

**7.2.4 Case-Control Studies of Glioma (WTR-EPI-006), Meningioma (WTR-EPI-007), Neuromas (Including Acoustic Neuroma) (WTR-EPI-008), Salivary Gland Tumors (Including the Parotid Gland) (WTR-EPI-009), Adult Onset Leukemia (WTR-EPI-010)**

Subject Area: The WTR, in response to the needs of its epidemiology research program, is soliciting proposals for specific research projects. The following background information and proposal details are intended to assist investigators interested in submitting proposals to conduct disease-specific case-control studies.

Background: In August 1994, the SAG published a research plan entitled "Potential Public Health Risks from Wireless Technology: Research Agenda for the Development of Data for Science-Based Decisionmaking," hereafter referred to as the Research Agenda. The Research Agenda outlined guiding principles for the development of a complete, relevant, credible, and rigorous scientific program for the evaluation of potential human health risks associated with the use of wireless technology.

Guiding Principle Number One of the Research Agenda outlined a three-tiered concept to be used in evaluating the priorities of the risk evaluation research plan. Wide use of wireless communication instruments makes essential the inclusion of epidemiological data for the development of a high quality database to be used for possible post-market surveillance and a determination of potential health risks. Tier II studies will, therefore, include cohort and case-control studies for the evaluation of general and specific potential causal associations between wireless technology use and adverse effects on human health.

Rationale for Selection of Case-control Studies: In January 1995, a working group made up of experts in the fields of cancer, epidemiology, and radiofrequency physics met to address the question of appropriate tissue/disease selection for the assessment of potential effects of wireless communication instrument use by humans. Dosimetric modeling studies (containing SAR distribution and level measurements), tissue specific tumor incidence, tumor latency, severity,

and prognosis were all considered in selecting tumor types for the evaluation of potential causal relationships in specific case-control studies.

Exposures from human use of wireless communication instruments are almost entirely restricted to the head (ratio of peak SAR) in the head to the whole-body average is as high as 1000:1); therefore, the focus of case-control studies will be tumor types associated with the brain and other tissues of the head. Gliomas (including glioblastoma multiforme), meningiomas, and neuromas were identified as the most common types of brain tumors in humans. In modeling studies, significant SAR levels are observed in the area of the parotid gland, making the evaluation of salivary gland tumors a relevant issue for this program. Finally, absorption of RFR in bony tissue of the head, which may contain areas of active bone marrow, raised the issue of potential effects of use of wireless technologies and adult-onset leukemia.

**Proposal Requirements:** Issues of potential biases from selection, misclassification and confounding should be addressed proactively. Sample size and power calculations should be included. A detailed rationale for interpretation of study results should be included and will be given significant weight during the evaluation process. Proposals must include a statement of qualifications and details pertaining to experience in conducting case-control studies. An outline of study design and methodology including protocol details should be included. A detailed cost estimate including labor, expenses, equipment, and overhead must be included in the proposal. Applicants are required to demonstrate a thorough knowledge of epidemiological concepts and biological endpoints, as well as consideration of the following required elements:

- (1) Demonstration of ability to conduct disease-specific case-control studies;
- (2) Demonstration of Good Epidemiology Practice (GEP) familiarity and previous compliance;
- (3) SOPs for all routine procedures to be used;
- (4) Description of methods to be used in the collection and evaluation of exposure data;
- (5) Procedures for data collection;
- (6) Procedures for statistical analysis including criteria for a positive response; and

- (7) Description of and rationale for selection of cases and controls including type of wireless technology(ies) to be included.

Proposals for studies involving the assessment of more than one endpoint will be welcomed. In addition, the WTR will support studies involving various types of wireless technologies, including analog, digital (CDMA and TDMA types), and GSM. All research will be conducted in accordance with GEPs in collaboration with the WTR's Quality Assurance Unit. In addition, a commitment to publication of the results in the peer-reviewed scientific literature is required.

**Submission Information:** Applications in duplicate (facsimile transmissions will not be accepted) must be received by October 1, 1995:

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Wireless Technology Research, L.L.C.  
1711 N St., NW, Suite 200  
Washington, DC 20036  
USA

Please include reference number WTR-TRP-006 to -010.

## 8.0 REFERENCES

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## **A.1 Good Laboratory Practice**

In the mid-1970s, the FDA published a set of GLP regulations and guidelines governing the conduct and reporting of non-clinical studies. Continuing interest in ensuring study integrity and data quality has prompted many amendments to the regulations, with the most recent publication dated April 1993. These regulations can be found in Part 58, Title 21, *Code of Federal Regulations* (CFR).

The scope of GLP regulations extends from the day-to-day, hands-on activities associated with study conduct to the responsibilities of management to ensure that all phases of the study are conducted in accordance with the study protocol, amendments, and the relevant Standard Operating Procedures (SOPs) of the laboratory.

More specifically, areas of regulatory emphasis include, but are not limited to the following: personnel qualifications, organization and layout of testing facility, responsibilities of the study director and the independent quality assurance unit, use and maintenance of equipment, review and compliance with SOPs, protocol design considerations, data entry, and archiving of records.

By closely monitoring the approach by which the study is designed, the methods of how the data are collected, and the manner in which the results are reported, one can ensure that the data generated are accurate and adequately support the safety-in-use of the test article. GLP compliance also extends to the need for adequate storage and retrievability of study records. If the results of a given study are questioned, it is of prime importance that the complete study be reproducible solely on the basis of the archived records.

## **A.2 Good Epidemiology Practice**

To standardize and improve the methods by which epidemiologic studies are conducted, guidelines have been developed to address epidemiological study issues. They range from the quality of the data to the appropriateness of the study design and the procedures employed

during the conduct of the study. These guidelines were developed to provide an alternative to the GLPs that would better address the specific issues faced by epidemiology researchers.

The “Guidelines for Good Epidemiology Practices (GEPs) for Occupational and Environmental Epidemiologic Research” were developed by the Chemical Manufacturers Association’s Epidemiology Task Force and published in *The Journal of Occupational Medicine*, Volume 33, Number 12, December 1991. The guidelines emphasize data quality and integrity and proper documentation of research methods. The GEPs propose minimum practices and procedures in the following areas: organization and personnel, facilities, resource commitment and contractors, protocol, review and approval of protocols and reports, study conduct, communication, archiving, and quality assurance.

Protocols should contain all relevant information, including a statement of intent or objectives of the study, a review of the pertinent scientific literature, a description of the study methodology, and methodologies for record keeping. The protocol should be accessible to all investigators and adhered to throughout the study.

SOPs must be written describing in detail the routine procedures involved in performing epidemiologic studies. Reproducibility, accuracy, and validity are ensured when SOPs provide clear descriptions of procedures and these procedures are followed precisely during the study. Change in SOPs should be maintained including revisions and dates of such revisions.

Epidemiological studies are dependent upon quality exposure data. The statement of research objectives, specific aims, and rationale should explain the design and conduct of the study in terms of the underlying biology.

The study report is the final product that should convey all important information and study results to interested readers. It is a summary of the completed study, including the study objectives, methods, results, and the principal investigator’s interpretation of the findings.

### **A.3 Good Clinical Practice**

Although no specific document outlines a set of guidelines called “good clinical practices,” the FDA has published guidelines for Clinical Investigations (21 CFR part 54).

A clinical study must have a complete protocol and both the protocol and study report must include a clear statement of the specific objectives of the study. A thorough description of the methods and the study design, including subject selection, assignment of subjects into study and control groups and assessment of subject response, must also be included. Results and an analysis of those results must be presented in the study report.

There must be an analysis of the results of the study adequate to assess the effects of the treatment. The protocol and report should describe the results and the analytical methods used to evaluate them, indicating statistical methods, comparability of test and control groups, and the effects of any interim data analyses performed.

To assure the protection of human subjects, participants are required to be informed on all aspects of the study, and investigators must obtain written informed consent from each participant (21 CFR 50, protection of human subjects). Institutional Review Board review and approval of the completed protocol are required in all studies involving human subjects.

### **A.4 Quality Assurance Under the WTR Program**

A table summarizing the specific areas of compliance required for the three types of studies is attached. An area where WTR specifically requires an extension of the requirements in the three documents relates to data entry. The regulation concerning data entry states that data entered in the data book will be dated on the day of entry and signed or initialed by the person entering the data. WTR will require that the principal investigator also sign or initial that the data was collected and entered according to the proper conduct of the study.

Specific requirements and guidelines for ensuring quality assurance and quality control of all research performed under the WTR program are:

- Under the WTR research program, all studies will be monitored by an independent Quality Assurance Unit (QAU) consisting of a person or persons not participating in the studies, to ensure compliance with regulatory guidelines. Usually this QAU is a part of the performing organization and monitors the studies for the management of the organization. However, due to the specialized nature of this research program, laboratories with the required scientific expertise may not have an independent QAU and establishing a QAU on site may be impractical. In these situations, the WTR, under the leadership of its quality assurance representative, will establish a QAU with the appropriate representation from the WTR intramural program staff and ad hoc members from the scientific community with the required expertise to evaluate compliance with good research practices. In either case, the QAU will be held responsible for assessing the quality of all aspects of the studies. A Quality Assurance Plan, which provides details of the quality assurance and quality control procedures for the studies, must be submitted by the QAU of the performing organization with its response to the RFP. If the organization responding to the RFP does not have an established QAU, it must detail its procedures related to quality control and request assistance in this area from WTR.
- SOPs must be prepared for all studies. Commonly, this will be the responsibility of the performing organization. Occasionally, when unique and specialized procedures are required, WTR staff will assist in developing SOPs before any studies are initiated. SOPs used in each WTR study will be maintained as WTR records for archiving purposes. These SOPs are subject to review by WTR personnel.
- The performing laboratory will maintain a file of QAU reports and responses (inspections, audits, periodic status) concerning studies. As the sponsor for the studies, WTR management, QA personnel, and the Project Officer will have access to the file for review purposes. The confidential, proprietary, and predecisional information contained

in this file will not be divulged by WTR reviewers. The file will not be revealed to any outside parties, including GLP compliance inspectors for the FDA or EPA.

- A performing laboratory can expect to have at least one QA monitoring site visit during the study and at least one per year for longer studies. During the visit, a team of three to eight QA professionals (WTR and/or support contract staff) will audit and inspect representative ongoing studies. Additional visits will be made as needed.

The participants of these QA inspection teams will depend upon the area of science being performed and the expertise required to evaluate compliance with guidelines. The teams will consist of core members, depending on the area of science, and ad hoc experts with the expertise to review scientific procedures. Investigators are encouraged to contact WTR staff during the proposal development process for assistance regarding the QA program. The participants for these teams are as follows:

Toxicology

- (1) Donald I. McRee, Ph.D., Chair  
Director of Extramural Research, WTR
- (2) Martha Embrey, M.P.H.  
Health & Environmental Sciences Group, Ltd.
- (3) Lori Martin, B.S.  
CanTox U.S., Inc.
- (4) Arthur Guy, Ph.D.  
WTR Member (Dosimetry)  
(or dosimetry expert)
- (5) Expert Consultant  
(Quality Assurance)
- (6) Ad hoc Scientific Experts  
(as required)

### Epidemiology

- (1) Donald I. McRee, Ph.D., Chair  
Director of Extramural Research, WTR
- (2) Rebecca Steffens, M.P.H.  
Health & Environmental Sciences Group, Ltd.
- (3) Arthur Guy, Ph.D.  
WTR Member (Dosimetry)  
(or dosimetry expert)
- (4) Expert Consultant  
(Quality Assurance)
- (5) Ad hoc Scientific Experts  
(as required)

### Clinical Studies

- (1) Donald I. McRee, Ph.D., Chair  
Director of Extramural Research, WTR
  - (2) Gretchen Findlay, B.S.  
Health & Environmental Sciences Group, Ltd.
  - (3) Arthur Guy, Ph.D.  
WTR Member (Dosimetry)  
(or dosimetry expert)
  - (4) Expert Consultant  
(Quality Assurance)
  - (5) Ad hoc Scientific Experts  
(as required)
- Quality assurance procedures require that the QAU from either the performing organization or WTR will develop and maintain specific quality assurance SOPs. These SOPs are to cover quality assurance activities that deal with the independent conduct of inspections, audits, and related activities applicable to studies performed for and by WTR. A historical file of these SOPs and all revisions thereof, including the dates of such revisions, will be maintained.

**Specific Areas of Compliance Required by Good Laboratory Practices,  
Good Epidemiology Practices and Clinical Investigations**

Toxicology Studies	Epidemiological Studies	Clinical Studies
Good Laboratory Practices	Guidelines for Good Epidemiological Practices	Clinical Investigations
<p>Nonclinical laboratory studies must meet criteria in the following areas:</p>	<p>Minimum practices and procedures for the following areas:</p>	<p>Obligations, commitments, and regulations governing conduct of clinical investigations:</p>
<ul style="list-style-type: none"> <li>I. Scope and Applicability</li> <li>II. Personnel</li> <li>III. Testing Facility Management</li> <li>IV. Study Director</li> <li>V. Quality Assurance Unit</li> <li>VI. Facilities</li> <li>VII. Equipment</li> <li>VIII. Standardization of Procedures</li> <li>IX. Reagents and Solutions</li> <li>X. Animal Care</li> <li>XI. Test and Control Articles</li> <li>XII. Protocol for and Conduct of Nonclinical Laboratory Study</li> <li>XIII. Records and Reports</li> <li>XIV. Disqualification</li> <li>XV. Effects of Disqualification</li> <li>XVI. Alternative and Additional Actions to Disqualification</li> <li>XVII. Reinstatement</li> </ul>	<ul style="list-style-type: none"> <li>I. Organization and Personnel               <ul style="list-style-type: none"> <li>A. Organizational Structure</li> <li>B. Personnel</li> </ul> </li> <li>II. Facilities, Resource Commitment, and Contractors</li> <li>III. Protocol</li> <li>IV. Review and Approval               <ul style="list-style-type: none"> <li>A. Scientific Review</li> <li>B. Ethical Review</li> <li>C. Administrative Review</li> </ul> </li> <li>V. Study Conduct               <ul style="list-style-type: none"> <li>A. Protection of Human Subjects</li> <li>B. Data Collection and Verification</li> <li>C. Analysis</li> <li>D. Study Report</li> </ul> </li> <li>VI. Communication of Results</li> <li>VII. Archiving</li> <li>VIII. Quality Assurance</li> </ul>	<ul style="list-style-type: none"> <li>1. Protocol for Conduct of Clinical Investigation               <ul style="list-style-type: none"> <li>A. Objective of Study</li> <li>B. Study Design</li> <li>C. Method of Selecting Subjects</li> <li>D. Methods Taken to Eliminate Bias</li> <li>E. Method of Assigning Treatment Groups</li> <li>F. Method of Data Analysis</li> </ul> </li> <li>II. Organization and Personnel (Institutional Review Board Approval)</li> <li>III. Consent of Human Subjects</li> <li>IV. Records and Reports</li> <li>V. Retention of Records (Archiving)</li> </ul>

Sec.

58.15 Inspection of a testing facility.

**Subpart B—Organization and Personnel**

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**Subpart C—Facilities**

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58.47 Facilities for handling test and control articles.  
58.49 Laboratory operation areas.  
58.51 Specimen and data storage facilities.

**Subpart D—Equipment**

58.61 Equipment design.  
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**Subpart E—Testing Facilities Operation**

58.81 Standard operating procedures.  
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58.90 Animal care.

**Subpart F—Test and Control Articles**

58.105 Test and control article characterization.  
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**Subpart G—Protocol for and Conduct of a Nonclinical Laboratory Study**

58.120 Protocol.  
58.130 Conduct of a nonclinical laboratory study.

**Subparts H-I—[Reserved]**

**Subpart J—Records and Reports**

58.185 Reporting of nonclinical laboratory study results.  
58.190 Storage and retrieval of records and data.  
58.195 Retention of records.

**Subpart K—Disqualification of Testing Facilities**

58.200 Purpose.  
58.202 Grounds for disqualification.  
58.204 Notice of and opportunity for hearing on proposed disqualification.  
58.206 Final order on disqualification.  
58.210 Actions upon disqualification.  
58.213 Public disclosure of information regarding disqualification.  
58.215 Alternative or additional actions to disqualification.

**PART 58—GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES**

**Subpart A—General Provisions**

Sec.

58.1 Scope.  
58.3 Definitions.  
58.10 Applicability to studies performed under grants and contracts.

## Sec.

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

58.219 Reinstatement of a disqualified testing facility.

**AUTHORITY:** Secs. 402, 406, 408, 409, 501, 502, 503, 505, 506, 507, 510, 512-516, 518-520, 701, 706, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 342, 346, 346a, 348, 351, 352, 353, 355, 356, 357, 360, 360b-360f, 360h-360j, 371, 376, 381); secs. 215, 351, 354-360F of the Public Health Service Act (42 U.S.C. 216, 262, 263b-263n).

**SOURCE:** 43 FR 60013, Dec. 22, 1978, unless otherwise noted.

### Subpart A—General Provisions

#### § 58.1 Scope.

(a) This part 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 color 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, 706, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33779, Sept. 4, 1987]

#### § 58.3 Definitions.

As used in this part, the following terms shall have the meanings specified:

(a) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 *et seq.*, as amended (21 U.S.C. 321-392)).

(b) *Test article* means any food additive, color 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 354-360F of the Public Health Service Act.

(c) *Control article* means any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any article other than a test article, feed, or water that is administered to the test system in the course of a nonclinical laboratory study for the purpose of establishing a basis for comparison with the test article.

(d) *Nonclinical laboratory study* 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 utilizing 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.

(e) *Application for research or marketing permit* includes:

(1) A color 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 recognized 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 §§ 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 § 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 an over-the-counter drug for human use, submitted as part of the procedures for classifying such drugs as generally recognized as safe and effec-

tive 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 § 314.300 of this chapter.

(10) A *Notice of Claimed Investigational Exemption for a 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 Premarket 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 procedures for establishing, amending, or repealing a performance standard for such devices, described in part 861.

(19) Data and 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 § 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 § 1010.5.

(f) *Sponsor* means:

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

(2) 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

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

(g) *Testing facility* means a person who actually conducts a nonclinical 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 nonclinical 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 nonclinical laboratory studies.

(h) *Person* includes an individual, partnership, corporation, association, scientific or 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. 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 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.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33779, Sept. 4, 1987; 54 FR 9039, Mar. 3, 1989]

**§ 58.10 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, 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 nonclinical 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 authorized employee of the Food and Drug Administration, at reasonable times and in a reasonable manner, to inspect the facility and to inspect (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 in inspection and copying requirements shall not apply to quality assurance unit records of findings and problems, or to actions recommended and taken.

(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 statute or regulation to submit the results of the study to the Food and Drug Administration.

**Subpart B—Organization and Personnel**

**§ 58.29 Personnel.**

(a) Each individual engaged in the conduct of or responsible for the supervision of a nonclinical laboratory study shall have education, training, and experience, or 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 nonclinical 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 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.

(f) 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 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 nonclinical laboratory study.

§ 58.31 Testing facility management.

For each nonclinical laboratory study, testing facility management shall:

(a) Designate a study director as described in § 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 § 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 nonclinical 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 results, and repre-

sents the single point of study control. The study director shall assure that:

(a) The protocol, including any change, is approved as provided by § 58.120 and is followed.

(b) All experimental data, including observations of unanticipated responses of the test system are accurately recorded and verified.

(c) 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.

(d) 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, practices, 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 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.

(2) Maintain copies of all protocols pertaining to all nonclinical laboratory studies for which the unit is responsible.

(3) 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, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for reinspection. 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.

(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 standard operating procedures were made without proper authorization 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 nonclinical 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 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 the 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.

(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]

### Subpart C—Facilities

#### § 58.41 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.

[52 FR 33780, Sept. 4, 1987]

#### § 58.43 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 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 minimize vermin infestation, odors, disease hazards, and environmental contamination.

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

**Food and Drug Administration, HHS**

**§ 58.81**

**§ 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 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.

**§ 58.49 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.

[52 FR 33780, Sept. 4, 1987]

**§ 58.51 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.

**Subpart D—Equipment**

**§ 58.61 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.

[52 FR 33780, Sept. 4, 1987]

**§ 58.63 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 required under § 58.81(b)(11) 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.

(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]

**Subpart E—Testing Facilities  
Operation**

**§ 58.81 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 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 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 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, 1987]

#### § 58.83 Reagents and solutions.

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

#### § 58.90 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 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 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 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.

(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 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 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 characterized by their labeling.

(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 provided by § 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, 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, 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 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.

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

**Subpart G—Protocol for and Conduct of a Nonclinical 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 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.

(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 nonclinical laboratory study.**

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

(b) The test 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 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 initialed 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.

(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]

**Subparts H-I—[Reserved]**

**Subpart J—Records and Reports**

**§ 58.185 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 as described in § 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 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.

[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, feces, 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 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 locations.

(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.

(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]