federal register

Monday
October 29, 1984

Part II

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 58

Good Laboratory Practice Regulations; Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 58

[Docket No. 83N-0142]

Good Laboratory Practice Regulations

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to revise the regulations that specify good laboratory practice for nonclinical laboratory studies. The revisions are based on an agency determination that several provisions of the regulations should be clarified, amended, or deleted to reduce regulatory burdens on testing facilities. Major changes are proposed in the provisions on quality assurance, protocol preparation, test and control article characterization, and retention of specimens and samples. The changes proposed will not compromise the regulations' objective, which is to ensure the quality and integrity of the safety data submitted in support of the approval of regulated products. The action is intended to reduce the burden of compliance with the regulations.

DATE: Comments by December 28, 1984.

ADDRESS: Written comments may be sent to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Paul D. Lepore, Bioresearch Monitoring Staff (HFC-30), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-2390.

SUPPLEMENTARY INFORMATION: FDA discussed the need for regulations on good laboratory practice for nonclinical laboratory studies (GLP's) in the preamble to the proposed regulations (41 FR 51206; November 19, 1976). Agency inspections of toxicology laboratories had revealed problems in the conduct of some nonclinical laboratory studies so severe that in many instances the studies could not be relied on for regulatory decisionmaking.

The importance of proper safety testing to the product approval process prompted the agency to begin its Toxicology Laboratory Monitoring Program. To ensure the quality and integrity of the safety data submitted to it in support of the approval of any application for a research or marketing permit, FDA issued regulations specifying standards for adequate safety testing, prepared an inventory of domestic and foreign toxicology laboratories engaged in safety testing, conducted training sessions for agency investigators to develop proficiency in evaluating testing facilities, and instituted a compliance program that provided for periodic inspections of the testing facilities.

These steps have been completed. In the **Federal Register** of December 22, 1978 (43 FR 60013), FDA issued final GLP regulations. The regulations, which were codified as 21 CFR Part 58, became effective on June 20, 1979. In the **Federal Register** of April 11, 1980 (45 FR 24865), FDA amended § 58.113(b) to delete the requirement that reserve samples of test and control article-carrier mixtures be retained.

FDA maintains an inventory of testing facilities that have been inspected for compliance with the GLP regulations. A recent listing contains entries for 475 laboratories, including 425 domestic and 49 foreign testing facilities. Affiliations for the listed domestic facilities are as follows: 165 sponsor laboratories, 174 contractor laboratories, 72 university laboratories, and 14 government laboratories. The inventory listing is updated quarterly to accommodate laboratories that have either ceased or begun work on products regulated by the agency.

FDA has conducted 17 training courses at its National Center for Toxicological Research in Jefferson, AR, to provide training in good laboratory practice and the associated laboratory inspection techniques as well as "hands-on" exercises in toxicology experimentation.

Finally, in 1976 the agency began an inspection program to assess laboratory compliance with the GLP regulations. Program features include biennial surveillance inspections to assess compliance with the procedural provisions of the GLP regulations and data audit inspections to assess the accuracy of the information contained in final study reports as required by § 58.185. By the end of the 1982 fiscal year, the agency had evaluated the reports of 710 laboratory inspections made under the Toxicology Laboratory Monitoring Program.

Background of This Proposal

Several circumstances have caused FDA to reevaluate the GLP regulations and to propose changes that allow laboratories greater flexibility in conducting nonclinical laboratory studies without compromising public protection. These circumstances include the satisfactory levels of laboratory compliance observed during agency inspections; the information received from regulated laboratories identifying particularly burdensome provisions of the GLP's and the principles of regulatory reform.

FDA's laboratory inspection experience has revealed that affected laboratories are in compliance with the GLP regulations and that the regulations can be streamlined without undermining the program. At the time of the November 19, 1976 proposal, the agency did not have complete information on the severity and pervasiveness of testing deficiencies. The available evidence showed, in a fraction of the testing industry, serious problems that required prompt and definitive correction. The agency now believes that the problems noted in the inspections made prior to 1976 were the exception rather than the rule. Seventy-two percent of the inspection reports evaluated by the agency since 1976 showed few or no substantial deviations from the GLP regulations. Four percent of the inspection reports evaluated since that time showed major deviations from the GLP regulations that required corrective action to be taken by a laboratory within a specified time frame, and 23 percent of the reports contained evidence of minor-to-significant deviations from the regulations that could be voluntarily corrected by the laboratory. These facts show that the Toxicology Laboratory Monitoring Program has met its objectives and that the regulated laboratories have made excellent progress in achieving full compliance with the GLP regulations. Because of the good record of industry compliance, FDA believes that the regulations can be simplified with no compromise to study quality.

The agency has received many questions and comments on the GLP regulations, and these communications are filed under Docket No. 76-0400 in the Dockets Management Branch (address above). Several comments stated that some provisions of the GLP regulations do not appear to make a significant contribution to the quality and integrity of the safety data derived from nonclinical laboratory studies. The agency has considered these comments in preparing this proposal.

In the **Federal Register** of the July 14, 1981 (46 FR 36333), the agency issued its plan for reviewing its rules to minimize regulatory burdens while maintaining an acceptable level of consumer protection. FDA received six comments suggesting that the GLP regulations be targeted for early review.

In view of the above, FDA established a GLP Review Task Team composed of members drawn from all agency units

involved in the Toxicology Laboratory Monitoring Program. The task team was asked to conduct a thorough review of the GLP regulations to identify provisions that could be amended or deleted to reduce regulatory burdens on the testing facilities without compromising study quality. Following its review, the task team prepared an issue paper that recommended that FDA amend 36 provisions of the regulations and that the agency prepare an appropriate **Federal Register** proposal. The issue paper has been placed on file in the Dockets Management Branch (address above) and is available for review between 9 a.m. and 4 p.m., Monday through Friday.

Public Comment

FDA invites comments on all aspects of this proposal. In addition, the agency invites interested persons to submit comments, data, and information on the need to revise any other provisions of 21 CFR Part 58. Comments supported by data, cost estimates, or other factual information about the impact of the regulations on various industries, product groups, and laboratories of different sizes would be especially useful. Any comments previously submitted need not be resubmitted because they are included in the docket file for this proposal. All comments received will be considered in preparing any final rule based on this proposal.

The Proposed Changes

Following is a discussion of the proposed changes in the GLP regulations.

1. Section 58.1 *Scope.* FDA proposes to make editorial changes in § 58.1 to clarify references in the GLP regulations to other parts of Title 21 of the Code of Federal Regulations. Elsewhere in Part 58, FDA also proposes to make appropriate changes to reflect new § 58.1(b).

2. Section 58.3 *Definitions:*

a. In § 58.3(c), FDA proposes to amend the definition of "control article" to exclude feed and water administered to the control groups of a test system. Section 58.3(c) currently defines control article as "* * * any other article other than a test article that is administered to the test system * * * for the purpose of establishing a basis for comparison with the test article." Because the control group of a test system provides the basis for comparison under the current definition, any article administered to the control group is a control article. For example, the following articles are ontrol articles under the existing egulations:

(1) The feed and water given to the control groups of animals in oral studies in which the test article is administered via the feed, via the drinking water, or by gavage or injection.

(2) The water used to prepare the test article mixtures in a gavage or injection study in animals when the water is administered to the control groups or used as an inoculum for the control plates/tubes (as is typical in mutagenicity studies).

Because the current definition of control article includes the substances in the situations described above, a variety of GLP provisions become operative. The feed and water must be characterized (§ 58.105(a)), tested for stability (§ 58.105(b)), stored appropriately (§ 58.105(c)), and sampled to provide reserve samples (§ 58.105(d)). In addition, strict accountability records must be maintained (§ 58.107). Some of these steps are not essential to study quality, while other are dealt with elsewhere in the GLP regulations. Therefore, the term control article should be reserved for those discrete substances/articles and vehicles administered to groups of the test system for providing a basis of comparision (commonly referred to as positive controls).

FDA believes that the proposed change will reduce recordkeeping for a large number of nonclinical laboratory studies. Reserve samples of feed and water administered to the control groups of the test system would not have to be retained; characterization and stability assessment would not have to be done; and strict accountability records of receipt, use, and disposition would not need to be generated and maintained for such articles.

b. In § 58.3(d), FDA proposes to modify the definition of "nonclinical laboratory study" to allow the conduct of several experiments using the same test article under a single, comprehensive protocol. For example, a battery of several studies of one test article conduct in several animal species to determine the safety of the test article could be conducted under one protocol. Similarly, where several test articles are to be studied concurrently using a single common procedure, e.g., mutagenicity testing, a single protocol could be developed and followed.

FDA believes that this approach will reduce the amount of required paperwork with no loss in the quality or accuracy of test article data developed by a testing facility.

c. In § 58.3(e), FDA proposes to delete from the definitions of "Application for research or marketing permit" those categories of data and information submitted as part of the procedures for classifying a prescription drug (current § 58.3(e)(8)) and a drug for animal use (current § 58.3(e)(12)) as generally recognized as safe and effective and not misbranded. The agency does not currently have or intend to have such procedures.

d. In new § 58.3(e)(8), FDA proposes to add a new category pertaining to data and information submitted as part of the procedures under 21 CFR Parts 109 and 509 for establishing a tolerance for unavoidable contaminants in human or animal food and food-packaging materials. The final regulations establishing Parts 109 and 509 were issued after FDA issued its GLP proposal. Therefore, the final GLP regulations did not include these procedures within the definitions of "Application for research or marketing permit." The agency proposes to correct the definition at this time.

e. In § 58.3(e) (17) and (18), FDA proposes to amend the definitions of "Application for research and marketing permit" for medical devices to refer to the appropriate medical device regulations that have been issued since the final GLP regulations were published.

3. Section 58.31 *Testing facility management.* FDA proposes to delete from § 58.31(b) the requirement that the replacement of a study director be documented as "raw data."

Section 58.31(b) requires that the replacement of a study director be documented and that the documentation be retained as a raw data record. The documentation required here is not necessary because a change of study director is recorded elsewhere in the laboratory's records (personnel files, Master Schedule Sheet).

4. Section 58.33 *Study director.* In § 58.33(b), FDA proposes to delete the phrase "and verified." Testing facilities have misconstrued the provision in § 58.33(b) that "All experimental data * * * are accurately recorded and verified" to mean that the study director is required personally to witness each data observation—an activity that is neither feasible nor required to ensure data accuracy.

The study director needs to assure that data collection procedures include the accurate recording of unforeseen circumstances. This responsibility is reflected in the revised provision.

5. Section 58.35 *Quality assurance unit:*

a. In § 58.35(a), FDA proposes to substitute "which" for the current phrase "composed of one or more individuals who" to make clear the

personnel who can perform quality assurance duties.

As written, the phrase has been misunderstood to mean that the Quality Assurance Unit (QAU) is to be composed of individuals whose only duties are quality assurance functions (in other words, the QAU is seen as a fixed, permanently staffed unit). In fact, the agency intended that § 58.35(a) only require that quality assurance activities be separated from study direction and conduct activities, i.e., a person who works on one study can perform quality assurance monitoring on any study in which he or she is not otherwise involved.

b. FDA proposes to delete the existing requirement in § 58.35(b)(1) that the status of the final report be a distinct entry on the Master Schedule Sheet. The agency believes this requirement is redundant because the other information required by § 58.35(b)(1), e.g., date study began and current status, provides the necessary information on final report status.

c. In § 58.35(b)(3), FDA proposes to modify the requirement that the QAU inspect each phase of a study at periodic intervals according to rigid schedules.

A review of the data collected during agency inspections of nonclinical testing facilities shows that this provision, as now worded, has been difficult to interpret and implement and that the requirements have been more rigid than is necessary. Indeed, on April 2, 1981, the Pharmaceutical Manufacturers Association (PMA) petitioned the agency to clarify the QAU inspection requirement described in § 58.35(b)(3). The petition sought relief from the requirement of frequent QAU inspection of routine repetitive study phases. The agency reviewed the facts of the PMA petition and concluded that testing facilities may have been overly strict in interpreting § 58.35(b)(3). Accordingly, the agency issued an advisory opinion letter (dated November 30, 1981, Docket No. 81P-0127) that declined to amend the GLP's because the relief sought was already available under the existing GLP provisions. In reviewing the PMA petition, the agency concluded that an inspection of each study phase was neither required nor necessary to ensure study quality. The agency therefore advised PMA that the inspection schedule should take into account the need for inspection of each study on a schedule adequate to assure the validity of the study being monitored. The changes proposed now are intended to clarify the pertinent provisions of § 58.35(b)(3) consistent with the advice given in the November 30, 1981 letter. The proposed changes will give the QAU reasonable leeway to identify critical study phases and to set reasonable inspection schedules so that studies can be monitored appropriately. In addition, the proposed changes will allow the QAU a measure of judgment in conducting its duties and will allow adjustment of monitoring activities to meet anticipated problems.

d. Current § 58.35(b) (4) and (7) contains information collection requirements that are subject to the Paperwork Reduction Act of 1980. FDA proposes to delete § 58.35(b)(4) which currently requires that the QAU submit periodic status reports to management and to the study director (remaining § 58.35(b) (5), (6), and (7) would be renumbered as (b) (4), (5), and (6) respectively). FDA also proposes to amend renumbered § 58.35(b)(6) to require that the QAU include, with the final report, a statement that identifies the phases of the study that were inspected and the frequency of inspection.

The agency believes that the periodic submission of routine QAU inspection reports to management and to the study director is not essential to assuring study quality, and that it will be sufficient to document such inspections. Proposed § 58.35(b)(6) provides that any final study report identify the phases inspected and cite the number of inspections conducted. Of primary importance is the requirement of § 58.35(b)(3) that any problems that are likely to affect study integrity be indentified and reported immediately so that prompt corrective action can be taken by the testing facility.

e. FDA proposes to delete § 58.35(e) which currently requires that all QAU records be kept in one location at testing facilities.

Section 58.190(b) requires that records be kept in such a way that they can be retrieved expediently. The agency believes that a single location for QAU records is not necessary so long as the records can be retrieved in accord with § 58.190(b) and so long as those records required to be made available to FDA investigators are easily accessible.

6. Section 58.41 *General.* FDA proposes to delete "location" as a consideration for a testing facility as specified in § 58.41.

The agency believes that "location" is not relevant to proper study conduct. Poorly located facilities may function adequately if the size, design, and construction are suitable to overcome the poor location.

7. Section 58.43 *Animal care facilities:*

a. In § 58.43(c), FDA proposes to modify the requirement that separate areas for the diagnosis, treatment, and control of laboratory animal diseases be provided.

The existing provision has been interpreted to require devoted laboratory areas for diagnosis, treatment, and control in every case, but a laboratory may elect to destroy diseased animals thereby obviating the need for the specified devoted areas. The agency believes that it is not cost-effective to require devoted space that will not be used and proposes to revise § 58.43(c) to require that such separate areas be provided "as appropriate."

b. In § 58.43, FDA proposes to delete paragraph (e) which currently requires that animal facilities be designed, constructed, and located so as to minimize disturbances that interfere with a study.

The agency believes that § 58.41, which requires that facilities be adequate for proper study conduct, is sufficient to cover this point.

8. Section 58.45 *Animal supply facilities.* FDA proposes to revise the specific refrigeration requirement for perishable supplies or feed to read, "Perishable supplies shall be preserved by appropriate means."

The existing provision requires refrigeration as the uniform method of choice for preserving perishable supplies and feed. In fact, a variety of storage procedures, e.g., dessication, room temperature-low humidity, constant temperature-constant humidity, can and need to be used depending on the stability characteristics of the perishable materials. The change is intended to permit the selection of the most appropriate storage method.

9. Section 58.47 *Facilities for handling test and control articles.* FDA proposes to make editorial changes in this section. The changes clarify the requirement that separate areas be provided for receipt, mixing, and storage of test and control articles and their mixtures as necessary to prevent contamination or mixups.

10. Section 58.49 *Laboratory operation areas.* FDA proposes to revise this section to delete paragraph (b). Paragraphs (a) and (b) each currently describe particular activities to illustrate the need for separate space. The activities are not all inclusive and the examples are not necessary for clarity. The revised section simply requires that separate space should exist, as needed, for the performance of both routine and specialized procedures.

11. Section 58.53 *Administrative and personnel facilities.* FDA proposes to delete § 58.53. The agency believes that the requirements for administrative and

personnel facilities are not a necessary part of these regulations.

12. Section 58.61 *Equipment design.* FDA proposes to delete the qualifying terms "automatic, mechanical, or electronic" from § 58.61. The proposed changes are editorial.

13. Section 58.63 *Maintenance and calibration of equipment.* FDA proposes to amend § 58.63(b) to allow that written standard operating procedures (SOP) for equipment need specify remedial action in the event of equipment failure or malfunction only when remedial action is appropriate to the specific piece of equipment. The change would allow SOP's for equipment to provide that laboratories may elect to discard rather than repair faulty equipment.

14. Section 58.81 *Standard operating procedures.* FDA proposes to delete the examples of SOP's listed in § 58.81(c). This is also an editorial change.

15. Section 58.90 *Animal care:*

a. In § 58.90(b), FDA proposes to modify the requirement that newly received animals be quarantined to require, instead, that newly received animals be isolated and that the health status of all newly received animals be evaluated in accordance with acceptable veterinary medical practice.

The term "quarantine" refers to a rigid set of procedures applied to animals prior to their use in any study. Such procedures include a mandatory holding period, a specified list of diagnostic procedures, and the use of specialized facilities and animal care practices. The agency believes that isolation and a health status evaluation conducted to prevent the entry of unhealthy animals into a study rather than rigid quarantine procedures will be sufficient to satisfy the intent of the regulations. The evaluation would be required to be in accord with acceptable veterinary practice and should be attuned to the specific study.

The proposed change would permit laboratories to develop specific isolation and health status evaluation procedures in concert with the age, species, and class of animals and with the type of study to be done.

b. In § 58.90(c), FDA proposes to require isolation of diseased animals only when necessary rather than in every case as now required in § 58.90(c).

Because the existing provision requires that animals contracting any disease that might interfere with the purpose of the study during a study be isolated, it also requires that the laboratory shall have a devoted area equipped to provide adequate isolation of diseased animals. The proposed change will permit several options for handling the diseased animals—they can be left in the experiment (if such action would not adversely affect the integrity of the study); they can be destroyed (in which case no isolation facilities would be required); or they may be isolated, treated, and returned to the study. These options will permit increased flexibility of laboratory operation.

16. Section 57.105 *Test and control article characterization:*

a. In § 58.105(a), FDA proposes to delete the phrase "before the initiation of the study." The change would permit test and control article characterization after completion of the study.

The course of new product development is a sequential process based on a logical series of experimental findings. For example, a potential new product is synthesized (or derived from fermentation or isolated from natural sources) and subjected to a battery of tests for pharmacologic/functional activity. If the product shows promising activity, it is then subjected to the sequence of tests necessary to establish the toxicologic profile, e.g., 30-day, subacute, chronic toxicology studies. If unusual toxicity is observed in any of the tests in the toxicologic profile, further product testing ends. Indeed, many products fail to reach the marketplace because unusual toxicity is observed in the early toxicology studies. Section 58.105(a) currently requires that, prior to initiating the first safety test in the toxicology profile, product sponsors shall fully characterize the test article. Such characterization is expensive, and it is currently being conducted on many products that are destined to fall by the wayside. The agency has been informed that the cost of test article characterization greatly exceeds the cost of conducting the initial safety studies that are done. Similar facts apply to control articles used in nonclinical laboratory studies. Characterization of such articles is expensive and need not be done unless the test article to which the control article is compared shows reasonable promise of reaching the marketplace.

The proposed change will permit the conduct of the characterization studies after the results of the initial toxicology studies are available. If these studies show unusual toxicity, and the product is dropped from further consideration, no characterization need be done. If the studies show promise, the product would need to be characterized in accord with the regulation. The proposed change is intended to reduce the regulatory burden by eliminating the need to characterize products not destined for marketing. The proposed change does not relieve the sponsor of submitting to the agency, in an application for a research or marketing permit, the complete characterizations as described in § 58.105(a).

b. In § 58.105(b), FDA corrects the typographical error in the first sentence by changing the word "or" to read "of."

17. Section 58.113 *Mixtures of articles with carriers.* FDA proposes to change § 58.113(a)(2) to clarify that stability data need be collected only as necessary to accommodate the conditions of use of a test article mixture. For example, test article mixtures that are prepared and dispensed on the same day require stability data to support only 1 day of use. Similarly, test article-feed mixtures that are to be used within 2 weeks require only 2 weeks of stability data. The agency has been informed that § 58.113(a)(2) has been interpreted to require the conduct of a formal stability trial sufficient to show long-term stability of the mixtures; such trials frequently take longer than the nonclinical laboratory study in which the mixture will be used. The revision makes it clear that although full long-term stability studies are not required, the term of the stability study may not be shorter than the actual term of use.

18. Section 58.120 *Protocol:*

a. Current § 58.120(a) contains information collection requirements that are subject to the Paperwork Reduction Act of 1980. In § 58.120(a), FDA proposes to replace the qualifying phrase "but shall not necessarily be limited to" with the words "as applicable." Section 58.120(a) now requires that each protocol contain entries for each of 16 listed items. FDA proposes to revise § 581.20(a) because some of the items are not necessary for all studies. For example, § 58.120(a)(9) requires a description of the diet used in a study as well as solvents, emulsifiers, and/or other materials used to dissolve or suspend the test articles before mixing with the carrier. Clearly, this section does not apply to radiation-emitting products. Likewise, dosage level (§ 58.120(a)(11)) is not necessary for all test articles, e.g., implantable medical devices.

The revision will permit the laboratory to identify in the protocol information that is applicable to the articles being tested, thereby eliminating unneeded protocol entries.

b. FDA proposes to delete § 58.120(a)(4), which currently requires that the protocol contain the proposed starting and completion dates for the study.

Section 58.120(b) requires the study director to issue a formal protocol

amendment whenever there is a change in the proposed time frame for the study. Because the actual scheduling of a study is a management prerogative, there is no need to have this information in the protocol. The elimination of the provision will simplify the protocol and eliminate the need for formal protocol amendments whenever study time frames change.

c. FDA also proposes to delete § 58.120(a)(5) which requires that the selection of the test system be justified in the protocol.

The existing provision confuses the purpose of the protocol. FDA believes that the protocol constitutes a plan of work rather than justification for use of a specific test system. Although use of a proper test system is essential to achieving the study's objectives, it is a scientific consideration that need not be stated in the protocol.

d. FDA also proposes to delete § 58.120(a)(10) which requires that route of administration and reason for its choice be listed in the protocol.

Section 58.120(a)(11), renumbered as proposed § 58.120(a)(8), requires that the method and frequency of administering the test or control article be identified in the protocol. Because this provision encompasses route of administration, the agency believes that § 58.120(a)(10) is redundant. Further, the agency believes that the reason for choosing a particular route of administration of the test or control article is a scientific study consideration that need not be stated in the protocol. It is, of course, a matter that needs to be discussed in the final report. For these reasons, FDA believes that § 58.120(a)(10) is unnecessary and should be removed from the GLP regulations.

e. Finally, FDA proposes to delete § 58.120(a)(12) which requires that the method by which test and control article absorption is determined be included because the information is not necessary in the protocol.

19. Section 58.130 *Conduct of a nonclinical laboratory study:*

a. FDA proposes to revise § 58.130(d) to provide that the records of gross findings observed at necropsy should be made available to the pathologist.

The agency believes that the need to provide necropsy findings to the pathologist is a scientific study consideration that should be assessed by management and the study director. Certain studies may require such findings to be kept from the pathologist; other studies may require informing the pathologist to achieve the study objectives. In either event, a determination should be based on the facts of a study. The proposed change provides that the pathologist may be informed of the necropsy findings whenever such procedure comports with the study objectives.

b. FDA proposes to revise § 58.130(e), renumbered as proposed § 58.130(d), to recognize that data may be generated by automated systems other than "computer driven." The terms "computer" or "computer driven" do not adequately provide for new technologies in data collection and storage methods. The agency believes that the proposed term "automated data collection" more accurately reflects current terminology in use by testing facilities.

20. Section 58.190 *Storage and retrieval of records and data:*

a. Current § 58.190(a) contains information collection requirements that are subject to the Paperwork Reduction Act of 1980. In § 58.190(a), FDA proposes to amend the provisions to allow specimens obtained from mutagenicity tests as well as wet specimens of blood, urine, feces, and biological fluids from any nonclinical laboratory study to be discarded after evaluation.

Section 58.190(a) currently requires a laboratory to retain in storage all specimens for the term specified in the regulations or for a term during which the quality of the specimens affords evaluation. This means that a laboratory is required to retain a specimen as long as the retention term of the most stable constituent. FDA proposes to exclude from the requirement specimens that are relatively fragile or contribute only in a minor way to safety evaluation. FDA believes that the current provision is burdensome and that allowing the listed specimens to be discarded will have no effect on study quality.

b. FDA proposes to revise § 58.190(e) to delete the provision that specifies index terms be used to catalogue archival contents.

The existing provision is too restrictive. The agency is not concerned about which index terms are used so long as the archival information can be retrieved expediently and proposed § 58.190(e) would so provide.

21. Section 58.195 *Retention of records:*

a. In § 58.195(c), FDA proposes to delete the examples. The examples do not clarify what materials from a study are to be retained.

b. FDA proposes to add new § 58.195(g) to clarify the fact that testing facilities may retain records either as original records or as true copies such as microfilm, microfiche, photocopies, or other accurate reproductions of the original records as contemplated in the definition of "raw data" set out in § 58.3(k). This provision merely parallels similar provisions for record retention contained in other regulations, e.g., 21 CFR Parts 211 and 820. The existing § 58.195(g) is redesignated as § 58.195(h).

Economic Assessment

FDA has examined the economic consequences of the proposed changes in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96–354). The agency tentatively concludes that the revisions would have favorable economic impacts on product sponsors and testing facilities without compromising the quality and integrity of the safety data submitted to support product approval. Although agency estimates are imprecise, cost savings are expected to accrue from changes affecting test and control articles ($5.6 million per year), from revisions in protocol requirements ($6.2 million per year), and from changes in quality assurance procedures ($12.9 million per year).

Accordingly, the agency concludes that the proposed revisions do not constitute a major rule as defined in Executive Order 12291 and that no regulatory flexibility analysis is required. The agency also certifies that the revisions will not have a significant impact on a substantial number of small entities. The vast majority of laboratories are not considered small businesses under the Regulatory Flexibility Act and the agency estimates that the impact on those laboratories that are small is not significant because toxicology testing is but a small portion of the work performed by many laboratories. The savings described above will accrue to all sponsors and testing facilities regardless of size. The agency's threshold assessment supporting these conclusions is on file with the Docket Management Branch (address above) and is available for public review between 9 a.m. and 4 p.m., Monday through Friday.

Environmental Impact

The agency has determined pursuant to 21 CFR 25.24(d)(14) (proposed December 11, 1979; 44 FR 71742) that this proposed action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Paperwork Reduction Act of 1980

Sections 58.35 (a), (b)(1), (3), and (6), 58.63(b), 58.90(c), 58.105(a), 58.120(a),

58.130(d), and 58.190 (a) and (e) of this proposed rule contain collection of information requirements. FDA has submitted a copy of this proposed rule to the Office of Management and Budget (OMB) for its review of these collection of information requirements under section 3504(h) of the Paperwork Reduction Act of 1980 as interpreted by OMB in 5 CFR Part 1320 (see 48 FR 13666; March 31, 1983). Other organizations and individuals desiring to submit comments on the collection of information requirements should direct them to the Dockets Management Branch (address above) and to the Office of Information and Regulatory Affairs, OMB, Rm. 3208, New Executive Office Bldg., Washington, DC 20503, Attn: Bruce Artim.

List of Subjects in 21 CFR Part 58

Laboratories.

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. 1785–1988 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, 263b–263n)) and under 21 CFR 5.11, it is proposed that Part 58 be amended as follows:

PART 58—GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES

1. In § 58.1 by designating the existing text as paragraph (a) and adding new paragraph (b), to read as follows:

§ 58.1 Scope.

* * * * *

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

2. In § 58.3 by revising paragraphs (c), (d), and (e)(8); removing paragraph (e)(12); by removing the phrase "of this chapter" in paragraph (e) (1) through (7), (9) through (11), (13), (14), (19), (21), and (22); by replacing "in section 513 of the act" with "in Part 860" in paragraph (e)(17); and by replacing "section 514 of the act" with "in Part 861" in paragraph (e)(18), as follows:

§ 58.3 Definitions.

* * * * *

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

(d) "Nonclinical laboratory study" means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.

(e) * * *

* * * * *

(8) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in Parts 109 and 509.

* * * * *

(12) [Reserved]

* * * * *

3. In § 58.31 by revising paragraph (b), to read as follows:

§ 58.31 Testing facility management.

* * * * *

(b) Replace the study director promptly if it becomes necessary to do so during the conduct of a study.

* * * * *

4. In § 58.33 by revising paragraph (b), to read as follows:

§ 58.33 Study director.

* * * * *

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

* * * * *

5. In § 58.35 by revising paragraphs (a) and (b) (1) and (3); removing paragraphs (b) (4) and (e); redesignating (b) (5), (6), and (7) as (b) (4), (5), and (6), respectively; and revising paragraph (b)(6), as redesignated, to read as follows:

§ 58.35 Quality assurance unit.

(a) A testing facility shall have a quality assurance unit which shall be responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the regulations in this part. For any given study the quality assurance unit shall be entirely separate from and independent of the personnel engaged in the direction and conduct of that sutdy.

(b) The quality assurance unit shall:

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

* * * * *

(3) Inspect each nonclinical laboratory study at intervals adequate to ensure the integrity of the study and maintain written and properly signed records of each periodic inspection showing the date of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for reinspection. Any problems found during the course of an inspection which are likely to affect study integrity shall be brought to the attention of the study director and management immediately.

* * * * *

(6) Prepare and sign a statement to be included with the final study report which shall identify the phases inspected and shall cite the number of inspections conducted.

* * * * *

6. By revising § 58.41, to read as follows:

§ 58.41 General.

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

7. In § 58.43 by revising the first sentence of paragraph (c) and by removing paragraph (e), as follows:

§ 58.43 Animal care facilities.

* * * * *

(c) Separate areas shall be provided, as appropriate, for the diagnosis, treatment, and control of laboratory animal diseases. * * *

* * * * *

8. In § 58.45 by revising the last sentence to read as follows:

§ 58.45 Animal supply facilities.

* * * Perishable supplies shall be preserved by appropriate means.

9. By revising § 58.47, to read as follows:

§ 58.47 Facilities for handling test and control articles.

As necessary to prevent contamination or mixups, there shall be separate areas for receipt and storage of test and control articles and their mixtures, and for mixing of test and control articles with carriers.

10. By revising § 58.49, to read as follows:

§ 58.49 Laboratory operation areas.

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

§ 58.53 [Removed]

11. By removing § 58.53 *Administrative and personnel facilities.*

12. By revising § 58.61, to read as follows:

§ 58.61 Equipment design.

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

13. In § 58.63(b) by revising the first sentence, to read as follows:

§ 58.63 Maintenance and calibration of equipment.

* * * * *

(b) The written standard operating procedures required under § 58.81(b)(11) shall set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration and/or standardization of equipment, and shall specify, when appropriate, remedial action to be taken in the event of failure or malfunction of equipment. * * *

* * * * *

14. In § 58.81(c) by revising the first sentence, to read as follows:

§ 58.81 Standard operating procedures.

* * * * *

(c) Each laboratory area shall have immediately available laboratory manuals and standard operating procedures relative to the laboratory procedures being performed. * * *

* * * *

15. In § 58.90 by revising paragraphs (b) and (c), to read as follows:

§ 58.90 Animal care.

* * * * *

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

(c) At the initiation of a nonclinical laboratory study, animals shall be free of any disease or condition that might interfere with the purpose or conduct of the study. If, during the course of the study, the animals contract such a disease or condition, the diseased animals shall be isolated, if necessary. These animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study. The diagnosis, authorizations of treatment, description of treatment, and each date of treatment shall be documented and shall be retained.

* * * * *

16. In § 58.105 by revising the first sentence of paragraph (a) and by changing in the first sentence of paragraph (b) "initiation or a nonclinical laboratory study" to "initiation of a nonclinical laboratory study", as follows:

§ 58.105 Test and control article characterization.

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

* * * * *

17. In § 58.113(a)(2) by revising the first sentence, to read as follows:

§ 58.113 Mixtures of articles and carriers.

(a) * * *

* * * * *

(2) To determine the stability of the test and control articles in the mixture as required by the conditions of the study.* * *

* * * * *

18. In § 58.120 by revising paragraph (a), to read as follows:

§ 58.120 Protocol.

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

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

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

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

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

(5) The procedure for identification of the test system.

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

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

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

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

(10) The records to be maintained.

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

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

19. In § 58.130 by revising paragraphs (d) and (e) to read as follows:

§ 58.130 Conduct of a nonclinical laboratory study.

* * * * *

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

(e) All data generated during the conduct of a nonclinical laboratory study, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and legibly in ink. All data entries shall be dated on the date of entry and signed or initiated by the person entering the data. Any change in entries shall be made so as not to obscure the original entry, shall indicated the reason for such change, and shall be dated and signed or identified at the time of the change. In automated data collection systems, the individual responsible for direct data imput shall be identified at the time of data input. Any change in automated

data entires shall be made so as to not obscure the original entry, shall indicate the reason for change, shall be dated, and the responsible individual shall be identified.

§ 58.185 [Amended]

20. In § 58.185 *Reporting of nonclinical laboratory study results* in paragraph (a)(14) and changing "§ 58.35(b)(7)" to read "§ 58.35(b)(6)."

21. In § 58.190 by revising paragraphs (a) and (e), to read as follows:

§ 58.190 Storage and retrieval of records and data.

(a) All raw data, documentation, protocols, specimens, except those obtained form mutagenicity tests and wet specimens of blood, urine, feces, and biological fluids, and final reports generated as a result of a nonclinical laboratory study shall be retained.

* * * * *

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

22. In § 58.195 by revising paragraph (c), redesignating paragraph (g) as paragraph (h), and adding new paragraph (g), to read as follows:

§ 58.195 Retention of records.

* * * * *

(c) Wet specimens, samples of test or control articles, samples of test or control article carrier mixtures and specially prepared material, which are relatively fragile and differ markedly in stability and quality during storage, shall be retained only as long as the quality of the preparation affords evaluation. In no case shall retention be required for longer periods than those set forth in paragraphs (a) and (b) of this section.

* * * * *

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

* * * * *

§ 58.204 [Amended]

23. In § 58.204 *Notice of and opportunity for hearing on proposed disqualification* in paragraph (b) by changing "Part 16 of this chapter" to read "Part 16."

§ 58.213 [Amended]

24. In § 58.213 *Public disclosure of information regarding disqualification* in paragraph (b) by changing "Part 20 of this chapter" to read "Part 20."

§ 58.219 [Amended]

25. In § 58.219 *Reinstatement of a disqualified testing facility* by changing "Part 20 of this chapter" to read "Part 20."

Interested persons may, on or before (Decemeber 28, 1984), submit to the Dockets Management Branch (address above) written comments regarding this proposed rule. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: August 27, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

[FR Doc. 84-28403 Filed 10-26-84; 8:45 am]

BILLING CODE 4160-01-M