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UNIT 03 (b): GOOD LABORATORY PRACTICES

Content

Good Laboratory Practices: General Provisions, Organization and Personnel, Facilities, Equipment, Testing Facilities Operation, Test and Control Articles, Protocol for Conduct of a Nonclinical Laboratory Study, Records and Reports, Disqualification of Testing Facilities

Introduction

In India, the Drugs & Cosmetic Rules, 1945 require that a manufacturer of drugs should provide and maintain adequate staff, premises and laboratory equipment for carrying out tests of strength, quality and purity of substances at the testing unit which should be separate from the manufacturing unit and head of the manufacturing unit.

It has been further provided under the said rules that the test requiring sophisticated instrumentation techniques or biological or microbiological methods other than sterility might be got carried out at the institutions approved by the Licensing Authority.

The Government of India, Ministry of Health & Family Welfare has notified the draft rules to amend the Drugs & Cosmetic Rules covering the Good Laboratory Practice (GLP) under schedule L-1.

GLPs are the guidelines for quality control and quality assurance in testing laboratories. GLP is a set of principles intended to support research or marketing permits for products regulated by government agencies.

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History of GLP

1. USFDA GLP

The formal concept of 'good laboratory practice' first evolved in the USA in the 1970s because of concerns about the validity of pre-clinical safety data submitted to the Food and Drug Administration (FDA) in the context of new drug applications (NDA).

FDA Investigation found,

- Inadequate characterization of test items and test systems
- Inadequate resources
- Poorly-designed protocols or not followed
- Equipment not properly calibrated
- Reports not sufficiently verified
- Archives inadequate

Non-US companies that wanted to do business with the United States or register their pharmacies in the United States had to comply with the United States GLP regulations.

They eventually started making GLP regulations in their home countries.

2. OECD GLP

In 1981, the principles of Good Laboratory Practice (GLP) have been developed by Organization for Economic Cooperation and Development (OECD) to promote the quality and validity of test data used for the determination of safety of chemicals and chemical products.

30 countries (the member states of the OECD) have signed an agreement binding them to OECD GLP Principles. Other non-OECD member states have also adopted the OECD GLP Principles.

The scope of the OECD GLP is that its principles are required to be followed by testing laboratories carrying out studies to be submitted to national authorities of OECD countries for the purpose of assessment of chemicals and other uses relating to the protection of man and environment.

Several countries require manufacturers of industrial chemicals, pharmaceutical, cosmetics, food products, feed additives, veterinary drugs, pesticides etc. to establish with the help of test data that use of these products does not pose any hazards to human health and the environment. This test data is required to be generated by OECD GLP compliant testing laboratory.

If manufacturer of items mentioned above wants to export the items to OECD or other countries which though not member but have opted for compliance to OECD GLP, will have to submit safety data which will be examined by regulatory authority of the concerned country.

In India, for applying for GLP compliance certificate and documents of GLP authority, readers may visit the website (www.indiaglp.gov.in).

GLP compliance certificate issued by National GLP Compliance Monitoring Authority is valid for a period of 3 years.

Definition of Good Laboratory Practices (GLP)

Good Laboratory Practice (GLP) is a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

Scope

GLP should be applied to the non-clinical safety testing of test items (natural or biological origin and living organisms) contained in:

- pharmaceutical products
- pesticide products
- cosmetic products
- veterinary drugs
- food and feed additives
- Industrial chemicals

Purpose

- To promote the development of quality test data.
- Comparable quality of test data to avoid duplicative testing.

- To avoid the creation of technical barriers to trade.
- Improve the protection of human health and the environment.
- Help scientists obtain results which are:
  - Reliable
  - Repeatable
  - Audible
  - Recognized by scientists worldwide

USFDA GLP has an element by the heading of "Organization and Personnel" and the requirements are given under the sub-headings:

- Personnel
- Testing facility management
- Study director; and
- Quality assurance unit

Under the OECD GLP, this subject matters has been covered under two elements, namely, "test facility organization and personnel" and "Quality Assurance Programme".In these elements responsibilities of different persons have been given and include the following.

- Test facility managements responsibilities
- Study director responsibilities
- Principle investigator's responsibilities
- Study personnel's responsibilities
- Responsibilities of quality assurance personnel

The Indian GLP has two more elements which relate to organization, personnel and quality assurance. These elements are:

- Personnel
- Internal quality system audits

General Provisions

Scope:

This parts prescribes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and colour additives, animal food additives, human and animal drugs, medical device for human use biological products and electronic products.

Definitions:

a) **Act** means the Federal Food, Drug and Cosmetic Act.

b) **Test article** means any food additive, colour additive, drug, biological product, electronic product, medical device for human use, or any other article subject to regulation under the act or under sections 351 and 354-360 F of the Public Health Service Act.

c) **Control article** means any food additive, colour additive, drug, biological product, electronic product, medical device for human use, or any article other than a test article for the purpose of establishing a basis for comparison with the test article.

d) **Non clinical laboratory study** means in vivo or in vitro experiments in which a test articles are studied prospectively in test systems under laboratory conditions to determine their safety.

e) Application for research and marketing permit includes:

1. A colour additive petition
2. A food additive petition
3. Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for use, which use results or may reasonably be expected to result.
4. Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted.
5. An investigational new drug application
6. A new drug application
7. Data and information regarding an over the counter drug for human use, generally recognized as safe and effective and not misbranded;
8. Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials.
9. Data and information regarding an antibiotic drug submitted as part of the procedures for issuing, amending, or repealing regulations for such drugs.
10. A notice of claimed Investigational Exemption for a new animal Drug
11. A new animal drug application
12. An application for a biological product license
13. An application for an investigational device exemption.
14. An application for a premarket approval of a medical device
15. A product development protocol for a medical device
16. Data and information regarding a medical device submitted as part of the procedures of classifying such device
17. Data and information regarding a medical device submitted as part of the procedures for establishing, amending or repealing performance standard for such devices.
18. Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption for notification of radiation safety defect or failure of compliance with a radiation safety performance standard.
19. Data and information regarding an electronic product submitted as part of the procedures for establishing, amending or repealing performance standard for such devices.

20. Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard.
21. Data and information regarding an electronic product submitted as part of the procedures for granting, amending or extending an exemption from any electronic product submitted as part of the procedures for granting, amending or extending an exemption from any electronic product performance standard.

f) **"Sponsor"** means:

I. A person who initiates and supports, by provision of financial or other resources, a clinical laboratory study;

II. A person who submits a nonclinical study to the Food and Drug Administration in support of an application for a research or marketing permit; or

III. A testing facility, if it both initiates and actually conducts the study.

g) **Testing facility** means a persons, premises and operational unit(s) that are necessary for conducting the non-clinical health and environmental safety study.

h) **Person** includes an individual, partnership, corporation, association, scientific and academic establishment, government agency, or organizational unit thereof, and any other legal entity.

i) **Test system** means any animal, plant, microorganism, or subparts thereof to which the test or control article is administered or added for study. Test system also includes appropriate groups or components of the system not treated with the test or control articles.

j) **Specimen** means any material derived from a test system for examination or analysis.

k) **Raw data** means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study.

Raw data may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments.

l) **Quality assurance** unit means any person or organizational element, except the study director, designated by testing facility management to perform the duties relating to quality assurance of nonclinical laboratory studies.

m) **Study director** means the individual responsible for the overall conduct of a nonclinical laboratory study.

n) **Batch** means a specific quantity or lot of a test or control article that has been characterized according to 58.105 (a).

o) **Study initiation date** means the date the protocol is signed by the study director.

p) **Study completion** date means the date the final report is signed by the study director.

Applicability to studies performed under grants and contracts

When a sponsor conducting a nonclinical laboratory study intended to be submitted to or reviewed by the Food and Drug Administration utilizes the services of a consulting laboratory, contracter, or grantee to perform an analysis or other service, it shall notify the consulting laboratory, contractor, or grantee that the service is part of a nonclinical laboratory study that must be conducted in compliance with the provisions of this part.

Inspection of a testing facility

a) A testing facility shall permit an authorized employee of the Food and Drug Administration, at reasonable times and in a reasonable manner, to inspect the facility and to inspect all records and specimens required to be maintained regarding studies within the scope of this part.

b) The food and Drug Administration will not consider a nonclinical laboratory study in support of an application for a research or marketing permit if the testing facility refuses to permit inspection. The determination that a nonclinical laboratory study will not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any applicable statue or regulation to submit the results of the study to the Food and Drug Administration.

Organization and Personnel

1. Personnel

- Each individual engaged in the conduct of or responsible for the supervision of a non-clinical laboratory study shall have education, training, and experience, or combination of all, to enable that individual to perform the assigned functions.
- Each testing facility shall maintain a current summary of training and experience and job description for each individual engaged in or supervising the conduct of nonclinical laboratory study.
- There shall be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol.
- Personnel shall take necessary personnel sanitation and health precautions designed to avoid contamination of test and control articles and test systems.
- Personnel engaged in a nonclinical laboratory study shall wear clothing appropriate for the duties they perform. Such clothing shall be changed as often as necessary to prevent microbiological, radiological, or chemical contamination of test systems and test and control articles.

- Any individual found at any time to have an illness that may adversely affect the quality and integrity of the nonclinical laboratory study shall be excluded from direct contact with test systems, test and control articles and any other operations or function that may adversely affect the study until the condition is corrected.

  All personnel shall be instructed to report to their immediate supervisors any health or medical conditions that may reasonably be considered to have an adverse effect on a nonclinical laboratory study.

2. Testing Facility Management

For each nonclinical laboratory study, testing facility management shall:

- Designate a study director, before the study is initiated.
- Replace the study director promptly if it becomes necessary to do so during the conduct of a study.
- Assure that there is a quality assurance unit.
- Assure that test and control articles or mixtures have been appropriately tested for identity, strength, purity, stability, and uniformity, as applicable.
- Assure that personnel, resources, facilities, equipment, materials, and methodologies are available as scheduled.
- Assure that personnel clearly understand the functions they are to perform.
- Assure that any deviations from these regulations reported by the quality assurance unit are communicated to the study director and corrective actions are taken and documented.

3. Study Director

For each nonclinical laboratory study, a scientist or other professional of appropriate education, training and experience, or combination of those, shall be identified as the study director.

The study director has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of results, and represents the single point of study control. The study director shall ensure that:

- The protocol, including any change, is approved as provided by 58.120 and is followed.
- All experimental data, including observations of unanticipated responses of the test system are accurately recorded and verified.
- Unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study are noted when they occur, and corrective action is taken and documented.
- Test systems are as specified in the protocol.

- All applicable good laboratory practice regulations are followed.

- All raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study.

4. Quality Assurance Unit

a) A testing facility shall have a quality assurance unit which shall be responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records and controls are in conformance with the regulations.

For any given study, the quality assurance unit shall be entirely separate from and independent of the personnel engaged in the direction and conduct of that study.

b) The quality assurance unit shall:

- Maintain a copy of a master schedule sheet of all nonclinical laboratory studies conducted at the testing facility indexed by test article and containing the test system, nature of study, date study was initiated, current status of each study, identity of the sponsor, and name of the study director.

- Maintain copies of all protocols pertaining to all nonclinical laboratory study for which the unit is responsible.

- Inspect each nonclinical laboratory study at intervals adequate to assure the integrity of the study and maintain written and properly signed records of each periodic inspection showing the date of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, finding and problems, action recommended and taken to resolve existing problems, and any scheduled date for reinsertion.

  Any problems found during the course of an inspection which are likely to affect study integrity shall be brought to the attention of the study director and management immediately.

- Periodically submit to management and the study director written status reports on each study, nothing any problems and the corrective actions taken.

- Determine that no deviations from approved protocols or standard operating procedures were made without proper authorization and documentation.

- Review the final study report to assure that such report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the nonclinical laboratory study.

- Prepare and sign a statement to be included with the final study report which shall specify the dates on those inspections were made and findings reported to management and to the study director.

c) The responsibilities and procedures applicable to the quality assurance unit, the records maintained by the quality assurance unit, and the method of indexing such records shall be in writing and shall be maintained.

These items including inspection dates, the study inspected, the phase or segment of the study inspected, and name of the individual performing the inspection shall be made available for inspection to authorized employees of the Food and Drug Administration.

d) A designated representative of the Food and Drug Administration shall have access to the written procedures established for the inspection and may request testing facility management to certify that inspections are being implemented, performed, documented, and followed up in accordance with this paragraph.

Facilities

1. General

Each testing facility shall be of suitable size and construction to facilitate the proper conduct of nonclinical laboratory studies. It shall be designed so that there is a degree of separation that will prevent any function or activity from having an adverse effect on the study.

2. Animal care facilities

a) A testing facility shall have a sufficient number of animal rooms or areas, as needed, to assure proper: (1) Separation of species or test systems, (2) isolation of individual projects, (3) quarantine of animals, and (4) routine or specialized housing of animals.

b) A testing facility shall have a number of animal rooms or areas separate from those described in paragraph (a) of this section to ensure isolation of studies being done with test systems or test and control articles known to be biohazardous, including volatile substances, aerosols, radioactive materials, and infectious agents.

c) Separate areas shall be provided, as appropriate, for the diagnosis, treatment, and control of laboratory animal diseases. These areas shall provide effective isolation for the housing of animals either known or suspected of being diseased, or of being carriers of disease, from other animals.

d) When animal are housed, facilities shall exist for the collection and disposable of all animal waste and refuse or for safe sanitary storage of waste before removal from the testing facility. Disposal facilities shall be so provided and operated as to minimize vermin infections, odors, disease hazards, and environmental contamination.

3. Animal supply facilities

There shall be storage areas, as needed, for feed, bedding, supplies, and equipment. Storage areas for feed and bedding shall be separated from areas housing the test systems and shall be protected against infestation or contamination. Perishable supplies shall be preserved by appropriate means.

4. Facilities for handling test and control articles

a) An necessary to prevent contamination or mixups, there shall be separate areas for:
   1. Receipt and storage of the test and control articles.
   2. Mixing of the test and control articles with a carrier, e.g., feed.
   3. Storage of the test and control article mixtures.

b) Storage areas for the test and/or control article and test and control mixtures shall be separate from areas housing the test systems and shall be adequate to preserve the identity, strength, purity, and stability of the articles and mixtures.

5. Laboratory operation areas

Separate laboratory space shall be provided, as needed, for the performance of the routine and specialized procedures required by nonclinical laboratory studies

6. Specimen and data storage facilities

Space shall be provided for archives, limited to access by authorized personnel only, for the storage and retrieval of all raw data and specimens from completed studies.

Equipment

1. Equipment design

Equipment used in the generation, measurement, or assessment of data and equipment used for facility environmental control shall be of appropriate design and adequate capacity to function according to the protocol and shall be suitably located for operation, inspection, cleaning, and maintenance.

2. Maintenance and calibration of equipment

a) Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized.

b) The written standard operating procedures shall set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration and/or standardization of equipment, and shall specify, when appropriate, remedial action to be taken in the event of failure or malfunction of equipment. The written standard operating procedures shall designate the person responsible for the performance of each operation.

c) Written records shall be maintained of all inspection, maintenance, testing, calibrating and/or standardizing operations.

These records, containing the date of the operation shall describe whether the maintenance operations were routine and followed the written standard operating procedures. Written

records shall be kept of nonroutine repairs performed on equipment as a result of failure and malfunction.

Such records shall document the nature of the defect, how and when the defect was discovered, and any remedial action taken in response to the defect.

Testing Facilities Operation

1. Standard operating procedures

a) A testing facility shall have standard operating procedures in writing setting forth nonclinical laboratory study methods that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study.

All deviations in a study from standard operating procedures shall be authorized by the study director and shall be documented in the raw data. Significant changes in established standard operating procedures shall be properly authorized in writing by management.

b) Standard operating procedures shall be established for, but not limited to, the following:
   1) Animal room preparation
   2) Animal care
   3) Receipt, identification, storage, handling, mixing, and method ofsampling of the test and control articles.
   4) Test system observations
   5) Laboratory tests
   6) Handling of animals found moribund or dead during study.
   7) Necropsy of animals or postmortem examination of animals.
   8) Collection and identification of specimens.
   9) Histopathology
   10) Data handling, storage, and retrieval.
   11) Maintenance and calibration of equipment
   12) Transfer, proper placement, and identification of animals.

c) Each laboratory area shall have immediately available laboratory manuals and standard operating procedures relative to the laboratory procedures being performed. Published literature may be used as a supplement to standard operating procedures.

d) A historical life of standard operating procedures, and all revisions thereof, including the dates of such revisions, shall be maintained.

2. Reagents and solutions

All reagents and solutions in the laboratory areas shall be labeled to indicate identity, titer or concentration, storage requirements, and expiration etc. Deteriorated or outdated reagents and solutions shall not be used.

3. Animal care

a) There shall be standard operating procedures for the housing, feeding, handling, and care of animals.

b) All newly received animals from outside sources shall be isolated and their health status shall be evaluated in accordance with acceptable veterinary medical practice.

c) At the initiation of nonclinical laboratory study, animals shall be free of any disease or condition that might interfere with the purpose or conduct of the study.

If, during the course of the study, the animals contract such a disease or condition, the diseased animals shall be isolated, if necessary. These animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study.

The diagnosis, authorizations of treatment, description of treatment, and each date of treatment shall be documented and shall be retained.

d) Warm-blooded animals, excluding suckling rodents, used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that require the animals to be removed from and returned to their home cages for any reason (e.g. cage cleaning, treatment, etc.), shall receive appropriate identification.

All information needed to specifically identify each animals within an animal-housing unit shall appear on the outside of that unit.

e) Animals of different species shall be housed in separate rooms when necessary. Animals of the same species, but used in different studies should not ordinarily be housed in the same room when inadvertent exposure to control or test articles or animal mixup could affect the outcome of either study.

If such mixed housing is necessary, adequate differentiation by space and identification shall be made.

f) Animal cages, racks and accessory equipment shall be cleaned and sanitized at appropriate intervals.

g) Feed and water used for the animals shall be analyzed periodically to ensure that contaminants known to be capable of interfering with the study and reasonably expected to be present in such feed or water are not present at levels above those specified in the protocol. Documentation of such analyses shall be maintained as raw data.

h) Bedding used in animal cages or pens shall not interfere with the purpose or conduct of the study and shall be changed as often as necessary to keep the animals dry and clean.

i) If any pest control materials are used, the use shall be documented. Cleaning and pest control materials that interfere with the study shall not be used.

Test and Control Articles

1. Test and control article characterization

a) The identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article shall be determined for each batch and shall be documented.

Methods of synthesis, fabrication, or deviation of the test and control articles shall be documented by the sponsor or the testing facility. In those cases where marketed products are used as control articles, such products will be characterized by their labelling.

b) The stability of each test or control article shall be determined by the testing facility or by the sponsor either: (1) Before study initiation, or (2) concomitantly according to written standard operating procedures, which provide for periodic analysis of each batch.

c) Each storage container for a test or control article shall be labeled by name, chemical abstract number or code number, batch number, expiration date, if any, and, where appropriate, storage conditions necessary to maintain the identity, strength, purity, and composition of the test or control article. Storage containers shall be assigned to a particular test article for the duration of the study.

d) For studies of more than 4 weeks' duration, reserve samples from each batch of test and control articles shall be retained for the period of time mentioned in guideline.

2. Test and control article handling

Procedures shall be established for a system for the handling of the test and control articles to ensure that:

a) There is proper storage.

b) Distribution is made in a manner designed to preclude the possibility of contamination, deterioration, or damage.

c) Proper identification is maintained throughout the distribution process.

d) The receipt and distribution of each batch is documented. Such documentation shall include the date and quantity of each batch distributed or returned.

3. Mixtures of articles with carriers

a) For each test or control article that is mixed with a carrier, tests by appropriate analytical methods shall be conducted:

1) To determine the uniformity of the mixture and to determine, periodically, the concentration of the test or control article in the mixture.

2) To determine the stability of the test and control articles in the mixture as required by the conditions of the study either:

I. Before study initiation
II. Concomitantly according to written standard operating procedures which provide for periodic analysis of the test and control articles in the mixture.

b) Where any of the components of the test or control article carrier mixture has an expiration date, that date shall be clearly shown on the container. If more than one component has an expiration date, the earliest date shall be shown.

Protocol for and Conduct of a Nonclinical Laboratory Study

1. Protocol

a) Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study. The protocol shall contain the following information:

1) A descriptive title and statement of the purpose of the study.

2) Identification of the test and control articles by name, chemical abstract number, or code number.

3) The name of the sponsor and the name and address of the testing facility at which the study is being conducted.

4) The number, body weight range, sex, source of supply, species, strain, substrain, and age of the test system.

5) The procedure for identification of the test system

6) A description of the experimental design, including the methods for the control of bias.

7) A description and/or identification of the diet used in the study as well as solvents, emulsifiers, and/or other materials used to solubilize or suspend the test or control articles before mixing with the carrier. The description shall include specifications for acceptable levels of contaminants that are reasonably expected to be present in the dietary materials and are known to be capable of interfering with the purpose or conduct of the study if present at levels greater than established by the specifications.

8) Each dosage level, expressed in milligrams per kilogram of body weight or other appropriate units, of the test or control article to be administered and the method and frequency of administration.

9) The type and frequency of tests, analyses, and measurements to be made.

10) The records to be maintained.

11) The date of approval of the protocol by the sponsor and the dated signature of the study director.

12) A statement of the proposed statistical methods to be used.

b) All changes in or revisions of an approved protocol and the reasons therefor shall be documented, signed by the study director, dated and maintained with the protocol.

2. Conduct of a nonclinical laboratory study

a) The nonclinical laboratory study shall be conducted in accordance with the protocol.

b) The test system shall be monitored in conformity with the protocol.

c) Specimens shall be identified by test system, study, nature, and date of collection. This information shall be located on the specimen container or shall accompany the specimens in a manner that avoids error in the recording and storage of data.

d) Records of gross finding for a specimen from postmortem observations should be available to a pathologist when examining that specimen histopathologically.

e) All data generated during the conduct of a nonclinical laboratory study, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and legibly in ink. All data entries shall be dated on the date of entry and signed or initiated by the person entering the data.

Any change in entries shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change.

In automated data collection systems, the individual responsible for direct data input shall be identified at the time of data input. Any change in automated data entries shall be made so as not to obscure the original entry, shall indicate the reason for change, shall be dated, and the responsible individual shall be identified.

Records and Reports

1. Reporting of nonclinical laboratory study results

a) A final report shall be prepared for each nonclinical laboratory study and shall include, but not necessarily be limited to the following:

1) Name and address of the facility performing the study and the dates on which the study was initiated and completed.

2) Objectives and procedures stated in the approved protocol, including any changes in the original protocol.

3) Statistical methods employed for analyzing the data.

4) The test and control articles identified by name, chemical abstracts number or code number, strength, purity, and composition or other appropriate characteristics.

5) Stability of the test and control articles under the conditions of administration.

6) A description of the methods used.

7) A description of the test system used. Where applicable, the final report shall include the number of animals used, sex, body weight range, source of supply, species,, strain and substrain, age, and procedure used for identification.

8) A description of the dosage, dosage regimen, route of administration, and duration.

9) A description of all circumstances that may have affected the quality or integrity of the data.

10) The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study.

11) A description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.

12) The signed and dated reports of each of the individual scientists or other professionals involved in the study.

13) The locations where all specimens, raw data, and the final report are to be stored.

14) The statement prepared and signed by the quality assurance unit.

b) The final report shall be signed and dated by the study director.

c) Corrections or additions to a final report shall be in the form of an amendment by the study director. The amendment shall clearly identified that part of the final report that is being added to or corrected and the reasons for the correction or addition, and shall be signed and dated by the person responsible.

2. Storage and retrieval of records and data

a) All raw data, documentation, protocols, final reports, and specimens generated as a result of nonclinical laboratory study shall be retained.

b) There shall be archives for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports. Conditions of storage shall minimize deterioration of the documents or specimens in accordance with the requirements for the time period of their retention and the nature of the documents or specimens. A testing

facility may contract with commercial archives to provide a repository for all material to be retained. Raw data and specimens may be retained elsewhere provided that the archives have specific reference to those other archives.

c) An individual shall be identified as responsible for the archives.

d) Only authorized personnel shall enter the archives.

e) Material retained or referred to in the archives shall be indexed to permit expedient retrieval.

3. Retention of records

a) Record retention requirements set forth in this section do.

b) Except as provided in paragraph (c) of this section, documentation records, raw data and specimens pertaining to the nonclinical laboratory study and required to be made by this part shall be retained in the archive(s) for whichever of the following period is shortest:

1) A period of at least 2 years following the date on which an application for a research or marketing permit in support of which the results of the nonclinical laboratory study were submitted, is approved by the Food and Drug Administration. This requirement does not apply to studies supporting investigational new drug applications (INDs) or application for investigational device exemptions (IDEs), records of which shall be governed by the provisions of paragraph (b)(2) of this section.

2) A period of at least 5 years following the date on which the results of the nonclinical laboratory study are submitted to the Food and Drug Administration in support of an application for a research or marketing permit.

3) In other situations (e.g where the nonclinical laboratory study does not result in the submission of the study in support of an application for a research or marketing permit), a period of at least 2 years following the date on which the study is completed, terminated, or discontinued.

c) Wet specimens (except those specimens obtained from mutagenicity tests and wet specimens of blood, urine, feces, and biological fluids), samples of test or control articles, and specially prepared material, which are relatively fragile and differ markedly in stability and quality during storage, shall be retained only as long as the quality of the preparation affords evaluation. In no case shall retention be required for longer periods than those set forth in paragraphs (a) and (b) of this section.

d) The master schedule sheet, copies of protocols, and records of quality assurance inspections shall be maintained by the quality assurance unit as an easily accessible system of records for the period of time specified in paragraphs (a) and (b) of this section.

e) Summaries of training and experience and job descriptions required to be maintained and may be retained along with all other testing facility employment records for the length of time specified in paragraphs (a) and (b) of this section.

f) Records and reports of the maintenance and calibration and inspection of equipment shall be retained for the length of time specified in paragraphs (a) and (b) of this section.

g) Records required by this part may be retained either as original records as or true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records.

h) If a facility conducting nonclinical testing goes out of business, all raw data, documentation, and other material shall be transferred to the archives of the sponsor of the study. The food and Drug Administration shall be notified in writing of such a transfer.

Disqualification of Testing Facilities

1. Purpose

a) The purpose of disqualification are:

1) To permit the exclusion from consideration of completed studies that were conducted by a testing facility which has failed to comply with the requirements of the good laboratory practice regulations until it can be adequately demonstrated that such noncompliance did not occur during, or did not affect the validity or acceptability of data generated by, a particular study; and

2) To exclude from consideration all studies completed after the date of disqualification until the facility can satisfy the Commissioner that it will conduct studies in compliance with such regulations.

b) The determination that a nonclinical laboratory study may not be considered in support of an application for a research or marketing permit des not, however, relieve the applicant for such a permit of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration

2. Grounds for disqualification

The commissioner may disqualify a testing facility upon finding all of the following.

3) The testing facility failed to comply with one or more of the regulations of this part.

4) The noncompliance adversely affected the validity of the nonclinical laboratory studies; and

5) Other lesser regulatory actions (e.g. warning or rejection of individual studies) have not been or will probably not be adequate to achieve compliance with the Good laboratory practice regulations.

3. Notice and opportunity for hearing on proposed disqualification

a) Whenever the Commissioner has information indicating that grounds in his opinion justify disqualification of a testing facility, he may issue to the testing facility a written notice proposing that the facility be disqualified.

b) A hearing on the disqualification shall be conducted in accordance with the requirements for a regulatory hearing.

4. Final order on disqualification

a) If the commissioner, after the regulatory hearing, or after the time for requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification processing, makes the finding, he shall issue a final order disqualifying the facility.

Such order shall include a statement of the basis for that determination. Upon issuing a final order, the Commissioner shall notify the testing facility of the action.

b) If the commissioner, after a regulatory hearing or after the time for requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification proceeding, does not make the findings , he shall issue a final order terminating the qualification proceeding.

Such order shall include a statement of the basis for that determination. Upon issuing a final order the commissioner shall notify the testing facility and provide a copy of the order.

5. Actions upon disqualification

a) Once a testing facility has been disqualified, each application for a research or marketing permit, whether approved or not, containing a relying upon any nonclinical laboratory study conducted by the disqualified testing facility may be examined to determine whether such study was or would be essential to decision.

If it is determined that a study was or would be essential, the Food and Drug Administration shall also determine whether the study is acceptable, notwithstanding the disqualification of the facility.

Any study done by a testing facility before or after disqualification may be presumed to be unacceptable, and the person relying on the study may be required to establish that the study was not affected by the circumstances that led to the disqualification, e.g., by submitting validating information.

If the study is then determined to be unacceptable, such data will be eliminated from consideration in support of the application; and such elimination may serve as new information justifying the termination or withdrawal of approval of the application.

b) No nonclinical laboratory study begun by a testing facility after the date of the facility's disqualification shall be considered in support of any application for a research or marketing permit.

The determination that a study may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.

6. Public disclosure of information regarding disqualification

a) Upon issuance of a final order disqualifying a testing facility, the commissioner may notify all or any interested persons. Such notice may be given at the discretion of the Commissioner whenever he believes that such disclosure would further the public interest or would promote compliance with the good laboratory practice regulations.

Such notice if, given, shall include a copy of the final order issued and shall state that the disqualification constitutes a determination by the Food and Drug Administration that nonclinical laboratory studies performed by the facility will not be considered by the Food and Drug Administration in support of any application for a research or marketing permit.

If such notice is sent to another Federal Government agency, the Food and Drug Administration will recommend that the agency also consider whether or not it should accept nonclinical laboratory studies performed by the testing facility.

If such notice is sent to any other person, it shall state that it is given because of the relationship between the testing facility and the person being notified and that the Food and Drug Administration is not advising or recommending that any action can be taken by the person notified.

b) A determination that a testing facility has been disqualified and the administrative record regarding such determination are disclosable to the public.

7. Alternative or additional actions to disqualification

a) Disqualification of a testing facility under this subpart is independent of, and neither in lieu of nor a precondition to, other proceeding or actions authorized by the act.

The Food and Drug Administration may at any time, institute against a testing facility and/or against the sponsor of a nonclinical laboratory study that has been submitted to the Food and Drug Administration any appropriate judicial proceeding (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and prior to, simultaneously with, or subsequent to, disqualification.

The Food and Drug Administration may also refer the matter to another Federal, State or local government law enforcement or regulatory agency for such action as that agency deems appropriate.

b) The Food and Drug Administration may refuse to consider any particular nonclinical laboratory study in support of an application for a research or marketing permit, if it finds that the study was not conducted in accordance with the good laboratory practice regulations, without qualifying the testing facility that conducted the study or undertaking other regulatory action.

8. Suspension or termination of a testing facility by a sponsor

Termination of a testing facility by a sponsor is independent of, and neither in lieu of nor a precondition to, proceeding or actions authorized by this subpart. If a sponsor terminates or suspends a testing facility from further participation in a nonclinical laboratory study that is being conducted as part of any application for a research or marketing permit that has been submitted to any Center of the Food and Drug Administration, it shall notify that Center in writing within 15 working days of the action; the notice shall include a statement of the reasons for such action. Suspension or termination of a testing facility by a sponsor does not relieve it of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.

9. Reinstatement of a disqualified testing facility

A testing facility that has been disqualified may be reinstated as an acceptable source of nonclinical laboratory studies to be submitted to the Food and Drug Administration if the Commissioner determines, upon an evaluation of the submission of the testing facility, that the facility can adequately assure that it will conduct future nonclinical laboratory studies in compliance with the good laboratory practice regulations, if any studies are currently being conducted, that the quality and integrity of such studies have not been seriously compromised.

A disqualified testing facility that wishes to be so reinstated shall present in writing to the Commissioner reasons why it believes it should be reinstated and a detailed description of the corrective actions it has taken or intends to take to assure that the acts or omissions which lead to its disqualification will not recur.

The Commissioner may condition reinstatement upon the testing facility being found in compliance with the good laboratory practice regulations upon an inspection.

If a testing facility is restated, the Commissioner shall so notify the testing facility and all organizations and persons who were notified. A determination that a testing facility has been reinstated is disclosable to the public.

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