

§ 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.

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

(1) A period of at least 2 years following the date on which an application for a research or marketing permit, in support of which the results of the nonclinical laboratory study were submitted, is approved by the Food and Drug Administration. This requirement does not apply to studies supporting investigational new drug applications (IND'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 on which the results of the nonclinical laboratory study are submitted to the Food and Drug Administration in support of an application for a research or marketing permit.

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

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

(d) The master schedule sheet, copies of protocols, and records of

quality assurance inspections, as required by § 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 § 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 nonclinical 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 Food and Drug Administration 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—Disqualification 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 adequately demonstrated that such noncompliance did not occur during, or did not affect the validity or acceptability of data generated by, a particular study; and (2) to exclude from consideration all studies completed after the date of disqualification until the facility can satisfy the Commissioner that it will conduct studies in compliance with such regulations.

(b) The determination that a 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 Food and Drug Administration.

§ 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 (or any other regulations regarding such facilities in this chapter):

(b) The noncompliance adversely affected the validity of the nonclinical 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 § 58.202 which in his opinion justify disqualification of a testing facility, he may issue to the testing facility a written notice proposing that the facility be disqualified.

(b) A hearing on the disqualification shall be conducted in accordance with the requirements for a regulatory hearing set forth in part 16 of this chapter.

§ 58.206 Final order on disqualification.

(a) If the Commissioner, after the regulatory hearing, or after the time for requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification proceeding, makes the findings required in § 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 § 58.202, he shall issue a 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 nonclinical 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 Food and Drug Administration shall also determine whether the study is acceptable, notwithstanding the disqualification of the facility. Any study done by a testing facility before or after disqualification may be presumed to be unacceptable, and the person relying on the study may be required to establish that the study was not affected by the circumstances that led to the disqualification, e.g., by submitting validating information. If the study is then determined to be unacceptable, such data such be eliminated from consideration in support of the application; and such elimination may serve as new information justifying the termination or withdrawal of approval of the application.

(b) No nonclinical laboratory study begun by a testing facility after the date of the facility's disqualification shall be considered in support of any application for a research or marketing permit, unless the facility has been reinstated under § 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 Food and Drug Administration.

§ 58.213 Public disclosure of information regarding disqualification.

(a) Upon issuance of a final order disqualifying a testing facility under § 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 Food and Drug Administration that nonclinical laboratory studies performed by the facility will not be considered by the Food and Drug Administration in support of any application for a research or marketing permit. If such notice is sent to another Federal Government agency, the Food and Drug Administration will recommend that the agency also consider whether or not it should accept nonclinical laboratory studies performed by the testing facility. If such notice is sent to any other person, it shall state that it is given because of the relationship between the testing facility and the person being notified and that the Food and Drug Administration is not advising or recommending that any action 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 precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, institute against a testing facility and/

or against the sponsor of a nonclinical laboratory study that has been submitted to the Food and Drug Administration any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and prior to, simultaneously with, or subsequent to, disqualification. The Food and Drug Administration may also refer the matter to another Federal, State, or local government law enforcement or regulatory agency for such action as that agency deems appropriate.

(b) The Food and Drug Administration may refuse to consider any particular nonclinical laboratory study in support of an application for a research or marketing permit, if it finds that the study was not conducted in accordance with the good laboratory practice regulations 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 facility 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 authorized by this subpart. If a sponsor terminates or suspends a testing facility from further participation in a nonclinical laboratory study that is being conducted as part of any application for a research or marketing permit that has been submitted to any Center of the Food and Drug Administration (whether approved or not), it shall notify that Center in writing within 15 working days of the action; the notice shall include a statement of the reasons for such action. Suspension or termination of a testing facility by a sponsor does not relieve it of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.

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

§ 58.219 Reinstatement of a disqualified testing facility.

A testing facility that has been disqualified may be reinstated as an ac-

Sec.

60.28 Time frame for determinatory review periods.

Subpart D—Due Diligence Petitions

60.30 Filing, format, and content of petitions.

60.32 Applicant response to petition.

60.34 FDA action on petitions.

60.36 Standard of due diligence.

Subpart E—Due Diligence Hearings

60.40 Request for hearing.

60.42 Notice of hearing.

60.44 Hearing procedures.

60.46 Administrative decision.

AUTHORITY: Secs. 409, 505, 507, 515, 520, 701, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 348, 355, 357, 360e, 360j, 371, 376); sec. 351 of the Public Health Service Act (42 U.S.C. 262); 35 U.S.C. 156.

SOURCE: 53 FR 7305, Mar. 7, 1988, unless otherwise noted.

Subpart A—General Provisions**§ 60.1 Scope.**

(a) This part sets forth procedures and requirements for the Food and Drug Administration's review of applications for the extension of the term of certain patents under 35 U.S.C. 156. Patent term restoration is available for certain patents related to drug products (as defined in 35 U.S.C. 156(f)(2)), and to medical devices, food additives, or color additives subject to regulation under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act. Food and Drug Administration actions in this area include:

(1) Assisting the United States Patent and Trademark Office in determining eligibility for patent term restoration;

(2) Determining the length of a product's regulatory review period;

(3) If petitioned, reviewing and ruling on due diligence challenges to the Food and Drug Administration's regulatory review period determinations; and

(4) Conducting hearings to review initial Food and Drug Administration findings on due diligence challenges.

(b) References in this part to the Code of Federal Regulations are to

Subpart C—Regulatory Review Period Determinations

60.20 FDA action on regulatory review period determinations.

60.22 Regulatory review period determinations.

60.24 Revision of regulatory review period determinations.

60.28 Final action on regulatory review period determinations.

Guidelines for Good Epidemiology Practices for Occupational and Environmental Epidemiologic Research

The Chemical Manufacturers Association's Epidemiology Task Group

The Guidelines for Good Epidemiology Practices (GEPs) for Occupational and Environmental Epidemiologic Research address the conduct of studies generally undertaken to answer questions about human health in relationship to the work place or the environment. The GEPs propose minimum practices and procedures that should be considered to help ensure the quality and integrity of data used in epidemiologic research and to provide adequate documentation of the research methods. The GEPs address the process of conducting individual epidemiologic studies and do not prescribe specific research methods.

The Guidelines for Good Epidemiology Practices propose minimum practices and procedures in the following areas:

- I. Organization and Personnel
- II. Facilities, Resource Commitment, and Contractors
- III. Protocol
- IV. Review and Approval
- V. Study Conduct
- VI. Communication
- VII. Archiving
- VIII. Quality Assurance

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Although the Guidelines for Good Epidemiology Practices will not guarantee good epidemiology, they do provide a useful framework for ensuring that all research issues are adequately addressed. This framework is proposed as a first step in improving epidemiologic research practices through adherence to sound scientific research principles.

Appendices provide an overview of standard operating procedures, a glossary of terms used in the Guidelines, and suggested references on occupational epidemiology methods.

Epidemiologic studies provide unique, valuable information about the relationship between human health and exposure to substances in the environment and the workplace. While the contributions of toxicology and epidemiology are complementary, there is general agreement that reliable human evidence (epidemiologic studies) should take precedence over animal data (toxicological studies) in public policy and regulatory decision making. However, because of the nonexperimental nature of occupational and environmental epidemiologic studies, scientific controversy often surrounds the interpretation and significance of epidemiologic study results. In addition, controversy frequently concerns the quality of the data used, the appropriateness of the study design, and the process used to conduct the study. The nonexperimental nature of the epidemiologic studies cannot be changed, but the value of such research can be improved. The Guidelines for Good Epidemiology Practices address those issues—data quality, study design, and study conduct—that are under the control of the investigator.

Goals for the Guidelines for Good Epidemiology Practices

The Guidelines for Good Epidemiology Practices (GEPs) address the conduct of studies generally under-

taken to answer questions about human health in relationship to the workplace or the environment. The GEPs propose minimum practices and procedures that should be considered to help ensure the quality and integrity of data used in epidemiologic research and to provide adequate documentation of the research methods. The GEPs address the process of conducting individual epidemiologic studies and do not prescribe specific research methods.

Although Guidelines for Good Epidemiology Practices will not guarantee good epidemiology, they will provide a framework within which these issues might be addressed. The Guidelines have the following goals:

1. To provide a framework to assist researchers in adhering to good epidemiologic research principles.
2. To promote sound epidemiologic research by encouraging quality data collection and analysis.
3. To facilitate the continued development of improved epidemiologic research methodology.
4. To provide a framework for evaluating epidemiologic studies.
5. To improve the acceptance of studies that use sound scientific methods.
6. To improve the utility of epidemiologic studies in the formulation of public policy.
7. To improve public confidence in epidemiology as a scientific discipline.
8. To facilitate the conservation of technical resources by promoting careful study design and planning of study conduct.

Alternative Guidelines

A number of other organizations have also become interested in developing or applying guidelines to epidemiologic research.^{1,2} The Office of Management and Budget (OMB) published "Guidelines for Federal Statistical Activities" in which they defined "statistics" as the quantitative results of a survey or study collected for the purposes of reporting population characteristics.³ The Environmental Protection Agency (EPA) recently modified both the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA) good laboratory practice standards (GLPs) to specifically include epidemiology.^{4,5} In response to comments, EPA states that "all studies, including epidemiologic studies . . . [should] be performed under GLP standards. EPA recognizes that in such studies data used may not have been generated in conformance with . . . GLP standards. However, it is

EPA's position that the study itself can be conducted and submitted to EPA in accordance with the GLP standards."

The GLPs are directed primarily at experimental laboratory research, often involving the use of animals or cell culture systems. The GLPs address issues that confront researchers conducting experimental toxicological research. The Guidelines for Good Epidemiology Practices were developed in part to provide an alternative to the GLPs that would appropriately address the issues confronted by epidemiology researchers conducting nonexperimental studies.

Scope and Application

The Guidelines for Good Epidemiology Practices can be applied to all types of occupational and environmental epidemiologic research. Epidemiologic studies often evolve through a number of stages that might include proposals, feasibility studies, and measurement instrument validation studies that precede the development of a protocol. The GEPs should encompass all activities that begin with protocol development.

Clearly, large complex studies will benefit from the careful planning and thorough documentation implicit in these guidelines. Adherence to the spirit of the guidelines will be beneficial for those activities preceding protocol development as well as more informal investigations such as health hazard assessments/evaluations or small cluster investigations. Even in circumstances of immediate public health concern, the guidelines will provide a useful framework to ensure that all research issues are adequately addressed.

Further Development of the Guidelines for GEPs

The current document is a first step in developing a framework for improving epidemiologic research practices through adherence to sound scientific research principles. The guidelines emphasize data quality and integrity and adequate documentation of research methods. These guidelines should evolve based on the experiences gained through their application to studies.

A Special Note to Readers: As an aid to readers, a glossary of terms is provided in Appendix 2. These definitions reflect the use of the terms in this document. In an effort to be concise and clear, some sections of the guidelines for GEPs include examples and/or further explanation of the issue. Examples or elaborative text appear in *italics*.

Guidelines for Good Epidemiology Practices for Occupational and Environmental Epidemiologic Research

I. Organization and Personnel

A. Organizational Structure

The organization or individual conducting the research shall be fully responsible for the operation and performance of the research. The organization shall be a legal entity with a governing body that sets policy and that is fully responsible for the administrative aspects of the organization and its related research activities.

The relationship, roles, and responsibilities of the organizations and/or individuals sponsoring or conducting the study should be carefully defined in writing.

For example, this should include delineating the roles and responsibilities to be assumed by the study sponsor and the contractor(s) in communicating various aspects of the study as well as data ownership, archiving, etc.

B. Personnel

Personnel engaged in epidemiologic research and related activities shall have the education, training, and/or experience necessary to competently perform the assigned functions. The organization shall maintain a current summary of training and experience of these personnel. A job description for each individual engaged in or supervising activities shall be maintained and updated periodically.

II. Facilities, Resource Commitment, and Contractors

A. Facilities

Adequate physical facilities shall be provided to all those engaged in epidemiologic research and related activities. Sufficient resources, eg, office space, relevant equipment, and office/professional supplies, shall be available to ensure timely completion of all studies. Suitable storage facilities shall be available to maintain research materials in a safe and secure environment.

B. Resource Commitment

Sufficient commitment shall be made at the beginning of each study to ensure its timely and proper completion (see section III(L): Protocol).

C. Contractors

For the purposes of ensuring and documenting the contractor's conformance with the Guidelines for Good Epidemiology Practices, it is recommended that the

study sponsor have the right during the course of the study, and for a reasonable period following completion of the study, to inspect the contractor's facilities, including equipment, technical records, and records relating to the work conducted under the sponsor's contract.

III. Protocol

Each study shall have a written protocol. This protocol must be approved before the study begins (see section IV: Review and Approval).

The protocol should include the following:

- A. A descriptive title.
- B. The names, titles, degrees, addresses, and affiliations of the study director, principal investigator, and all co-investigators.
- C. The name(s) and address(es) of the sponsor(s).
- D. An abstract of the protocol.
- E. The proposed study tasks and milestones, including study approval data (date protocol signed by all signatories), study start date (first date that the protocol is implemented), periodic progress review dates, and completion date.
- F. A statement of research objectives, specific aims, and rationale.

The statement should identify the immediate purpose of the investigation. For example, it might also indicate whether the study will be exploratory data analysis, hypothesis testing, or a combination of both as well as whether the proposed study will address previously unanswered questions, will attempt to corroborate or confirm previous findings, or will be routine epidemiologic surveillance.

- G. A critical review of the relevant literature to evaluate applicable findings.

For example, the literature review should encompass animal and human experiments, clinical studies, vital statistics, and previous epidemiologic studies. The literature review should be of sufficient depth to identify potential confounders and effect modifiers and to determine areas where new knowledge is needed.

- H. A description of the research methods, including:
 1. The overall research design and strategy and reasons for choosing the proposed study design.

For example, case-control, cohort, cross-sectional, nested case-control, or other hybrid designs.

2. The data sources for exposure, health status, and risk factors.

For example, questionnaires, biological measurements, exposure/work history record reviews, or exposure/disease registries.

3. Clear definitions of health outcomes, exposure, and other measured risk factors as well as selection criteria, as appropriate, for exposed and nonexposed persons, morbidity or mortality cases, and referent groups.
4. Projected study size and, if appropriate, statistical power.

5. The methods to be used in assembling the study data.

This should include a description of, or reference to, methods used to control, measure, or reduce various forms of error—eg, bias due to selection, misclassification, interviewer, or confounding—and its impact on the study. Pretesting procedures for research instruments and any manuals and formal training to be provided to interviewers, abstractors, coders, or data entry personnel should be described or referenced.

6. Procedures for handling the data in the analysis.

This should include a description of procedures for defining or categorizing exposure and health outcome variables for purposes of analysis. It should also include provisions for assessing dose-response relationships and treatment of potentially confounding and effect modifying variables.

7. Methods for data analysis.

This should include procedures to control, if possible, sources of bias and their influence on results and a description of planned comparisons and methods for analyzing and presenting results.

8. Major limitations of the study design, data sources, and analytic methods.

9. Criteria for interpreting the results.

This should include a brief discussion of the characteristics of the proposed study design, including limitations, that will influence the discussion of the results. It also should state criteria for assessing biological plausibility, internal and external consistency of the findings, and causal inference. The statistical tests to be applied to the data and procedures for obtaining point estimates and confidence intervals of measures of occurrence or association should also be described.

- I. A description of plans for protecting human subjects.

This should include information about whether study subjects will be placed at risk as a result of the study, under what circumstances in-

formed consent will be required, and provisions for maintaining confidentiality of information on study subjects.

(See section IV: Review and Approval; section V: Study Conduct; section VI: Communication; and section VII: Archiving.)

- J. A description of, or reference to, quality assurance and quality control procedures for all phases of the study. As appropriate, include certification and/or qualifications of any supporting laboratory or research groups (see section VIII: Quality Assurance).

- K. A description of plans for disseminating and communicating study results (see section VI: Communication).

- L. Resources required to conduct the study.

Describe, for example, time, personnel, and equipment required to conduct the study, including a brief description of the role of each of the personnel assigned to the research project.

- M. The bibliographic references.

- N. Addenda, as appropriate.

For example, correspondence, collaborative agreements, institutional approvals, and samples of the informed consent forms, questionnaires, and representative samples of other documents to be used in the study.

- O. A dated protocol review and approval sign-off sheet for the study director, principal investigator, co-investigators, and all reviewers (see section IV: Review and Approval).

- P. Dated amendments to the protocol.

IV. Review and Approval

Review of study protocols and final reports should encompass all aspects of a study outlined in the Guidelines for Good Epidemiology Practices (see section III: Protocol and section V(D): Study Conduct). All reviews should be conducted in a timely fashion. It may be appropriate to involve worker or community representatives in the planning and review of the protocol and study results.

A. Scientific Review

The study protocol shall receive appropriate scientific review by qualified person(s) who are not part of the investigative team to ensure that the study is designed to address the objectives of the research and that the protocol is written according to Guidelines for Good Epidemiology Practices. The nature and circumstances of this review shall be documented (see section III: Protocol).

The scientific aspects of the completed study shall receive appropriate technical review to ensure that the

abstract, summary, and conclusions are supported by the underlying data, methods, and analyses (see section V: Study Conduct).

B. Ethical Review

The ethical aspects of each study protocol shall be reviewed by an institutional review board or other comparable review procedure.

This review should consider:

1. Obligations to research subjects.

For example, protecting the welfare of study subjects; the need for, and content of, communications and informed consent; protecting privacy; and maintaining confidentiality.

2. Obligations to society.

For example, avoiding conflicts of interest; avoiding partiality; disseminating the study's findings; data sharing; and pursuing responsibilities with due diligence.

3. Obligations to funders and employers.

For example, specifying obligations in contractual form of how research is to be conducted and how it may involve ethical, technical, administrative, or legal responsibilities; presenting methods and alternatives; and protecting privileged information.

4. Obligations to colleagues.

For example, promoting and preserving public confidence in epidemiologic research while not over- or underestimating the methods or results of epidemiologic inquiry; reporting methods and results; and disseminating the study's findings.

C. Administrative Review

The administrative aspects of the study protocol shall receive appropriate review and written approval by sponsors, contractors, and associated third parties to ensure that sufficient resources are available to complete the study in a timely and proper fashion.

Reports shall include a statement that the study was completed in accordance with the protocol, including any approved modifications to the protocol, and in accordance with the GEPs. Any deviations from the GEPs shall be explained and documented (see section VIII: Quality Assurance).

V. Study Conduct

While the study director shall be responsible for the overall research program, the principal investigator shall be responsible for the individual research project, including the day-to-day conduct of the study, interpretation of the study data, and preparation of a final report. These responsibilities extend to all aspects of

the study including periodic reporting of study progress as well as quality assurance. In some situations, the study director and the principal investigator may be the same person.

To ensure the proper conduct of the study, personnel shall adhere to sound research principles and practices established according to the protocol.

A protocol must be approved before the study begins. The study shall be conducted in accordance with the protocol; all deviations from the protocol shall be properly documented and authorized by the principal investigator.

If a decision is made not to complete a research project, the reasons for that decision shall be put in writing, dated, and signed by the responsible party, ie, the individual who makes the decision to terminate the study.

A. Protection of Human Subjects

Procedures for protecting human subjects shall be followed (see section III(I): Protocol and section IV(B): Review and Approval). Confidential information about study subjects shall be protected using established procedures.

If stipulated by the study protocol and/or required by an institutional review board, each study subject shall be informed about the purpose of the study and any risks associated with participating in the study. Written consent, if required, shall be obtained from each study subject before he/she participates in the study.

Written consent shall include at a minimum:

1. Purpose of the research or study.
2. Name(s), address(es), and phone number(s) of personnel available to answer questions about the research and the rights of study subjects.
3. Expected duration of subject's participation.
4. Eligibility requirements for study participation.
5. Possible benefits to the study subject or others of study results.
6. Statement on the voluntary nature of participation in the study and the right of the study subject to discontinue participation at any time.
7. Statement of confidentiality of records identifying the study subject, including reasonable exceptions to absolute confidentiality, eg, sharing of information with the study subject's personal physician or as required by court order.
8. Description of any foreseeable risks or discomforts to the study subject.
9. Statement of availability of results.

B. Data Collection and Verification

All data collected for the study should be recorded directly, accurately, promptly, and legibly. The individual(s) responsible for the integrity of the data, computerized and hard copy, shall be identified.

All procedures used to verify and promote the quality and integrity of the data shall be outlined in writing (see section VIII: Quality Assurance). An historical file of these procedures shall be maintained, including all revisions and the dates of such revisions. Any changes in data entries shall be documented.

C. Analysis

All data management and statistical analysis programs and packages used in the analyses should be documented. All dated versions used in research shall be kept with accompanying documentation (see section VII: Archiving).

D. Study Report

Completed studies shall be summarized in a final report that accurately and completely presents the study objectives, methods, results, and the principal investigator's interpretation of the findings.

The final report shall include at a minimum:

1. A descriptive title.
2. An abstract.
3. Purpose (objectives) of the research as stated in the protocol.
4. The names, titles, degrees, addresses and affiliations of the study director, principal investigator, and all co-investigators.
5. Name(s) and address(es) of sponsor(s).
6. Dates on which the study was initiated and completed.
7. Introduction with background, purpose, and specific aims of the study.
8. A description of the research methods, including:
 - a. the selection of study subjects and controls,
 - b. the data collection methods used,
 - c. the transformations, calculations, or operations on the data, and
 - d. statistical methods used in data analyses.
9. A description of circumstances that may have affected the quality or integrity of the data (see section VIII: Quality Assurance).
10. A summary and analyses of the data.

Include sufficient tables, graphs, and illustrations to present the pertinent data and to reflect the analyses performed.
11. A statement of the conclusions drawn from the analyses of the data.
12. A discussion of the implication of study results.

Cite prior research in support of and in contrast to present findings. Discuss possible biases and limitations in present research.
13. References.
14. A statement describing the location where all source data and the final report are stored. (see section VIII: Archiving).
15. A dated study report review sign-off sheet for the study director, principal investigator, co-investigators, and reviewers and/or auditors (see section IV: Review and Approval and section VIII: Quality Assurance).

VI. Communication

Each organization shall predetermine procedures under which communications of the intent, conduct, results, and interpretations of an epidemiologic study will occur, including what function individuals associated with the research must fulfill. These individuals should include the principal investigator, study director, and/or the sponsor. This procedure may be documented in the form of a company standard operating procedure, in the study protocol, or through contractual agreement.

Government agencies shall be informed of study results in a manner that complies with applicable regulatory requirements.

Scientific peers shall be informed of study results by publication in the scientific literature or presentations at scientific conferences, workshops, or symposia, to the extent possible.

All study subjects shall be informed of the study results and any interpretation of the study findings and conclusions, to the extent possible. Study subjects may be informed in person, through meetings, video tapes, letters, newsletters, summary reports, or other appropriate communication. Information about study results shall be provided in language appropriate for the audience.

VII. Archiving

There shall be physically secure archives for the orderly storage and expedient retrieval of all study related material. An index shall be prepared to identify the archived contents, to identify their location, and to identify by name and location any materials that by their general nature are not retained in the study archive.

Access to the archives shall be controlled and limited to authorized personnel only. Special procedures may be necessary to ensure that access to confidential information is limited and that the confidentiality of information about study subjects is protected (see section III(I): Protocol).

At a minimum, the study archive should contain, or refer to, the following:

- A. Study protocol and copies of all approved modifications.
- B. A final report of the study.

- C. All source data and, where feasible, specimens. A printed sample of the master computer data file(s) with reference to the location of the machine readable master.

If the data include any employee medical records subject to the Access to Employee Medical Records Regulation (29 CFR 1910.20), the records shall be retained according to the provisions of this rule.

- D. Documentation adequate to identify and locate all computer programs and statistical procedures used, including version numbers where appropriate (see section V(C): Study Conduct).
- E. Copies of computer printouts, including relevant execution code, that form the basis of any tables, graphs, discussions, or interpretations in the final report. Any manually developed calculations shall be documented on a work sheet and similarly retained.
- F. Correspondence pertaining to the study, standard operating procedures, informed consent releases, copies of all relevant representative material, copies of signed institutional review board and other external reviewer reports, and copies of all quality assurance reports and audits.
- Include, for example, questionnaires, name, make and model numbers of relevant measurement instruments, calibration information and procedures.*
- G. Original documents for the following research materials shall be included in the archives:
1. Laboratory/research notebooks.
 2. Coder modification notebooks.
 3. Signed and dated copies of the research protocol and final report.

VIII. Quality Assurance

Written procedures shall be established to ensure the quality of the data used in a study (see section III(J): Protocol and section V: Study Conduct). These procedures shall address data collection and completeness, coding and computer input, storage and retrieval, and data validation and analysis. Any deviations from the GEPs shall be explained and documented in the final report (see section IV(C): Review and Approval).

An individual who is not part of the investigative team should be assigned as a study quality assurance auditor. This individual shall, no less than annually, review study compliance with the written quality assurance procedures. The study quality assurance auditor shall prepare a written summary of the audit. The principal investigator should respond in writing to the audit report, including any remedial actions taken.

Quality assurance activities shall address the preceding sections of these guidelines as well as monitor conformance with established standard operating proce-

dures (SOPs) (see Appendix 1: Standard Operating Procedures).

APPENDICES

Appendix 1: Standard Operating Procedures

Appendix 2: Glossary of Terms Used in the Guidelines for Good Epidemiology Practices

Appendix 3: Suggested References on Occupational Epidemiology Methods

Appendix 1

Standard Operating Procedures

The Guidelines for Good Epidemiology Practices address the conduct of epidemiologic studies rather than the management of epidemiologic research programs. Many of the suggested guideline requirements can be fulfilled by reference to standard operating procedures for the research program.

Standard operating procedures (SOPs) are written, detailed descriptions of routine procedures involved in performing epidemiologic studies. Reproducibility, accuracy, and validity are ensured when SOPs are designed to clearly reflect each facility's research procedures. It should be the responsibility of a designated individual to develop and continuously review and update SOPs pertaining to his area of responsibility. Signatures of approval from the department's managing personnel or appropriate designees should be obtained for all new and updated versions. Significant changes in established SOPs should be maintained, including all revisions and the dates of such revisions. The manual of SOPs should be readily available to all research and administrative personnel.

Standard operating procedures should include:

1. A statement of the purpose of the standard operating procedure.
2. A detailed description of the procedure.
3. The person responsible or the training level required to perform the procedure.
4. The date of issue (effective date).
5. The issue number/revision number.
6. Signature of preparer.
7. Authorizing/reviewing signature of management.

Examples of research program activities for which SOPs could be established include:

1. Procedures for collecting raw data.
2. Procedures for validating the completeness of the study population.
3. Procedures for coding death certificates.
4. Procedures for assessing error rates in data abstraction and coding.

5. Security procedures for ensuring the integrity of the raw data and computer records.
6. Procedures for archive management.
7. Procedures for standard industrial hygiene sampling and analytic methods.
8. Procedures for scientific review.
9. Required composition of scientific review boards.
10. Procedures for data analysis.
11. Procedures for communications.

Appendix 2

Glossary of Terms Used in the Guidelines for Good Epidemiology Practices

The definitions below reflect the use of these terms in the Guidelines for Good Epidemiology Practices. These terms may have additional or different meanings in another context.

Descriptive Studies—a description of the population under study and the occurrence of disease or disease-related phenomena in populations. The latter may be presented as incidence or prevalence rates according to basic group characteristics such as age, sex, race, and/or geographic area.⁶

Epidemiologic Surveillance—periodic scrutiny of a defined population using epidemiologic techniques to detect changes and trends in the distribution of morbidity, mortality, or disease risk factors within that population.

Exploratory Data Analysis—analysis of a data set without a predetermined hypothesis, sometimes referred to as a descriptive study. This can be done with or without tests for statistical significance. Exploratory data analysis can be used to generate hypotheses, to suggest the most appropriate analytical techniques, to set priorities for future research, and to help focus subsequent analyses. A study may be a hybrid design and combine both exploratory data analysis and tests of the null hypothesis.

Hypothesis Testing Study—an analytic study that, through the use of tests of statistical significance, seeks to refute specific predetermined null hypotheses; the process of answering a specific *a priori* question or group of questions. A study may be a hybrid design and combine both exploratory data analysis and tests of the null hypothesis.

Legal Entity—legal existence. An entity, other than a natural person, who has sufficient existence in legal contemplation that it can function legally, be sued or sue, and make decisions through agents as in the law of corporations.

Null Hypothesis—the study question stated in a null fashion so that it can be tested for statistical significance, eg, tested to determine whether the results might occur by chance alone.⁷

Principal Investigator—the research investigator who has direct responsibility for the initiation, conduct, analysis, and interpretation of a specific study or investigation.

Quality Assurance—the overall program that ensures conformance to established performance standards. The quality assurance process encompasses all aspects of the research operation from the protocol to the final report.

Scientific Review—critical evaluation of a scientific study or investigation at any stage of development by peers of the principal investigator.

Standard Operating Procedure (SOP)—any standard method or process for conducting or accomplishing a routine research procedure not unique to a specific study.

Study—epidemiologic research relating to the distribution and determinants of health-related outcomes in specified populations and the application of this research to control of health problems.

Study Director—the research director, manager, or administrator who is responsible for managing the research program and who provides oversight of studies or investigations conducted within the research program.

Appendix 3

Suggested Bibliography on Occupational Epidemiology Methods

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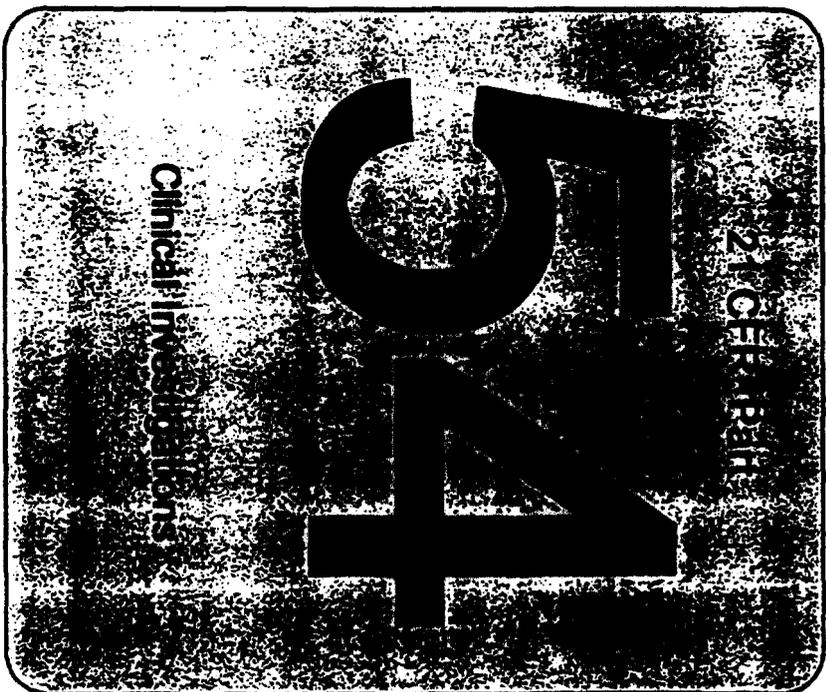
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PART 54--CLINICAL INVESTIGATIONS

Subpart A--General Provisions

Secs.

- 54.1 Scope.
- 54.2 Exemptions.
- 54.3 Definitions.
- 54.15 Inspection of facilities and records.

Subpart B--Organization and Personnel

- 54.25 Institutional review board.

Subparts C-E--(Reserved)

Subpart F--Test Articles

- 54.102 Use of test article by unauthorized persons.
- 54.108 Records of receipt and disposition of test articles.
- 54.116 Handling of controlled substances.
- 54.118 Promotion of test articles.

Subpart G--Protocol for Conduct of a Clinical Investigation

- 54.120 Protocol.
- 54.130 Conduct of a clinical investigation.
- 58.132 Withdrawal, withholding and discard periods for clinical investigations in food-producing animals.

Subpart H--Subjects in Clinical Investigations

- 54.142 Consent of human subjects.
- 54.143 Owner consent regarding animal subjects.
- 54.155 Records regarding subjects.

Subpart I (Reserved)

Subpart J--Records and Reports

- 54.185 Reporting of results of a clinical investigation.
- 54.195 Retention of records.

Subpart K--Disqualification of a Clinical Investigator

- 54.200 Purpose.
- 54.202 Grounds for disqualification.
- 54.204 Notice of and opportunity for hearing on proposed disqualification.
- 54.206 Final order on disqualification.
- 54.210 Actions upon disqualification.
- 54.213 Public disclosure of information regarding disqualification.
- 54.215 Alternative or additional actions to disqualification.
- 54.217 Suspension or termination of an investigator by a sponsor.
- 54.219 Reinstatement of a disqualified clinical investigator.

AUTHORITY: Sec. 406, 408, 409, 502, 503, 505, 506, 507, 510, 512-516, 518-520, 601, 701(a), 706, and 801. Pub. L. 717, 52 Stat. 1049-1054 as amended, 1055, 1058 as amended, 55 Stat. 851, 59 Stat. 1049-1054 as amended, 1055, 1058 as amended, 55 Stat. 1785-1788 as amended, 74 Stat. 399-403 as amended, 76 Stat. 794 as amended, 82 Stat. 343-351, 90 Stat. 539-574 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 357, 360, 360b-360f, 360H-360J, 361, 371(a), 376, and 381); secs. 215, 351, 354-360F, Pub. L. 410, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended (42 U.S.C. 216, 262, 263b-263n).

Subpart A—General Provisions

§54.1 Scope.

(a) This part contains the general obligations and commitments of, and regulations governing conduct of, persons who conduct clinical investigations regulated by the Food and Drug Administration under section 505(i), 507(d), 512(j), and 520(g) of the Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, medical devices for human use, and electronic products. Additional specific obligations and commitments of, and regulations governing conduct of persons who conduct clinical investigations involving particular test articles and products may also be found in other parts of this chapter, e.g. parts 312, 511, and 812. Compliance with these parts is intended to protect the rights and safety of subjects involved in such investigations and to help assure the quality and integrity of the data filed pursuant to sections 406, 408, 409, 502, 503, 505, 506, 507, 510, 512, 513-516, 518-520, 607, 706, and 801 of the Act and sections 351 and 354-360 of the Public Health Service Act.

§54.2 Exemption

Any investigator subject to the requirements of this part, or the sponsor of such investigator, may request the Food and Drug Administration for a waiver of any specific requirements. Such a request shall be submitted in writing as part of an application for a research permit in accordance with §§312.1, 511.1, or part 812 of this chapter and shall set forth the basis for the applicant's belief that compliance with a particular requirement is not necessary either to protect the rights and safety of subjects involved in the particular clinical investigation or to help assure the quality and integrity of the data

produced in the investigation. The Commissioner may, in the Commissioner's discretion, grant in writing a request for a waiver of certain requirements if he agrees with the applicant that compliance with those requirements in the course of the particular clinical investigation is not necessary. In the case of applications for a research permit granted on an emergency basis, such request for waiver may be made over the telephone and be granted orally by the agency at the same time the emergency application is approved on an oral basis. Written confirmation shall be included in the official application submitted subsequently to this emergency authorization of such application.

§54.3 Definitions.

As used in this part:

(a) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902), 52 Stat. 1040-1059, as amended (21 U.S.C. 321-392).

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

(1) A color additive petition, described in Part 71 of this chapter.

(2) A food additive petition, described in Parts 171 and 571 of this chapter.

(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 that 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 §170.30 and §570.30 of this chapter.

(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 of this chapter.

(5) Data and information regarding a substance submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in §180.1 of this chapter.

(6) Data and information regarding a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.

(7) A "Notice of Claimed Investigational Exemption for a New Drug", described in Part 312 of this chapter.

(8) A new drug application, described in Part 314 of this chapter.

(9) Data and information regarding the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in Part 320 of this chapter.

(10) 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 effective and not misbranded, described in Part 330 of this chapter.

(11) Data and information regarding a prescription drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in this chapter.

(12) Data and information regarding an antibiotic submitted as part of the procedures for issuing, amending, or repealing regulations for such drugs, described in Part 340 of this chapter.

(13) A "Notice of Claimed Investigational Exemption for a New Animal Drug", described in Part 511 of this chapter.

(14) A new animal drug application, described in Part 514 of this chapter.

(15) Data and information regarding a drug for animal use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in this chapter.

(16) An application for a biological product license, described in Part 601 of this chapter.

(17) Data and information regarding a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in Part 601 of this chapter.

(18) Data and information regarding a cosmetic submitted as part of the procedures for demonstrating that the product or any ingredient is "hypoallergenic", described in §701.100 of this chapter.

(19) Data and information regarding an in vitro diagnostic product submitted as part of the procedures for establishing, amending, or repealing a standard for such products, described in Part 809 of this chapter.

(20) An "Application for an Investigational Device Exemption", described in Part 812 of this chapter.

(21) Data and information regarding a medical device submitted as part of the procedures for classifying such devices, described in section 513 of the act.

(22) Data and information regarding a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for such device, described in section 514 of the act.

(23) An application for premarket approval of a medical device, described in section 515 of the act.

(24) A product development protocol for a medical device, described in section 515 of the act.

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

(26) 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 of this chapter.

(27) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in §1010.5 of this chapter.

(c) *Clinical investigation* means any experiment involving a test article, which experiment is either subject to requirements for prior submission to the Food and Drug Administration under section 505(l), section 507(d), section 512(j), or section 520(g) of the act, or which experiment is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provision of Part 58 of this chapter.

(d) *Contract research organization* means a person who assumes one or more of the obligations of a sponsor as an independent contractor with the sponsor, e.g., design of protocol, selection and/or monitoring of investigators, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

(e) *Investigator* means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject).

(f) *Monitor*, when used as a noun, means a designated individual selected by a sponsor or contract research organization to oversee the progress of a clinical investigation. The monitor may be a full-time employee of a sponsor or contract research organization or a consultant to the sponsor or

contract research organization. "Monitor", when used as a verb, means the act of overseeing the progress of a clinical investigation in accordance with §52.29.

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

(h) *Sponsor* means a person who initiates a clinical investigation, but who does not actually conduct the investigation (i.e., the test article is administered or dispensed to or used involving a subject under the immediate direction of another individual). A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(i) *Sponsor investigator* means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual (e.g., corporation or agency). The obligations of a sponsor-investigator under this part include those of a sponsor except where a sponsor-investigator is explicitly exempted from certain obligations under §52.15.

(j) *Subject* means an individual who is or becomes a participant in a clinical investigation, either as a recipient of the test article or as a human control. A subject may be either a healthy human being or healthy or unhealthy animal, or a patient to whom the test article might offer a therapeutic benefit or provide diagnostic information. The term "subject" applies both to human beings and to other animals; whenever only human subjects are referred to, the adjective "human" shall be used. The term "subject", when applied to animals other than man, may apply to individuals and/or groups based upon whether an individual or group response is being measured.

(k) *Test Article* means any drug (including a biological product for human use), medical device, human or animal food additive, color additive, cosmetic, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360f of the Public Health Service Act.

§54.16 Inspection of facilities and records.

(a) An investigator shall permit an authorized employee of the Food and Drug Administration, at reasonable times and in a reasonable manner:

(1) To inspect the facilities utilized by the investigator for the clinical investigation;

(2) For purposes of verification of case reports and other information prepared for the sponsor as part of the data and information to be submitted by the sponsor to the Food and Drug Administration;

(i) To inspect records required to be made or kept by the investigator as part of or relevant to the investigation;

(ii) To copy such records that do not identify the names of human subjects or from which the identifying information has been deleted; and

(iii) To copy such records that identify the human subjects, without deletion of the identifying information, but only upon notice that the Food and Drug Administration has reason to believe that the consent of human subjects was not obtained, that the reports submitted by the investigator to the sponsor (or to the institution review board) do not represent actual cases or actual results obtained, or that such reports or other required records appear to be otherwise false or misleading.

(b) An investigator shall permit authorized representative of the sponsor (e.g., the monitor selected under §52.28 of this chapter), at reasonable times and in a reasonable manner, to inspect the facilities utilized by the investigator for the clinical investigation and to inspect, for purposes of verifica-

tion of case reports and other information prepared for the sponsor, the records required to be made or kept by the investigator as part of the investigation.

(c) The Food and Drug Administration will not accept a clinical investigation as evidence in support of an application for a research or marketing permit if the investigator who conducted the investigation refuses to permit an inspection under this section. The determination that a clinical investigation may not be accepted 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 statute or regulation to submit the results of the investigation to the Food and Drug Administration.

Subpart B--Organization and Personnel

§54.25 Institutional review board.

If the clinical investigation is subject to an institutional review requirement under either parts 312 or 812 of this chapter or any other applicable regulation in this chapter:

(a) An investigator shall submit the proposed clinical investigation (including the protocol of the investigation, a report of prior investigations if a medical device for human use, and the materials to be used in obtaining the consent of the human subjects, described in §54.142(b)) for review by the board, and shall obtain the approval of the board, before any human subjects are allowed to participate in, or requested formally (i.e., in accordance with §310.102 or subpart F of part 812 of this chapter, whichever is applicable) to consent to participate in, the investigation.

(b) An investigator shall submit any proposed change in or deviation from the protocol of the clinical investigation for review by the board if the change or deviation may increase the risk to human subjects in the study or may adversely affect the validity of the investigation or the rights of the human subjects, and shall obtain the approval of the board before

such change or deviation is implemented. When the change or deviation is done to eliminate or reduce the risk to human subjects, it may be implemented before review or approval by the board; the investigator shall notify the board of the change or deviation in writing within 10 working days after implementation.

(c) In obtaining the consent of subjects, an investigator shall not use a form that has not been approved by the board.

(d) An investigator shall submit to the board the progress report required in §54.185(a). An investigator shall submit to the board the final report required in §54.185(b). An investigator shall submit to the board any special report relating to adverse effects required by §54.185(c), or any information regarding similar reports received from the sponsor, as soon as possible and in no event later than 10 working days after the investigator discovers the information or is notified of it by the sponsor, e.g., when uncovered by another investigator or in a non-clinical laboratory study.

(e) An investigator shall provide accurate and adequate information regarding the clinical investigation to the board in response to its request.

(f) An investigator shall maintain records of all submissions to, and all actions by, the board regarding the clinical investigation.

Subparts C-E--(Reserved)

Subpart F--Test Articles

§54.102 Use of test article by unauthorized persons.

An investigator shall only permit a test article to be administered or dispensed to or used involving subjects who are under his or her personal supervision or under the supervision of another investigator who is responsible to him or her and, if it is a test article intended for use in humans, who is named by the investigator in his or her signed statement undertaking the obligations of an investigator or sponsor-investigator, e.g., forms FD-1571 and FD-1572 in §312 of this chapter. An investigator shall not supply a test article to any other person for administration to or use upon subjects or for any other purpose, without the prior authorization of the sponsor.

§54.108 Records of receipt and disposition of test articles.

An investigator shall return to the sponsor any unused or reusable supply of a test article, or otherwise dispose of the article as authorized in writing by the sponsor, upon request of the sponsor, upon completion, suspension, termination, or discontinuance of the clinical investigation, or upon termination or withdrawal by the Food and Drug Administration of the exemption under which the investigation is being conducted.

§54.116 Handling of controlled substances.

If a test article is a substance listed in any schedule of the Controlled Substance Act (21 U.S.C. 801 note; 21 CFT Part 1308), the investigator shall take reasonable precautions to prevent theft or diversion of the article into illicit channels, including storage of the substance in a cabinet or other enclosure, which is substantially constructed and securely locked and to which access is restricted by the investigator.

§54.118 Promotion of test articles.

An investigator shall not represent in a promotional context that an unmarked test article is safe or effective for the purposes for which it is under investigation or otherwise promote or commercialize the article. This requirement is not intended to restrict the full exchange of scientific information concerning the article, including dissemination of scientific findings in scientific or lay communications media; its interest is to restrict promotional claims of safety or effectiveness and to preclude commercial use or test-marketing of the article before authorization for marketing by the Food and Drug Administration.

Subpart G--Protocol for and Conduct of a Clinical Investigation

§54.120 Protocol.

(a) Each clinical investigation shall have a written protocol.

(b) All changes or revisions to a protocol, and reasons therefore, shall be documented by the investigator, dated, and maintained with the protocol.

§54.130 Conduct of a clinical investigation.

A clinical investigation shall be conducted in accordance with the protocol. An investigator shall not implement a change in the protocol, or otherwise deviate from such protocol, if the change or deviation may increase the risk to subjects in the study or may adversely affect the validity of the investigation or the rights of the human subjects, without the prior review and written approval of the sponsor of the investigation and, when such review is required under either §312.1 or Part 812 or any other applicable regulation in this

chapter, by an institutional review board. When the change is made to eliminate or reduce the risk to human subjects, it may be implemented before review or approval by the sponsor and the board; the investigator shall notify the sponsor and the board of the change or deviation in writing within 10 working days after implementation.

§54.132 Withdrawal, withholding, and discard periods for clinical investigations in food-producing animals.

An investigator in a clinical investigation that includes food-producing animals as subjects shall not offer the animals for slaughter for food purposes, or otherwise offer for food purposes edible products from the animals, without prior authorization from the Food and Drug Administration or the U. S. Department of Agriculture, and shall observe the authorized withdrawal, withholding, or discard time periods.

Subpart H--Subjects in Clinical Investigations

§54.142 Consent of human subjects.

(a) An investigator shall inform each human subject (or, where appropriate the legal representative of the human subject), including any human subject used as a control, that the test article is being used for research purposes, provide the other information required by §310.102(h) or subpart F or part 812 of this chapter, whichever is applicable.

(b) An investigator shall provide to the sponsor, and to the institutional review board, if any, a copy of any written materials to be given or read to the human subject, or the subject's legal representative, regarding the information required to be given by §310.102(h) or subpart F of part 812 of this chapter (whichever is applicable), and a copy of any form to be used to document the consent of such subject or the subject's legal representative.

§54.143 Owner consent regarding animal subjects.

An investigator shall inform the owner or owners of each animal subject that the test article is being used for research purposes in a clinical investigation, and shall obtain and properly document the consent of each owner or owners.

§54.155 Records regarding subjects.

(a) An investigator shall maintain adequate and accurate records on which case reports on each subject (including a subject used as a control) are based, which shall include the following:

(1) Detailed medical history records which contain:

(i) Medical history before the subject's involvement in the clinical investigation which includes basic identifying information linking the subject's record to the subject's case report forms submitted to the Food and Drug Administration, results of all diagnostic tests performed, diagnoses made, therapy provided, and other data on the condition of the subject.

(ii) Medical history during the subject's involvement in the clinical investigation, which includes all data described in paragraph (a)(1)(i) of this section as it relates to the exposure of the subject to the test or control article, and to any concomitantly or concurrently administered therapy, including the date (and time, if relevant) of each dispensing or administration and the quantity dispensed or administered; and, all relevant observations and data on the condition of the subject throughout the subject's participation in the investigation, including the appearance of factors that might alter the effects of the test article (e.g., development of an apparently unrelated intercurrent illness).

(2) Any documentation regarding the consent of the human subject required under §31012 or subpart F or part 812 of this chapter, whichever is applicable.

(b) In research in animals other than man, where a group response (rather than an individual response) is an appropriate measurement, the records required in this section may be maintained on each group for the specific measurement rather than on each individual subject in the group.

Subpart I--(Reserved)

Subpart J--Records and Reports

§54.185 Reporting of results of a clinical investigation

(a) An investigator shall make accurate and adequate reports to the sponsor, and to any institutional review board that has reviewed and is continuing to review the investigation, on the progress of the clinical investigation at appropriate intervals not exceeding 1 year.

(b) An investigator shall make an accurate and adequate final report to the sponsor, and to any institutional review board that has reviewed and is continuing to review the investigation, within 3 months after the completion, termination or discontinuation of the entire clinical investigation or of such investigator's participation in it, whichever is sooner. This report shall include all case reports not provided to the sponsor in periodic or special reports.

(c) An investigator shall make an accurate and adequate special report to the sponsor, and to any institutional review board that has reviewed and is continuing to review the investigation, on any serious adverse effect, death, or life-threatening problems that may reasonably be regarded as caused by or associated with the test article and which was not previously anticipated (in nature, severity or degree of incidence) in the written information on the article provided to the investigator by the sponsor. Such reports shall be made

as soon as possible and in no event later than 10 working days after the investigator discovers the serious adverse effect, death, or medical problem.

(d) An investigator shall retain a copy of each report he or she submits to the sponsor and to an institutional review board under this section.

§54.196 Retention of records.

(a) An investigator shall retain the records required by this part or by any other regulations in this chapter regarding clinical investigations (e.g., parts 312, 511, and 812) for whichever of the following periods is shortest:

(1) A period of 2 years following the date on which the test article is approved by the Food and Drug Administration for marketing for the purposes that were the subject of the investigation;

(2) A period of 5 years following the date on which the results of the investigation are submitted to the Food and Drug Administration in support of or as part of an application for a research or marketing permit for the test article for the purposes that were the subject of the investigation; or

(3) In other situations (e.g., where the investigation does not result in the submission of the data from the investigation in support of or as part of an application for a research or marketing permit), a period of 2 years following the date on which the entire clinical investigation (not merely the investigator's portion of an investigation involving more than one investigator) is complete, terminated, or discontinued, or the exemption under which the investigation is being conducted is terminated or withdrawn by the Food and Drug Administration.

(b) In the event the investigator retires, relocates, or for any other reason withdraws from the responsibility for maintaining the records for the period of time required, custody of the records may be transferred to any other person who will

accept responsibility for the records, e.g., the sponsor, an institutional review board, or another investigator. Notice of such transfer shall be given in writing to the sponsor.

Subpart K--Disqualification of a Clinical Investigator

§54.200 Purpose

The purposes of disqualification of an investigator who has failed to comply with any of the regulations set forth in this part, or other regulations governing the conduct of investigators in this chapter, may be one or both of the following:

(a) To preclude him or her from conducting clinical investigations subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), 512(j), or 520(g) of the act until such time as it becomes likely that he or she will abide by such regulations or that such violations will not recur. The determination to disqualify an investigator does not constitute a finding or recommendation that the investigator is not qualified to practice or teach medicine or should be subject to other sanctions by other persons, such as licensing boards or employers.

(b) To preclude the consideration of any clinical investigations in support of applications for a research or marketing permit from the Food and Drug Administration, which investigations have been conducted by the investigator, until such time that it becomes likely that he or she will abide by such regulations or that such violations will not recur or that it can be adequately demonstrated that such violations did not occur during or affect the validity or acceptability of a particular investigation or investigations. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant from such a permit of any obligation under any other applicable statute or regulation to submit the results of the investigation to the Food and Drug Administration.

§54.202 Grounds for disqualification.

The commissioner may disqualify an investigator upon finding all of the following:

(a) The investigator failed to comply with any of the regulations set forth in this part or other regulations regarding the conduct of investigators in this chapter.

(b) The noncompliance adversely affected the validity of the clinical investigation or the rights of the human subjects, or the safety of the subjects; and

(c) Other lesser regulatory actions, e.g., warnings or rejection of data from individual investigations, have not been or will probably not be adequate to assure that the investigator will comply with such regulations in the future.

§54.204 Notice of and opportunity for hearing on proposed disqualification.

(a) Whenever the Commissioner has information indicating that grounds exist under §54.202 which in the Commissioner's opinion may justify disqualification of an investigator, the Commissioner may issue to the investigator a written notice proposing the investigator be disqualified.

(b) A hearing on the disqualification of an investigator shall be conducted in accordance with the requirements for a regulatory hearing set forth in part 16 of this chapter.

§54.206 Final order on disqualification.

(a) If the Commissioner, after the regulatory hearing or after the time for requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification proceeding, makes the findings required in §54.202, the Commissioner shall issue a final order disqualifying the investigator. Such order shall include a statement of the basis for that determination and shall prescribe any actions (set forth in §54.210(b)) to be taken with

regard to ongoing clinical investigations being conducted by the investigator. Upon issuing a final order, the Commissioner shall notify (with a copy of the order) the investigator of the action, as well as the sponsor of each clinical investigation subject to requirements for prior submission to the Food and Drug Administration that was being conducted by the investigator and has not been terminated or discontinued or as to which the exemption under which it is being conducted has not been terminated or withdrawn by the Food and Drug Administration.

(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 proceedings, determines not to make the findings required in §54.202, the Commissioner shall issue a 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 investigator and provide a copy of the order.

§54.210 Actions upon disqualification.

(a) No clinical investigation subject to requirements for prior submission to the Food and Drug Administration will be authorized by the Commissioner if such investigation is to be conducted, in whole or in part, by a disqualified investigator.

(b) The Commissioner, after considering the nature of each ongoing clinical investigation subject to requirements for prior submission to the Food and Drug Administration that is being performed by the investigator, the number of subjects involved, the risks to them from suspension of the investigation, and the need for involvement of an acceptable investigator, may direct, in the final order disqualifying an investigator under §54.206(a), that one or more of the following actions be taken with regard to each such investigation: