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NONCLINICAL LABORATORIES STUDIES

Proposed Regulations for Good Laboratory Practice

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 3e, 8, 121, 312, 314, 430, 431, 514]

[Docket No. 76N-0400]

NONCLINICAL LABORATORY STUDIES

Proposed Regulations for Good Laboratory Practice Regulations

The Food and Drug Administration (FDA) proposes to establish good laboratory practice regulations for methods to be used in, and the facilities and controls to be used for, conducting nonclinical laboratory studies to assure the quality and integrity of 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 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360b–360f, 360h–360j, 376, and 387) and sections 351 and 354–360F of the Public Health Service Act (42 U.S.C. 262 and 263b–263n). Interested persons have until March 21, 1977, to submit comments. The Commissioner of Food and Drugs also announces that a public hearing to discuss the views of interested persons on the proposed regulations will be scheduled early in 1977 and will be subject to a notice to be published in the FEDERAL REGISTER at a later date.

The Commissioner fully appreciates that the agency's establishment of regulations governing the conduct of nonclinical laboratory studies represents a major new initiative for FDA that will have significant impact on the private testing community. He is convinced, as is the Congress of the United States, that deficiencies discovered in the current conduct of such testing, both in the private sector and in government, require this initiative to be pursued vigorously. Decisions about the safety of consumer products that are based, wholly or in part, on data derived from such testing are too important for the agency to accept anything less than the best scientific data that can be obtained. At the same time, the Commissioner wants the final good laboratory practice regulations to be both sound scientifically and realistic.

The Commissioner encourages all interested persons to comment on this proposal in detail and at length, and invites suggestions for improvements. To assure that all interested persons are given the opportunity for personal participation in developing regulations governing the conduct of nonclinical laboratory studies, the Commissioner announces that he will hold a public hearing on this proposal approximately 60 days after the date of publication in the FEDERAL REGISTER. A notice of the exact time and place for the hearing will appear in the FEDERAL REGISTER approximately 30 days after the date of publication of this proposal.

An earlier draft of this proposal was forwarded to other Federal agencies for information and comment. As of October 15, 1976, comments were received from the National Institutes of Health, the National Cancer Institutes, the National Institute for Occupational Safety and Health, the Environmental Protection Agency, the Consumer Product Safety Commission, and the Department of Agriculture. In addition, the Center for Disease Control submitted a draft of regulations that it proposes to publish under the authority of the Clinical Laboratories Improvement Act. Where possible, these comments and proposals were considered and are reflected in the current proposal. Outstanding issues will be addressed and discussed in the preamble to the final regulation. The comments of the other agencies have been put on display in the office of the Hearing Clerk, Food and Drug Administration.

The Federal Food, Drug, and Cosmetic Act and the Public Health Service Act impose on manufacturers the burden of demonstrating that their products meet the safety and effectiveness requirements of the law and that they are not misbranded for their intended use. To ensure the highest degree of consumer protection, FDA requires that extensive animal and other types of testing be performed. Although FDA itself carries out independent testing of certain types of products and validates testing systems, it lacks the resources to conduct its own testing of all products requiring toxicological studies; the responsibility for such testing is one assigned by law to the manufacturers of regulated products. Instead, FDA may prescribe the type and extent of testing deemed necessary for a determination of safety and utility of a product, and then require that these be conducted by or on behalf of the person desiring to market a regulated product. These studies may have to be submitted to FDA before the product is marketed, or after marketing has begun in order to justify continued distribution; in a few cases, the studies are not submitted but must be available to FDA upon request. The adequacy and validity of nonclinical laboratory tests therefore remain the responsibility of the sponsor of the product, as part of establishing the marketability of the product under the Federal Food, Drug, and Cosmetic Act and/or the Public Health Service Act. While the sponsor of a product is generally its manufacturer, other persons such as distributors, government agencies, and users or consumers may seek to attain FDA approval or acceptance of a product. Thus, in this preamble, the reader should understand that the terms "sponsor" and "manufacturer" are frequently, but not always, used interchangeably.

The testing required for products is established by the legal requirements applicable to the product and by the available technology to fulfill these requirements. Testing may include physical and chemical studies, nonclinical laboratory studies, and clinical trials in humans or animals in whom the product is intended to be used. The nonclinical laboratory data submitted to or reviewed by FDA encompass a wide variety of tests and procedures performed on animals and other biological test systems to delineate the toxicity and other effects of a regulated product. Primarily, these tests are intended to assess acute, subchronic and chronic toxicity of the product to humans or animals, including reproductive, teratogenic, carcinogenic and mutagenic effects as well as degenerative disorders, based upon the appearance of these effects in laboratory animals. Nonclinical laboratory investigations also involve biochemistry, nutrition, immunology, microbiology and other disciplines that may indicate the toxic potential, the functionality, or the effectiveness of a regulated product, and that may contribute to a decision on the risks and benefits of the product to humans and animals. Data may be derived from either in vivo or in vitro tests or procedures involving exposure of the product to laboratory animals.

As one example of the regulatory need for scientific research data, all new drugs and most biologics must undergo extensive testing in animals or other biological test systems to determine the toxicity profiles and other possible short- and long-term adverse effects, including the possibility of carcinogenicity whenever the drug is intended for chronic use in humans. Preclinical studies of drugs are of particular importance in deciding whether a new drug can be safely tested in humans to assess its potential use as a therapeutic agent.

With regard to drugs intended for veterinary use, studies are conducted in laboratory animals and target animal species to develop data on the safety and effectiveness of the drug in the animal. If the target species is a food-producing animal, data relating to human safety as a result of use of the drug in the animal is also needed.

The Medical Device Amendments of 1976 (Pub. L. 94-295) to the Federal Food, Drug, and Cosmetic Act require safety and effectiveness data for premarket approval of certain devices, as a prerequisite to the development of product performance standards, and for other purposes. Such data may be obtained from in vivo and in vitro studies involving animals, as well as from physical and chemical experiments and clinical trials in humans.

Similarly, animal testing is essential in assessing the potential for toxic effects, including teratogenicity and carcinogenicity, of food additives and color additives. Such testing cannot ethically or practically be conducted in humans; therefore, animal data are essential for a determination of the safety of these substances.

The importance of toxicological and other laboratory data derived from animal studies and other biological test systems to decisions on safety, effectiveness, and functionality of drugs, biological products, devices, food additives, color additives, and other regulated products demands that these studies be conducted according to scientifically sound protocols and scientifically proper procedures to ensure the quality and integrity of the resulting data. Such studies require the combined efforts of toxicologists, pathol-

ogists, statisticians, other professionals, animal care experts, and technical personnel.

A testing facility is any institution that collects safety data for submission to FDA in support of products either prior to or following approval for marketing. The primary types of institutions involved are laboratories of manufacturing firms, or those of contract research and development or testing companies. Also included, to the extent that they collect safety and efficacy data submitted to FDA in support of petitions for regulated products, are veterinary and medical clinics, universities and State experimental stations, State and Federal government research laboratories, private and public hospitals and foreign establishments of any of the foregoing types. The facility may range in size from the large corporation to an individual who may perform safety studies on behalf of a sponsoring institution.

The Commissioner recognizes that this proposed definition is broad and may include facilities to which application of these regulations would not be necessary or appropriate. For example, a university laboratory may screen dozens of chemical compounds in rodents to determine whether any have pharmacological activity, with only those showing any promise being further tested in animals. Although such studies are important to evaluating the safety of drugs prior to conducting trials involving human subjects, they are not often of critical importance because subsequent and more rigorous animal studies are conducted before FDA review is sought. The need for detailed regulation of studies performed by such a laboratory appears small; in any case, such studies would be subject to internal review if they are submitted to the agency as part of an application, and audits of supporting documentation, when desirable, will remain a central feature of FDA acceptance of scientific data. As discussed below, the Commissioner specifically invites comments on whether, and if so how, certain types of testing facilities should be excluded from these regulations.

STATEMENT OF THE PROBLEM

Until recently, FDA has assumed that nonclinical laboratory studies submitted in support of a regulated product resulted from the application of appropriate experimental procedures by a testing facility. In an effort to evaluate these data properly, and to assure their authenticity and reliability, the agency employs a compliance program for nonclinical laboratories that provides for in-depth examination of nonclinical studies performed at the product sponsor's facilities as well as those performed at contract testing laboratories. The type of investigation performed under this program consists, for the most part, of "for-cause" inspections that are initiated at the request of an agency unit because of questions arising from submitted data. The selection of a laboratory for this type of inspection is usually based on the appearance of one or more of the following:

1. Inconsistencies in the data;
2. Data of questionable validity;
3. A study of questionable purpose or design; and
4. Simultaneous performance of an unusually large number of complex studies.

The objective of this program has been to achieve assurance of the quality of the data from nonclinical studies submitted to FDA. To accomplish this, the current practices and procedures of the nonclinical laboratory are assessed to determine if the laboratory is capable of performing investigations in support of agency regulated products, by assuring that physical facilities and equipment are sufficient and properly maintained, that the staff is qualified by training and experience, that the investigational procedures are scientifically valid, and that complete and accurate laboratory records are maintained. The "for-cause" inspections are being conducted in the absence of published regulations for acceptable laboratory practice and without a systematic program for auditing all test facilities.

Recent FDA experiences have identified significant problems in the manner in which nonclinical laboratory studies are being performed. Deficiencies were found during inspections of the testing facilities of major pharmaceutical firms, inspections of several private contract testing facilities, and internal reviews of toxicity studies of color additives conducted by FDA. How widespread or serious the problems are is not known at this time. The agency is concerned, however, that significant deviations in the quality and integrity of reported data might be of a greater magnitude and scope than had previously been assumed. The following are the more important deficiencies in the animal testing procedures that have been observed:

1. Experiments were poorly conceived, carelessly executed, or inaccurately analyzed or reported. For example, FDA found: Original autopsy records for certain studies were either unavailable or were apparently transcribed to new records several years after the autopsies; pathology reports submitted to the agency were inconsistent with the original autopsy records; microscopic examinations of tissue slides were conducted by more than one pathologist, each of whom came to different conclusions, yet only the conclusions favorable to the drug were submitted to the agency; in one long-term toxicity and carcinogenicity study, there was not a complete set of records for any single animal in the study, despite the fact that the records were required for proper analysis of the study and were represented to the agency to exist; and, in the same long-term toxicity and carcinogenicity study, the protocol required daily physical examination of the animals, yet the agency was unable to find any records to indicate that these examinations were carried out.

2. Technical personnel were unaware of the importance of protocol adherence, accurate observations, accurate administration of the test substance, and accurate recordkeeping and record transcription. Examples of these deficiencies include: Certain employees of a firm were unable to explain the procedures used to record data; records of laboratory observations were neither dated nor signed; employees were unable to account for discrepancies between raw data and final reports submitted to the agency; animals were observed and recorded as normal for a variety of factors, including appearance, awareness, appetite, and thirst, when in fact the animals were dead; and, drugs under study were administered to animals in a manner that made it impossible to determine how much, if any, of the required dosage was actually ingested by the animal.

3. Management did not assure critical review of data or proper supervision of personnel. For example, in one toxicity study involving rats, gross changes of tissue began to appear, yet management was not made aware of these alarming changes for approximately 4 to 8 months; and, in another study, a drug was determined to be a tumorigen, yet this information was not promptly given to the agency.

4. Studies were impaired by protocol designs that did not allow the evaluation of all available data. In one situation, protocols were discovered that called for looking at all the high-dose and control animals for tumorigenicity while the protocols did not require that all the low- and mid-dose animals be observed as well.

5. Assurance could not be given for the scientific qualifications and adequate training of personnel involved in the research study. At one firm, the reproduction and teratology studies were conducted and laboratory personnel were overseen by a senior scientist who did not have the proper qualifications or background to be conducting and supervising these critical studies. In another case, necropsies were being performed by people without the proper training, as was recognized by a senior scientist who reviewed the work.

6. There was a disregard for the need to observe proper laboratory, animal care, and data management procedures. Illustrations of these deficiencies are: Treatment and control animals were not properly identified; weighings of the animals were not accurately recorded; animals were fixed in toto and not necropsied for several months; one study was discontinued because a disease, unrelated to the drug under study, killed most of the animals in the study, yet none of the animal records contained any observations of symptoms of the disease; and a laboratory was sprayed and fogged with pesticides while the animals were present in the laboratory.

7. Sponsors failed to monitor adequately the studies performed in whole or in part by contract testing laboratories. For example: a contract laboratory failed to make a slide of lesions for histopathological examination, despite the fact that this was called for in the proto-

col, and management failed to adequately monitor the study; in one study done by a contract laboratory, although the management had serious questions about the conduct of the study, they never questioned nor exercised any control over the operating investigator; in another study done by a contract laboratory, FDA was told that animal tissues had been examined histopathologically when a review of the contract laboratory's original records indicate that these tissue samples were never even collected; and, in another study done by a contract laboratory the problem of autolysis of the animals was so extensive that the study should have been considered unacceptable, yet the final study report made no mention of this fact.

8. Firms failed to verify the accuracy and completeness of scientific data in reports of nonclinical laboratory studies in a systematic manner before submission to FDA. Examples of such failure include: Significant discrepancies found between gross observations on pathology sheets when compared with the individual pathology summaries submitted to the agency; inconsistent progress reports of the same study submitted to FDA; and one firm submitted a study utilizing the wrong data and the wrong animal identification numbers which were easily discovered by the agency, yet management did not check the data used.

In testimony before both the United States Senate Subcommittee on Health of the Committee on Labor and Public Welfare and United States Senate Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary on July 10, 1975, January 20, 1976, April 8, 1976, and July 19, 1976, the Commissioner of Food and Drugs summarized the problems that have arisen regarding the integrity of data submitted to FDA in support of the safety of regulated products, and expressed concern about the absence of industry-wide standards for conducting animal or other test system studies intended to be submitted to FDA. Copies of this testimony and pertinent underlying information that can be made public at this time have been put on display in the office of the Hearing Clerk, Food and Drug Administration.

Responses to the Problem

As a consequence of the Commissioner's testimony, Congress has approved a substantial increase in the FDA budget of approximately 16.6 million dollars for the fiscal year 1977 with the directive that FDA utilize the resources to ensure the quality and integrity of data submitted to the agency in support of products regulated by FDA.

In anticipation of this action, the Commissioner has established a "Bioresearch Monitoring Program" to develop and implement an agency-wide program for dealing with the full range of anticipated problems in all aspects of preclinical testing and clinical research relating to FDA-regulated products. The program is managed by an intra-agency Steering Committee headed by the FDA Associate Commissioner for Compliance and includes as its members: All Bureau Directors, the Executive Director of Regional Operations, the Director of the National Center for Toxicological Research, the Chief Counsel, the Associate Commissioner for Administration, the Associate Commissioner for Medical Affairs, the Associate Commissioner for Science, and the Assistant Commissioner for Planning and Evaluation. Elements of the Bioresearch Monitoring Program are being developed by several task forces, including a Toxicology Laboratory Monitoring Task Force. This task force was assigned the responsibility for developing an agency strategy to ensure the quality and integrity of the nonclinical laboratory studies that support the safety of FDA-regulated products. To meet these goals, the task force proposed that the following steps be taken:

1. Develop good laboratory practice regulations, analogous to existing good manufacturing practice regulations, which would delineate proper procedures for conducting nonclinical studies. These regulations would include standards for animal facilities, animal care practices, training and qualification of personnel, recording and handling of data, administration of the test and control substance, maintenance of records, and reporting of results.

2. Develop an agency-wide compliance program that would include regular inspections of nonclinical laboratories.

3. Establish a specific course for training agency investigators in evaluating testing facilities and their compliance with good laboratory practice regulations.

4. Identify the facilities involved in nonclinical testing of regulated products.

During this same period of time, the Pharmaceutical Manufacturers Association and G. D. Searle & Co. independently, and without request from the agency, each submitted proposals for guidelines describing good laboratory practice for nonclinical laboratory studies on drugs. These submissions were considered by the Toxicology Laboratory Monitoring Task Force. Copies of these submissions, together with all subsequent correspondence, have been placed on display with the Hearing Clerk, Food and Drug Administration.

Alternative Proposals

After an analysis of the recommendations of the Toxicology Laboratory Monitoring Task Force and the experiences of FDA summarized previously, the Commissioner has considered a variety of alternative approaches to promote the quality and integrity of nonclinical data submitted to FDA in support of regulated products.

Existing procedures lead to laboratory inspections by the agency only after the data have been submitted and reviewed, and then only if the data are critical to making a regulatory decision and if certain aspects of the data cause the agency to suspect that the findings are not accurate or valid. This suspicion triggers a "for cause" inspection of the laboratory to determine the causes of the perceived experimental deficiencies. The results of the inspection then determine the types of agency actions that are taken, e.g., agency refusal to accept the data in support of a product approval or withdrawal of approval of a marketed product. This procedure is no longer sufficient. The agency must have a systematic method for achieving the objective of accurate and valid studies on which to make regulatory decisions. Consumer protection mandates an efficient and effective regulatory scheme to attain the highest quality of research.

The regulated industry is entitled to know the expected standards of performance, the criteria and procedure to be used to evaluate this performance and the sanctions that may be imposed for inadequate performance.

One of the alternative approaches considered by the Commissioner would shift all or part of the burden for nonclinical laboratory testing from product sponsors to the agency and would require FDA to test every regulated product that is proposed for approval. This approach would entail an enormous expenditure of agency resources because of the spectrum of regulated products, the diversity of the kinds of data needed, and the number of products submitted to the agency for approval; furthermore, it would necessitate congressional authorization. At the present time, the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act impose the responsibility and burden for establishing the safety, and often the effectiveness or functionality, of a product on the persons who intend market and promote the use of the product.

The Commissioner also considered having the agency prescribe, by regulation, rigid test protocols, standard and nonroutine laboratory operating procedures, and methods for study implementation and conduct. By this approach, the agency would be assured of the uniformity of testing being performed but not necessarily of the quality of the studies or their appropriateness in all instances. Use of informed scientific judgment would be limited and innovation in test protocols and procedures might be stifled. A further disadvantage of this approach is that it could not readily encompass the full range of unique problems encountered in the testing of all agency regulated products.

Licensing of testing facilities was also considered as a means for ensuring the quality and integrity of nonclinical data. This approach would require the establishment of standards for licensing as well as licensing procedure, i.e., approval of a license application by the agency, possibly with an inspection and the issuance of a license before studies could commence. It has been the experience of the agency that licensing procedures are effective for those types of testing laboratories where strict controls are necessary and where uniform procedures are followed. However, as a result of the diversity in size and nature of nonclin

testing facilities, licensing procedures would be expected to be time consuming and not cost effective. For these reasons, the Commissioner believes that procedures more efficient than licensing could be designed to achieve agency objectives.

The Commissioner has also rejected an alternative that would require full-time on-site monitoring of nonclinical testing facilities by the agency, in a manner analogous to meat processing inspections by the Department of Agriculture. The diversity and distribution of nonclinical laboratory studies among testing facilities would cause difficulties in assignment and efficient utilization of highly trained FDA inspectional personnel. More importantly, the high cost of such a program would vastly outweigh any conceivable benefits to FDA, the testing facility, and the public.

Finally, the Commissioner has rejected the concept of voluntary standard setting by the use of industry-wide guidelines promulgated by the industry, a scientific society, or the agency. Although guidelines can be effective in improving industry practices, they cannot be lawfully enforced. The seriousness of the problems recently uncovered by the agency demands the use of an approach that will directly and promptly achieve compliance by all affected testing facilities. The Commissioner believes this cannot be achieved by voluntary guidelines, regardless of their scientific merit.

The good laboratory practice approach proposed by the Commissioner:

1. Is process-oriented rather than product- or person-oriented. Quality data accrue as a result of proper utilization of and control over the facilities, personnel, and procedures involved in the study. These factors are susceptible to inspection, evaluation and, if necessary, correction without regard to either the importance of a particular study to a regulatory decision or whether the study is ongoing or completed. Thus, periodic inspection of the laboratory processes by FDA can provide significant impact on the quality and integrity of the data generated by these processes.

2. Does not interfere with needed flexibility of laboratory operation, nor does it stifle the use of informed scientific judgment. It does not, for example, freeze protocol design nor preclude technological advances. The good laboratory practice approach provides an objective standard of laboratory performance which can be uniformly and equitably applied to every testing facility, regardless of factors such as the type of products studied and the purposes of the studies.

3. Provides for the design and implementation of an effective compliance program that will permit the general upgrading of testing facilities and the submission of high quality studies with an optimum allocation of resources and a minimum of regulatory and bureaucratic controls.

4. Is similar to other regulatory programs undertaken by the agency, and will use to the fullest possible extent prior experiences, existing procedures and organizational structures, and tested regulatory mechanisms. Thus the approach is a practical one for the agency.

5. Is within the legal mandates and resources of FDA.

6. Parallels conclusions reached by members of the regulated industry regarding ways to improve nonclinical laboratory operations.

The disadvantages of the existing and alternative approaches and the advantages of the good laboratory practice approach have led the Commissioner to agree with the recommendations of the Toxicology Laboratory Monitoring Task Force to promote the quality and integrity of the nonclinical laboratory studies that are submitted to FDA in support of regulated products.

At the same time, however, the Commissioner sees value in maintaining the ongoing program of "for cause" inspections in those cases where review of submitted data justifies such an approach.

The Commissioner proposes to establish a new Part 3e in Title 21 of the Code of Federal Regulations to address various aspects of bioresearch monitoring. This proposed new part is being designated Part 3e under Subchapter A—General until recodification of all of Subchapters A and B is completed. When this proposal becomes a final regulation, it will be redesignated and placed in the recodified scheme of Subchapter A. This proposal lists definitions applicable to the part, presents the good laboratory practice regulations, and establishes procedures for the disqualification of testing facilities. Additionally, this proposal contains specific amendments needed for conformance to existing regulations.

The Commissioner wishes to emphasize that the purpose of the proposed good laboratory practice regulations is to ensure, as far as possible, the quality and integrity of nonclinical laboratory data submitted to FDA in support of products regulated for protection of the public health under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. The proposed regulations would be applied only to the conduct of certain laboratory studies which are intended for submission to FDA. Specifically excluded would be, for instance, basic research on the causes of a disease or medical condition, experiments conducted as part of a regulatory activity (e.g., studies to determine whether a drug product conforms to applicable compendial and license standards), studies to determine physical characteristics of a test substance independent of any test system (e.g., to determine the stability of a chemical or the tensile strength of a plastic), clinical or field trials utilizing humans or animals, and basic research studies submitted to FDA that are designed to elucidate the pharmacological activity of drugs intended for human use. It is quite probable that the good laboratory practice regulations may be utilized by other Federal regulatory agencies as standards for determining the acceptability of nonclinical laboratory studies in support of products regulated by those agencies, and even by Federal agencies which support nonclinical laboratory studies by grant or contract as standards for the acceptability of grant applicants and contract bidders. The proposed good laboratory practice regulations reflect the current best efforts of FDA to develop a practical, feasible and effective regulatory program, using information about problems in the performance of nonclinical laboratory studies now known to the agency.

The agency wishes to obtain additional information about the current status and laboratory practices of nonclinical testing facilities. The agency is also interested in evaluating the good laboratory practice regulations proposed below and in identifying any unanticipated difficulties in implementing an agency-wide monitoring and compliance program for testing facilities. Therefore, during the months of November and December 1976 and January 1977, the agency will conduct surveillance inspections of a substantial number of previously uninspected testing facilities. During these inspections, FDA inspection teams will evaluate current practice in light of the proposed regulations, recognizing that the proposed regulations may undergo changes before their publication in final form.

Regulatory action will not be initiated against any testing facility or study solely on the grounds of deviations from the proposed good laboratory practice regulations. However, the agency may well conduct a followup audit of studies that it believes may have been compromised as a result of conditions or practices found at a testing facility. The agency could initiate regulatory action against approved products as a result of deficiencies discovered in such an audit. Should the agency discover evidence of withholding of information required to be submitted to FDA, or misrepresentation of data actually submitted, the Commissioner will seriously consider recommending criminal enforcement proceedings.

The agency will consider the experience gained from, and the findings made during, these surveillance inspections in preparing the final good laboratory practice regulations. This pilot phase of the program may be extended for an additional period of time if it becomes necessary to collect more information.

The Commissioner urges testing facilities and other interested components of the industry, as well as the public generally, to study this proposal carefully and to consider whether the specific requirements proposed, as well as the general approach selected, will achieve the objectives of the agency and the public. A wide spectrum of views is sought, and all interested persons are encouraged to file comments on each aspect encompassed by this proposal, making specific suggestions, whenever possible, for improving the proposed regulations or providing an alternate approach. The Commissioner will consider quite carefully the information provided in comments from the public and industry, as well as in the public hearing

on this proposal to be held in early 1977, before any final good laboratory practice regulations will be promulgated.

Scope

This proposal sets forth definitions and standards for the following: organization and personnel, buildings and facilities, equipment, testing facility operations, quality assurance, protocols, study implementation and conduct, recording and handling of data, records and reports. The proposal also describes the administrative sanctions that may be imposed, as well as the procedures involved, in the event of noncompliance. These proposed regulations would be applicable to any prospective nonclinical laboratory study conducted to obtain data for submission to FDA in support of a product regulated under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. As discussed above, basic research, preliminary exploratory studies, studies relating to regulatory compliance activities, studies to determine physical or chemical characteristics of a test substance independent of any test system, and clinical or field trials involving humans or animals are not included.

The Commissioner is aware that, as drafted, the regulations would apply to many types of testing facilities, that is, to any laboratory performing a "nonclinical laboratory study," which is broadly defined to include experiments to evaluate the safety of an article regulated by FDA, or to evaluate the functionality and/or effectiveness of such an article when inadequate functionality or effectiveness may result in a safety hazard. The Commissioner recognizes that this approach may encompass within the scope of the regulations certain types of testing facilities and/or certain categories of studies that should not be included.

These regulations are intended to ensure, as far as possible, the quality and integrity of test data that are submitted to FDA and become the basis for regulatory decisions made by the agency. These regulations are not intended to inhibit scientific study or burden laboratories with unnecessary and inappropriate requirements. Because FDA has not previously undertaken a survey of the types of laboratories performing studies to be submitted to FDA, or a comprehensive review of the varieties of studies being submitted, the Commissioner lacks the complete information essential to making any final determination as to which laboratories and/or studies should be subject to the regulations, and which should not. He specifically solicits comments addressed to this point.

To aid interested persons, the Commissioner notes that these regulations are a product of agency experience in reviewing long-term toxicology studies in animals, e.g., teratogenicity, mutagenicity, and carcinogenicity studies; these experiences, discussed above, clearly indicate the need for regulations for laboratories conducting such studies. Other laboratories conduct studies, that, while important to FDA decisionmaking, are not pivotal because subsequent studies ordinarily supersede them (e.g., early pharmacological screening studies) or are not included in the toxicology testing monitoring program because they are subject to other monitoring programs, e.g., studies utilizing human subjects and clinical or field trials in animals, and studies to determine physical or chemical characteristics of a regulated article. The Commissioner believes that the proposed regulations are probably inappropriate to laboratories conducting such studies, and unnecessary to assure the quality and integrity of the data, given other FDA monitoring and review activities.

Between these groups, there exists, at least in theory, a spectrum of studies and laboratories doing work similar to either long-term toxicology studies or to basic research or research subject to other FDA review. It would be valuable for FDA to receive comments addressing (1) the types of studies conducted that do not fall in either category, and whether they are sufficiently similar to the types of long-term safety studies on which the regulations were based to make their inclusion within the scope of the regulations appropriate; (2) whether exemptions from, or modifications of, certain of the specific requirements proposed in this notice would make inclusion of other types of studies appropriate, e.g., waiver of protocol and quality assurance unit requirements with retention of animal care and recordkeeping requirements; and (3) whether individual testing facilities tend to specialize in certain types of studies (e.g., commercial laboratories and long-term toxicology testing, and university laboratories and basic research studies), which might permit FDA to define the scope of the regulations by type of facility rather than, as proposed, by type of study performed. In addition, the Commissioner recommends that persons commenting on specific details of this proposal distinguish, when appropriate, between the advisability of the proposal when applied to e.g., commercial laboratories performing long-term toxicology studies, and its advisability when applied to, e.g., nonprofit laboratories in university settings.

Definitions

Section 3e.3 contains proposed definitions of all of the special terms used in Part 3e. Many of the proposed definitions pertain to technical terms that can be variably or imprecisely interpreted by persons affected by the proposed regulations. These terms are defined to provide a common basis of understanding for the agency, the regulated industry, and the general public. In addition, other definitions have been proposed for maintaining consistency with definitions used in other FDA regulations and for more precisely describing the extent and applicability of the proposed regulations.

In proposed § 3e.3(a), the term "act" is limited to the Federal Food, Drug, and Cosmetic Act, as amended. Other statutes when used will be mentioned by name, e.g., the Public Health Service Act.

In § 3e.3 (b) and (c), the Commissioner proposes to define the terms "test substance" and "control substance." The first includes any food additive, color additive, botanical material, drug, biological product, radiation-emitting product, medical device, or other article regulated by FDA, and would include such articles even before formal regulation has begun, e.g., a chemical that is being tested for possible use as a food additive and that is subsequently included in a food additive petition. The term "control substance" is defined to refer to materials administered to the test system to establish a basis for comparison with the test substance.

In proposed § 3e.3(d), in term "nonclinical laboratory study" is defined as any in vivo or in vitro experiment in which a test substance is studied prospectively in a test system under laboratory conditions to determine its safety. The term also includes those experiments intended to assess the functionality and/or effectiveness of a test substance where inadequate functionality or effectiveness of the test substance may result in a safety or health hazard. The term does not include research studies utilizing human subjects or clinical studies or field trials in animals. Further, the term does not apply to basic exploratory studies carried out to determine whether a test substance has any potential utility. The broad definition of "nonclinical laboratory study" is intended to include studies submitted to FDA to support an application for permission to market a product but which need not be conducted under a "Notice of Claimed Investigational Exemption for a New Drug" (IND) under section 505(i) or 507(d) of the act, the "Notice of Claimed Investigational Exemption for a New Animal Drug (INAD) under section 512(j) of the act, or the "Application for Investigational Device Exemption" (IDE) under section 520(g) of the act.

A unique concept required by the decision to make these proposed regulations agency-wide in scope is the term "application for research or marketing permit" in § 3e.3(e). This definition includes all of the various requirements for submission of scientific data and information to the agency under its regulatory jurisdiction, even though in certain cases no permission is technically required from FDA for the conduct of a proposed activity with a particular product, i.e., carrying out research or continuing marketing of a product. The term is intended solely as a shorthand way of referring to at least 23 separate categories of data and information that are now, or in the near future will become, subject to requirements for submission to the agency. These include:

(1) A color additive petition, (2) a food additive petition, (3) data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for use that may reasonably be expected to result, directly or indirectly, in its becoming a component or

otherwise affect the characteristics of any food, described in § 121.3 (21 CFR 121.3), (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 § 121.4000 (21 CFR 121.4000), (5) an IND, (6) a new drug application (NDA), (7) data and information for classifying an over-the-counter drug (OTC) as generally recognized as safe, effective, and not misbranded as part of the OTC review, (8) data and information regarding a prescription drug for human use to be submitted as part of procedures similar to that in the OTC review for classification as generally recognized as safe, effective, and not misbranded, (9) data and information regarding an antibiotic drug submitted as part of the procedures for issuing, amending, or repealing antibiotic drug regulations, (10) an INAD, (11) a new animal drug application (NADA), (12) data and information regarding a drug for veterinary use submitted as part of procedures similar to that in the OTC review for classifying such drugs as generally recognized as safe, effective, and not misbranded, (13) an application for biological product license, (14) data and information regarding a biological product submitted as part of the procedures for determining that licensed products are safe, effective and not misbranded, under Part 601 (21 CFR Part 601), (15) data and information regarding an in vitro diagnostic product submitted as part of the procedures for establishing, amending, or repealing standards for such products, (16) an IDE, (17) an application for premarket approval of a medical device, (18) a product development protocol for a medical device, (19) data and information regarding a medical device submitted as part of the procedures for classifying such devices, (20) data and information regarding a medical device submitted as part of the procedures for establishing amending, or repealing a standards for such devices, (21) data and information regarding a radiation-emitting product submitted as part of the procedures for establishing, amending, or repealing a standard for such products, as described in section 358 of the Public Health Service Act, (22) data and information regarding a radiation-emitting product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in § 1010.4 (21 CFR 1010.4), and (23) data and information regarding a radiation-emitting product submitted as part of the procedures for granting, amending, or extending an exemption from radiation safety performance standards, as described in § 1010.5 (21 CFR 1010.5).

Definitions are proposed in § 3e.3 (f), (g), and (h) to describe regulated facilities and operations. The term "sponsor" in paragraph (f) applies both to the person who initiates and supports, financially or otherwise, a nonclinical laboratory study, and to the person who submits such a study to the agency in support of an application for a research or marketing permit. The term "testing facility" as defined in paragraph (g) means a person who actually performs the nonclinical laboratory study. It would include those facilities required to register under section 510 of the act, provided that these establishments conduct nonclinical laboratory studies, as well as any consulting laboratory described in section 704 of the act. If a person both initiates and carries out a study (e.g., a pharmaceutical manufacturer with an in-house animal toxicology operation), he is considered to be both a "sponsor" and a "testing facility" for purposes of the good laboratory practice regulations. The term "person" in paragraph (h) includes an individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit thereof, and any other legal entity.

The term "test system" as proposed in § 3e.3(i) refers to any biological, chemical or physical system as well as its component parts with or in which test or control substances are studied or analyzed. Also included in the definition are groups or components of the system not treated with the test or control substances.

In § 3e.3(k) the term "raw data" means any laboratory worksheets, records, memoranda, notes, or certified copies thereof that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. "Raw data" may include photographs, microfilm or microfiche copies, computer printouts (derived from on-line data recording systems), magnetic media including dictated observations, and recorded data from automated instruments.

Paragraphs (l) and (m) of § 3e.3 provide definitions for the "quality assurance unit" and the "study director," respectively, encompassing the concept that quality assurance and study direction responsibilities are to be vested in different individuals within a testing facility. Thus, either a portion or all of an individual's time may be expended in quality assurance activities, or the quality assurance unit may be a group of individuals operating within a distinct facility. The terms do not permit a single individual to perform quality assurance and study direction for the same nonclinical laboratory study.

Organization and Personnel

Many of the problems that arise in the conduct of nonclinical laboratory studies can be directly or indirectly attributed to personnel that are unqualified, insufficient in number, or improperly supervised. For example, recent FDA investigations revealed that some necropsies and recording of observations were being performed by inadequately trained personnel. Further, the observations were altered before submission to FDA by a professional person who was not present during the necropsies. To assure that nonclinical laboratory studies are valid, personnel must be qualified by education, training, and/or experience to follow directions and perform test procedures properly.

Proposed § 3e.29 provides that each person engaged in or responsible for supervising the conduct of a nonclinical laboratory study have the education, training, and experience, or combination thereof, to perform the assigned functions. Although not required by the proposed regulations, it is recommended that each employee be knowledgeable in the good laboratory practice regulations as they relate to the employee's function. Training in good laboratory practice and specific laboratory procedures should be provided on a periodic basis by well-qualified individuals.

To enable FDA to determine the adequacy and competency of personnel, proposed § 3e.29(b) requires the testing facility to maintain a curriculum vitae and job description for each person engaged in or responsible for supervising the conduct of a nonclinical laboratory study.

An adequate number of personnel minimizes the loss of data resulting from haste or inability to perform a procedure within an appropriate time frame. A recent FDA investigation revealed that the microscopic examination of tissues was delayed several months because of an insufficient number of qualified personnel; when finally studied, a serious and unexpectedly high incidence of tumors was discovered. Under proposed § 3e.29 (c), a sufficient number of personnel is to be available to ensure timely and proper performance of activities specified by the protocol.

In addition, proposed § 3e.29 (d), (e), and (f) require personnel to practice good sanitation and health habits, wear clothing appropriate for the duties they perform, and change such clothing as often as necessary. Adequate sanitation and health practices on the part of personnel can prevent the transmission of diseases or parasitic infestation from humans to the test systems.

Study director. Experience has shown that unless responsibility for the proper conduct of a study is assigned to one person, there is a potential for conflicting instructions and poor protocol implementation. Records of one long-term animal study examined by agency personnel revealed that for a major portion of the study there was no individual responsible for the overall conduct of the study.

Proposed § 3e.31 provides that each nonclinical laboratory study shall have a study director who is a scientist or other professional person of appropriate education, training, and experience or combination thereof and who is responsible for the overall conduct of the study. The study director would be responsible for assuring that the approved protocol is followed, test substances are characterized, test systems are appropriate for the study, personnel involved in the study clearly understand their functions and are qualified to perform them, data are accurately and promptly verified and

recorded, health hazards to the test system which appear during the study are recognized and removed, good laboratory practices are followed, the studies are conducted in a manner that is safe for laboratory personnel, and the required data have been transmitted to the archives for storage.

Quality assurance unit. Experience has shown that detailed protocols and written standard operating procedures alone will not ensure the quality and integrity of the results of a nonclinical laboratory study. A mechanism is needed to monitor ongoing studies to determine that the protocols and written standard operating procedures have been followed. The experience of FDA with quality control units in manufacturing facilities has shown this mechanism to be effective. Thus, these proposed good laboratory practice regulations provide for a quality assurance unit in each testing facility. This unit would report to management and provide a focal point for FDA inspection of studies.

Proposed § 3e.33 requires the establishment of a quality assurance unit within the testing facility that is charged with the responsibility for assuring that the facilities, equipment, personnel, methods, practices, procedures, records, and controls are designed and function in conformance with good laboratory practice regulations and the protocols for individual nonclinical laboratory studies. The quality assurance unit would be required to inspect periodically each phase of a study and to document the inspection. Written reports giving the status of each study, the problems noted, and the actions taken to resolve the problems would be required to be submitted to management periodically. For any study lasting more than 6 months, the quality assurance unit is required to perform an in-depth evaluation of the study to detect, at an early stage, errors in recording data, and unusual patterns of events, lack of conformity to the protocol, and deviations from good laboratory practice and standard operating procedures. A master schedule sheet of all studies conducted at a testing facility must be maintained showing the current status of each study. All records required to be maintained by the quality assurance unit are to be made available for inspection to authorized FDA employees.

The Commissioner believes that it is essential that nonclinical laboratory studies be conducted according to scientifically sound protocols and with detailed attention to their quality control. The Commissioner further believes that inspection by a quality assurance unit will provide assurance to the agency that a study was conducted in a manner that ensures the quality and integrity of the results.

The Commissioner points out that the primary role of the quality assurance unit is that of monitoring the performance of the research and the methods employed. The regulations do not place with the quality assurance unit the responsibility for accepting or rejecting a specific study design or its results or for approving or rejecting standard operating procedures.

Access to professional assistance. Unforeseen problems or circumstances may arise at any time in the course of a nonclinical laboratory study. If these problems or circumstances are not corrected or changed, the quality and integrity of the entire study might be jeopardized. Often the solution of these problems may require trained professional judgment. For this reason, proposed § 3e.35 provides for the availability of a scientist or other professional to respond to requests from technicians or less experienced personnel for assistance or consultation. The scientist or other professional may be the study director or any other individual accessible in person or by telephone who is qualified to provide the required assistance or to refer the problem to some other individual who is qualified to respond.

FACILITIES

Adequate facilities are essential to the quality and integrity of data obtained in nonclinical laboratory studies. Such facilities allow for the separation of animal and other test systems as well as for the isolation of diseased animals, thus minimizing the transmission of infectious diseases and preventing uncontrolled effects upon the animal. Separate and properly designed areas for the storage of supplies are necessary for the prevention of deterioration of perishable supplies and for the preparation of test and control substances before administration to preclude contamination and mixups. Provision for separate or well-defined areas for different studies minimizes the potential for inadvertent exposure of the test system to substances other than the test substances. Adequate facilities also protect personnel from exposure to harmful substances and help prevent transmission of diseases or contamination from man or the environment to the test system and vice versa. Appropriate areas for waste disposal and sanitation practices decrease chances of adverse effects to personnel and test systems as well as to the environment.

Proposed Subpart C sets forth the functional areas considered essential in a testing facility for the proper conduct of a nonclinical laboratory study. The proposed regulations require separate areas for the (1) receipt and quarantine of animals, (2) housing and care of animals, (3) storage of feed, bedding, supplies, and equipment, (4) receipt, storage, and mixing of the test substance, (5) laboratory testing operations, (6) cleaning, sterilizing, and maintaining of laboratory equipment, (7) specimen and data storage, and (8) administration and personnel.

Proposed § 3e.43 requires that environmental control of animal rooms or areas be in compliance with the Animal Welfare Act of 1970 (Pub. L. 91-579) as set forth in 9 CFR Part 3. Where specifications regarding housing of certain species of animals are not set forth by that act, the recommendations contained in HEW Publication No. (NIH) 74-23 entitled "Guide for the Care and Use of Laboratory Animals" are to be used. Copies of this publication may be obtained from: Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402. A copy has been placed on display with the Hearing Clerk, Food and Drug Administration.

The proposed regulation requires that separate areas are to be provided for (1) effective isolation of animals either known or suspected of being diseased, or of being disease carriers, from animals that are in good health and (2) for isolation of studies being done with test substances known to be infectious to both man and animals to protect personnel and to prevent cross-infection. Further, the proposed regulation requires that animals be separated by species when necessary, e.g., to protect against interspecies transmission of infectious diseases. In this connection, it is known that rabbits frequently harbor organisms that are infectious to cats, primates, guinea pigs, and other species and, therefore, should be housed in separate rooms.

The proposed regulation specifies that animal facilities are to be designed, constructed, and located so as to minimize disturbances to laboratory personnel and animals. Excessive noise levels may interfere with data collection and recordkeeping and may result in errors caused by employee fatigue and distraction. In addition, loud intermittent noises may cause undue stress to the animals.

Proposed § 3e.45 requires that storage areas for feed and bedding be separated from areas housing the test systems and that the storage area be protected against infestation or contamination. Refrigerated storage would be provided for perishable foods, such as meats, fruits, and vegetables.

Proposed § 3e.47 requires that to prevent contamination or mixups of test and control substances there shall be separate or defined areas for: (1) The receipt and storage of the test and control substances, (2) mixing of those substances with a carrier, e.g., feed, and (3) the storage of the test and/or control substance mixtures. In addition, storage areas for the test and control substances and test and control substance mixtures are to be separated from test system housing areas to prevent inadvertent exposure of the test systems to the test or control substance and are to be adequate to maintain the identity, strength, quality, purity, and stability of the substances and mixtures.

Proposed § 3e.49 deals with the areas within a facility in which the routine laboratory procedures are performed, e.g., biochemistry, hematology, histopathology procedures, as well as requiring specialized areas for performing activities such as aseptic surgery, intensive care, necropsy, histology and radiography. Special areas are required for the use of radioactive and biohazardous materials, volatile agents, and hazardous aerosols to protect personnel and test systems from unnecessary radiation exposure, contamination, or infection.

Guidelines for handling biohazardous materials are located in: (1) "National Cancer Institute Safety Standards for Research Involving Chemical Carcinogens," HEW Publication (NIH) 76-900, June 2, 1975, (2) "National Cancer Institute Safety Standards for Research Involving Oncogenic Viruses," HEW Publication (NIH) 76-790, October 3, 1974, (3) "Classification of Etiologic Agents on the Basis of Hazard," 3d Ed., HEW, Center for Disease Control, May 1974, and (4) National Institutes of Health Recombinant DNA Research Guidelines published in the FEDERAL REGISTER of July 7, 1976 (41 FR 27902). Copies of the first three publications may be obtained from: Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402. Copies of all these documents have been placed on display with the Hearing Clerk, Food and Drug Administration.

Space and facilities (e.g., mechanical glassware washing equipment, autoclaves, sinks), separate from the areas housing the test systems, are required for cleaning, sterilizing, and maintaining equipment and supplies.

Proposed § 3e.51 requires space, limited to access by authorized personnel only, for the storage and retrieval of all raw data and specimens.

Proposed § 3e.53 requires space in the testing facility for administrative, supervisory, and directional functions. Space for washing and toilet facilities is also required.

Separate space for each of the areas mentioned above is required in order to minimize external factors that might adversely affect test systems or in some other way compromise the conduct of the nonclinical laboratory study.

The Commissioner concludes that facilities that are in accordance with proposed Subpart C will promote the quality and integrity of nonclinical laboratory study results by prohibiting or minimizing infection, contamination, mixups, inadvertent exposure to substances other than the test substances, interspecies transmission of disease, environmental stresses, deterioration of materials and supplies, and will protect personnel from exposure to harmful substances.

EQUIPMENT

The design and condition of equipment are critical to the reliability of the results obtained from nonclinical laboratory studies. Inadequately designed or faulty equipment can prevent the accomplishment of the stated objectives of a given study. Equipment used in the care and treatment of animals must be designed so that it does not adversely affect the health of the animals or the integrity of the study. Equipment used in the preparation or administration of the test substance must be designed to minimize chances of contamination or inaccurate dosage. Equipment must be cleaned, maintained, tested, calibrated, and repaired to prevent errors and malfunctions resulting in lost or inaccurate data. Regular scheduling of equipment maintenance, written maintenance procedures and records of performed maintenance are necessary to ensure that laboratory equipment is kept in good operating condition.

In the course of inspections of nonclinical testing facilities, FDA personnel observed mixing equipment encrusted with material from previous use as well as mixers that were not electrically grounded. Ungrounded mixers may allow a buildup of electrostatic charges that could lead to improper mixing.

Proposed § 3e.61 sets forth requirements for the design, and § 3e.63 describes the required cleaning, maintenance, and calibration of the equipment in a testing facility. Proposed § 3e.63 also specifies the records of such activities which are required to be kept. These requirements extend to equipment used in the care of the test system as well as that used in conducting laboratory procedures. Written standard operating procedures are required assigning responsibility for cleaning, maintaining, inspecting, and testing equipment. Periodic calibration of automatic, mechanical, and electronic equipment is required.

TESTING FACILITY OPERATIONS

The existence of written standard operating procedures can prevent the introduction of systematic errors in data, resulting from variations among individuals performing test procedures, and the loss of data through incomplete data collection methods. Accordingly, standard operating procedures should cover animal care; receipt, storage, testing, mixing, and administration of the test and control substances; calibration of instruments and equipment; test system observations; laboratory tests; handling of animals found moribund or dead during the study; necropsy or postmortem examinations of animals; preparation of specimens; histopathology; data handling, storage, and retrieval; and preparation and validation of the final report. Agency investigations have shown that in certain instances written standard operating procedures did not even exist for some of these areas. For example, histopathology is an extremely important indicator of the effects of a biological effect upon a tissue or cell. Careful preparation, cutting, sectioning, mounting, staining, and interpretation of histologic slides from animal tissues to determine the changes occurring in test animals during the study is crucial if the scientist is to obtain valid information. Valuable histopathological information has been lost in studies because these functions were not performed properly.

Proposed § 3e.81 requires written standard operating procedures setting forth in detail the methods for performing the various laboratory operations. Such written standard operating procedures shall include methods for all sampling, testing, or other laboratory control mechanisms as well as for preparing and maintaining any records and reports required by these regulations. Deviations from these operating procedures for a given study must be properly authorized by the study director. Significant changes to the testing facilities standard operating procedures must be authorized by management.

The standard operating procedures relative to the laboratory operations being performed are to be available in the immediate work area of the laboratory personnel at all times.

The Commissioner concludes the proposed § 3e.81 will reduce errors in data generation, collection, and reporting by ensuring that all personnel associated with a nonclinical laboratory study are familiar with and use the same standard operating procedures.

Proposed § 3e.83 describes procedures for handling reagents and solutions to assure their proper and reliable use. This provision is intended to minimize chances for error in laboratory tests resulting from the use of reagents that are contaminated or deteriorated.

Animal care. Observing proper animal care procedures is an essential element in the conduct of any research involving animals. Factors such as the caging and housing system used, sanitation practices, diet, handling, humidity, lighting, temperature, and noise control are capable of markedly affecting experimental results in laboratory animals. In addition, concern for the quality and health of laboratory animals is both a humane and a scientific consideration.

Quarantine of newly received animals is essential to prevent diseased animals from being used in studies and the transmission of disease to animals already in the facility. Animals received by one facility recently inspected by FDA were in poor physical condition upon receipt but nevertheless were used in a study shortly after receipt.

Proper identification of animals can prevent loss of data or misinterpretation of results due to mixups. Laboratory inspections have shown that as a result of improper identification in nonclinical laboratory studies some animals have been reported to have died more than once.

It is possible that the presence of certain environmental contaminants, e.g., pesticides and chlorinated hydrocarbons, in the feed or drinking water of laboratory animals can alter or mask the response of these animals to test or control substances. Therefore, it is important to ascertain and control the quantities of these substances in animal feed and drinking water.

Proposed § 3e.90 sets forth the requirements for the care and handling of animals used as the test systems in a nonclinical laboratory study. Requirements regarding housing, feeding, and handling are to be consistent with existing standards. Copies of these standards identified in the regulation have been placed on display with the Hearing Clerk, Food and Drug Administration. Deviation from such standards, e.g., use of restraining devices, is acceptable provided there is adequate documentation of the need for the deviation.

The proposal specifies that all newly received animals must be placed in quarantine until their health status has been evaluated in accordance with acceptable veterinary medical practice.

Proposed § 3e.90 sets forth requirements for the unique individual identification of animals either in accordance with the Animal Welfare Act, or for species not required to be so identified by that act, identification by a number that identifies the shipment or purchase order number on receipt of the animal. A unique permanently attached identification number, e.g., tattoo, neck chain, ear tag, ear punch, etc., would be required for animals that are moved from one cage to another during a study or if such animals are used in laboratory procedures that require manipulations and observations over extended periods of time. Further, animals should not be moved to a new location or placed under different environmental conditions during a study without written permission from the study director.

Proposed § 3e.90(i) also sets forth requirements for the periodic analyses of the feed and drinking water used for animals to ensure that known interfering contaminants are not present at a level above predetermined specifications.

The Commissioner contends that inadequate animal identification and animal care practices are a recurring problem adversely affecting the quality and integrity of data from many nonclinical laboratory studies and that proposed § 3e.90 would reduce this problem.

Test and Control Substances

In any toxicological study there must be assurance that the test system is properly exposed to the substance being tested. For this reason, the identity, strength, quality, purity, and stability of the test substance must be known. It was found in recent investigations by the agency that different batches of a test substance used in a long-term animal study did not meet the sponsor's specifications for identity. If a control substance is used in the nonclinical laboratory study, its identity, strength, quality, purity, and stability must also be known. This ensures that interfering impurities are not present in the test or control substance and that neither substance has deteriorated during the period of administration. There must be asurance in any study that the test system receives a known amount of the substance being tested. Therefore, procedures to ensure the uniformify and potency of the test or control substance-carrier mixtures are necessary.

Proposed § 3e.105 sets forth the procedures to be followed regarding the identification and testing of test and control substances. Proposed § 3e.107 describes requirements for the handling of these substances is general, and § 3e.115, for the handling of carcinogenic substances.

The mixture of test or control substances into carriers (e.g., when incorporated into feed) is discussed in proposed § 3e.113. The uniformity and concentration of the substances in the diet mix must be determined before the start of the study. In addition, random samples of each batch of the test or control substance mixture should be analyzed periodically during the course of the study to ensure that the proper mixing and formulation procedures are being used.

The Commissioner concludes that this proposed Subpart F will increase the likelihood that a nonclinical laboratory study of a characterized test or control substance will allow the relationship between dose and biological response to be determined.

Protocols for and Conduct of Nonclinical Laboratory Studies

One important element of any nonclinical laboratory study is the preparation of a protocol defining its objective and stating how it is to be attained. Investigations by FDA of long-term animal studies have shown that protocols were occasionally put in writing only after the study had been initiated. In addition, other studies were identified for which no written protocols were available. A written approved protocol is essential to ensure that all operations needed to fulfill the stated objectives are performed. The Commissioner encourages multidisciplinary consultation in the development and review of a protocol. For example, statisticians can provide valuable input by assuring that the hypothesis of the study can be tested by the proposed experimental design.

A testing facility should have an available mechanism for systematically evaluating and approving initial protocols as well as subsequent changes in the protocol while a study is in progress. Past experience has shown that unauthorized deviations from protocols have occurred during the conduct of some nonclinical laboratory studies and therefore have compromised the quality and integrity of the study.

Proposed § 3e.120 requires that each nonclinical laboratory study have a written protocol that clearly indicates the objectives and procedures for the conduct of the study and sets forth the minimum information to be contained in such a protocol. Changes or revisions to an approved protocol are to be documented, dated, and signed by the study director.

While this proposed section establishes the informational content of protocols, the responsibility for good experimental design resides with members of the scientific community. The Commissioner emphasizes that FDA's concern in the good laboratory practice regulations is not the design of a particular protocol or the prohibition of changes in the protocol. Rather it is the existence of a detailed written protocol before the initiation of any nonclinical laboratory study, the approval of changes in the protocol in writing before their implementation, and the conduct of the study according to the protocol and any amendments.

Conduct of study. A recurrent problem area in the conduct of a nonclinical laboratory study is loss or inaccurate recording of data as a result of inadequate recording procedures. Recent FDA inspections have also revealed observations made on scraps of paper or pocket notebooks for later transfer to date sheets. In addition, data sheets did not show the name of the individual making the observation.

Proposed § 3e.130(b) specifies that test systems shall be monitored in conformity with the protocol. For example, an acceptable protocol would direct that moribund animals should either be sacrificed or placed in isolation and observed carefully at least twice daily so that they can be found shortly after death to avoid autolyzed tissue. It should also direct that if an animal is found dead outside of normal working hours and a qualified person is not available to perform necropsy, then the carcass should be immediately preserved at a temperature between 2° and 8° C (36° and 46° F) and necropsied on the next day. Qualified personnel should be available to monitor and necropsy moribund and/or dead animals on weekends or holidays.

Proposed § 3e.130(c) sets forth the manner in which specimens are to be identified. Such identification will minimize the assignment of specimens to the wrong test system of study.

Proposed § 3e.130(d) requires that records of post-mortem observations be available to a pathologist when examining a specimen histopathologically. This will increase the pathologists's ability to describe correctly the microscopic findings and correlate them with the gross observations.

Proposed § 3e.130(e) requires that all data generated during the conduct of a nonclinical laboratory study, except those that are generated as direct computer input, are to be recorded directly, promptly, and accurately in ink in bound books are prenumbered pages or on worksheets that are to be bound during or at the conclusion of the study. All data entries are to be dated on the day of entry and signed, or identified in the case of direct computer input, by the person generating the data. Any changes in an entry are to be made in such a manner so as not to obscure the original entry, the reason for such change must be indicated, and the change shall be dated and signed, or identified in the case of direct computer input, by the person making the change.

Proposed § 3e.130(f) requires that all recorded data be reviewed, signed, and dated by a person, other than the person entering the data, responsible for the performance and evaluation of the activity from which the data were derived to assure adherence to procedures.

The Commissioner concludes that by specifying stringent controls on data collection and recording, as provided in proposed § 3e.130, adherence to the protocol in the conduct of the study will be promoted, and loss and inaccurate recording of data will be minimized.

Records and Reports

Reporting of nonclinical laboratory study results. Complete and accurate reports of studies are essential to agency decisions. The agency therefore insists that the final report include all pertinent material, results, observations, and conclusions of a study and that it documen-

fully and completely all of the conditions and circumstances under which a study was conducted.

Proposed § 3e.185 sets forth information that must be included in a final nonclinical laboratory study report. The final report would have to be signed and dated by the study director and each segment (report of each individual scientist and other professional person) signed and dated by the responsible scientist or other professional person.

It is also proposed that corrections or additions to a final report be in the form of an amendment of the study director clearly identifying that part of the report that is being added to or corrected and the reasons for the correction or addition. The amendment is to be signed by the person responsible for the correction or addition and dated.

The Commissioner feels that a final report prepared according to proposed § 3e.185 is essential to accurate interpretation of the study results and use of the study in regulatory decisionmaking.

Storage and retrieval of records and data. Proper storage of the records and data from a nonclinical laboratory study allows the reconstruction of the study for the purpose of assessing the quality and integrity of the results or the reinterpretation of the data in the light of later findings. The accessibility of such records allows FDA to assess the study and its acceptability in support of the safety of regulated products.

Proposed § 3e.190 sets forth the requirements for the storage and retrieval of those data that are to be retained in an archive, either at the testing facility or elsewhere, e.g., the sponsor's establishment. All raw data, documentation and other information, protocols, specimens, and the reports generated during and as a result of a nonclinical laboratory study would be required by this proposal to be retained and stored in an archive for the length of time specified in proposed § 3e.195(a) and shall be retrievable for inspection by authorized FDA employees upon request.

Proposed § 3e.190 specifies that an individual be identified as responsible for the archives. Data stored in the archives would be required to be indexed by test substance, date of study, test system species, and nature of the study.

Retention of records. Records of a nonclinical laboratory study should be retained for as long as possible or as long as their quality allows evaluation. Practical considerations dictate that minimum periods of retention be established and that these periods correspond to the time periods during which any question pertaining to the safety of the substance is under active consideration.

The Commissioner therefore proposes in § 3e.195(a) to establish minimum record retention requirements. All data and information required by the good laboratory practice regulations shall be retained for one of the following three alternative periods, whichever is shortest, except as otherwise noted:

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 FDA;

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

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.

Proposed § 3e.195(b) specifies that wet specimens, samples of test or control substance carrier mixtures and specially prepared material (e.g., histochemical, electron microscopic, blood mounts and teratological preparations and uteri from dominant lethal mutagenesis tests), which are relatively fragile and differ markedly in stability and quality during storage should be retained only as long as their quality allows evaluation.

The Commissioner proposes in § 3e.195(c) that the records of inspection or evaluation of a nonclinical laboratory study by the quality assurance unit and the master schedule sheet required to be maintained by proposed § 3e.33(b) be retained in the files of the quality assurance unit for the appropriate length of time specified in § 3e.195(a).

Proposed § 3e.195(d) specifies that curricula vitae and job descriptions required by proposed § 3e.29(b) may be retained with all other testing facility employment records rather than in the archives, provided the names of the persons involved in the conduct of each nonclinical laboratory study are included as part of the data required to be stored in the archives. The last available curriculum vitae and job description for an employee who has terminated employment shall be retained for the length of time specified in § 3e.195(a).

Proposed § 3e.195(e) also requires records and reports of the maintenance, cleaning, calibration, and inspection of equipment to be retained for the length of time in accordance with § 3e.195(a).

The Commissioner believes that proper storage of records and data under proposed §§ 3e.190 and 3e.195 will alleviate previous difficulties encountered by FDA in verifying the results of nonclinical laboratory studies.

Compliance and Enforcement

At least as important as determining how to improve the process by which nonclinical laboratory studies are performed is determining how to provide incentives to testing facilities to carry out the improvements found to be necessary or desirable. Many actions are available, and each has an appropriate place in FDA's compliance program. These include:

1. Notifying the testing facility of deficiencies observed during an inspection. It will be the practice of an FDA investigator to do this before leaving the premises upon concluding an inspection.

2. Issuing more formal warnings that important discrepancies between the conditions observed and regultory requirements must be corrected for the testing facility to avoid more serious regulatory action. This step generally will be accomplished by regulatory correspondence.

3. Determining that one or more specific nonclinical laboratory studies will not be considered by FDA in support of an application for a research or marketing permit. This would not mean that the data from completed studies need not be submitted to FDA. The usual rule that all data and information relevant to a particular article (e.g., a proposed or marketed product) must be submitted remains in effect. See, for example, proposed 21 CFR 2.7 (contents of a citizen petition for FDA action, as published in the Federal Register of September 3, 1975 (40 FR 40682)); 21 CFR 312.1(a)(5) and (6) (significant adverse findings regarding a drug in an IND study); 21 CFR 310.300(a) (1) and (2) (results from published and unpublished human and animal experience and studies on drugs with approved NDA's); and 21 CFR 809.30(c)(18) submission of data and information on in vitro diagnostic products in connection with development of a standard). Findings that the study is not acceptable in support of an application for a research or marketing permit means that the agency will not authorize further testing or future marketing if the claim for safety of the product is based upon that study. Valid data and information in an otherwise unacceptable study which are adverse to the product, however, may serve as the basis for regulatory action.

This disparity in treatment merely reflects the fact that a technically bad study can never establish the absence of a safety risk but may establish the presence of a previously unsuspected hazard. It reflects current agency policy; even in situations where the scientific quality of an investigational drug study is not in question, FDA may receive data but not use it in support of a decision to approve testing or commercial distribution of a drug because of ethical improprieties in the conduct of the study. (See 21 CFR 312.20.)

Rejection of a particular study from consideration in support of an application is provided for by statute in the procedures and criteria for determining whether the application is approvable under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act; for example, a determination that a faulty study precludes a finding that a new drug is safe can be made in accordance with the procedures set forth in section 505(d) of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 314. Accordingly, no special procedures need be prescribed. The standards for good laboratory practice represent amplification of the legal requirements regarding evidence of safety necessary to approve an application for a research or marketing permit.

4. Disqualifying a testing facility as a source of data and information in sup-

port of any application for a research or marketing permit. In such a case, which should be uncommon, the determination that data generated by the testing facility are not acceptable in support of an application is not limited to a particular study but may extend to all studies performed by the facility. This sanction would be utilized when the deficiencies found at a facility are of such a widespread or fundamental nature that the quality and integrity of every study being conducted by the facility has probably been compromised, or when the facility has failed to comply with the good laboratory practice regulations after previous warning from FDA. Unlike rejection of a specific study and legal prosecution, disqualification is not explicitly provided for by statute and thus necessitates the promulgation of regulations describing the procedures and substantive grounds for imposing this sanction; much of the remainder of this preamble is devoted to this matter. This extensive discussion should not, however, be read as implying that disqualification is the exclusive or primary administrative action for noncompliance with good laboratory practice. Disqualification is designed to provide FDA with an enforcement tool that is more efficient and effective than a study-by-study review when it becomes apparent that a testing facility is not capable of producing accurate and valid test results.

5. Prosecuting the testing facility and/or the sponsor of the nonclinical laboratory study for violations of Federal criminal laws, including section 301(e) of the Federal Food, Drug, and Cosmetic Act (failure to make a report required under certain other sections of the act, because a grossly erroneous or inadequate report does not fulfill the statutory obligation) and 18 U.S.C. 1001 (submission of a false report to the government). Even where the testing facility is not under a direct statutory obligation to submit information to FDA, and in fact does not send data to the agency but merely transmits them to the sponsor, the facility is likely to be aware that FDA will be the ultimate recipient. In such cases, it may be liable for aiding and abetting in the violation (18 U.S.C. 2) or for causing the violation to be made by a third party (see *United States* v. *Dotterweich*, 320 U.S. 277 (1943); and *United States* v. *Park*, 421 U.S. 658 (1975)).

The Commissioner is aware of the wide range of severity in these sanctions. He has directed the preparation of a compliance program which will identify the administrative and legal sanctions, which FDA may invoke upon findings of nonconformance with the provisions of these regulations. These sanctions and the internal procedures by which they will be applied will be contained in an FDA Compliance Program Guide to be made publicly available upon its completion (now projected for late next year). An understanding of this document should assuage fears that firms not in compliance with the good laboratory practice regulations immediately after they become effective will be subject to extreme penalties. The Commissioner recognizes that many testing facilities do not now meet, and perhaps for several months will not be able to meet, the standards set forth in these proposed good laboratory practice regulations. The same will be true of FDA facilities for test validation and product testing, which will be subject to the same standards and the same rigorous inspections that are applied to, or conducted at, private testing facilities. The proposed regulations articulate certain standards that are not currently widely observed in the conduct of nonclinical laboratory studies, e.g., maintenance of a quality assurance unit. The Commissioner understands that it will take time to establish such operations, and he is of the opinion that, during the initial stages of monitoring of private testing facilities, FDA must play an important informational and educational role. The series of initial inspections that the agency plans as a pilot program will evaluate laboratory performance in reference to these proposed regulations, but the primary objectives will be to evaluate the adequacy of these standards and to assess the status of the private testing laboratories generally. Failure to meet the standards set forth in the proposed regulations will not provide an independent basis for regulatory action.

The Commissioner emphasizes, however, that he will not hesitate to initiate appropriate regulatory action based upon the findings of violations of law or serious deficiencies in the conduct or reporting of tests submitted to FDA, including any inspection conducted during the pilot program. For example, if agency inspectors should discover evidence that data required to be submitted to FDA has been unlawfully withheld or that data has been misrepresented or falsified, all available legal sanctions will be considered. Similarly, if an inspection should reveal deficiencies in a submitted study, or studies, that are so serious the agency cannot properly rely on the findings reported, the Commissioner or the appropriate Bureau will consider necessary administrative action with respect to the product involved, such as initiating proceedings to withdraw approval for marketing.

The experience of FDA in enforcing regulations pertaining to the conduct of persons carrying out studies subject to the agency's jurisdiction has indicated a need for administrative sanctions in addition to court enforcement proceedings. Criminal prosecutions for violating these regulations are serious; they necessitate the expenditure of significant resources; and they usually are inappropriate when noncompliance does not reflect criminal intent, bad faith, or gross negligence. Consequently, such actions are generally indicated only for serious offenses, such as flagrant violations or deliberate falsification of data. Less serious offenses or first violations should be handled through a system that is more expeditious and less costly, but equally effective in providing incentives to compliance.

One such system is termed the "disqualification process." It has been used in the past by FDA to obtain compliance with the requirements of the law regarding clinical investigators, and is currently codified in 21 CFR 312.1(c) and 511.1(c). A revision of these regulations is now being prepared in the agency. The revised version will be similar to the disqualification regulations proposed for use by the Bureau of Medical Devices and Diagnostic Products under the Medical Device Amendments of 1976. (See proposed 21 CFR 812.119 published in the FEDERAL REGISTER of August 20, 1976 (41 FR 35282).) Disqualification, in the case of clinical investigators, has simply meant that an investigator is no longer eligible to receive investigational drugs under his own or someone else's IND or INAD. It imposes no fine; it attaches no financial liability, except to the extent that an investigator may be unable to fulfill a research contract; it does not revoke a medical license or institutional privileges. The disqualification of an investigator is intended to achieve two objectives: First, it precludes a disqualified investigator from access to any investigational article until he can demonstrate his ability and willingness to conform to the standards for conducting investigational studies essential to assure scientifically sound and ethical research; second, disqualification provides a mechanism for refusing to accept data prepared by the investigator in support of an application for a research or marketing permit.

The concept of disqualification appears reasonably applicable to the area of nonclinical laboratory studies. First, in both situations the agency is concerned with compliance by a particular group of investigators with the applicable regulatory standards. Second, in both situations the regulatory standards focus on the process by which scientific data are generated; that is, the regulatory requirements are designed so that, if good faith compliance occurs and the protocol is scientifically sound, there is reasonable assurance that the data generated are scientifically valid. Third, disqualification eliminates the need for an in-depth FDA audit and review of each study performed by the disqualified person. Having found, for example, that inadequate records were made in several studies, FDA can properly presume that records in all of the researcher's other studies are likely to be inadequate. Disqualification shifts the responsibility of validating data to the person offering them, and reduces the burdens on FDA in determining whether to accept the data. Fourth, utilizing the same process in both areas offers an advantage because many participants in the development and marketing of products regulated by the agency, including sponsors, investigators, and agency officials, are familiar with it. Finally, the disqualification process provides the person an opportunity to be heard before the agency in his own behalf. The Commissioner is aware that in some instances, the sponsor of a nonclinical laboratory study performed by

an independent contract testing facility has little or no interest in defending the quality of the study or the conduct of the facility. The sponsor may, for example, perceive his best interests lie in acquiescing to the agency's challenge to the study; in these circumstances, the person whose work is being questioned would be denied any meaningful opportunity to explain or justify the activities that are in doubt. Disqualification creates a forum for just such an exchange, which is important for fairness to all concerned.

There is one critical difference between the effects of disqualification of clinical investigators and disqualification of nonclinical testing facilities. A disquaified investigator is denied access to investigational articles because FDA permission is required before he can be included in an IND, INAD, or IDE. A disqualified testing facility is not denied access to test substances, because prior FDA permission to distribute or receive these is not legally required. In both cases, however, disqualification would preclude consideration of the investigator's or facility's data in support of an application for a research or marketing permit. This result, which is most critical to the decisionmaking process at FDA, also provides a most effective administrative sanction for significant noncompliance that cannot be or has not been remedied by lesser agency actions, e.g., warnings or rejection of a particular study.

For these reasons, the Commissioner is proposing to adopt the disqualification mechanism as the ultimate administratives action for serious noncompliance with good laboratory parctice regulations, except where criminal or injunctive action is clearly warranted.

Disqualification of testing facilities. The regulations governing disqualification of testing facilities are proposed to be set forth in Subpart K of Part 3e. Section 3e.200 is proposed to codify the purposes of disqualification to state clearly the meaning of this administrative action.

Grounds for disqualification. The Commisioner proposes in § 3e.202 to set forth grounds upon which a nonclinical testing facility may be disqualified and the results of its studies ruled unacceptable to support applications for a research or marketing permit from the agency. The primary function of the regulations on nonclinical laboratory studies is to assure that the results of such studies are reliable and can be utilized in making judgments about the safety and proper labeling of products regulated by the agency. Proposed § 3e.202 contains 16 specific grounds for disqualification:

1. The testing facility utilized personnel in carrying out studies who did not satisfy the provisions of § 3e.29, whether through lack of qualifications or insufficiency in number, resulting in an inability to ensure accurate performance of the duties specified in the protocol.

2. The testing facility, in conducting studies, failed to designate a study director, as provirded for in § 3e.31.

3. The testing facility conducted studies without a suitable mechanism for quality assurance as provided for in § 3e.33.

4. The testing facility conducted studies in physical facilities which did not satisfy the provisions of Subpart C, and the deficiencies in size or design were severe enough to call into question the quality and integrity of the laboratory study and of the data collected.

5. The testing facility conducted studies with equipment that did not meet the requirements of Subpart D and thus may have adversely affected the health of the test system, the nature and administration of the test and control substances, or the accuracy and precision of data collection operations.

6. The testing facilities carried out studies in the absence of or without regard to written standard operating procedures for certain critical operations as set forth in § 3e.81, resulting in the potential introduction of unknown variations in study conduct.

7. The animals used by the testing facilities in studies were not housed, fed, watered, handled, and identified in accordance with § 3e.90 and such deficiencies were sufficiently severe to alter or mask effects of the test or control substance upon the animals or to prevent adequate identification of treated and nontreated animals.

8. The testing facility did not have or did not follow procedures necessary for determining and documenting the identity, strength, quality, and purity of test and control substances and the uniformity and concentration of test and control substance carrier mixtures as set forth in Subpart F, calling into question any quantitative conclusions relating to dose response.

9. Nonclinical laboratory studies were conducted by the testing facility in the absence of a written protocol containing the information set forth in § 3e.120. Protocols are of great importance, and the absence of protocols is always sufficiently serious to justify disqualification.

10. The testing facility did not collect, review, sign, and date all data generated in nonclinical laboratory studies in accordance with § 3e.130 and such deficiencies are sufficiently severe as to call into question the validity of data upon which substantive final conclusions on the safety of the test substance are based.

11. The testing facility did not monitor test systems in conformity with protocols, and specimens were not properly identified in accordance with § 3e.130; and such deviations were sufficiently severe as to call into question the validity of data on which substantive conclusions are based.

12. The final study reports prepared by the testing facility do not meet the requirements of § 3e.185 and as a result are misleading or inconclusive with regard to the objectives, procedures, results and implications of the studies.

13. The raw data, documentation, information, protocol, final reports, and specimens generated during nonclinical laboratory studies have not been retained by the testing facility in accordance with § 3e.190, resulting in a loss of ability to review the conclusions and assess the quality and integrity of the studies.

14. The raw data, documentation, information, protocol, final reports, and specimens generated during nonclinical laboratory studies have not been retained by the testing facility for the minimum period of time specified in § 3e.195.

15. The testing facility refused to permit an inspection of the facilities used in studies, or an inspection and copying of records and reports made during or on completion of the studies, by an authorized representative of the sponsor, if any, or by FDA. As discussed below in this preamble, the agency must be able to verify submitted data before it can rely upon such data to reach a regulatory decision.

16. The testing facility falsified any record or report or deliberately withheld any report required by the good laboratory practice regulations.

Notice of and opportunity for a hearing on proposed disqualification. The Commissioner proposes to establish a uniform procedure to be followed by the various FDA Bureaus regulating or reviewing nonclinical laboratory studies on products and test substances subject to FDA jurisdiction. Each Bureau will be initially responsible for administering good laboratory practice requirements for the products and substances under its purview, as part of receiving applications for research and marketing permits submitted to that Bureau. In those cases where rejection of specific studies and other remedies are inadequate to achieve compliance, however, action will be referred to the office of the Commissioner. Under the proposed regulations, disqualification would be proposed by the Associate Commissioner for Compliance. After consideration of the recommendations of the Bureaus involved, notice of the proposed action would be provided to the testing facility; there would be an opportunity for a regulatory hearing before the Commissioner or a person designated by him; and final action on the proposed disqualification would be taken only by the Commissioner.

The written notice issued to the testing facility upon commencement of a disqualification proceeding shall contain the following items of information, in accordance with 21 CFR 2.510(a):

(1) The notice shall specify the facts and set forth the specific paragraphs of § 3e.202 which are believed to justify disqualification.

(2) The notice shall state that the testing facility has an opportunity for a regulatory hearing on the proposed disqualification before the Commissioner, or a person designated by him, and that such hearing will be conducted in accordance with Subpart F of 21 CFR Part 2, the FDA procedural regulations.

(3) The notice shall state the time within which a hearing may be requested, which shall be not less than 3 working days from the receipt of the notice.

(4) The notice shall contain the name, address, and telephone number of the FDA official who has been designated by the Commissioner as presiding officer for the regulatory hearing and to whom any request may be filed by registered mail, telegram, telex, personal delivery, or any other mode of written communication.

In the past under the disqualification regulations pertaining to clinical investigators, the Bureau of Drugs has provided an "informal" conference with the officer who issued the notice before the "formal" disqualification hearing (see 21 CFR 312.1(c)(1)). The conferences frequently had many formal trappings, such as stenographic transcripts. The conferences were often followed by the contemplated hearing by the officer deciding on the disqualification. This process doubled the time and expense of all the parties—FDA, the investigator, and the sponsor, if it were involved—without discernible benefit. The Commissioner has therefore decided not to provide for such an informal conference in these regulations. The procedures proposed should provide adequate flexibility and fairness to all parties.

FINAL ORDER ON DISQUALIFICATION

If, after the regulatory hearing or after the time for requesting a hearing expires without a request being made, the Commissioner determines, upon an evaluation of the administrative record, that the testing facility is responsible for any of the acts or omissions specified in the notice proposing disqualification and has not adequately explained its conduct, he shall prepare and issue a final order disqualifying the facility. Proposed § 3e.206 provides that the final order shall include a statement of the basis for the disqualification. Once a final order has been issued, the Commissioner shall so notify the testing facility.

If, after the regulatory hearing or after the time for requesting a hearing expires without a request being made, the Commissioner determines, upon reviewing the administrative record, that the testing facility is not responsible for the acts or omissions specified in the notice proposing disqualification, or that the facility is responsible but has adequately explained its conduct, he shall issue a final order terminating the disqualification proceeding and shall include a statement of the basis for his decision to terminate the proceeding. After such a final order has been issued, the Commissioner shall so notify the testing facility.

Actions upon disqualification. Once a testing facility has been disqualified, proposed § 3e.210 provides that each application for a research or marketing permit, approved or not, that contains or relies upon any nonclinical laboratory study performed by that testing facility may be examined to determine whether the study was, or would be, essential to FDA's decision to approve the application. If it is determined that, without the results of the study, an investigational study would not have been allowed to proceed or that a product application or monograph would not have been approved, FDA will then determine whether the study is acceptable, notwithstanding disqualification. 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 disqualification. This may include requiring the sponsor or applicant to submit validating information. If FDA determines that the study is not acceptable, the study will be eliminated from consideration of the application for a research or marketing permit. Elimination of such data will serve as "new information" justifying termination of an investigational study (e.g., IND or IDE), the withdrawal of approval of a product license (e.g., NDA or biological product license), or the revocation of a product, monograph, or standard (e.g., antibiotic monograph, in vitro diagnostic product standard or a radiation-emitting product standard).

The Commissioner advises that it is not necessary that a testing facility be disqualified in order for the agency to reject consideration of a particular nonclinical laboratory study in support of an application for a research or marketing permit. The criteria set forth in the statute and regulations applicable to each type of application, together with the good laboratory practice regulations, will still be used to judge the scientific validity and meaning of nonclinical laboratory studies. The agency may apply the good laboratory practice regulations to a particular study and determine that the study is so inadequate that it will not support a claim of safety of a product. If the sponsor of a product or a testing facility that conducted the study wishes to contest this finding, the opportunity to do so will be provided in the procedures for denying or withdrawing the approval of the application. The Commissioner believes that it is not in the public interest to provide a two-step process whereby a particular study would be disqualified under procedures similar to those proposed in Subpart K and then the application itself would be denied under procedures set forth in other regulations. Efficiency and fairness to all concerned suggest that these issues be resolved at the same time in one proceeding, if that is required; it may be that, although a particular study is not acceptable, other data and information in the application will support a product's safety, and therefore no proceeding is necessary to rule on the acceptability of the particular study. Likewise, the agency may choose to reject individual studies without disqualifying the testing facility, when, for example, the studies were performed at a period when the facility was not in compliance with good laboratory practice regulations but has since come into compliance. The Commissioner further advises that it is likely that the usual formal regulatory action taken for noncompliance with good laboratory practice regulations will be rejection of individual studies and that disqualification of the testing facility will be reserved for those cases where the rejection of a particular study is an inadequate regulatory response.

Public disclosure of information upon disqualification. The Food and Drug Administration believes that information regarding the disqualification of a testing facility should be transmitted to other Federal agencies supporting nonclinical laboratory research or reviewing such studies for regulatory purposes and, where appropriate, to others such as State and local licensing authorities. It is recognized, however, that the consequences of such notice are obvious and could include termination of a grant or contract, disciplinary proceedings by licensing boards or professional societies, and other damage to the reputation and business of the testing facility.

In 1971 the Supreme Court held, in "Wisconsin v. Constantineau," 400 U.S. 433: "Where a person's good name, reputation, honor, or integrity is at stake because of what the government is doing to him, notice and an opportunity to be heard are essential." That notice must include a full statement of the consequences of the decision once reached. The Chief Counsel of the FDA has advised that the agency, because of the "Constantineau" decision, may not affirmatively notify persons with whom the disqualified testing facility has professional relations of FDA's administrative action, without first warning the testing facility that such notice is one of the consequences of disqualification. Moreover, this warning should be given both in FDA regulations and in the notice to the facility at the time disqualification is proposed. Only by having such notice can the testing facility make a determination as to whether and how to protest its rights.

The Commissioner proposes in § 3e.213 (a) to authorize the FDA to notify other Federal agencies or other persons, such as appropriate State or local licensing authority, that a testing facility has been disqualified by FDA when the Commissioner believes that such disclosure would further the public interest or would promote compliance with the good laboratory practice regulations. This determination is within the discretion of the Commissioner and may be made after consideration of the circumstances justifying the disqualification, the mitigating conditions, and the degree to which other institutions or persons have an involvement in the ongoing activities of the testing facilities. Because notification of disqualification, without more information, might unduly prejudice the testing facility, the Commissioner shall provide a copy of the final order issued under proposed § 3e.206(a) and shall state that the disqualification constitutes a determination by FDA that a nonclinical laboratory study performed by the testing facility will not be considered by the agency in support of any application for a research or marketing permit. If notice is sent to another Federal government

agency, FDA will recommend that that agency also consider whether it should accept nonclinical laboratory studies performed by that testing facility. If notice is sent to anyone else (e.g., a State or local licensing authority), FDA will not advise or recommend that any action be taken upon the matter. A copy of each notification shall be given to the testing facility.

A determination that a testing facility has been disqualified and the administrative record regarding such determination are disclosable to the public under the Freedom of Information Act (5 U.S.C. 552) and under FDA public information regulations (21 CFR Part 4) as records relating to the administrative enforcement action that has been completed. This is stated in proposed § 3e.213(b).

Alternative or additional actions to disqualification. Since disqualification of a testing facility may be neither a sufficient nor an appropriate sanction in every case, the Commissioner believes that disqualification must be independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the law. Proposed § 3e.215 makes clear, therefore, that FDA may at any time institute against a testing facility, and/or against the sponsor of a nonclinical laboratory study that has been submitted to FDA, 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. This would, of course, include refusal to consider a particular study in support of a particular application, the regulatory action which probably will be most commonly used in the near future for significant noncompliance with good laboratory practice regulations.

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

Suspension or termination of testing facility by a sponsor. Because the Commissioner believes it is important that the sponsor of a nonclinical laboratory study be able to terminate or suspend a testing facility at any time from further participation in the study it is conducting for the sponsor, proposed § 3e.217 makes clear that the sponsor has such authority and may suspend or terminate the facility, whether or not FDA has commenced any action to disqualify that facility. Further, in taking such action, the sponsor is not limited to the grounds or required to use the procedures for disqualification that are set forth in the proposed regulation. The sponsor is required, however, to advise FDA of this action, including the reasons for it, within 5 working days if the study is being conducted as part of any application for a research or marketing permit already submitted to FDA. Even where a sponsor terminates or suspends a testing facility's work, the sponsor must retain all reports on the work and, when otherwise required by FDA (e.g., as part of an application for a research or marketing permit), submit such reports to the agency.

Reinstatement of a disqualified testing facility. Under this proposal, disqualification serves as a barrier to having the results of future nonclinical laboratory studies considered in support of applications for research or marketing permits for an indefinite period of time until the testing facility is reinstated by the agency. The Commissioner is of the opinion that disqualification should be of indeterminate duration. The sanction is not a punishment for past actions but a remedial action to prevent future violations and to assure that data in support of applications is produced under circumstances that increase the likelihood of their scientific validity. It accomplishes this by limiting the facility's ability to conduct further testing that might be submitted to the FDA until it comes into compliance, and by providing a deterrent to others to avoid violations. Thus, disqualification should continue until the agency finds that the testing facility can fulfill the requirements imposed under the good laboratory practice regulations and will do so in the future.

Proposed § 3e.219 authorizes the Commissioner to reinstate a testing facility (i.e., determine that its studies may once again be considered in support of applications for research or marketing permits), if he finds that the facility can provide adequate assurances that it will conduct future studies in compliance with the requirements of the good laboratory practice regulations. A testing facility that wishes to be reinstated shall explain to the Commissioner why it believes it should be reinstated, including a detailed description of the corrective actions it has taken or intends to take to assure that the acts or omissions which led to its disqualification will not recur. Reinstatement may be contingent upon the facility's passing an FDA inspection during the study. In fairness to the testing facility, all persons or organizations notified under proposed § 3e.213(a) of the facility's previous disqualification must be notified when that facility is later reinstated; the proposed § 3e.219 so provides.

A determination that a testing facility has been reinstated is disclosable to the public under the Freedom of Information Act (5 U.S.C. 552) and under Part 4 (21 CFR Part 4) as records relating to completed administrative enforcement actions.

LEGAL AUTHORITY

The results of literally hundreds of nonclinical laboratory studies are submitted to FDA each year by persons seeking regulatory action by the agency. To obtain a marketing license, animal test data are offered to support the safety of a product, e.g., a food or color additive, a drug or biologic for human or veterinary use, or a medical device. Even where a license is not required or already has issued, such data may be relied upon to demonstrate the bioavailability of a marketed drug, the general recognition of safety of a product, or the absence of any need for premarket approval or a product standard for a device. Given the enormous volume of nonclinical laboratory studies filed with FDA, the varieties of scientific and regulatory review that must be devoted to these studies apart from determining the basic validity, e.g., to interpret the results and to evaluate the status of the affected products in light of the results, and the limited resources within the agency, the Commissioner believes that FDA must have a way to screen those studies that are likely to be unreliable and therefore warrant little further evaluation from those that are acceptable. The promulgation of good laboratory practice regulations provides one set of criteria for making this judgment. While compliance with the regulations does not guarantee the quality and integrity of a nonclinical laboratory study, failure to comply increases substantially the probability that the results will not be of high quality and integrity. Moreover, as noted elsewhere in this preamble, the regulations reflect principles recognized by the scientific community as essential to sound nonclinical research. Thus, these regulations will assist FDA in identifying those studies that cannot be considered in support of an application for a research or marketing permit.

Under section 701(a) of the act (21 U.S.C. 371(a)), the Commissioner is empowered to promulgate regulations for the efficient enforcement of the act. Previously, the Commissioner has issued regulations (21 CFR 314.111(a)(5)) for determining whether a clinical investigation of a drug intended for human use, among other things, was scientifically reliable and valid (in the words of section 505(d) of the act, "adequate and well-controlled") to support approval of the drug. These regulations were also issued under section 701(a) of the act and have been upheld by the Supreme Court (see *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); see also *Upjohn Co.* v. *Finch*, 422 F.2d 944 (6th Cir. 1970) and *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del. 1970)).

The Commissioner has therefore concluded that legal authority to promulgate good laboratory practice regulations exists under section 701(a) of the act, as essential to enforcement of the agency's responsibilities under sections 406, 408, 409, 502, 503, 505, 506, 507, 510, 512, 513, 514, 515, 516, 518, 519, 520, 706, and 801 of the Federal Food, Drug, and Cosmetic Act, as well as the responsibilities of FDA under sections 351 and 354–360F of the Public Health Service Act. Regardless of whether such regulations would have been necessary before the discovery of serious and apparently widespread problems with the reliability of nonclinical laboratory studies, it is now imperative that FDA establish regulations to reduce these problems.

It follows from the authority to promulgate good laboratory practice regulations that FDA also has authority to prescribe the terms on which it will accept data generated by nonclinical testing facilities. Therefore, the proposed regulations provide in § e3.15 that the agency will not consider a nonclinica

laboratory study in support of an application for a research or marketing permit unless the testing facility that conducted the study consents to FDA inspection, and in § 3e.202(o) that the agency may disqualify a testing facility that refuses to permit an inspection. The Commissioner believes this does not infringe on any right or obligations of a testing facility. The facility may at any time withdraw its consent to inspection, either to exercise its own rights or to protect the confidentiality of a sponsor who has forbidden any release of information under its grant or contract. In this event, however, FDA will not consider the results of the study and may consider disqualifying the facility as a future source of nonclinical laboratory studies. This may adversely affect the status of an application submitted by a third person, e.g., the sponsor of a study under a contract, but this is strictly a matter between those parties. In proposed § 3e.10, the Commissioner advises all persons who sponsor or perform under contract nonclinical laboratory studies that may be submitted to FDA to consider inclusion in the contract of provisions regarding FDA inspections. Such provision is especially important if the testing facility is not otherwise aware that the results of the study may be submitted to FDA.

Inspections of many, perhaps most, testing facilities will not be conditioned upon consent. Under section 704(a) of the act, FDA may inspect establishments, including consulting laboratories, in which certain drugs and devices are processed or held, and may examine research data that would be subject to reporting and inspection pursuant to section 505 (i) or (j) or 507 (d) or (g) of the act. In addition, any establishment registered under section 510(h) of the act is subject to inspection under section 704 of the act. Thus, most manufacturing firms that conduct in-house nonclinical laboratory studies on drugs and devices, and those contract laboratories working for such firms, would be subject to FDA inspection whether or not they consented.

The Commissioner has reviewed the potential environmental impact of the proposed regulation and has concluded that the proposed action will not significantly affect the quality of the human environment and that an environmental impact statement is not required. Copies of the environmental impact analysis report and environmental impact assessments are on file with the Hearing Clerk, Food and Drug Administration.

For reasons set forth in the agency's inflation impact assessment on file with the Hearing Clerk, it is believed that this proposal would not cause a major inflation impact, as defined by Executive Order 11821, OMB Circular A-107, and the Guidelines issued by the Department of Health, Education, and Welfare.

However, the Commissioner recognizes that these proposed regulations may have economic, or inflation, implications for laboratories engaged in toxicity testing on animals. The extent of the impact on laboratories cannot be precisely estimated at this time because the degree to which laboratories will have to modify their present laboratory procedures to comply with the proposed standards is unknown. Also, little has been published about the economic characteristics of the laboratories, such as their revenues, number of employees, operating costs, and so forth. These data are necessary to evaluate the potential impact of the proposed regulations according to the six criteria that have been established for determining whether a major impact has been caused.

The agency plans to inspect a statistically drawn sample of nonclinical laboratories before issuing a final regulation on good laboratory practices. The inspections will provide information on the congruence or disparity between current procedures and proposed standards. More data are needed, however, to precisely estimate the inflation impact of these proposed regulations. For example, an inflation impact analysis requires information on projected costs for laboratory modifications as well as general information about the economic characteristics of the industry. Consequently, the Commissioner invites comments from industry, consumers, and other parties which would address the following:

1. Added operating and capital costs that would be incurred to comply with the proposed regulations.

2. Number of employees, if any, that would be hired or released for reasons related to the proposal.

3. Competitive advantage or disadvantage attributable to the proposal.

4. Characteristics of the nonclinical laboratory industry as a whole, such as number of laboratories affected by the proposal, employment, annual revenues.

5. Suggestions for reasonable alternatives and a comparative analysis of their costs and benefits. Respondents should cite specific provisions of the proposed regulations and how they have been interpreted when submitting materials pertaining to impact. Estimates should be documented.

The Commissioner will make publicly available a report on the inflation impact of these regulations at the time they are made final.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 512–516, 518–520, 701(a), 706, and 801, 52 Stat. 1049–1053 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511–517 as amended, 72 Stat. 1785–1788 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, 356, 357, 360, 360b–360f, 360h–360j, 371(a), 376, and 381)) and the Public Health Service Act (secs. 215, 351, 354–360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173–1186 as amended (42 U.S.C. 216, 262, 236b–236n)) and under authority delegated to him (21 CFR 5.1) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)), the Commissioner proposes that Chapter I of Title 21 of the Code of Federal Regulations be amended as follows:

SUBCHAPTER A—GENERAL

1. By establishing new Part 3e to read as follows:

PART 3e—GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES

Subpart A—General Provisions

Subpart B—Organization and Personnel

Subpart C—Facilities

Subpart D—Equipment

Subpart E—Testing Facility Operation

Subpart F—Test and Control Substances

Subpart G—Protocol For and Conduct of A Nonclinical Laboratory Study

Subparts H–I—[Reserved]

Subpart J—Records and Reports

Subpart K—Disqualification of Testing Facilities

AUTHORITY: Secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 512–516, 518–520, 701(a), 706, and 801, Pub. L. 717, 52 Stat. 1049–1053 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511–517 as amended, 72 Stat. 1785–1788 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, 356, 357, 360, 360b–360f, 360h–360j, 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

§ 3e.1 Scope.

This part contains good laboratory practices for conducting nonclinical laboratory studies that support application for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, human and animal drugs, medical devices, biological products and radiation-emitting 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.

§ 3e.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 (21 U.S.C. 321).

(b) "Test substance" means any food additive, color additive, drug, botanical material, biological product, radiation-emitting product, medical device, 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 substance" means any food additive, color additive, drug, botanical material, biological product, radiation-emitting product, medical device, or any other article other than a test substance 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 substance.

(d) "Nonclinical laboratory study" means any in vivo or in vitro experiment in which a test substance is studied prospectively in a test system under laboratory conditions to determine its safety. The term also includes such experiments intended to assess the functionality and/or effectiveness of a test substance where inadequate functionality or effectiveness of the test substance may result in a safety or health hazard. 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 or not a test substance has any potential utility or to determine physical or chemical characteristics of a test substance independent of any test system, e.g., to determine the stability of a chemical or the tensile strength of a plastic.

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

(1) A color additive petition, described in Part 8 of this chapter.

(2) A food additive petition, described in Part 121 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, which results may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in § 121.3 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 § 121.4000 of this chapter.

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

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

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

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

(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 Part 430 of this chapter.

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

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

(12) Data and information regarding a drug for veterinary 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.

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

(14) 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.

(15) 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.

(16) An "application for an investigational device exemption," described in Part 812 of this chapter.

(17) An "Application for Premarket Approval of a Medical Device," described in this chapter.

(18) A "Product Development Protocol for a Medical Device," described in this chapter.

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

(20) Data and information regarding a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for such devices, described in this chapter.

(21) Data and information regarding a radiation-emitting 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.

(22) Data and information regarding a radiation-emitting 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.

(23) Data and information regarding a radiation-emitting 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.

(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.

(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 substance 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, cellular, subcellular, chemical or physical system, e.g., container being tested for extractables, and any components or subparts of such a system to which the test or control substance is administered or added for study or analysis. "Test system" also includes appropriate groups or components of the system not treated with the test or control substances.

(j) "Specimen" means any material, tissue, tissue block, or slide derived from a test system for examination or analysis.

(k) "Raw data" means any laboratory worksheets, records, memoranda, notes, or certified copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. "Raw data" may include photographs, microfilm or microfiche copies, computer printouts (derived from on-line data recording systems), magnetic media, including dictated observations, and re-

corded data from automated instruments.

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

(m) "Study director" means any scientist or other professional person of appropriate education, training, and experience, or combination thereof, responsible for the implementation of the protocol of a nonclinical laboratory study.

§ 3e.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.

§ 3e.15 Inspection of a testing facility.

A testing facility shall permit an authorized employee of the sponsor of a nonclinical laboratory study, or the Food and Drug Administration, at reasonable times and in a reasonable manner, to inspect the facility and to inspect and copy records required to be maintained regarding the study under this part. 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.

Subpart B—Organization and Personnel

§ 3e.29 Personnel.

(a) Each person 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 person to perform the assigned functions.

(b) Each testing facility shall maintain a current curriculum vitae and job description for each person engaged in or supervising the conduct of a nonclinical laboratory study. The testing facility shall also retain the last available curriculum vitae and job description for such person after termination of employment, as specified in § 3e.195(d).

(c) There shall be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol.

(d) Employees shall practice good sanitation and health habits.

(e) Personnel engaged in a nonclinical laboratory study shall wear laboratory clothing appropriate for the duties they perform. Such clothing shall be changed as often as necessary to prevent microbiological or chemical contamination of test systems.

(f) Any person 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 substances, and any other operation or function that may adversely affect the study until the condition is corrected. The reporting and/or treatment of an illness shall be documented in the records of the nonclinical laboratory study. All employees shall be instructed to report to supervisory personnel any health or medical conditions that may reasonably be considered to have an adverse effect on a nonclinical laboratory study.

§ 3e.31 Study director.

(a) Before the initiation of a 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 ultimate responsibility for implementation of the protocol and conduct of the study and shall assure that:

(1) The approved protocol, including any approved change, is followed.

(2) Test and control substances or mixtures have been appropriately tested for identity, strength, quality, purity, stability, and uniformity.

(3) Test systems are appropriate.

(4) Personnel, resources, facilities, and methodologies are available as scheduled.

(5) Personnel clearly understand the functions they are to perform.

(6) All data are accurately recorded and verified.

(7) Unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study are noted and documented.

(8) The occurrence of an unforeseen health hazard to the test system is recognized and promptly reported to the appropriate supervisor and that corrective action taken is documented.

(9) The responses of the test system, whether anticipated or not, are documented.

(10) All applicable good laboratory practice regulations are followed.

(11) The study is conducted in a manner that is safe for laboratory personnel.

(12) All raw data, documentation, and other information to be retained, protocols, specimens, and final reports are transferred to the archives during or at the close of the study.

(b) The study director shall be replaced promptly if it becomes necessary during the conduct of a study, and justification for this replacement shall be documented and maintained as raw data.

§ 3e.33 Quality assurance unit.

(a) A testing facility shall have a quality assurance unit composed of one or more individuals who shall be responsible for assuring that the facilities, equipment, personnel (including personnel safety), methods, practices, records, and controls are in conformance with the regulations of this part and for assuring the quality and integrity of the data obtained from a nonclinical laboratory study and for adherence to protocols and standard operating procedures. Each facility's quality assurance unit shall also monitor the quality and integrity of any nonclinical laboratory studies or portions thereof done by contractors or grantees.

(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 substance and containing the test system, nature of study (e.g., chronic, acute, reproduction, or taratology), animal species, date study was initiated, current status of each study, name of the sponsor, name of the study director, and whether the final study report has been approved or disapproved for submission to the sponsor.

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

(3) Inspect each phase of a nonclinical laboratory study periodically 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 shall be brought to the attention of the study director and management immediately.

(4) Perform a complete evaluation every 3 months of all phases of all studie lasting more than 6 months. Studies last ing less than 6 months shall be evaluated more frequently than every 3 months.

(5) Periodically submit to management and the study director written status reports on each study, noting any problems and the corrective actions taken.

(6) Assure that no deviations from approved protocols or standard operating procedures have been made without proper prior authorization.

(7) Review the final study report to assure that such report accurately describes the methods, standard operating procedures, observations, results, and raw data of the nonclinical laboratory study.

(c) The responsibilities and procedures applicable to the quality assurance unit, a list of the records maintained by the quality assurance unit, and the method of indexing such records shall be in writing and shall be maintained and made available for inspection to authorized employees of the Food and Drug Administration.

§ 3e.35 Access to professional assistance.

A scientist or other professional of appropriate education, training, and experience, or combination thereof, shall be available to respond to requests from technicians or less experienced personnel for assistance or consultation and to handle any unforeseen issues.

Subpart C—Facilities

§ 3e.41 General.

Each testing facility shall be of suitable size, construction, and location to facilitate the proper conduct of nonclinical laboratory studies. It shall be designed so that there shall be defined (and, where required, separate) areas for each of the functions described in this subpart.

§ 3e.43 Animal care facilities.

(a) A testing facility shall have a sufficient number of animal rooms or areas to assure separation of species or test systems and isolation of individual projects to receive, quarantine, and isolate the animals and to provide for their routine or specialized housing. Structural requirements and environmental control of these rooms or areas for animals shall comply with the provisions of the Animal Welfare Act of 1970 (Pub. L. 91-579) as set forth in 9 CFR Part 3. Space requirements for the primary enclosure shall also be as specified in 9 CFR Part 3, except that where specifications regarding housing of certain species of animals are not set forth, the recommendations contained in HEW Publication No. (NIH) 74-23 entitled "Guide for the Care and Use of Laboratory Animals" shall be used.

(b) A testing facility shall also 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 substances known to be infectious or otherwise harmful to either man or animals.

(c) An area near the animal housing areas shall be provided for the diagnosis, treatment, and control of laboratory animal diseases. This area shall provide effective isolation for the housing of animals either known or suspected of being diseased, or of being carriers of disease, from animals that are in good health.

(d) 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.

(e) Animal facilities shall be designed, constructed, and located so as to minimize disturbances that interfere with the study.

§ 3e.45 Animal supply facilities.

There shall be storage areas 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. Refrigeration shall be provided for perishable supplies or feed.

§ 3e.47 Facilities for handling test and control substances.

(a) To prevent contamination or mix-ups, there shall be separate or defined areas for:

(1) Receipt and storage of the test and control substances.

(2) Mixing of the test and control substance with a carrier, e.g., feed.

(3) Storage of the test and control substance mixture.

(b) Storage areas for the test and/or control substances and test and control substance mixtures shall be separated from areas housing the test systems and shall be adequate to preserve the identity, strength, quality, purity and stability of the substances and mixtures.

§ 3e.49 Laboratory operation areas.

(a) Separate laboratory space shall be provided for the performance of the routine procedures or categories of procedures required by nonclinical laboratory studies, including specialized areas near animal housing areas for performing activities such as aseptic surgery, intensive care, necropsy, histology and radiography.

(b) Specialized areas shall be provided for the handling of volatile agents or hazardous aerosols. Special procedures shall be employed for the handling of other biohazardous materials.

(c) If radioactive materials are to be used, special facilities or areas and licensing of persons to possess and use radioactive materials shall be in accordance with regulations set forth by the Nuclear Regulatory Commission in Title 10 of the Code of Federal Regulations or the requirements of an agreement State.

(d) Space and facilities separate from the housing areas for the test systems shall be provided for cleaning, sterilizing, and maintaining equipment and supplies used during the course of the study.

§ 3e.51 Specimen and data storage facilities.

There shall be facilities, limited to access by authorized personnel only, for the storage and retrieval of all raw data and specimens.

§ 3e.53 Administrative and personnel facilities.

(a) There shall be space provided for the administration, supervision, and direction of the testing facility.

(b) Locker and shower facilities as needed, toilet facilities with hot and cold water, soap or detergent, and air driers or single service towels shall be provided. These facilities shall be in accordance with regulations set forth by the Occupational Safety and Health Administration under Title 29 of the Code of Federal Regulations.

Subpart D—Equipment

§ 3e.61 Equipment design.

(a) Equipment used in the testing facility, including equipment for laboratory environmental control, shall be of appropriate design and adequate capacity and shall be suitably located to facilitate operation, cleaning and maintenance.

(b) Equipment and materials used in the maintenance of test systems shall be of appropriate design to maintain the health of the test system and to facilitate cleaning and maintenance.

(c) Equipment and materials used to prepare and administer the test and/or control substances shall be of adequate design to assure accurate administration of the quantity of test and control substances that are specified in the protocol for the nonclinical laboratory study. Such equipment shall be of appropriate design to preclude contamination of the test and control substances and to facilitate cleaning and maintenance.

(d) Automatic, mechanical, or electronic equipment used in the generation, measurement, or assessment of data during a nonclinical laboratory study shall be of adequate design to perform the intended functions.

§ 3e.63 Maintenance and calibration of equipment.

(a) Equipment shall be inspected, cleaned, and maintained regularly; equipment used for the generation, measurement, or assessment of data shall be tested and calibrated regularly. When appropriate, proper maintenance shall include pest control that minimizes risk to the health of the test system and to the conduct of the study. Cleaning and pest control materials or any other materials that could interfere with the conduct of the study or the health of the test system should be avoided wherever possible.

(b) There shall be written standard operating procedures which set forth in detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, and calibration of equipment, and which specify remedial action to be taken in the event of failure or malfunction of equipment. The written standard operating procedures shall designate the individual who is responsible for the performance of each operation, and copies of the standard operating procedures shall be made available to laboratory personnel.

(c) Written records shall be maintained of all inspection, cleaning, maintenance, testing and calibrating operations. These records, containing the date of the operation, shall describe whether the maintenance operations were routine and followed the written standard operating procedures. If cleaning or pest control materials are used which might interfere with the conduct of the study or constitute a hazard to the test system, there shall be adequate documentation of the material and procedures used, e.g., name of the material, date and method of application, and statement as to whether test systems were present and if so how contamination was prevented. 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.

Subpart E—Testing Facilities Operation

§ 3e.81 Standard operating procedures.

(a) A testing facility shall have written standard operating procedures setting forth nonclinical laboratory study methods that it is satisfied are adequate

to ensure the quality and integrity of the data generated in the course of the study. Any deviation from a standard operating procedure authorized by the study director shall be documented in the study data and reported in writing to the quality assurance unit. Significant changes to such 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, sampling, testing and administration of the test and control substances. The testing program shall be designed to establish the identity, strength, quality and purity of the test and control substances, to assess stability characteristics, where possible, and to establish storage conditions and expiration dates, where appropriate.

(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) Preparation of specimens.

(9) Histopathology.

(10) Personnel health and safety.

(11) Data handling, storage, and retrieval.

(12) Preparation and validation of final study report.

(c) Each appropriate laboratory area shall have available at all times in the immediate bench area of personnel, laboratory manuals and standard operating procedures relative to the laboratory procedures being performed, e.g., toxicology, histology, clinical chemistry, hematology, teratology, necropsy. Textbooks may be used as supplements to such written description but may not be used in lieu thereof.

(d) A historical file of standard operating procedures annotating effective dates and dates of revisions shall be maintained.

§ 3e.83 Reagents and solutions.

All reagents and solutions in the laboratory areas shall be labeled to indicate identity, and when relevant, titer or concentration, storage requirements, method of preparation, expiration date, if appropriate, and other pertinent information. Deteriorated materials and materials of substandard quality shall be removed from the laboratory and shall not be used in a nonclinical laboratory study except to conduct studies on the toxicity of such materials.

§ 3e.90 Animal care.

(a) All animals under the care of the testing facility shall be housed, fed, and handled in compliance with standards set forth by the Animal Welfare Act of 1970 under 9 CFR Part 3, or, where standards are not indicated in 9 CFR Part 3, they shall be housed, fed, and handled in a manner consistent with the recommendations in HEW Publication (NIH) No. 74-23 "Guide for the Care and Use of Laboratory Animals." All animals for which there are no specific regulations shall be housed, fed, and handled in compliance with Subpart E of 9 CFR Part 3, the recommendations of HEW Publication No. (NIH) 74-23 and the National Academy of Sciences/National Research Council "Standards for the Breeding, Care and Management of Syrian Hamsters (1960); Laboratory Mice (1962); Laboratory Rats (1962); Guinea Pigs (1964); Laboratory Cats (1964); Laboratory Dogs (1964); Laboratory Rabbits (1965)." Should these guidelines and standards be revised, animal care shall be in accordance with such revisions. If the nonclinical laboratory study so requires, deviation from the standards, e.g., use of restraining devices, shall be acceptable provided there is adequate documentation of the need for such deviation. Such documentation shall be retained as part of the records of the study.

(b) All newly received animals from outside sources shall be placed in quarantine until their health status has been evaluated. This evaluation shall be in accordance with acceptable veterinary medical practice.

(c) Animals either known or suspected of being diseased or of being carriers of a disease shall be isolated from animals that are in good health. Management of such diseased animals shall be carried out as recommended in HEW Publication No. (NIH) 74-23 and subsequent revisions.

(d) Animals shall be free of any naturally occurring disease or condition that might interfere with the purpose or conduct of the nonclinical laboratory study. If necessary, animals utilized as test systems in nonclinical laboratory studies may be treated for disease or signs of disease as long as 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.

(e) Rodents and other homeothermic species that are not required by the Animal Welfare Act of 1970 to be individually identified by a tatto or official tag shall be identified on receipt by a number that identifies the shipment or purchase order number. If such animals are used in laboratory procedures that require manipulations and observations over an extended period of time or in nonclinical laboratory studies that require the animals to be removed from and returned to their home cages for any reason (e.g., cage cleaning, treatment, etc.), they shall receive a unique permanently attached identification number, e.g., number tatto, neck chain, ear tag, ear punch, etc. The identification number shall appear on the outside of the animal housing unit and with all data recorded for the animal. The study director of the nonclinical laboratory study shall ensure that all animals are uniquely and permanently identified. At necropsy, the identification number of the animal shall accompany all specimens to minimize the possibility of mixup of tissue following necropsy.

(f) 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 substances 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 to avoid any intermixing of test animals.

(g) If it is necessary to transfer animals being used in laboratory studies to clean cages, proper placement of animals shall be checked by comparison of the identification on the animal and on the cage. There shall be a procedure for verification of transfer and proper placement of animals. Animals shall not be moved to a new location or placed under different environmental conditions during a nonclinical laboratory study without written permission from the study director, and such written permission shall be maintained as raw data.

(h) Animal cages, racks and accessory equipment shall be cleaned and sanitized at appropriate intervals as recommended in HEW Publication No. (NIH) 74-23 and subsequent revisions.

(i) Feed and water used for the animals shall be analyzed periodically to ensure that known interfering contaminants are not present at a level above predetermined specifications. Documentation of such analyses shall be maintained as raw data.

(j) The shelf life of each batch of animal feed shall be indicated by an expiration date. A batch of feed shall not be used after the expiration date.

(k) Bedding used in animal cages or pens shall not interfere with the purpose or conduct of the study and shall be changed at least once per week or as often as necessary to keep the animals dry and clean.

Subpart F—Test and Control Substances

§ 3e.105 Test and control substance characterization.

(a) The identity, strength, quality and purity of each batch of a test or control substance shall be determined and documented by the testing facility before the initiation of the study unless this determination with verifying documentation has not been done by the sponsor. The records of these analyses shall be retained by the testing facility or the sponsor. Other substances contained in the test and control substances including their amount and the method of assay shall be documented as well as the method of synthesis or origin of the test and control substances; such documentation shall be maintained as raw data.

(b) Where possible, the stability of each test or control substance shall be determined by the testing facility or by the sponsor before initiation of a nonclinical laboratory study unless the purpose of the study is to determine stability. If the stability of the test and control substances cannot be accurately deter-

mined before initiation of a study, written standard operating procedures shall be established and followed to provide for periodic re-analysis of each batch to reasonably assure that its identity, strength, quality, and purity conform to specifications.

(c) The test and control substances shall be derived from the smallest number of production batches consistent with their stability and necessary to fulfill the requirements of the study.

(d) Each container for a test or control substance shall be labeled by name or code number, expiration date, if any, and appropriate storage conditions necessary to maintain the identity, strength, quality, and purity of the test or control substance.

(e) For nonclinical laboratory studies in which the dosage regimen extends more than 4 weeks duration, an appropriately identified reserve sample selected at random from each batch of a test or control substance to be used in a study shall be taken, stored in an identical immediate container under conditions consistent with the labeling, and analyzed at the time the batch is depleted, at the termination of the study, or at the expiration date, whichever occurs first to assure that the identity, strength, quality, purity, and stability conform to established specifications. The date and results of the analysis shall be recorded and maintained.

(f) Batches returned from distribution shall be quarantined in a separate and identifiable area. The reason for the return and the source of the returned batch shall be documented. If a batch is to be redistributed, it shall be re-analyzed to determine conformance to established specifications for identity, strength, quality, and purity. If the batch meets all appropriate standards and specifications, it may be redistributed. If the results of the analysis do not indicate conformance with appropriate standards and specifications and such results would affect laboratory studies and/or implicate associated batches, an appropriate investigation shall be made, and corrective action shall be taken, and documented. All documentation regarding the distribution, redistribution, or corrective action pertaining to the test or control substance shall be retained as raw data.

§ 3e.107 Test and control substance handling.

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

(a) There is proper storage at all times to maintain the identity, strength, quality, purity, and stability.

(b) Distribution is made in a manner designed to preclude the possibility of contamination.

(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.

§ 3e.113 Mixtures of substances with carriers.

For each batch of the test or control substance that is mixed with a carrier (e.g., feed) before administration:

(a) Tests by appropriate analytical methods shall be conducted:

(1) To determine the adequacy of mixing to ensure uniformity and to determine the concentration of the test or control substance in the mixture. If the nonclinical study is to be performed as a blind study, enough individual samples of each batch of the mixture shall be returned to the sponsor for analysis. A periodic check of the uniformity of a test or control substance/carrier mix shall be made.

(2) To assess the stability characteristics of the test or control substance/carrier mix to establish storage conditions and an expiration date. The expiration date shall be clearly shown on the container for each batch of test or control substance/carrier mixture.

(3) To determine the release of the test or control substance from the carrier.

(b) A sample of each batch of test or control substance mixture shall be taken and retained for testing, if required. These samples shall be retained for the period of time as provided by § 3e.195.

§ 3e.115 Handling of carcinogenic substances.

The general safety principles set forth in the "National Cancer Institute Safety Standards for Research Involving Chemical Carcinogens," HEW Publication No. (NIH) 75-900, shall be followed in the handling, storage and disposal of known or suspected chemical carcinogens used as the test or control substance in a nonclinical laboratory study.

Subpart G—Protocol For and Conduct of A Nonclinical Laboratory Study

§ 3e.120 Protocol.

(a) Each nonclinical laboratory study shall have an approved written protocol that clearly indicates the objectives and all methods, including statistical methods, for the conduct of the study. The protocol shall contain but not be limited to the following information:

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

(2) Identification of the test and control substance by name and/or code number.

(3) The stability of the test and control substances in terms of the methods to be employed.

(4) The name of the study director, the names of other scientists or professional persons involved, and the names of laboratory assistants and animal care personnel.

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

(6) The proposed starting date and date of completion of the study.

(7) The proposed date for submission of the final study report to management or to the sponsor.

(8) The number, body weight range, sex, source of supply, species, strain and substrain, age of the test system, and justification for selection.

(9) The procedure for the unique identification, if needed, of the test system to be used in the study.

(10) A description of the method of randomization, if any, of the test system with justification for the selected method.

(11) A description and/or identification of the diet used in the study as well as solvents, emulsifiers and/or other material(s) used to solubilize or suspend the test or control substance before mixing with the carrier.

(12) The route of administration and the reason for its choice.

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

(14) Method by which the degree of absorption of the test and control substance will be determined if necessary to achieve the objectives of the study.

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

(16) The records to be maintained.

(17) Nonroutine procedures required to assure personnel health and safety.

(18) The date of approval of the protocol by the sponsor and the signature of the study director.

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

§ 3e.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 shall 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 as direct computer input, shall be recorded directly, promptly, and accurately in ink in bound books with prenumbered pages or on worksheets that shall be bound during or at the conclusion of the nonclinical laboratory study. All appropriate computer and machine output shall be bound during or at the conclusion of the study. All data entries shall be dated on the day of entry and signed or initialed by the person entering the data. Any change in entries for whatever reason (e.g., to correct an error or transposition)

shall be made in such a manner 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 data input. In computer driven data collection systems, the operator responsible for direct data input shall be identified at the time of data input. Any change in computer entries for whatever reason (e.g., to correct an error or transposition) shall be made in such a manner so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and the responsible individual shall be identified.

(f) All recorded data shall be reviewed, signed, and dated by a person, other than the person making the entry, responsible for the performance and evaluation of the activity from which the data were derived at appropriate intervals to assure adherence to procedures and to verify observations.

Subparts H–I—[Reserved]

Subpart J—Records and Reports

§ 3e.185 Reporting of nonclinical laboratory study results.

(a) A final report shall be prepared for each nonclinical laboratory study and shall accurately describe 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 to the original protocol.

(3) Raw data generated while conducting the study and any transformations, calculations, or operations performed on the data.

(4) Statistical methods employed for analyzing the data.

(5) The test and control substances identified by name and/or code number, strength, quality, and purity.

(6) Stability of the test and control substances under the conditions of administration.

(7) Methods used.

(8) Test system used. When animals are used, include the number in the study, sex, body weight range, source of supply, species, strain and substrain, age, and procedure used for the unique identification of test system.

(9) Dosage, dosage regimen, route of administration, and duration.

(10) Any unforeseen circumstances that may have affected the quality or integrity of the nonclinical laboratory study.

(11) The name of the study director.

(12) A summary of the data, an analysis of the data, and a statement of the conclusions drawn from the analysis.

(13) The reports of each of the individual scientists or other professionals involved in the study, e.g., pathologist, statistician. The dated signature of the study director and of all scientists and other professionals on their respective segments.

(14) The location where all raw data and the final report are to be stored.

(b) 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.

§ 3e.190 Storage and retrieval of records and data.

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

(b) There shall be an archive of adequate space and design to facilitate the orderly storage and expedient retrieval of all raw data, documentation and other information, protocols, specimens, and final reports. Specimens may be retained in other designated locations provided the archives have specific reference to those other locations and the specimens are not intermingled. 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 by this esection. If this material is not stored in an archive belonging to the research facility or sponsor, the name and address of the archive in which materials are stored shall be provided to the sponsor in the submission of the final report of the nonclinical laboratory study.

(c) All raw data and specimens, except as indicated in paragraph (b) of this section, shall be maintained in the archives after completion and reporting of the study. If documents or specimens are not physically present in the archives, appropriate and specific reference to those materials required to be maintained shall be located in the files of the archives. At the completion of the study, if the sponsor requests all materials that are required to be maintained in the archives of the testing facility to be transferred to the archives of the sponsor for storage, duplicates of the transmitted materials shall be maintained where the nature of the material permits.

(d) An individual shall be identified to be responsible for the archives.

(e) Only authorized personnel shall enter those secured areas designated as the archives for the purpose of controlling the storage and retrieval procedures established.

(f) All stored documents and specimens resulting from a nonclinical laboratory study shall be indexed by test substance, date of study, test system species, and nature of study.

(g) All raw data, documentation and other information, protocols, specimens, and final reports generated during and as a result of a nonclinical laboratory study required to be retained by this subpart shall be made available for inspection to authorized employees of the Food and Drug Administration.

§ 3e.195 Retention of records.

(a) Except as provided in paragraph (b) of this section, raw data, documentation and other information, protocols, final reports, and specimens pertaining to a nonclinical laboratory study and required to be made by this part shall be retained in the archives 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;

(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; or

(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.

(b) Wet specimens, samples of test or control substance carrier mixtures and specially prepared material (e.g., histochemical, electron microscopic, blood mounts, teratological preparations, and uteri from dominant lethal mutagenesis tests), which are relatively fragil and differ markedly in stability and quality during storage, shall be retained only as long as the quality of the preparation affords evaluation.

(c) The master schedule sheet, records of inspection or evaluation of a study and copies of status reports by the quality assurance unit, as required by § 3e.33(b), shall be maintained by the quality assurance unit as an easily accessible system of records for the period of time specified in paragraph (a) of this section.

(d) Curricula vitae and job descriptions required to be maintained by § 3e.29(b) may be retained along with all other testing facility employment records, provided the names of the persons involved in the conduct of a nonclinical laboratory study are included as part of the data required to be stored in the archives. The testing facility shall retain the last available curriculum vitae and job description for an employee after termination of employment for the length of time specified in paragraph (a) of this section.

(e) Records and reports of the maintenance and cleaning and of the calibration and inspection of equipment, as required by § 3e.63(b) and (c), shall be retained for the length of time specified in paragraph (a) of this section.

(f) If a facility conducting nonclinical research goes out of business, all raw data, documentation, and other material specified in this section shall be trans-

ferred to the archives of the sponsor of the study, or to an appropriate third party, e.g., a commercial storage facility or a university. The Food and Drug Administration shall be notified in writing of such a transfer.

Subpart K—Disqualification of Testing Facilities

§ 3e.200 Purpose.

The purpose of disqualification is to preclude the consideration of nonclinical laboratory studies in support of an application for a research or marketing permit from the Food and Drug Administration, which studies have been conducted by a testing facility that has failed to comply with the good laboratory practice regulations set forth in this part, until it becomes likely that the facility will abide by such regulations or that such violations will not recur. The sanction of disqualification is intended to be used in those situations where other 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. The determination that a nonclinical 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.

§ 3e.202 Grounds for disqualification.

The Commissioner may disqualify a testing facility upon finding one or more of the following:

(a) The testing facility utilized personnel in carrying out studies who were inadequate in number or insufficiently trained to ensure the accurate performance of activities specified by the protocol as provided by § 3e.29.

(b) The testing facility conducted nonclinical laboratory studies without designated study directors as provided for in § 3e.31.

(c) The testing facility conducted studies without a suitable mechanism for quality assurance as specified in § 3e.33.

(d) The testing facility conducted studies in physical facilities that were not of suitable size and construction or location and design to facilitate the proper conduct of nonclinical laboratory studies as set forth in Subpart C of this part, and these deficiencies may have adversely affected the health of the test systems or the quality and the integrity of the data generated in such studies. A facility shall be determined not suitable unless it provides separate and adequate areas for animal care; receipt, storage and distribution of supplies; receipt, storage and mixing of test and control substances; laboratory operations; specimen and data storage; administrative and personnel facilities and appropriate sanitation and waste disposal facilities.

(e) The testing facility conducted studies with equipment that was not of appropriate design or adequate capacity to facilitate operation, cleaning and maintenance; to maintain the health of the test system; to ensure accurate administration of the test or control substances; or to ensure accurate and precise measurement or assessment of data consistent with Subpart D of this part, and these deficiencies may have adversely affected the health of the test systems or the quality and the integrity of the data generated in such studies.

(f) The testing facility carried out studies in the absence of or without regard to written standard operating procedures as required in § 3e.81, and such deficiences may have adversely affected the health of the test system or the quality and integrity of the data generated in such studies.

(g) The animals used by the testing facility in the studies were not housed, fed, watered, handled or identified in accordance with § 3e.90, and such deficiencies may have adversely affected the health of the test system or the quality and integrity of that data generated in such studies.

(h) The testing facility did not have or did not follow procedures for determining and documenting the identity, strength, quality, and purity of test and control substances and uniformity and concentration of test and control substance/carrier mixtures were not determined and documented in conformance with Subpart F of this part, or did not take adequate precautions to ensure that test systems were not treated with test or control substances or test or control substance/carrier mixtures which had deteriorated or were contaminated, thus calling into question the validity of conclusions based on the data generated in studies conducted by that facility.

(i) The testing facility conducted studies that did not have protocols consistent with § 3e.120.

(j) The testing facility did not collect, review, sign and date all data in accordance with § 3e.130, and such deficiencies may have adversely affected the quality and integrity of data generated in studies conducted by that facility.

(k) The testing facility did not monitor test systems in conformity with the protocol and did not appropriately identify specimens as specified in § 3e.130, and such deficiencies may have adversely affected the quality and integrity of data generated in studies conducted by that facility.

(l) The testing facility, in preparing final study reports, did not accurately describe the objectives and procedures of the studies, the raw data generated while conducting the studies, the methods and test systems used, the test and control substances, and any unforeseen circumstances that may have affected the quality and integrity of the data as specified in § 3e.185, thus calling into question the validity of conclusions based on the data generated in studies conducted by that facility.

(m) Raw data, documentation, information, protocols, specimens and final reports generated during nonclinical laboratory studies have not been retained by the testing facility in an archive of adequate space and design as provided for in § 3e.190.

(n) Raw data, documentation, information, protocols, final reports and specimens generated during nonclinical laboratory studies have not been retained by the testing facility for the minimum period of time designated in § 3e.195.

(o) The testing facility refused to permit an inspection of the facilities used in studies, or an inspection and the copying of records and reports made during or on completion of the studies, by an authorized representative of the sponsor, if any, or by the Food and Drug Administration.

(p) The testing facility falsified any record or report, or deliberately withheld any report, required by the good laboratory practice regulations.

§ 3e.204 Notice of and opportunity for hearing on proposed disqualification.

(a) Whenever the Associate Commissioner for Compliance has information indicating that grounds exist under § 3e.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 Subpart F of Part 2 of this chapter.

§ 3e.206 Final order on disqualification.

(a) If, after the regulatory hearing or after the time for requesting a hearing expires without a request being made, the Commissioner determines, upon an evaluation of the administrative record of the disqualification proceedings, that the testing facility is responsible for any of the acts or omissions specified in the notice issued pursuant to § 3e.204(a) and has failed to furnish an adequate explanation for such acts or omissions, the Commissioner 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, after a regulatory hearing or after the time for requesting a hearing expires without a request being made, the Commissioner determines, upon an evaluation of the administrative record of the disqualification proceeding, that the testing facility is not responsible for any of the acts or omissions specified in the notice issued pursuant to § 3e.204(a), or is so responsible but has furnished an adequate explanation for such acts or omissions, 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 (with a copy of the order) the testing facility.

§ 3e.210 Actions upon disqualification.

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 those studies were 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 will be eliminated from consideration in support of the application; and such elimination may serve as new information justifying the termination or withdrawal of approval of the application.

§ 3e.213 Public disclosure of information upon disqualification.

(a) Upon issuance of a final order disqualifying a testing facility under § 3e.206 (a), the Commissioner may notify other Federal government departments or agencies that support, regulate, or review nonclinical laboratory studies possibly conducted by the disqualified testing facility. The Commissioner may also, where appropriate, notify State and local licensing authorities, that the facility has been disqualified by the Food and Drug Administration. 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 § 3e.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 that agency also consider whether or not it should accept nonclinical laboratory studies performed by the testing facility. If such notice is sent to a State or local licensing authority, the Food and Drug Administration will not advise or recommend 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 4 of this chapter.

§ 3e.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 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.

§ 3e.217 Suspension or termination of a testing facility by a sponsor.

The sponsor of any nonclinical laboratory study may at any time terminate or suspend a testing facility from further participation in any nonclinical laboratory study it is conducting for the sponsor, whether or not the Food and Drug Administration has commenced any action to disqualify the facility. The sponsor need not utilize either the grounds or the procedures for disqualification set forth in 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 Bureau of the Food and Drug Administration (whether approved or not), it shall notify that Bureau in writing within 5 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.

§ 3e.219 Reinstatement of a disqualified testing facility.

A testing facility that has been disqualified may be reinstated as an acceptable source of nonclinical laboratory studies to be submitted to the Food and Drug Administration if the Commissioner determines, upon an evaluation of the submission of the testing facility, that the facility can adequately assure that it will conduct future nonclinical laboratory studies in compliance with the good laboratory practice regulations set forth in this part and, if any studies are currently being conducted, that the quality and integrity of such studies have not been seriously compromised. A disqualified testing facility that wishes to be so reinstated shall present in writing to the Commissioner reasons why it believes it should be reinstated and a detailed description of the corrective actions it has taken or intends to take to assure that the acts or omissions which led to its disqualification will not recur. The Commissioner may condition reinstatement upon the testing facility being found in compliance with the good laboratory practice regulations upon an inspection. If a testing facility is reinstated, the Commissioner shall so notify the testing facility and all organizations and persons who were notified, under § 3e.213, of the disqualification of the testing facility has been reinstated is disclosable to the public under Part 4 of this chapter.

PART 8—COLOR ADDITIVES

2. In § 8.4 by adding new paragraph (g) to read as follows:

§ 8.4 Petitions proposing regulations for color additives.

* * * * *

(g) Petitions filed with the Commissioner under section 706(b) of the act shall include a statement that all nonclinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies have not been conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations shall be described in detail.

3. In § 8.8 by redesignating paragraph (b) as (b)(1) and by adding new paragraph (b)(2) to read as follows:

§ 8.8 Extension of time for studying petitions; substantive amendments; withdrawal of petitions without prejudice.

* * * * *

(b) *Substantive amendments.* (1) * * *

(2) Additional information or data submitted in support of filed petitions shall include a statement that all nonclinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies have not been conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations shall be described in detail.

* * * * *

SUBCHAPTER B—FOOD AND FOOD PRODUCTS

PART 121—FOOD ADDITIVES

4. In § 121.51 by adding new paragraph (m) to read as follows:

§ 121.51 Petitions proposing regulations for food additives.

(m) Petitions filed with the Commissioner under section 409(b) of the act shall include a statement that all nonclinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations as

set forth in Part 3e of this chapter, or, if such studies have not been conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations shall be described in detail.

5. In § 121.53 by designating the existing text as paragraph (a) and by adding new paragraph (b) to read as follows:

§ 121.53 Substantive amendments to petitions.

* * * * *

(b) Additional information and data submitted in support of filed petitions shall include a statement that all nonclinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or if such studies have not been conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations shall be described in detail.

SUBCHAPTER D—DRUGS FOR HUMAN USE

PART 312—NEW DRUGS FOR INVESTIGATIONAL USE

6. In § 312.1 by adding new item 16 to Form FD-1571 in paragraph (a)(2); in paragraph (d)(11) by adding the word "or" after the final semicolon; and by adding new paragraph (d)(12) to read as follows:

§ 312.1 Conditions for exemption of new drugs for investigational use.

(a) * * *

(2) * * *

Form FD-1571 * * *

16. A statement that all nonclinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations set forth in Part 3e of this chapter, or, if such studies have not been conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations shall be described in detail.

* * * * *

(d) * * *

(12) All nonclinical laboratory studies were not conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies were not conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations were not described in detail.

* * * * *

PART 314—NEW DRUG APPLICATIONS

7. In § 314.1 by adding new item 16 to Form FD-356H in paragraph (c)(2), by redesignating paragraph (f)(7) as (f)(8) and by adding a new paragraph (f)(7) to read as follows:

§ 314.1 Applications.

* * * * *

(c) * * *

(2) * * *

Form FD-356H—Rev. 1974 * * *

16. *Nonclinical laboratory studies.* A statement that all nonclinical laboratory studies contained in the application were conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies have not been conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations shall be described in detail.

* * * * *

(f) * * *

(7) A statement that all nonclinical laboratory studies contained in the application were conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies have not been conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations shall be described in detail.

* * * * *

8. In § 314.8 by adding new paragraph (l) to read as follows:

§ 314.8 Supplemental applications.

* * * * *

(l) A supplemental application that contains nonclinical laboratory studies shall include a statement by the applicant that all of these studies were conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies have not been conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations shall be described in detail.

9. In § 314.9 by adding paragraph (c) to read as follows:

§ 314.9 Insufficient information in application.

* * * * *

(c) The information contained in an application shall be considered insufficient to determine whether a drug is safe and effective for use unless the applicant includes a statement that all nonclinical laboratory studies contained in the application were conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies have not been conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations shall be described in detail.

10. In § 314.12 by adding new paragraph (c) to read as follows:

§ 314.12 Untrue statements in application.

* * * * *

(c) All nonclinical laboratory studies contained in the application were not conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies were not conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations were not described in detail.

11. In § 314.110 by adding new paragraph (a)(9) to read as follows:

§ 314.110 Reasons for refusing to file applications.

(a) * * *

(9) The applicant fails to include in the application a statement that all nonclinical laboratory studies contained in the application were conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies were not conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations were not described in detail.

* * * * *

12. In § 314.111 by striking the period at the end of paragraph (a)(7), adding in lieu thereof a semicolon and the word "or" and adding new paragraph (a)(8) to read as follows:

§ 314.111 Refusal to approve the application.

(a) * * *

(8) Any nonclinical laboratory study contained in the application was not conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such study was not conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations were not described in detail.

* * * * *

13. In § 314.115 by adding new paragraph (c)(5) to read as follows:

§ 314.115 Withdrawal of approval of an application.

* * * * *

(c) * * *

(5) That any nonclinical laboratory study contained in the application was not conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies have not been conducted in compliance with such practice, differences between the practices used in conducting the study and the good laboratory practice regulations shall be described in detail.

* * * * *

PART 430—ANTIBIOTIC DRUGS; GENERAL

14. In § 430.20 by adding new paragraph (h) to read as follows:

§ 430.20 Procedures for the issuance, amendment, or repeal of regulations.

* * * * *

(h) No regulation providing for the certification of an antibiotic drug for human use shall be issued or amended unless the nonclinical laboratory studies

on which the issuance or amendment of the regulation is based were conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies have not been conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations shall be described in detail.

PART 431—CERTIFICATION OF ANTIBIOTIC DRUGS

15. In § 431.17 by adding new paragraph (j) to read as follows:

§ 431.17 New antibiotic and antibiotic-containing products.

* * * * *

(j) A statement that all nonclinical laboratory studies contained in the request have been conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies have not been conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations shall be described in detail.

SUBCHAPTER E—ANIMAL DRUGS, FEEDS, AND RELATED PRODUCTS

PART 514—NEW ANIMAL DRUG APPLICATION

16. In § 514.1 by adding new paragraph (b)(12)(iii) to read as follows:

§ 514.1 Applications.

* * * * *

(b) * * *

(12) * * *

(iii) A statement that all nonclinical laboratory studies contained in the application were conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies have not been conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations shall be described in detail.

* * * * *

17. In § 514.8 by adding new paragraph (l) to read as follows:

§ 514.8 Supplemental new animal drug applications.

* * * * *

(l) A supplemental application that contains nonclinical laboratory studies shall include a statement by the applicant that all of the studies were conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies have not been conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations shall be described in detail.

18. In § 514.15 by adding new paragraph (c) to read as follows:

§ 514.15 Untrue statements in applications.

* * * * *

(c) All nonclinical laboratory studies contained in the application were not conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies were not conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations were not described in detail.

19. In § 514.110 by adding new paragraph (b)(8) to read as follows:

§ 514.110 Reasons for refusing to file applications.

* * * * *

(b) * * *

(8) It fails to include a statement that all nonclinical laboratory studies contained in the application were conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such studies were not conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations were not described in detail.

* * * * *

20. In § 514.111 by adding new paragraph (a)(10) to read as follows:

§ 514.111 Refusal to approve an application.

(a) * * *

(10) Any nonclinical laboratory study contained in the application was not conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such study was not conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations were not described in detail.

* * * * *

21. In § 514.115 by adding new paragraph (b)(4) to read as follows:

§ 514.115 Withdrawal of approval of applications.

* * * * *

(b) * * *

(4) That any nonclinical laboratory study contained in the application was not conducted in compliance with the good laboratory practice regulations as set forth in Part 3e of this chapter, or, if such study was not conducted in compliance with such regulations, differences between the practices used in conducting the study and the good laboratory practice regulations were not described in detail.

* * * * *

Interested persons may, on or before March 21, 1977, submit to the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, written comments (preferably in quintuplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: November 12, 1976.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

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