31 March, 2011
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The Director-General
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

The Director-General
Manufacturing Industries Bureau
Ministry of Economy, Trade and Industry

The Director-General
Environmental Policy Bureau
Ministry of the Environment

Notice of the Good Laboratory Practice for test facilities conducting tests of New Chemical Substances etc.

With the enforcement of the *Act for the Partial Revision of the Act on the Evaluation of Chemical Substances and the Regulation of Their Manufacture, etc.* (Act No. 39 of 20th May, 2009), the test facility prescribed in Article 7 of *the Ministerial Ordinance Specifying Items for Tests Pertaining to New Chemical Substances and Studies Pertaining to the Hazardous Properties of Priority Assessment Chemical Substances and Monitoring Chemical Substances* (Prime Minister's Office, Ministry of Health and Welfare, Ministry of International Trade and Industries, Ministerial Ordinance No. 1 of 13th July, 1974), shall be those which comply, in principle, with following standards (hereinafter referred to as "Test Facility conducting the Studies pertaining to New Chemical Substances etc.") effective on and after 1st April 2011.

With regard to the *Notice of the Good Laboratory Practice for test facilities conducting tests of New Chemical Substances etc.* (Yakuhatsu No. 1121003, 21st November, 2003; Seikyoku No. 3, 17th November, 2003; Kampoki No. 031121004), it shall be repealed effective on 31st March, 2011.

The Good Laboratory Practice for test facilities conducting tests of New Chemical Substances etc.

Chapter 1. General Rules

Purposes

Article 1. These standards are established in order to ensure the quality of the study results by prescribing basic principles to be followed by the test facility when conducting the studies stipulated in the *Ministerial Ordinance Specifying Items for Tests Pertaining to New Chemical Substances and Studies Pertaining to the Hazardous Properties of Priority Assessment Chemical Substances and Monitoring Chemical Substances* (Prime Minister's Office, Ministry of Health and Welfare, Ministry of International Trade and Industries, Ministerial Ordinance No. 1 of 13th July, 1974).

Scope

Article 2. These standards shall apply to the studies stipulated in the Ministerial Ordinance Specifying Items for Tests Pertaining to New Chemical Substances and Studies Pertaining to the Hazardous Properties of Priority Assessment Chemical Substances and Monitoring Chemical Substances.

Definition of Terms

Article 3. The meaning of the key terms used in these standards shall be as described respectively in following matters.

(1) Safety study (hereinafter referred to as "study") means an experiment or set of experiments to obtain data on the properties or the safety of the test substance intended for submission to Ministry of Health, Labour and Welfare, Ministry of Economy, Trade and Industry, and Ministry of the Environment, associated with the report.

(2) Test facility means the persons, premises and its operational unit(s) that are necessary for conducting the study. For a study which is conducted at more than one site (hereinafter referred to as a "Multi-Site Study"), the test facility comprises the sites, which individually or collectively can be considered to be test facilities.

(3) Test Facility Management means the person(s) who has the authority and responsibility for the organisation and functioning of the test facility according to these standards.

(4) Test Site Management (limited to cases where he is appointed) means the person(s) responsible for ensuring that the delegated test facility are conducted in accordance with these standards.

(5) Sponsor means an entity which commissions the study to the test facility.

(6) Study Director means the individual responsible for the overall conduct of the study.

(7) Principal Investigator (limited to cases where he is appointed) means an individual who, for a Multi-Site Study, acts on behalf of the Study Director and has a certain responsibility for delegated phases of the study. The Study Director’s responsibility for the overall conduct of the study cannot be delegated to the Principal Investigator(s); this includes approval of the study plan and its amendments, approval of the final report and ensuring that these standards are followed.

(8) Quality Assurance Unit means an organisation which is independent of study conduct and is designed to assure the Test Facility Management of compliance with these standards.

(9) Standard Operating Procedures (SOPs) means documents which describe how to perform activities not specified in detail in study plans or test guidelines.

(10) Master schedule means a compilation of information to assist in the assessment of workload and for the tracking of studies at a relevant test facility.

(11) Study plan means a document which defines the objectives and experimental design for the conduct of the study, and, if any amendments are made, includes those amendments.

(12) Study plan amendment means an intended change to the study plan after the study initiation date.

(13) Study plan deviation means an unintended departure from the study plan after the study initiation date.

(14) Test system means any system of analytical or measurement equipment for physical/chemical data collection (hereinafter referred to as "physical/chemical test systems"), any system of animal/botanical/microbial organisms to be used in a study, or part of thereof, or any system of cultured cells (hereinafter referred to as "biological test systems") or a combination thereof used in a study.

(15) Raw data means the results of the original observations, and all original test facility records and documentation, or verified copies thereof, which are necessary for the reconstruction of the study and its evaluation. Raw data also include, for example, photographs, microfilm, microfiche copies, computer records, recording tapes, recorded data from automated instruments, or any other electronic medium that has been recognised as capable of providing secure storage of information for a time period as stated in Article 32, below.

(16) Specimen means any material derived from a test system for examination, analysis, or retention.

(17) Experimental starting date means the date on which the first study-specific data are collected.

(18) Experimental completion date means the last date on which data are collected from the study.

(19) Study initiation date means the date the Study Director signs or stamps the study plan.

(20) Study completion date means the date the Study Director signs or stamps the final report.

(21) Test substance means a chemical substance that is the subject of a study.

(22) Reference substance means any chemical substance used to compare with the test substance.

(23) Batch means a specific quantity or lot of a test substance or reference substance produced within a certain period of time in such a way that it could be expected to be of a uniform character.

(24) Vehicle means any substance which serves as a carrier used to mix, disperse, or solubilise the test substance or reference substance to facilitate the exposure or administration to the test system.

Chapter 2. Organisation and Personnel

Test Facility Management's Responsibilities

Article 4. Each Test Facility Management should ensure that these standards are complied with, in its test facility and, at a minimum, it should:

(1) ensure that a statement exists which identifies the individual(s) within a test facility who fulfil the responsibilities of management as defined by these standards;

(2) ensure that a sufficient number of qualified personnel, appropriate facilities, equipment, and materials are available for the timely and proper conduct of the study;

(3) ensure the maintenance of a record of the qualifications, training, experience and job description for each professional and technical individual;

(4) ensure that personnel clearly understand the functions they are to perform and, where necessary, provide training for these functions;

(5) ensure that appropriate and technically valid Standard Operating Procedures are established and followed, and approve all original and revised Standard Operating Procedures;

(6) ensure that a Quality Assurance Personnel is designated and assure that the quality assurance responsibility is being performed in accordance with these standards;

(7) designate an individual with the appropriate qualifications, training, and experiences as the Study Director before each study is initiated. Replacement of a Study Director should be done according to established procedures, and should be documented.

(8) ensure the documented approval of the study plan by the Study Director;

(9) ensure that the Study Director has made the approved study plan available to the Quality Assurance personnel;

(10) ensure the maintenance of a historical file of all Standard Operating Procedures;

(11) designate a person responsible for the management of archive(s);

(12) maintain a master schedule;

(13) ensure that test facility supplies meet requirements appropriate to their use in a study;

(14) ensure that test and reference substances are appropriately characterised and controlled;

(15) establish the procedures to ensure that computerised systems are suitable for their intended purpose, and are validated, operated and maintained in accordance with these standards.

(16) 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 the delegated phase(s) of the study. Replacement of a Principal Investigator should be done according to established procedures, and should be documented.

(17) ensure for a Multi-Site Study that clear lines of communication exist between the Study Director, Principal Investigator(s) (limited to cases where he is appointed), the Quality Assurance personnel and study personnel;

Test Site Management's Responsibilities

Article 5. When a phase of a study is conducted at any of the test facilities, each Test Site Management (limited to cases where he is appointed) should have all the responsibilities as defined in Article 4 with the following exceptions: (6), (7), (8), (9), (16) and (17).

Study Director's Responsibilities

Article 6. The Study Director is the single point of study control and has the responsibility for the overall conduct

of the study and for its final report. These responsibilities should include at a minimum, the following functions. The Study Director should:

(1) approve the study plan and any amendments to the study plan by dating and affixing signature or stamp (seal); amendments to the study plan, if any, should clearly state the details of and reasons for the amendments.

(2) ensure that the Quality Assurance Unit have a copy of the study plan and any amendments in a timely manner and communicate effectively with the Quality Assurance Unit as required during the conduct of the study;

(3) ensure that study plans and amendments and Standard Operating Procedures are available to study personnel;

(4) ensure that the procedures specified in the study plan are followed, and when any deviations from the study plan and Standard Operating Procedures are found, record and assess the impact on the quality and integrity of the study, and take appropriate corrective action if necessary; Above should be documented.

(5) ensure that all raw data generated are fully documented and recorded on paper or in appropriate electronic media;

(6) ensure that necessary measures have been taken in order for the computerised systems used in the study to work properly;

(7) sign or stamp 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 these standards;

(8) ensure that after completion (including termination) of the study, the study plan, the final report, raw data and supporting materials are archived;

(9) keep him/her away from work to avoid any possible adverse influence on the study, if the study personnel has any health problem which could affect adversely the conduct of the study, until it improves.

(10) ensure that the study plan and the final report for a Multi-Site Study identify and define the role of any Principal Investigator(s) (limited to cases where he is appointed) and any test facilities involved in the conduct of the study;

Principal Investigator’s Responsibilities

Article 7. The Principal Investigator (limited to cases where he is appointed) will ensure that the delegated phases of the study are conducted in accordance with these standards.

Study Personnel's Responsibilities

Article 8. Study personnel's responsibilities are as follows:

(1) All personnel involved in the conduct of the study must be knowledgeable in those parts of these standards which are applicable to their involvement in the study.

(2) Study personnel will comply with the study plan and appropriate Standard Operating Procedures

applicable to their involvement in the study. Any deviation from these instructions should be documented and communicated directly to the Study Director, and/or if appropriate, the Principal Investigator(s).

(3) All study personnel are responsible for recording raw data promptly and accurately and in compliance with these standards, 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 study. Study personnel having any health problems which could affect adversely the conduct of the study should communicate that to the appropriate person.

Chapter 3. Quality Assurance Unit

General

Article 9. The test facility should have documented Quality Assurance Provisions to assure that studies performed are in compliance with these standards.

2. The Quality Assurance Unit should comprise individuals who are designated by and directly responsible to the Test Facility Management and who are familiar with the test procedures.

3. The persons in charge above should not be involved in the conduct of the study being assured.

4. Quality Assurance Standard Operating Procedures should specify, at a minimum, the following functions:

(1) Study audits or inspections

(2) Inspection of the test facility and of the archive(s)

(3) Audit of the final report

(4) Preparation of the Quality Assurance Report

(5) Audits or inspections mainly for the process related to the quality of the study

5. Every time the Standard Operating Procedures in the preceding paragraph is prepared or revised, it shall be retained with the date and reason.

Quality Assurance Personnel's Responsibilities

Article 10. Quality Assurance Personnel’s responsibilities include, at a minimum, the following functions. They should:

(1) maintain copies of all approved study plans, Standard Operating Procedures and an up-to-date copy of the master schedule;

(2) verify that the study plan contains the information required for compliance with these standards. This verification should be documented;

(3) conduct audits or inspections to determine if all studies are conducted in accordance with these standards. Audits or inspections should also determine that study plans and Standard Operating Procedures have been made available to study personnel and are being followed. The results of these audits and inspections should be documented and retained;

(4) promptly report any audit or inspection results in writing to the Test Facility Management and to the Study Director, and to the Test Site Management and to the Principal Investigator(s), when applicable. If a problem which is sufficiently serious to affect the quality of the study is found, the recommendations for the solution should be made to the Test Facility Management and the Study Director along with the follow-up audit or inspection schedule. The details of these events should be documented.

(5) audit 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 studies;

(6) if it is found that the final report contents are appropriate, promptly report any audit or inspection results in writing to the Test Facility Management and to the Study Director, when applicable, to the Test Site Management and, to the Principal Investigator(s);

(7) prepare and sign or stamp a quality assurance statement, to be included in the final report, which specifies the types of audits/inspections and their dates, including the phase(s) of the study audited or inspected, and the dates that audit/inspection results were reported to the Test Facility Management and the Study Director and Principal Investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data.

Chapter 4. Facilities

General

Article 11. The test facility should be of suitable size, construction and location to meet the requirements of the study and to minimise disturbance that would interfere with the validity of the study.

2. Different activities are appropriately separated in the test facility in order to conduct each study properly.

Test System Facilities

Article 12. Test system facilities should conform to the following criteria:

(1) The test facility should have a sufficient number of rooms, areas or space to assure appropriate conduct of the study.

(2) In order to prevent any untoward effects on the test system, the test facility should have appropriate rooms, areas, space, installations or structure to assure the isolation of the test systems as needed and depending on the nature of test. Suitable rooms or areas should be available for the diagnosis, treatment and control of diseases, in order to ensure that there is no unacceptable degree of deterioration of the 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/or deterioration.

Facilities for Handling Test and Reference Substances

Article 13. To prevent contamination or mix-ups, there should be rooms or areas separately from test system facilities having the following functions;

(1) Receipt and storage of the test and/or reference substances.

(2) Mixing of a test or reference substance with a vehicle.

(3) Storage of the mixture of a test or reference substance with a vehicle.

2. The above-mentioned storage rooms or areas should be adequate to preserve identity, concentration, purity, and stability of the test and reference substances and each of their mixtures with a vehicle, and should have the capacity to store hazardous substances, that could adversely affect the test systems, separately form the test systems.

Archive Facilities

Article 14. Archive facilities should be provided for the secure storage and retrieval of study plans, raw data, final reports, samples of test substances and specimens. Archive design and archive conditions should protect contents from untimely deterioration (including the contract archiving services).

Waste Disposal Facilities

Article 15. Handling and disposal of wastes should be carried out in such a way as not to jeopardise the integrity of studies. This includes provision for appropriate collection, storage and disposal facilities, and decontamination and transportation procedures.

Chapter 5. Apparatus, Equipment, Reagents, and Materials

Apparatus and Equipment

Article 16. Apparatus, including validated computerised systems, used for the generation, storage and retrieval of data, and for controlling environmental factors relevant to the study, should be suitably located and of appropriate design and adequate capacity.

2. Apparatus and equipment used in a 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, comply with national or international standards of measurement.

3. In cases where apparatus and/or equipment are repaired due to failure or breakage, the date, the details and personnel involved should be recorded and retained.

Reagents

Article 17. Chemicals, reagents, and solutions should be labelled to indicate name, source of supply, concentration, date of preparation, expiry date and specific storage instructions.

2. Although altered or expired reagents should not be used in a study, the expiry date may be extended on the basis of documented evaluation or analysis.

Materials

Article 18. Apparatus, equipment and materials used in a study should not interfere adversely with the test systems.

Chapter 6. Test Systems

Physical/Chemical Test Systems

Article 19. The physical/chemical test systems should comply with the following matters;

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

(2) Apparatus and equipment used for the measurements of physical/chemical data should be maintained and regulated in good condition according to Standard Operating Procedures. In cases where apparatus and/or equipment are repaired due to failure or breakage, the date, the details and personnel involved should be documented and retained.

(3) The accuracy of physical/chemical test systems should be checked by measuring the reference substance, provided, however, that this shall not apply if the verification is not required in the study method.

Biological Test Systems

Article 20. The biological test systems should comply with the following matters;

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

(2) Newly received biological test systems should be monitored for abnormalities in a suitable housing or containers so as to avoid contamination or infection to other biological test systems and the results should be recorded.

(3) In the preceding item, if there is any unusual mortality or morbidity affecting the whole lot of the test system, the said lot should not be used in the studies and, when appropriate, should be humanely destroyed.

(4) At the experimental starting date, the relevant biological test system should be free of any disease or condition that might interfere with the purpose or conduct of the study.

(5) Biological test systems that become diseased or injured during the course of a 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 study should be recorded.

(6) Records of source, date of receipt, and condition on receipt of biological test systems should be maintained.

(7) Biological test systems should be acclimatised to the test environment for an adequate period before the first exposure or administration of the test or reference substance.

(8) All information needed to properly identify the biological test systems should appear on their housing or containers. Individual biological test systems that are to be removed from their housing or containers during the

conduct of the study should bear appropriate identification.

(9) During use, housing or containers for test systems should be cleaned at appropriate intervals and kept in sanitised conditions. Any material that comes into contact with the test system should be free of contaminants at levels that would interfere with the study. Bedding for animals should be changed when appropriate. Use of pest control agents should be documented.

Chapter 7. Test and Reference Substances

Receipt, Handling, Sampling and Storage

Article 21. Records including test substance and reference substance characterisation, date of receipt, expiry date, quantities received and used in studies should be maintained.

2. Handling, sampling, and storage procedures should be identified in order that the homogeneity and stability are assured as much as possible and contamination or mix-ups are precluded.

3. Storage container(s) should carry identification code, expiry date and specific storage instructions.

Characterisation

Article 22. Each test and reference substance should be appropriately identified with an identification code, Chemical Abstracts Service Registry Number (CAS number), name and biological parameters.

2. For each study, the identity, including lot number, purity, composition, concentrations, or other characteristics to appropriately define each lot of the test or reference substances should be known.

3. In cases where the test substance 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 substance subject to the study.

4. The stability of test and reference substances under storage and test conditions should be known for all studies.

5. If the test substance is exposed or administered after mixing with a vehicle, the homogeneity, concentration and stability of the test substance in that vehicle should be determined.

6. A sample for analytical purposes from each batch of the test substance should be retained for all studies except short-term studies.

Chapter 8. Standard Operating Procedures

General

Article 23. 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 that test facility.

2. Revisions to Standard Operating Procedures should require written approval of the Test Facility Management.

3. Every time the Standard Operating Procedures is prepared or revised, it shall be retained with the date and

reason.

4. Each separate test facility unit or area should have immediately available current Standard Operating Procedures relevant to the activities being performed therein. Published analytical methods, articles and manuals may be used as supplements to these Standard Operating Procedures.

5. Deviations from Standard Operating Procedures related to the study should be documented and should be acknowledged by the Study Director and, if appointed, the Principal Investigator(s).

Matters to be Described in Standard Operating Procedures

Article 24. Standard Operating Procedures should be available for, at a minimum, the following categories of test facility activities.

(1) Test and Reference Substances
Receipt, identification, labelling, handling, sampling, storage and mixing with vehicle

(2) Apparatus and Equipment
Operation, checking, cleaning, maintenance and calibration

(3) Computerised Systems
Validation, operation, checking, maintenance, , security, change control and back-up

(4) Reagents etc.
Preparation, storage and labelling

(5) Record Keeping, Reporting, Storage, and Retrieval
Identification code, data collection, preparation of reports, indexing systems, handling of data (including the use of computerised systems)

(6) Test System (where appropriate)
a. Room or area and environmental room conditions for the test system.
b. Procedures for receipt, transfer, proper placement, characterisation, identification and care of the test system
c. Test system preparation, observations and examinations, before, during and at the conclusion of the study
d. Handling of test system individuals found moribund or dead during the study
e. Collection, identification and handling of specimens (including necropsy and histopathology)
f. Siting and placement of test systems in test plots.

(7) Quality Assurance Unit
Operation of Quality Assurance Unit in planning, scheduling, performing, documenting and reporting audits or inspections

(8) Protective measures concerning safety and hygiene

Chapter 9. Performance of the Study

Study Plan

Article 25. For each study, a written plan should exist prior to the initiation of the study. The study plan should be

approved by dating and signing or placing a stamp by the Study Director on it and verified for compliance with these standards by Quality Assurance personnel as specified in the Article 10 above.

Amendments to the Study Plan

Article 26. Amendments to the study plan should be justified in writing and approved by dating and signing or placing a stamp by the Study Director on it and maintained with the original study plan.

2. Deviations from the study plan should be documented with the reason and approved by dating and signing or placing a stamp on it in a timely fashion by the Study Director and/or, if appointed, Principal Investigator(s) and maintained with the study raw data.

Content of the Study Plan

Article 27. The study plan should contain, at a minimum, the following information:

(1) Identification of the Study, the Test substance and Reference substance
  a. Title ;
  b. The nature and purpose of the study;
  c. Name, abbreviation, or identification code of test and reference substances;

(2) Information Concerning the Test Facility and the Sponsor;
  a. Name and address of the Test Facility and the Sponsor;
  b. Name and affiliation of the Study Director;
  c. Name and affiliation of Principal Investigator(s) (limited to cases where he is appointed) and the phase(s) of the study delegated by the Study Director and under the responsibility of the Principal Investigator(s).;

(3) Dates
  a. The date of approval of the study plan by signing or placing a stamp by the Study Director on it.
  b. The proposed experimental starting and completion dates.

(4) Test Methods
  Test method to be used and test guideline to be referred to.

(5) Issues (where applicable)
  a. The justification for selection of the test system;
  b. Characterisation of the test system, such as the species, strain, substrain, source of supply, number, body weight range, sex, age and other pertinent information;
  c. The method of exposure or administration and the reason for its choice;
  d. The dose levels and/or concentration(s), frequency and duration of exposure or administration;
  e. Detailed information on the experimental design, including a description of the chronological procedure of the study; analysis, measurements, observations and examinations to be performed; type and frequency of analysis; , and statistical methods to be used.

(6) Records
  A list of records and materials to be retained.

Conduct of the Study

Article 28. Implementation of the Study should comply with the following matters;

(1) The study should be conducted in accordance with the Study Plan and the Standard Operating Procedures under the Study Director's guidance, supervision and control.

(2) A unique identification code should be given to each study and the code should be displayed on the relevant records or specimens. The code should enable the specimens to confirm their origin.

(3) Except for direct computer inputs, all data generated during the conduct of the study should be recorded directly, promptly, accurately, legibly, and indelibly by the individual involved in the study. These entries should be signed and dated, or have a stamp placed on them.

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

(5) When data are input directly in a computer, the individual(s) responsible for the data entries should confirm whether the accurate data are input and record the date of entry and their own names.

(6) Any changes of the data directly entered into a computer should be securely recorded along with reason for the change(s), date, personnel involved. And, where possible, the records of the change(s) are made searchable retrospectively by entering separately.

Chapter 10. Reporting of Study Results

General

Article 29. Reporting of the study results should comply with the following matters;

(1) A final report should be prepared for each study.

(2) The final report should be dated and signed or stamped by the Study Director to indicate acceptance of responsibility for the validity of the data. It should be stated that the relevant study has been conducted according to these standards.

(3) When the reports related to the relevant study prepared by the Principal Investigators (limited to cases where they are appointed) or other scientists involved are attached to a final report, the relevant reports should be dated and signed or stamped by the preparer.

(4) Corrections and additions to a final report should be in the form of amendments without obscuring the previous entry. Amendments should clearly specify the reason for the corrections or additions and should be dated and signed or stamped by the Study Director. Any corrections and additions to a final report should be notified to the Quality Assurance Unit.

Attachment of Quality Assurance Statement

Article 30. The final report should include a Quality Assurance Statement listing the following matters with signature or stamp by Quality Assurance personnel. This statement would also serve to confirm that the final report reflects the raw data.

(1) Types of audits or inspections made and their date

(2) Phase(s) of the study audited or inspected

(3) Date of any audit or inspection results which were reported to the Test Facility Management and to the Study Director and, if appointed, Principal Investigator(s).

Content of the Final Report

Article 31. The final report should include, at a minimum, the following information:

(1) Identification of the Study, the Test and Reference Substances
a. Title and the purpose of study;
b. Name, abbreviation, or identification code of test and reference substances;
c. Characterisation of the test substance (including purity, stability and homogeneity);

(2) Information Concerning the Test Facility and the Sponsor;
a. Name and address of the test facility and the sponsor;
b. Name and affiliation of the Study Director;
c. Name(s) and affiliation(s) of the Principal Investigator(s) (limited to cases where he is appointed) and the phase(s) of the study delegated;
d. Name(s) of Study Personnel and their split of work;
e. Names and affiliations of specialists and the part(s) of the final report to which they contributed.

(3) Dates
a. Study initiation date;
b. Experimental starting and completion dates;

(4) Description of Materials and Test Methods
a. Description of materials used;
b. Reference to test method and test guidelines;

(5) Any environmental factors which might interfere adversely with the quality of the study results.

(6) Results
a. A summary of results;
b. All information and data required by the study plan;
c. A description of the results (including determinations of statistical testing);
d. An evaluation, consideration, and conclusion based on the results;

(7) Storage
The location(s) where the study plan, samples of test and reference substances, specimens, raw data and the final report are to be stored.

Chapter 11. Storage and Retention of Records and Materials

Retention Period

Article 32. The following records and materials should be retained in the archives for the period specified below;

(1) Master schedule;

(2) The study plan, raw data, and the final report of each study;

(3) Records of all audits or inspections performed by the Quality Assurance Unit;

(4) Records of qualifications, training, experience and job descriptions of personnel;

(5) Records and reports of the maintenance and calibration of apparatus;

(6) Validation documentation for computerised systems;

(7) The historical file of all Standard Operating Procedures;

(8) Environmental monitoring records;

The archive materials listed (1) to (8) above should be retained for 10 years after receiving the notification according to the provisions of Item 1 or 2 of Article 4; Item 2, 3 or 8 of Article 5; Item 3 of Article 10; or Item 2 of Article 14 of the Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc (Act No.117 of 16th October, 1973, hereinafter referred to as "Chemical Substance Control Low (CSCL)")

(9) Test and reference substances, and any other samples;

(10) Specimens;

The archive materials listed (9) and (10) should be retained for 10 years after receiving the notification according to the provisions of Item 1 or 2 of Article 4; Item 2, 3 or 8 of Article 5; Item3 of Article 10 or Item 2 of Article 14 of CSCL, or for as long as they can be kept under ideal conditions without deterioration of their quality, whichever is shorter.

Manner of Archiving

Article 33. Operation of archiving should comply with the following matters;

(1) Records and materials retained in the archives should be indexed so as to facilitate orderly storage and retrieval.

(2) Test Facility Management should designate the person responsible for the management of archive(s) in archive facilities. Standard Operating Procedures related to archiving should be prepared.

(3) Only personnel authorised by the person responsible for the management of archive(s) or Test Facility Management should have access to the archives. Access into the archives and movement of material in and out of the archives should be properly recorded.

Transfer of Archiving Materials

Article 34. 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(s) of the study(ies).

Chapter 12. Miscellaneous

Confirmation with the Sponsor

Article 35. In cases where a test facility is commissioned a study, the test facility should confirm with the sponsor in advance whether the relevant study should be conducted according to these standards.

Reference Matters

Article 36. In these standards, any other guidance matters required in conducting specific studies are given in the

Annexes attached thereto.

Annex 1. Further Requirements for Conducting the Biodegradation Test

Chapter 1. Equipment, Apparatus, Materials, and Reagents

Equipment and Apparatus

Article 1. Equipment used for the sludge culturing should be carefully maintained to avoid disturbance due to external factors that would interfere physically, chemically or biologically with the activated sludge.

Materials

Article 2. Any equipment and apparatus that come into contact with the activated sludge and the test substance should be made of materials that would not affect the viability of the activated sludge and the identification and determination of quantity of the test substance.

Chapter 2. Test Systems

Handling of Activated Sludge

Article 3. Observation and analytical results of activated sludge which is kept in the culture vessels for sludge shall be recorded and retained.

Chapter 3. Standard Operating Procedures

Matters Stipulating Standard Operating Procedures

Article 4. For Biodegradation Test, with respect to handling of test systems, Standard Operating Procedures should be supplemented with the following matters;.

(1) Sampling or receiving and transporting of sludge

(2) Preparation and culture of sludge

(3) Determination of concentration of suspended solids in activated sludge

(4) Maintenance and observation of the sludge in the equipment used for the sludge culturing

(5) Inoculation of activated sludge

(6) Maintenance and observation of the activated sludge in the closed oxygen consumption respirometer

2. For the Degradation Study, with respect to examination and analysis, the Standard Operating Procedures should be supplemented with the following matters

(1) Pre-analysis storage of the contents of culture bottles

(2) Waste disposal after the analysis

Chapter 4. Planning and Performance of Study

Study Plan

Article 5. For the Degradation Study, a Study Plan should be supplemented with the following matters;

(1) Source of sludge, concentration of suspended solids in activated sludge inoculated and other parameters relating to the sludge

(2) Test temperature, concentration of the test substance and other test conditions

Annex 2. Further Requirements for Conducting the Bioconcentration Test of Chemical Substances in Fish

Chapter 1. Equipment, Apparatus, Materials, and Reagents

Apparatus and Equipment

Article 1. Water tanks for acclimation and water tanks for testing should be carefully maintained to avoid disturbance due to external factors that would interfere physically, chemically or biologically with the test fish.

Materials

Article 2. Any equipment and apparatus that come into contact with the test fish and the test substance should be made of materials that would not affect the condition of the fish and the identification and determination of quantity of the test substance.

Chapter 2. Test Systems

Handling of Test Fish

Article 3. Newly received lots of fish should be treated in the other holding ponds or acclimation tank of other lots of fish until the individual fish found with observable disease, weakness, or damaged gills or skin are removed.

2. Observation results and treatment status of test fish before and during the study should be recoded and retained.[1]

Chapter 3. Standard Operating Procedures

Matters Stipulating Standard Operating Procedures

Article 4. For conducting the Concentration Test of Chemical Substances in Fish (hereinafter referred to as "Bioconcentration Test"), with regard to handling of test systems, Standard Operating Procedures should be supplemented with the following matters;

(1) Selection of fish species

(2) Determination of test method (including uptake and depuration periods, and sampling of test fish)

(3) Receiving and transferring test fish

(4) Selection of test fish

(5) Holding of test fish

(6) Dipping and dosing to test fish

(7) Sterilisation and disinfection of test fish

(8) Acclimation of test fish

(9) Management and observation of test fish from experimental starting date until experimental completion date

(10) Sampling and weighing of test fish

(11) Determination of lipid content in test fish

(12) Determination of test substance concentration in the water of test tanks

(13) Acute fish toxicity test for setting dose levels to be used in the Bioconcentration Test

2. For the Bioconcentration Test, with respect to examination and analysis, the Standard Operating Procedures should be supplemented with the following matters;

(1) Homogenisation of test fish tissue and extraction with solvents, and other pretreatment

(2) Pre-analysis storage of test fish (including the homogenate)

(3) Waste disposal after analysis

Chapter 4. Planning and Performance of Study

Study Plan

Article 5. For the Bioconcentration Test, a Study Plan should be supplemented with the following matters;

(1) Source, holding condition, acclimation condition and any other parameters related to the test fish

(2) Test temperature, concentration of the test substance, justification for setting the uptake and depuration periods, quality of test water, supplying method of test substance and test water, and any other parameters related to the test conditions

Chapter 5. Reporting of Study Results

Matters to be Described in the Final Report

Article 6. For the Bioconcentration Test, the final report should be supplemented with the following matters;

(1) Test fish

(2) Determination of test method (including uptake and depuration periods, its reason, and sampling of test fish)

Annex 3. Further Requirements for Conducting the Determination of 1-Octanol/Water Partition

Coefficients Study

Chapter 1. Standard Operating Procedure

Matters Stipulating by Standard Operating Procedures

Article 1. For conducting the Determination of 1-Octanol/Water Partition Coefficients Test (hereinafter referred to as "Partition Coefficient Determination Test"), with respect to handling of test systems, Standard Operating Procedures should be supplemented with the following matters;

(1) Estimation of the partition coefficient

(2) Preparation and/or saturation of solvent

(3) Preparation of test substance solution and reference substance , and their storage

(4) Solvent amount, solvent volume ratio, and amount of test substance used in the test

(5) Establishment of the partition equilibrium (shaking and phase separation)

2. For conducting the Partition Determination Coefficient Test, with respect to examination and analysis, the Standard Operating Procedures should be supplemented with the following matters;

(1) Sampling of 1-octanol phase and water phase and pre-analysis preparation

(2) Waste disposal after analysis

Annex 4. Further Requirements for Conducting the Chemical Substances' Chronic Toxicity Study, the Test on the Impact on Reproductive Potential and Later Generations, the Teratogenicity Test, the Mutagenicity Test, the Carcinogenicity Test, the Test on *in vivo* Fate, the Pharmacological Test and the Repeated Dose Toxicity Test in Mammals

Chapter 1. Facilities

Test Facilities

Article 1. The Test Facility for conducting the Chemical Substances' Chronic Toxicity Study, the Test on the Impact on Reproductive Potential and Later Generations, the Teratogenicity Test, the Mutagenicity Test, the Carcinogenicity Test, the Test on in vivo Fate, the Pharmacological Test and the Repeated Dose Toxicity Test in Mammals (hereinafter referred to as" Toxicity Tests") should have the facilities and areas as described respectively in following matters;

(1) Animal breeding facilities, etc.

a. The test facility should have an animal breeding facility of suitable size and construction which provides equipment or apparatus for controlling the environment as necessary with respect to temperature, humidity, ventilation, and lighting.

b. Animal breeding facilities should have a sufficient number of animal rooms or areas, fulfiling the following requirements when necessary;

(i) Capacity to separate and breed animals by species or other biological test systems
(ii) Capacity to separate and breed animals by the study plan
(iii) Quarantine of animals

c. The test facility should have specialised animal rooms or areas where studies can be conducted in isolation from other studies in conducting the studies using test or reference substances such as volatile substances, aerosols, or radioactive materials, etc. and materials known to be biohazardous, such as infection agents, to that test system.

d. Suitable facilities should be available for the isolation and treatment of animals with diseases.

(2) Facilities for supplies for animals

a. The test facility should have storage areas, as needed, for animal feed, bedding, supplies and apparatus. In this case, storage areas for feed and bedding should be separated from areas housing the test systems and should be protected against contamination. Refrigeration should be provided for perishable supplies or feed.

(3) Areas for experimental procedures

a. The test facility should have separate operating areas, as needed, for carrying out periodic measurements and other operations such as biochemical tests, histopathology, surgery and necropsy.

b. There should be specialised areas for the test using constituents of animals or microorganisms in a test facility.

c. The test facility should have areas separated for cleaning, sterilising and maintaining supplies and apparatus used during the conduct of a study.

Chapter 2. Equipment, Apparatus and Reagents

Materials

Article 2. Regarding materials used in toxicity tests, the following matters should be implemented;

(1) Necessary measures should be taken, at appropriate intervals, to ensure that animal cages, pens, racks and accessory equipment are kept clean and sanitary.

(2) Bedding used in animal cages or pens should not interfere with the purpose or conduct of the study and should be changed, as often as necessary, to keep the rearing environment dry and clean.

(3) Feed and water for the animals should be analyzed periodically to ensure that contaminants which can interfere with the study and can be reasonably expected to be present in such feed or water are not present at levels above those specified in the study plan. In this case, documentation of such analysis should be maintained as raw data.

(4) Detergents or pest control agents that interfere with the study should not be used. If such materials are used, it should be documented.

Chapter 3. Test and Reference Substances

Handling of Test and Reference Substances

Article 3. Regarding handling methods for the test and reference substances at test facilities, the following matters should be implemented;

(1) Test and reference substances should be distributed in a manner designed to preclude the possibility of

contamination or deterioration.

(2) Proper labelling should be done in the distribution process.

(3) The date and quantity should be documented for each lot when substances are distributed or returned.

Mixing with Vehicle

Article 4. When each test or reference substance is used as a mixture with a vehicle, the stability of the test or reference substance in the mixture should be, in principle, measured before the study. If there are circumstances which make it impossible to measure the stability of the mixture before the study, Standard Operating Procedures concerning the measurement of the stability should be established and followed to provide for periodic analysis.[2]

2. When feed is employed as a vehicle, the homogeneity and concentration of the test or reference substance when mixed with feed should be measured periodically.

3. When any of the components of the mixture of a test or reference substance with a vehicle has an expiry date, the date should be clearly indicated on the container. If more than one component has an expiry date, the earliest date should be indicated.

Chapter 4. Test Systems

Animal Husbandry

Article 5. Animals to be used in a toxicity test should be raised and managed appropriately in compliance with the following matters;

(1) All newly received animals from outside sources should have their health status evaluated, and those animals observed to have diseases or morbidity that might interfere with the purpose or conduct of a study should be isolated from the healthy animals and should not be used.

(2) If, during the course of a study, animals are found to develop diseases or morbidity that might interfere with the purpose or conduct of the study, such animals should be isolated from the other animals. If necessary, the isolated animals may be approved by the Study Director to be treated for diseases provided that such treatment does not interfere with the study. In this case, the reason for the treatment, approval of such treatment, method of treatment, prescription of remedies, each date of treatment and treatment outcomes should be recorded and maintained.

(3) Animals should be acclimated to the study environment for an appropriate period before the study.

(4) Animals should, as necessary, be appropriately identified by tattoo, ear punch, ear tag, colour code, or other means.

(5) For animals used in a study, information identifying all animals within an animal room should be indicated on the outside of cages, pens or racks to preclude errors in housing, as necessary.

(6) Animals of different species should be housed in separate rooms, in principle.

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[2] As a standard manner of operation, SOP should be prepared for the measurement of the stability for a particular test substance, however, it is unreasonable to relate it to the inability to measure the stability of the mixture before the initiation of the study.

(7) If animals of the same species housed in the same room are to be used in different studies, separation and identification by adequate space should be made.

Chapter 5. Standard Operating Procedures

Matters Stipulating by Standard Operating Procedures

Article 6. For Toxicity Tests, Standard Operating Procedures should be supplemented with the following matters;

(1) Animal breeding facility maintenance and animal husbandry management.

(2) Identification, housing, placement and transfer of test animals.

(3) Observation of common symptom of test animals, etc..

(4) Handling of moribund or dead animals.

(5) Necropsy or post-mortem examination of animals.

(6) Collection and identification of specimens.

(7) Histopathology inspection.

(8) Other necessary matters.

Chapter 6. Planning and Performance of a Study

Matters to be Described in the Study Plan

Article 7. For Toxicity Tests, the study plan should be supplemented with the following matters;

(1) Reason for selection of the test system.

(2) Species, strain, number, age, sex, body weight range and source of supply of the test system.

(3) Method for identification of the test system.

(4) Methods used in the experimental design to minimise bias.

(5) Feed (the description should include determination of acceptable levels of potential contaminants that are known to be capable of interfering with the purpose or conduct of the study if present above certain levels) and other vehicles.

(6) Route of administration of the test and reference substances, and the reason for its selection.

(7) Dosage levels of the test and reference substances, and the method, frequency and duration of their administration, as well as the reason for their selections.

(8) Method of determining the rate of absorption of the test and reference substances in the test systems, if necessary, to achieve the objectives of the study.

(9) Other necessary matters.

Conduct of a Study

Article 8. The specimens should be labelled by an appropriate method, specifying the nature of the study, identification number of the test system and their date of collection.

2. When a specimen of tissue is examined for histopathological study, records of gross necropsy findings for that specimen should be available to the person in charge of the examination.

Chapter 7. Reporting of Study Results

Matters to be Included in Final Report

Article 9. For Toxicity Tests, the final report should be supplemented with the following matters~~;~~

(1) Stability of the test and reference substances under the conditions of their administration.

(2) The species, strain, number, age, sex, body weight range, source of supply, date of receipt and housing conditions of the test system.

(3) The route, dosage levels, method, frequency, and duration of administration of the test or reference substance.

(4) Reason for the dosage levels of the test or reference substance.

(5) Other necessary matters.

Chapter 8. Storage of Samples and Materials

Storage

Article 10. Conditions of storage should be designed so as to minimise damage or deterioration of documents or specimens during the retention period.

Retention Period of Specimens

Article 11. Wet specimens which differ markedly in quality during storage, such as histochemical, electron microscopic, hematological or teratological specimens, and specially prepared specimens should be maintained only as long as the quality of the specimens withstands evaluation. This period is regarded as conforming to the requirements stipulated in the standards.

Annex 5 Further Requirements for Conducting the Algal Growth Inhibition Test, the Daphnia sp. Acute Immobilisation Test, the Fish Acute Toxicity Test, the Daphnia magna Reproduction Test, the Test of Effects on survival and Growth in Fish Early Life Stage and the Test of Effects on Chironomid survival and Growth

Chapter 1. Facilities

Test Facilities

Article 1. The test facility for conducting the Algae Growth Inhibition Test, the Daphnia sp. Acute Immobilisation Test, the Fish Acute Toxicity Test, the *Daphnia magna* Reproduction Test, the Test of Effects on Survival and Growth in Fish Early Life Stage and Test of Effects on Chironomid survival and Growth should have the facility(ies) and area(s) as described in the following matters;

(1) Facility for maintaining of test organisms etc.

a. The test facility should have an organisms maintaining facility which provides equipment or apparatus for controlling the environment as necessary with respect to temperature, humidity, ventilation, and lighting.

b. Organisms maintaining facility should have rooms or areas, fulfiling the following requirements when necessary;

(i) Capacity to separate by species or biological test systems.

(ii) Capacity to separate by the study plan.

c. The test facility should have specialised rooms or areas where studies can be conducted in isolation from other studies in conducting the studies using test or reference substances such as volatile substances, aerosols or radioactive materials, etc. and materials known to be biohazardous, such as infection agents, to that test system.

d. Suitable facilities should be available for the isolation of test organisms with diseases.

(2) Facilities for supplies for test organisms

The test facility should have storage areas, as needed, for test organisms feed, supplies and apparatus.

(3) Facilities for experimental procedures

a. The test facility should have separate operating areas, as needed, for carrying out periodic measurements and other operations such as counting and observations of organisms.

b. The test facility should have areas separated for cleaning, sterilising and maintaining supplies and apparatus used during the conduct of a study.

Chapter 2. Equipment, Instruments and Reagents

Materials

Article 2. Regarding materials used in Aquatic Toxicity Tests, the following matters should be implemented;

(1) Necessary measures should be taken at appropriate intervals to ensure that vessels, racks and accessory equipment are kept clean and sanitary.

(2) Water used for the experiments should be analyzed periodically to ensure that contaminants which can interfere with the study and can be reasonably expected to be present in such water are not present at levels above those considered to be a problem. In this case, documentation of such analysis should be maintained as raw data.

(3) If detergents or pest control agents are used, it should be recorded.

Chapter 3. Test and Reference Substances

Handling of Test and Reference Substances

Article 3. Regarding handling methods for the test and reference substances at test facilities, the following matters should be implemented;

(1) Test and reference substances should be distributed in a manner designed to preclude the possibility of contamination or deterioration.

(2) Proper labelling should be done in the distribution process.

(3) The date and quantity should be documented for each lot when substances are distributed or returned.

Chapter 4. Test Systems

Animal Husbandry

Article 4. Organisms to be used in Aquatic Toxicity Tests should be raised and managed appropriately in compliance with the following matters;

(1) All newly received organisms from outside sources should have their health status evaluated, and those organisms observed to have diseases or morbidity that might interfere with the purpose or conduct of a study should be isolated from the healthy organisms and should not be used.

(2) If, during the course of a study, animals are found to develop diseases or morbidity that might interfere with the purpose or conduct of the study, such organisms should be isolated from the other organisms and should not be used.

(3) Organisms to be assigned to the study should be observed for their health prior to or during the conduct of the study, and observed results and abnormalities, if any, should be documented and retained.

(4) Organisms of different species should be housed in separate rooms or containers.

(5) If animals of the same species housed in the same room are to be used in different studies, separation and identification by aquarium/vessel should be made after exposure to the test substance.

(6) For the species that might be capable of survival and propagation outside of the test facility, necessary measures should be taken to ensure their containment to avoid escape during maintaining or study periods.

(7) Any biological waste remaining after completion of the study should processed appropriately and discarded accordingly.

Repeatability of Test Ssystem

Article 5. In order to evaluate the repeatability of the test system, a sensitivity test on the organisms to be used in the study should be confirmed at each occasion of the study conduct or at regular intervals (e.g., every six months), provided that, for the Chironomid study for the effects on life or growth, the population from the same supply source that was confirmed for sensitivity does not need such testing. Specifically, a toxicity study should be conducted with the reference substance and its results should be recorded together with the background data (averages and standard deviations) and those records shall be retained. If it is concluded that repeatability of the test system is not attained, those populations should not be used in the study.

Chapter 5. Standard Operating Procedures

Matters Stipulating Standard Operating Procedures

Article 6. For the Aquatic Toxicity Tests, Standard Operating Procedures should be supplemented with the following matters;

(1) Test organisms rearing room and husbandry management.

(2) Receipt, identification, selection, housing and transfer of test organisms.

(3) Acclimation and sensitivity test of test organisms.

(4) Management and observation of organisms during the test period.

(5) Determination of the test substance concentration in the test solution contained in test vessels.

(6) Handling of moribund or dead animals.

(7) Other necessary matters.

Chapter 6. Planning and Performance of a Study

Matters to be described in the Study Plan

Article 7. For Aquatic Organisms Toxicity Tests, the study plan should be supplemented with the following matters;

(1) Test temperature, test water type and any other conditions related to the conduct of the study.

(2) Any other necessary matters.

Chapter 7. Reporting of Study Results

Matters to be Described in the Final Report

Article 8. With regard to the Aquatic Toxicity Tests, the final report should be supplemented with the following matters;

(1) Stability of the test substance under the exposure conditions.

(2) Records regarding the date of receipt of the test system, historical data of the sensitivity test, and acclimation conditions, where appropriate.

(3) Other necessary matters.

Chapter 8. Storage of Samples and Materials

Storage

Article 9. Conditions for storage should be designed so as to minimise damage or deterioration of documents during the retention period.

Annex 6. Further Requirements f for Conducting the Avian Reproduction Toxicity Test

Chapter 1. Facilities

Test Facilities

Article 1. The test facility for conducting the Avian Reproduction Toxicity Test (hereinafter referred to as "Birds Reproduction Test") should have facility(ies) and area(s) as described in following matters;

(1) Bird maintaining facilities

a. The test facility should have a bird maintaining facility of suitable size and construction which provides equipment or apparatus for controlling the environment as necessary with respect to temperature, humidity, ventilation, and lighting

b. Bird maintaining facilities should have a sufficient number of animal rooms or areas, fulfiling the following requirements when necessary;

(i) An adequate separation of bird species or test systems.

(ii) An adequate separation of birds by the study plan.

(iii) Quarantine of birds.

c. The test facility should have specialised bird rooms or areas where studies can be conducted in isolation from other studies in conducting studies using test or reference substances such as volatile substances, aerosols, or radioactive materials, etc. and materials known to be biohazardous, such as infection agents, to that test system.

d. Suitable facilities should be available for the isolation and treatment of birds with diseases.

(2) Facilities for supplies for birds

The test facility should have storage areas, as needed, for bird feed, bedding, supplies and apparatus. In this case, storage areas for feed and bedding should be separated from areas housing the test systems and should be protected against contamination. Refrigeration should be provided for perishable supplies or feed.

(3) Facilities for experimental procedures

a. The test facility should have separate operating areas, as needed, for carrying out periodic measurements and other operations such as histopathology and necropsy.

b. The test facility should have areas separated for cleaning, sterilising and maintaining supplies and apparatus used during the conduct of a study.

Chapter 2. Equipment, Instruments and Reagents

Materials

Article 2. Regarding materials used in Birds Reproduction Test, the following matters should be implemented;

(1) Necessary measures should be taken, at appropriate intervals, to ensure that bird cages, racks and accessory equipment are kept clean and sanitary.

(2) Bedding used in bird cages should not interfere with the purpose or conduct of the study and should be changed, as often as necessary, to keep the rearing environment dry and clean.

(3) Feed and water for the birds should be analyzed periodically to ensure that contaminants which can interfere with the study and can be reasonably expected to be present in such feed or water are not present at levels above those considered to be a problem. In this case, documentation of such analysis should be maintained as raw data.

(4) Detergents or pest control agents that interfere with the study should not be used. If such materials are used, it should be documented.

Chapter 3. Test and Reference Substances

Handling of Test and Reference Substances

Article 3. Regarding handling methods for the test and reference substances at test facilities, the following matters should be implemented;

(1) Test and reference substances should be distributed in a manner designed to preclude the possibility of contamination or deterioration.

(2) Proper labelling should be done in the distribution process.

(3) The data and quantity should be documented for each lot when substances are distributed or returned.

Mixing with Feed

Article 4. For each test or reference substance that is mixed with a vehicle, the homogeneity of the test or reference substance in the mixture should be measured, and the stability of the test substance or reference substance in the mixture should be measured periodically.

2. Where any of the components of the mixture of a test or reference substance with a vehicle has an expiry date, that date should be clearly indicated on the container. If more than one component has an expiry date, the earliest date should be indicated.

Chapter 4. Test Systems

Bird Husbandry

Article 5. Birds to be used in the Birds Reproduction Test should be raised and managed appropriately in compliance with the following matters;

(1) All newly received birds from outside sources should have their health status evaluated, and those birds observed to have diseases or morbidity that might interfere with the purpose or conduct of a study should be isolated from the healthy birds and should not be used.

(2) If, during the course of a study, birds are found to develop diseases or morbidity that might interfere with the purpose or conduct of the study, such birds should be isolated from the other birds. If necessary, the isolated birds may be approved by the Study Director to be treated for diseases provided that such treatment does not interfere with the study. In this case, the reason for the treatment, approval of such treatment, method of treatment, prescription of remedies, each date of treatment and treatment outcomes should be recorded and maintained.

(3) Birds should be acclimated to the study environment for an appropriate period before the study.

(4) Birds should, as necessary, be appropriately identified by leg ring, wing band, colour code, or other means.

(5) For birds used in a study, information identifying birds within a room should be indicated on the outside of cages or racks to preclude errors in housing, as necessary.

(6) Birds to be assigned to the study should be observed for their health prior to or during the conduct of the study, and observed results and abnormalities, if any, should be documented and retained.

(7) Birds of different species should be housed in separate rooms, in principle.

(8) If birds of the same species housed in the same room are to be used in different studies, separation and identification by adequate space should be made.

(9) For the species that might be capable of survival and propagation in external environment, necessary measures should be taken to ensure their containment to avoid escape to the outside of the test facility during breeding or study periods.

(10) Any biological waste remaining after completion of the study should processed appropriately and discarded accordingly.

Chapter 5. Standard Operating Procedures

Matters Stipulating the Standard Operating Procedures

Article 6. For Birds Reproduction Test, Standard Operating Procedures should be supplemented with the following matters;

(1) Bird breeding facility maintenance and bird husbandry management.

(2) Receipt, identification, selection, housing and transfer of birds.

(3) Acclimation of birds.

(4) Observation of birds, such as common symptom of birds, etc.

(5) Determination of test substance concentration in feed.

(6) Handling of moribund or dead birds.

(7) Necropsy and postmortem examination of birds.

(8) Collection and identification of specimens.

(9) Pathological examinations.

(10) Other necessary matters.

Chapter 6. Planning and Performance of a Study

Matters to be Described in the Study Plan

Article 7. For Birds Reproduction Tests, the study plan should be supplemented with the following matters.

(1) Reason for selection of the test system.

(2) Species, strain, number, age, sex, body weight range and source of supply of the test system.

(3) Method for identification of the test system.

(4) Methods in the experimental design to minimise bias.

(5) Feed (the description should include determination of acceptable levels of potential contaminants that known to be capable of interfering with the purpose or conduct of the study if present above certain levels) and other vehicles.

(6) Route of administration of the test and reference substances, and the reason for its selection.

(7) Dosage levels of the test and reference substances, and the method, frequency and duration of administration, as well as the reason for their selections.

(8) Method of determining the rate of absorption of the test and reference substances in the test systems, if necessary, to achieve the objectives of the study.

(9) Test temperature, humidity, ventilations, lighting, type of feed, any other conditions related to the conduct of the study.

(10) Other necessary matters.

Conduct of a Study

Article 8. The specimens should be labelled by an appropriate method, specifying nature of the study, identification number of the test system and their date of collection.

Chapter 7. Reporting of Study Results

Matters to be Described in the Final Report

Article 9. With regard to the Birds Reproduction Test, the final report should be prepared and supplemented with following information:

(1) Stability of test and reference substances under the conditions of their administration.

(2) The species, strain, number, age, sex, body weight range, source of supply, date of receipt and housing conditions of the test system.

(3) The route, dosage levels, the method, frequency, and duration of administration of the test or control substance.

(4) Reason for the dosage levels of the test or reference substance.

(5) Other necessary matters.

Chapter 8. Storage of Samples and Materials

Storage

Article 10. Conditions of storage should be designed so as to minimise damage or deterioration of documents or specimens during the retention period.

Retention Period of Specimens

Article 11. The retention periods of wet specimens which differ markedly in quality during storage, and specially

prepared specimens, should be only as long as the quality withstands evaluation. This retention period is regarded as conforming to the requirements stipulated in the standards.