

21 CFR 58 - Good Laboratory Practice Regulations

Reg. No.	Regulatory Text
	Subpart A - General Provisions
58.1	Scope <p>(a) This part prescribes good laboratory practices for conducting non-clinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the FDA, including food and colour additives, animal food additives, human and animal drugs, medical devices for human use, biological products, and electronic products. Compliance with this part is intended to assure the quality and integrity of the safety data filed pursuant to sections 406, 408, 409, 502, 503, 505, 506, 507, 510, 512-516, 518-520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354 - 360F of the Public Health Service Act.</p> <p>(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter 1 of title 21, unless otherwise noted.</p> <p>[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33779, Sept. 4, 1987]</p>
58.3	Definitions <p>As used in this part, the following terms shall have the meanings specified:</p> <p>(a) <i>Act</i> means the Federal Food, Drug, and Cosmetic Act, as amended (sections 201-902, 52 Stat. 1040 <i>et seq.</i>, as amended (21 U.S.C. 321-392)).</p> <p>(b) <i>Test article</i> means any food additive, colour additive, drug, biological product, electronic product, medical device for human use, or any other article to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act.</p> <p>(c) <i>Control article</i> means any food additive, colour additive, drug, biological product, electronic product, medical device for human use or any other article, feed, or water that is administered to the test system in the course of a non-clinical laboratory study for the purpose of establishing a basis for comparison with the test article.</p> <p>(d) <i>Non-clinical laboratory study</i> means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilising human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.</p> <p>(e) <i>Applications for research or marketing research permit</i> includes:</p> <ol style="list-style-type: none">(1) A colour additive petition, described in part 71.(2) A food additive petition, described in parts 171 and 571.(3) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognised as safe for use, which use results or may reasonably be expected to result, directly or indirectly, in its becoming a

component or otherwise affecting the characteristics of any food, described in paragraphs 170.35 and 570.35.

(4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in paragraph 180.1

(5) an *investigational new drug application*, described in part 312 of this chapter.

(6) A *new drug application*, described in part 314.

(7) Data and information regarding as over the counter drug for human use, submitted as part of the process for classifying such drugs as generally recognised as safe and effective and not misbranded, described in part 330.

(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, described in parts 109 and 509.

(9) Data and information regarding an antibiotic drug submitted as part of the procedures for issuing, amending, or repealing regulations for such drugs, described in paragraph 314.300 of this chapter.

(10) A *Notice of Claimed Investigational Exemption for New Animal Drug*, described in part 511.

(11) A *new animal drug application*, described in part 514.

(12) [Reserved]

(13) An *application for a biological product license*, described in part 601.

(14) An *application for an investigational device exemption*, described in part 812.

(15) An *Application for Pre-market Approval of a medical Device*, described in section 515 of the act.

(16) A *Product Development Protocol for a Medical Device*, described in section 515 of the act.

(17) Data and information regarding a medical device submitted as part of the procedures for classifying such devices, described in part 860.

(18) Data and information regarding a medical device submitted as part of the procedure for establishing, amending, or repealing a performance standard for such devices, described in part 861.

(19) Data and electronic information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in subpart D of part 1003.

(20) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such product, described in section 358 of the Public Health Service Act.

(21) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard as described in paragraph 1010.4.

(22) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from any electronic product performance standard, as described in paragraph 1010.5.

(f) *Sponsor* means:

(1) A person who initiates and supports, by provision of financial or other resources, a non-clinical laboratory study;

(2) A person who submits a non-clinical study to the Food and Drug Administration in support of an application for a research or marketing permit; or

(3) A testing facility, if it both initiates and actually conducts the study.

(g) *Testing facility* means a person who actually conducts a non-clinical laboratory study, i.e., actually uses the test article in a test system. *Testing facility* includes any establishment required to register under section 510 of the act that conducts non-clinical laboratory studies and any consulting laboratory described in section 704 of the act that conducts such studies. *Testing facility* encompasses only those operational units that are being or have been used to conduct non-clinical laboratory studies.

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

(i) *Test system* means any animal, plant, micro-organism, 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 non-clinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. **In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature),** the exact copy or exact transcript may be substituted for the original source as raw data. *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 organisational element except the study director, designated by testing facility management to perform the duties relating to quality assurance of non-clinical laboratory studies.

(m) *Study director* means the individual responsible for the overall conduct of a non-clinical laboratory study.

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

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 3379, Sept. 4, 1987; 54 FR 9039, Mar.3, 1989]

58.10 Applicability to studies performed under grants and contracts.

When a sponsor conducting a non-clinical laboratory study intended to be submitted to or reviewed by the FDA utilises the services of a consulting laboratory, contractor, 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 non-clinical laboratory study that must be conducted in compliance with the provisions of this part.

58.15**Inspection of a testing facility**

(a) A testing facility shall permit an authorised employee of the FDA, at reasonable times and in a reasonable manner, to inspect the facility (and in the case of records also to copy) all records and specimens required to be maintained regarding studies within the scope of this part. The records inspection and copying requirements shall not apply to quality assurance unit records of findings and problems, or to actions recommended and taken.

(b) The FDA will not consider a non-clinical 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 non-clinical 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 statute or regulation to submit the results of the study to the FDA.

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Subpart B - Organisation and Personnel

58.29 Personnel

- (a) 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 a combination thereof, to enable that individual to perform the assigned functions.
- (b) 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 a non-clinical laboratory study.
- (c) There shall be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol.
- (d) Personnel shall take necessary personal sanitation and health precautions designed to avoid contamination of test and control articles and test systems.
- (e) Personnel engaged in a non-clinical 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.
- (f) Any individual found at any time to have an illness that may adversely affect the quality and integrity of the non-clinical laboratory study shall be excluded from direct contact with test systems, test and control articles and any other operation 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 non-clinical laboratory study.

58.31 Testing facility management

For each non-clinical laboratory study, testing facility management shall:

- (a) Designate a study director as described in paragraph 58.33, before the study is initiated.
- (b) Replace the study director promptly if it becomes necessary to do so during the conduct of a study.
- (c) Assure that there is a quality assurance unit as described in paragraph 58.35.
- (d) Assure that test and control articles or mixtures have been appropriately tested for identity, strength, purity, stability, and uniformity, as applicable.
- (e) Assure that personnel, resources, facilities, equipment, materials and methodologies are available as scheduled.
- (f) Assure that personnel clearly understand the functions they are to perform.
- (g) 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.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

58.33**Study director.**

For each non-clinical laboratory study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, 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 the results, and represents the single point of study control. The study director shall assure that:

- (a) The protocol including any change, is approved as provided by paragraph 58.120 and is followed.
- (b) All experimental data, including observations of unanticipated response of the test system are accurately recorded and verified.
- (c) Unforeseen circumstances that may affect the quality and integrity if the non-clinical laboratory study are noted when they occur, and corrective action is taken and documented.
- (d) The test systems are as specified in the protocol.
- (e) All applicable good laboratory practice regulations are followed.
- (f) All raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study.

[43 FR 60013, Dec. 22, 1978; 44 FR 17657, Mar. 23, 1979]

58.35**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, practice, records, and controls are in conformance with the regulations in this part. 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:

- (1) Maintain a copy of a master schedule sheet of all non-clinical 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, the identity of the sponsor, and name of the study director.
- (2) Maintain copies of all protocols pertaining to all non-clinical laboratory studies for which the unit is responsible.
- (3) Inspect each non-clinical 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, findings and problems, action recommended and taken to resolve existing problems and any scheduled date for re-inspection. Any problems found during inspection which are likely to affect study integrity shall be brought to the attention of the study director and management immediately.
- (4) Periodically submit to management and the study director written status reports on each study, noting any problems and the corrective actions taken.
- (5) Determine that no deviations from approved protocols or standing operating procedures were made without proper authorisation and documentation.

(6) 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 non-clinical laboratory study.

(7) Prepare and sign a statement to be included with the final study report which shall specify the dates inspections were made and finding 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, and the name of the individual performing the inspection shall be made available for inspection to authorised employees of the FDA.

(d) A designated representative of the FDA 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.

[Information collection requirements approved by the Office of Management and Budget under control number 0910-0203]

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

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Subpart C - Facilities

58.41 General

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

[52 FR 33780, Sept. 4, 1987]

58.43 Animal care facilities

(a) A testing facility shall have 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 specialised 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 control articles known to be bio-hazardous, including volatile substances, aerosols, radioactive materials, and infectious agents.

(c) Separate areas shall be provided, as proposed, for the diagnosis, treatment, and control of laboratory animal disease. 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 animals are housed, facilities shall exist for the collection and disposal 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 minimise vermin infestation, odours, disease hazards, and environmental contamination.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept.4, 1987]

58.45 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.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

58.47 Facilities for handling test and control articles

(a) As necessary to prevent contamination or mix-ups, 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.

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58.49	<p>Laboratory operation areas</p> <p>Separate laboratory space shall be provided, as needed, for the performance of the routine and specialised procedures required by non-clinical laboratory studies.</p> <p>[52 FR 33780, Sept. 4, 1987]</p>
58.51	<p>Specimen and data storage facilities</p> <p>Space shall be provided for archives, limited access by authorised personnel only, for the storage and retrieval of all raw data and specimens from completed studies.</p> <p>Subpart D - Equipment</p>
58.61	<p>Equipment design</p> <p>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.</p> <p>[52 FR 33780, Sept. 4, 1987]</p>
58.63	<p>Maintenance and calibration of equipment</p> <p>(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 standardised.</p> <p>(b) The written standard operating procedures required under paragraph 58.81(b)(11) shall be set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration, and/or standardisation 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.</p> <p>(c) Written records shall be maintained of all inspection, maintenance, testing, calibration and/or standardising 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 non-routine 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.</p> <p>(Information collection requirements approved by the Office of Management and Budget under control number 0910-0203)</p> <p>[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]</p>

Subpart E - Testing Facilities Operation

58.81 Standard operating procedures.

(a) A testing facility shall have standard operating procedures in writing setting forth non-clinical laboratory study methods that management is satisfied are adequate to ensure 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 authorised by the study director and shall be documented in the raw data. Significant changes in established operating procedures shall be properly authorised 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 of sampling 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 post mortem 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 file of standard operating procedures, and all revisions thereof, including the dates of such revisions, shall be maintained.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1978]

58.83 Reagents and solutions

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

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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 a non-clinical 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, authorisation 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 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 animal 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 mix-up 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 sanitised at appropriate intervals.
- (g) Feed and water used for the animals shall be analysed periodically to ensure that contaminants known to be capable of interfering with study and reasonably expected to be present in such feed or water are not present in levels above those specified in the protocol. Documentation of such analyses shall be maintained as raw data.
- (h) Bedding used in animal cages shall not interfere with 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.

(Information collection requirements approved by the Office of Management and Budget under control number 0910-0203)

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987; 54 FR 15924, Apr. 20, 1989; 56 FR 32088, July 15, 1991]

Subpart F - Test and Control Articles

58.105

Test and control article characterisation

- (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 derivation 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 characterised 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 labelled 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 provided by paragraph 58.195.

(Information collection requirements approved by the Office of Management and Budget under control number 0910-0203)

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987]

58.107 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.

58.113 Mixtures of articles with carriers.

- (a) For each test or control article that is mixed with a carrier, test 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, or
- (ii) Concomitantly according to written standard operating procedures which provide for periodic analysis of the test and control articles in the mixture.
- (b) [Reserved]
- (c) Where any of the components of the test 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.

[43 FR 60013, Dec. 22, 1978, as amended at 45 FR 24865, Apr. 11, 1980; 52 FR 33781, Sept. 4, 1987]

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Subpart G - Protocol for and Conduct of a Non-clinical Laboratory Study

58.120

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, as applicable, 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 the identification of the system.
 - (6) A description of the experimental design, including the methods for the control 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 solubilise or suspend the test or control particles before mixing with the carrier. The description shall include specification 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, and 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 of an approved protocol and the reasons therefore shall be documented, signed by the study director, dated, and maintained with the protocol.

(Information collection requirements approved by the Office of Management and Budget under control number 0910-0203)

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987]

58.130

Conduct of a non-clinical laboratory study.

- (a) The non-clinical laboratory study shall be conducted in accordance with the protocol.
- (b) The systems 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 specimen in a manner

that precludes error in the recording and storage of data.

(d) Records of gross findings for a specimen from post-mortem observations should be available to a pathologist when examining that specimen histopathologically.

(e) All data generated during the conduct of a non-clinical 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 initialled by the person entering the data. Any change in these 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 the data input. Any change in automated data entries shall be made so as not to obscure the original entry, shall indicate the reason for the change, shall be dated, and the responsible individual shall be identified.

(Information collection requirements approved by the Office of Management and Budget under control number 0910-0203)

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987]

Reg. No.

Regulatory Text
Subparts H - I (Reserved)

Subparts J - Records and Reports

58.185 Reporting of non-clinical laboratory study results.

- (a) A final report shall be prepared for each non-clinical laboratory study and shall include, but 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 analysing 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 sub-strain, age, and procedure used for the 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 as described in paragraph 58.35(b)(7).
- (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 identify that part of the 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.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987]

58.190 Storage and retrieval of records and data.

- (a) All raw data, documentation, protocols, final reports, and specimens (except those specimens obtained from mutagenicity tests and wet specimens of blood urine, faeces, and biological fluids) generated as a result of a non-clinical 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 minimise 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 locations.

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

(d) Only authorised personnel shall enter the archives.

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

(Information collection requirements approved by the Office of Management and Budget under control number 0910-0203)

[43 FR. 60013, Dec. 22, 1978, as amended at 52 FR. 33781, Sept. 4, 1987]

58.195 Retention of records.

(a) Record retention requirements set forth in this section do not supersede the record retention requirements of any other regulations in this chapter.

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(b) Except as provided in paragraph (c) of this section, documentation records, raw data and specimens pertaining to a non-clinical laboratory study and required to be made by this part shall be retained in the archive(s) for whichever of the following periods is the 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 non-clinical laboratory study were submitted, is approved by the FDA. This requirement does not apply to studies supporting investigational new drug applications for investigational device exemptions (IDE's) or applications for investigational device exemptions (IDE's), 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 of which the results of the non-clinical laboratory study are submitted to the FDA in support of an application for a research or marketing permit.

(3) In other situations (e.g., where the non-clinical 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 faeces, and biological fluids), samples of tests, 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 record of quality assurance inspections, as required by paragraph 58.35(c) 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 by paragraph 58.29(b) 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 as required by 58.63(b) and (c), shall be retained for the length of time specified in paragraph (b) of this section.

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

(h) If a facility conducting non-clinical testing goes out of business, all raw data, documentation and other material specified in this section shall be transferred to the archives of the sponsor of the study. The FDA shall be notified in writing of such a transfer.

[43 FR. 60013, Dec. 22, 1978, as amended at 52 FR. 33781, Sept. 4, 1987; 54 FR 9039, Mar. 3, 1989]

Subpart K - Disqualifications of Testing Facilities

58.200 Purpose

(a) The purposes 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 demonstrated that such non-compliance 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 will conduct studies in compliance with such regulations.

(b) The determination that a non-clinical laboratory 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 FDA.

58.202 Grounds for disqualification

The Commissioner may disqualify a testing facility upon finding all of the following:

(a) The testing facility failed to comply with one or more of the regulations set forth in this part of (or any other regulations regarding such facilities in this chapter);

(b) The non-compliance adversely affected the validity of the non-clinical laboratory studies; and

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

58.204 Notice of and opportunity for hearing on proposed disqualification.

(a) Whenever the Commissioner has information indicating that grounds exist under paragraph 58.202 which in his opinion justify disqualification of a testing facility, h 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 set forth in part 16 of this chapter.

Reg. No.
58.206

Regulatory Text
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 disqualification proceeding, makes the findings required in paragraph 58.202, 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 (with a copy of the order) 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 required in paragraph 58.202 he shall issue final order terminating the disqualification 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.

58.210 **Actions upon disqualification.**

(a) Once a testing facility has been disqualified, each application for a research or marketing permit, whether approved or not, containing or relying upon any non-clinical laboratory study conducted by the disqualified testing facility may be examined to determine whether such study was or would be essential to a decision. If it is determined that a study was or would be essential the FDA 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 non-clinical 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, unless the facility has been reinstated under paragraph 58.219. 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 FDA.

[43 FR 60013, Dec. 22, 1978, as amended at 59 FR 13200 Mar. 21, 1994]

58.213 **Public disclosure of information regarding disqualification.**

(a) Upon issuance of a final order disqualifying a testing facility under paragraph 58.206(a), 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 set forth in this part. Such notice, if given, shall include a copy of the final order issued under 58.206(a) and shall state that the disqualification constitutes a determination by the FDA that non-clinical laboratory studies performed by the facility will not be considered by the FDA in support of any application for a research or marketing permit. If such notice is sent to another FDA agency, the FDA will recommend that the agency also consider Whether or not it should accept non-clinical 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 FDA is not advising or recommending that any action 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 under part 20 of this chapter.

58.215 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 pre-condition to, other proceedings or actions authorised by the act. The FDA may, at any time, institute against a testing facility and/or against the sponsor of a non-clinical laboratory study that has been submitted to the FDA any appropriate judicial proceedings (civil or criminal) and other appropriate regulatory action, in addition to or in lieu of, and prior to, simultaneously with, or subsequent to, disqualification. The FDA 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 FDA may refuse to consider any particular non-clinical 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 set forth in this part, without disqualifying the testing facility that conducted the study or undertaking other regulatory action.

58.217 Suspension or termination of a testing by a sponsor.

Termination of a testing facility by a sponsor is independent of, and neither in lieu of nor a precondition to, proceedings or actions authorised by this subpart. If a sponsor terminates or suspends a testing facility from the further participation in a non-clinical laboratory study that is being conducted as part of any application for a research or marketing permit that has been submitted to any Centre of the FDA (whether approved or not), it shall notify that Centre 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 FDA.

[43 FR. 60013, Dec. 22, 1978, as amended at 50 FR. 8995, Mar. 6, 1985]

Reg. No.
58.219

Regulatory Text
Reinstatement of a disqualified testing facility.

A testing facility that has been disqualified may be reinstated as an acceptable source of non-clinical laboratory studies to be submitted to the FDA 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 non-clinical laboratory studies in compliance with the good laboratory practice regulations set forth in this part and, 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 led to its disqualification do 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 reinstated, the Commissioner shall so notify the testing facility and all organisations and persons who were notified, under paragraph 58.213 of the disqualification of the testing facility. A determination that a testing facility has been reinstated is disclosable to the public under part 20 of this chapter.