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**Part VI**

**Department of  
Health and Human  
Services**

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**Food and Drug Administration**

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**21 CFR Part 58  
Good Laboratory Practice Regulations;  
Final 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:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing a final rule that amends the regulations that specify good laboratory practice (GLP) for nonclinical laboratory studies. The amendments clarify, delete, or amend several provisions of the GLP regulations to reduce the regulatory burden on testing facilities. The changes will also achieve a substantial reduction in the paperwork burden imposed upon the regulated industries by the current regulations. Significant changes are made in the provisions respecting quality assurance, protocol preparation, test and control article characterization, and retention of specimens and samples based on FDA's experience in implementing the regulations. The agency has determined that the changes will not compromise the objective of the GLP regulations, which is to assure the quality and integrity of the safety data submitted in support of the approval of regulated products.

**EFFECTIVE DATE:** October 5, 1987.

**FOR FURTHER INFORMATION CONTACT:**

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**SUPPLEMENTARY INFORMATION:**

**Background**

In the *Federal Register* of October 29, 1984 (49 FR 43530), FDA published a proposal to amend the agency's regulations in 21 CFR Part 58, which prescribe good laboratory practice for conducting nonclinical laboratory studies (the GLP regulations). The proposal was the result of an evaluation of the GLP regulations and of the data obtained by the agency's inspection program to assess laboratory compliance with the regulations. The evaluation led the agency to conclude that some of the provisions of the regulations could be revised to permit nonclinical testing laboratories greater flexibility in conducting nonclinical laboratory studies without compromising public protection. FDA invited comments on all aspects of the proposal and provided 60 days for interested persons to submit comments.

views, data, and information on the need to revise any other provisions of Part 58.

**Comments**

FDA received 33 comments: 19 from manufacturers of articles regulated by FDA, 4 from associations, 8 from foreign or domestic testing or consulting laboratories, and 2 from individuals within FDA. The majority of these comments endorsed the proposed changes. Many of the comments suggested additional revisions to the GLP regulations or modifications to the proposed changes. A summary of the comments received by FDA during the comment period and the agency's response to them follows.

**General**

1. One comment urged FDA to initiate training procedures for its field personnel so that the regulated community would obtain maximum benefit from the revisions to the GLP regulations.

FDA agrees that agency field personnel who conduct inspections of nonclinical testing laboratories need to understand the specific requirements of the GLP regulations to follow appropriate inspectional practices and procedures. FDA has, to date, 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. FDA intends to continue to provide such training for its personnel.

2. Eight comments urged FDA to encourage the Environmental Protection Agency (EPA) to adopt similar revisions to its good laboratory practice standards. The comments noted that unless EPA amends its good laboratory practice standards to conform them to FDA's GLP regulations, nonclinical laboratories will still be required to comply with EPA's more stringent requirements. Therefore, regardless of any changes that FDA makes in its regulations, laboratories will not benefit from the revisions unless the EPA regulations are similarly revised.

FDA recognizes that certain nonclinical laboratories that are subject to FDA's regulations are also subject to the good laboratory practice standards established by EPA under the Federal Insecticide, Fungicide and Rodenticide Act (7 U.S.C. 135 et seq.) and the Toxic Substances Control Act (15 U.S.C. 2600 et seq.). When this final rule becomes effective, some of the provisions of the GLP regulations will differ from the good laboratory practice standards established by EPA. FDA has consulted

with EPA officials respecting the changes to FDA's regulations effected by this final rule and will cooperate fully with EPA when that agency propose to revise its regulations.

**Scope**

3. Except for editorial changes to § 58.1, FDA did not propose to change the scope of Part 58. One comment, however, urged the agency to revise § 58.1 further to make clear that batch release safety tests performed on specific batches of biological products intended for use in clinical trials after tests to establish the basic safety profile have been conducted are subject to the GLP regulations.

FDA declines to change final § 58.1 on the ground that the studies described by the comment are within the current scope of Part 58. The animal tests performed with an investigational biological product prior to licensing, including the batch release safety tests, are intended to establish the safety of the product. Accordingly, any such test would constitute a nonclinical laboratory study as defined in § 58.3(d). Because such test would also be intended to support a marketing application for a product regulated by FDA, it would be subject to the GLP regulations.

**Definitions**

4. Four comments endorsed FDA's proposal to change the definition of "control article" in § 58.3(c) to exclude from the definition feed and water administered to control groups of a test system. One comment, however, expressed concern that, by relaxing essential standards, the proposed change would compromise the quality of the animal test.

FDA does not agree that excluding feed and water from the definition of "control article" will compromise test quality. The regulations will continue to contain provisions adequate to control the use of feed and water in a nonclinical laboratory study. For example, § 58.31(e) requires management to assure that materials are available as scheduled, § 58.45 provides for proper feed storage, § 58.81(b)(2) requires the preparation of standard operating procedures for animal care (e.g., nutrition), § 58.90(g) requires periodic analysis of feed and water for interfering contaminants, and final § 58.120(a)(7) (formerly § 58.120(a)(9)) requires the protocol to contain a description or an identification of the diet, including specifications for acceptable levels of contaminants. Other sections of the regulations also

apply to feed or water that is used as a carrier for the test or control article. For example, § 58.31(d) requires management to assure that test and control article mixtures have been appropriately tested, § 58.47 requires that a testing facility include storage areas that are adequate to preserve the identity, strength, purity, and stability of such mixtures, and § 58.113 requires the laboratory to conduct appropriate analyses for uniformity of the mixture, as well as concentration and stability of the test article in the mixture. As discussed at length in the preamble to the proposal (49 FR 43531), the amendment to § 58.3(c) will mean that the feed and water provided to the control groups of a test system will not be subject to certain provisions of the regulations, e.g., those requiring control articles to be characterized and tested for stability (§ 58.105), retained as reserve samples (§ 58.195), or accountable with respect to use (§ 58.107). As discussed above, however, the regulations will continue to require the provision of adequate supplies of feed and water, a description of the feed, proper storage, and use accountability procedures as directed by the protocol, and standard operating procedures. Further, only feed and water shown to be free from unacceptable contamination may be used in a study.

For the reasons above, FDA concludes that the change to § 58.3(c) will not compromise the quality of the animal test and that the term "control article" should be reserved for the discrete substances/articles and vehicles other than feed and water administered to groups of the test system to provide a basis of comparison with the test article.

5. Four comments on proposed § 58.3(d) endorsed FDA's proposal to allow laboratories to conduct several experiments using the same test article under a single, comprehensive protocol. One comment, however, expressed concern that by amending the definition of "nonclinical laboratory study," FDA may inadvertently encourage laboratories to establish protocols that (1) are too brief to assure the quality and integrity of safety data developed through a study conducted under the protocol, or (2) do not describe study procedures in sufficient detail for such assurance, because lengthy "umbrella protocols" may be difficult to administer and track during the amendment process.

Under the revised definition in § 58.3(d), a single "umbrella" protocol may be used for concurrent testing of more than one test article using a single common procedure, e.g., mutagenicity

testing, or for a battery of studies of one test article conducted in several test systems. Section 58.120 requires that each study have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study, and § 58.33 requires the study director to assure that the protocol is approved and followed.

FDA notes that the changed definition of "nonclinical laboratory study" does not require any laboratory to establish "umbrella" protocols—it only allows it as an option. The agency recognizes that a longer, more complex protocol might be more difficult to manage than a simpler one; however, using an "umbrella" protocol should be more efficient than using several closely related protocols. The quality or accuracy of test data and procedures should not be compromised, while the paperwork burden should be reduced. In any event, the laboratory remains responsible for assuring that the validity of any study that it conducts is not adversely affected due to an inadequate protocol.

6. One comment urged FDA to revise further the definition of nonclinical laboratory study to define the terms "study initiation" and "study termination."

FDA recognizes that differing words and phrases are used within the GLP regulations to denote dates respecting significant events that occur during a laboratory study. For this reason, the agency agrees that it may be useful to add to the regulations definitions of the terms "study initiation" and "study completion."

FDA advises that the study initiation date represents the date on which the study director has completed plans in preparation for the technical conduct of a study (see § 58.33) and on which, under § 58.31(e), management is required to make certain that personnel, resources, facilities, equipment, materials, and methodologies for the study are available as scheduled. On the study initiation date, the study is entered on the master schedule sheet (see § 58.35(b)(1)). After this date, any protocol changes are to be made only in accordance with the procedure described in § 58.120(b). Accordingly, FDA is adding new § 58.3(o) to define "study initiation" to mean the date the protocol is signed by the study director.

The study completion date is the date on which the study director signs the final report (see final § 58.185(b)). On the study completion date, the study director is required to make certain that raw data, documentation, protocols, specimens, and final reports are

transferred to the archives (see § 58.33(f)), and under § 58.35, the quality assurance unit may retire the study from the master schedule sheet. This date also specifies the beginning of the record retention period under § 58.195(b). After the study completion date, final reports may be amended only in accordance with the procedure described in § 58.185(c). Accordingly, FDA is adding new § 58.3(p) to define "study completion" to mean the date the final report is signed by the study director. As a necessary conforming amendment, FDA is also amending § 58.185(b) to provide that the final report shall contain the dated signature of the study director.

FDA advises that the phrase "close of the study" as used in § 58.33(f) refers to the study completion date. Also, the terms "terminate" and "discontinue" as used in § 58.195(b)(3) are used in their ordinary senses to mean stop, cease, break off, or give up, denoting that a study has been ended before the planned study completion date. For these reasons, FDA believes that these terms do not need any further definition to make clear their meanings.

7a. Three comments urged FDA to expand the definition of "raw data" under § 58.3(k) to provide that the computer record of "hand-recorded data entered into the computer verbatim and verified" could be substituted for the original source as raw data.

FDA does not agree that the computer record of hand-recorded data may be considered as raw data. Individuals who enter data from a laboratory study into the computer commonly do not have any knowledge of the conditions under which the data were collected and may not understand the data originator's notations that regularly are included on the hand-recorded data sheets. The probability of error in data entry is greatly increased under these circumstances.

7b. One comment urged the agency to revise § 58.3(k) to make clear that the term "raw data" as it pertains to the findings of the histopathological examinations refers only to the signed and dated final report of the pathologist.

FDA does not agree that it needs to amend the definition of raw data relative to the findings of histopathological examinations. In pertinent part, § 58.3(k) defines raw data as laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities and are necessary for the reconstruction and evaluation of the final report. Although the notes taken by a pathologist during

histopathological examination of slides are indeed the result of original observations; these notes are not necessary for the reconstruction and evaluation of the final report. The final report is evaluated by an analysis of the pathology syndrome as described in the pathologist's report, which is required under § 58.185(a)(12). Further, because § 58.190(a) requires histopathological blocks, tissues, and slides to be retained as specimens, the final report can be reconstructed by verification of the pathology findings by, e.g., a second pathologist or by a team of pathologists.

The pathologist's interim notes, therefore, which are subject to frequent changes as the pathologist refines the diagnosis, are not raw data because they do not contribute to study reconstruction. Accordingly, only the signed and dated final report of the pathologist comprises raw data respecting the histopathological evaluation of tissue specimens.

#### Testing Facility Management

8. One comment objected to FDA's proposal to delete the provision in § 58.31(b) that requires testing facility management to document as "raw data" the replacement of a study director. The comment argued that it could be difficult to retrieve such documentation if data were transferred to another location after completion of a study.

FDA proposed to delete the requirement in § 58.31(b) to document study director replacement as "raw data" in the agency's belief that other provisions of the GLP regulations adequately require documentation of this event. The agency continues to believe that the requirement in § 58.31(b) is redundant to such other provisions and is not necessary to assure the quality and integrity of the safety data developed through a study conducted by a laboratory. For example, § 58.35(b)(1) provides that the master schedule sheet shall contain the name of the study director. Thus, replacement of the study director would necessitate an updating of the master schedule sheet. The master schedule sheet itself is "raw data" because it is a record that is the result of laboratory activities and is necessary for the reconstruction of the study. Also, § 58.120(b) requires that any change in an approved protocol and the reason or reasons for the change are to be documented. Because § 58.120(a)(11) of the final rule (previously § 58.120(a)(15)) requires that the protocol contain the dated signature of the study director, replacement of the study director would constitute such a change. Other provisions of the regulations require the quality assurance

unit to retain the master schedule sheet and copies of protocols as an easily accessible system of records for a specified period after completion of the study (§ 58.195(d)). Therefore, it should not be difficult to identify the term of each study director even if records are transferred elsewhere after study completion.

#### Study Director

9. Several comments objected to § 58.33 in its entirety on the grounds that (1) the regulation does not clearly define the responsibility of the study director and (2) the wording of the regulation implies that the study director must be technically competent in all areas of a study. One comment argued that the study director should be responsible only for "coordinating" the technical conduct, interpretation, analysis, documentation, and reporting of results.

FDA discussed at length in the preamble to the GLP final rule the intent of § 58.33 and the requirements applicable to the individual who is designated the study director for any study (43 FR 59986, 59995; December 22, 1978). As discussed in that preamble, the study director represents the single, fixed point of responsibility for overall conduct of each study. Although "coordination" of the pieces of a study logically is part of the study director's responsibilities, to limit his or her responsibilities to mere "coordination" would compromise public protection if another person were not such designated fixed point and would add an unnecessary burden if FDA were to require a laboratory to employ an additional person to provide such a point. The study director is charged with the technical conduct of a study, including interpretation, analysis, documentation, and reporting of results. FDA does not intend, however, that the individual is to be technically competent in all areas of a study. FDA's inspectional experiences have demonstrated that if responsibility for proper study conduct is not assigned to one person, a potential exists for the issuance of conflicting instructions and improper protocol implementation.

FDA concludes that the comments did not provide any new data or information to negate the agency's original determinations and that it should retain § 58.33 as it was established in the December 22, 1978, final rule.

10. One comment objected to FDA's proposal to delete the phrase "and verified" from § 58.33(b), which currently requires that the study director assure that all experimental data are "verified" as well as accurately recorded. The comment argued that

removing the study director's obligation to assure that the data have been verified would dilute the responsibility of the study director for proper conduct of the study.

FDA has carefully reevaluated its proposal to remove the phrase "and verified" from § 58.33(b). FDA proposed to delete the phrase from the regulation in response to arguments from management of testing facilities that they misinterpreted the provision, apparently believing that it required the study director personally to witness each data observation. FDA did not intend the provision to so require. Rather, the agency regards the study director as responsible for assuring that all experimental data are verified.

Ordinarily the verification required by § 58.33(b) is obtained by the individual collecting the data, using data verification procedures described in the protocol or in the specific standard operating procedure, and by the individual's supervisor as part of the supervisory quality control procedures. "Verified" is used to describe the study director's responsibility to assure the accurate recording of data. Verification in this sense does not require the study director to observe every data collection event but does require the study director to make certain that the study conduct procedures designated in the protocol for a study and the standard operating procedures established for a study are followed. For all these reasons, FDA has decided to retain the phrase "and verified" to confirm the need for data verification in nonclinical laboratory studies.

11. Two comments urged that the study director's responsibility for assuring placement in the archives of the study records specified under § 58.33(f) be transferred to testing facility management under § 58.31. The comments argued that raw data and documentation are under the immediate control of facility management rather than the study director.

The change suggested by the comments would conflict with the study director's responsibility identified in § 58.33 of representing the single point of study control (see paragraph 9 of this preamble). The archived materials of each study, including raw data and documentation, constitute lasting proof of study validity. The transfer of such materials to the archives is a critical step in study control that assures that the archived materials are complete and adequate for study reconstruction. Indeed, these revised regulations further emphasize the study director's control function by defining the study

completion date as the date the final report is signed and dated by the study director; after this date, the study director assures that all required materials are transferred to the archives. Consequently, FDA declines to accept the change proposed by the comments.

#### *Quality Assurance Unit*

12. FDA received eight comments regarding § 58.35(a), which sets forth the composition and function of the Quality Assurance Unit (QAU). One comment endorsed FDA's proposal 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. The comment suggested, however, that the agency use the term "function" or "activity" in § 58.35(a) in place of the current term "unit" to make it clear that quality assurance monitoring need not be performed by individuals of a permanently staffed unit. Four comments disagreed strongly with the proposed change to § 58.35(a), arguing that the change inappropriately implies that assurance of a well-conducted study does not require special training or experience. The comments also asserted that verifiable data are produced as a result of the current requirement for an independent, fixed and permanently staffed quality assurance unit. Other comments argued that individuals should not monitor studies similar to their own work. Some comments requested further clarification of the required composition of the QAU.

FDA does not believe that identification of the quality assurance unit as a "function" or "activity" would serve to clarify the composition or function of the QAU. FDA never has intended that the QAU necessarily has to be a separate entity or a permanently staffed "unit" (see 43 FR 59996). "Quality assurance unit" has become an accepted term to describe those individuals responsible for quality assurance as described in § 58.35. FDA also does not agree that the proposed revision to § 58.35(a) implies that assurance of a well-conducted study does not require special training or experience on the part of individuals monitoring the conduct and reporting of a nonclinical laboratory study. FDA continues to believe that well-qualified and trained personnel are essential to quality assurance under the GLP regulations and that one of management's most important responsibilities in maintaining effective quality assurance is to provide an adequate number of such personnel (§ 58.31 (c) and (e)).

FDA concludes from the comments that the requirements set forth in § 58.35(a) have been misinterpreted in some instances to mean that the regulations require that the QAU be composed of individuals whose sole duties are in quality assurance. In fact, the agency intends only that quality assurance activities be separated from study direction and conduct activities; that is, a trained and qualified person who works on one study can perform quality assurance duties on any study in which he or she is not involved. FDA's reason for requiring separation of quality assurance functions from study conduct functions is fundamental—to assure that quality assurance personnel can act candidly, without bias or a real or perceived conflict of interest. In effecting the separation required by the GLP regulations, FDA was aware that many small laboratories could not afford the operation of a permanently staffed QAU. For this reason, the agency concluded that the separation of functions on a study-by-study basis as permitted in the existing and revised regulations would provide effective quality assurance. The agency's intent in defining the composition and function of the QAU was discussed at length in the preamble to the current GLP regulations (see 43 FR 59996). FDA believes that the change now being made more clearly reflects the agency's original intent.

13. One comment recommended that FDA delete the word "sheet" from the term "master schedule sheet" in § 58.35(b)(1) on the ground that there are methods for maintaining a master schedule other than use of an actual "sheet."

FDA acknowledges that current technology allows for various methods for maintaining a master schedule, ranging from sophisticated computerized procedures to procedures whereby such information is contained in written records. Regardless of the method utilized, however, the master schedule information is "raw data" within the meaning of the GLP regulations and copies of the master schedule are required to be retained in the study archives in accordance with § 58.195(b). The agency is, therefore, retaining the term "master schedule sheet" to emphasize that the master schedule constitutes raw data subject to agency inspection and that the records must be retained.

14. One comment suggested that FDA delete the current provision in § 58.35(b)(1), which requires a laboratory to include the name of the sponsor of each study on the master schedule sheet for all studies conducted

at the facility. The comment urged the agency to allow sponsor identification by code.

FDA agrees that including the sponsors' name on the master schedule sheet is not essential either for the conduct of management's functions listed in § 58.31 or for the conduct of proper quality assurance under § 58.35. Sponsor identification by code is an adequate procedure, provided that the name of any sponsor is made available to FDA upon request. Accordingly, FDA is amending § 58.35(b)(1) to read " \* \* \* identity of the sponsor \* \* \*."

15. One comment suggested that FDA further revise § 58.35(b)(1) to allow the master schedule sheet to be indexed by study number rather than test article on the ground that multiple studies may be performed on each test article.

FDA recognizes that a nonclinical laboratory may have in progress several studies on each test article that is listed on the master schedule sheet. The agency concludes, however, that indexing by study number alone and not by test article would be inappropriate. The master schedule sheet is the mechanism through which the QAU can assure management that the facilities are adequate and that there are sufficient numbers of qualified personnel available to accomplish the scheduled work (see 43 FR 59997). In addition, § 58.31(e) requires management to assure that study materials (e.g., test articles) are available as scheduled. The use of study numbers rather than test articles as index terms would, therefore, frustrate a major purpose of the master schedule sheet and impede the conduct of an important management function.

16. Three comments endorsed FDA's proposal to delete the current requirement under § 58.35(b)(1) that the status of the final report be a distinct entry on the master schedule sheet. One comment, however, objected to the proposal on the basis that frequently there are delays in completing the final report, and the study status often is different from the expected date of completion of the report.

FDA believes that the comment that objected to the proposal misconstrued the purpose of revising § 58.35(b)(1). Section 58.35(b)(1) currently requires that the master schedule sheet contain separate headings for the "current status" of the study and for the "status of the final report" of the study. FDA considers the preparation of the final report to be a study event, current status of which should be reflected on the master schedule sheet. Preparation of the final report is similar to other study

events (e.g., test article-mixture preparation, test system dosing, in life observations) that are listed under "current status." Under this revision to § 58.35(b)(1), the master schedule sheet would contain the same information respecting the final report as is required under the current GLP regulations, but the information would be included only under the "current status" heading. The agency advises that "expected date of completion of a final report" is not a "status" entry. Such information has not been required in the past nor is this information being required now.

17. FDA proposed to revise § 58.35(b)(3) to provide specifically that the QAU need only inspect "each nonclinical laboratory study" on a schedule adequate to assure the integrity of the study. Four comments recommended that the agency further revise the regulation to substitute the word "studies" for the phrase "each nonclinical laboratory study" alleging that inspection of multiple short duration studies can result in expenditure of significant time and effort with little derived benefit. Two comments argued that inspection of short duration studies conducted repeatedly at the same facility by the same personnel is not necessary and suggested that, in lieu of requiring inspection of each study, standard operating procedures be developed to determine the inspection frequency of various types of studies. These comments also recommended that such inspections be used to demonstrate compliance of other similar studies conducted in the same time frame.

FDA does not agree with the comments. The quality of each nonclinical laboratory study submitted to the agency in support of an application for a research or marketing permit for a product regulated by FDA is critical to a determination of the safety of the product. The principle of quality assurance advanced in the GLP regulations is to inspect studies to identify and correct problems in a timely fashion. FDA is convinced that such problems can be detected only through a program of vigorous inspection of each study. This does not mean, however, that every phase of every study needs to be inspected by the QAU (see paragraph 18 of this preamble).

18. Two comments disagreed with FDA's proposal to modify the current requirement in § 58.35(b)(3) that the QAU inspect each phase of a study at specified intervals. The comments argued that elimination of specified quality assurance inspection intervals may result in decreased compliance by

cost-cutting laboratories. Another comment urged FDA to identify the critical phases of a nonclinical laboratory study to be inspected by the QAU.

Section 58.35(b)(3) currently provides that the QAU is to inspect at periodic intervals each phase of a nonclinical laboratory study. For studies lasting more than 6 months, the inspections are to be conducted every 3 months. For studies lasting less than 6 months, the inspections are to be conducted at intervals adequate to assure the integrity of the study (including each phase at least once). The term "each phase" was intended to emphasize the need for repeated surveillance so that the QAU observes at least once during the course of the study each critical operation. The term "periodic" was included in the regulation to indicate the need for more than one inspection of certain repetitive, continuing operations. In light of current information, however, FDA does not believe that such a rigid schedule is essential to assure study quality. The agency has learned through its inspection program that the quality of toxicology testing is much higher than that envisioned in 1976 when FDA proposed to establish the GLP regulations (see 41 FR 51206, 51207-51208; November 19, 1976).

Contemporary concepts of quality assurance emphasize the effectiveness of thorough, in-depth inspections of study processes (i.e., all operations required to accomplish a study phase) in place of quick, spot checks of individual operations with a study. Thorough examination of personnel, facilities, equipment, standard operating procedures, data collection procedures, raw data books, and other features associated with a study phase can achieve more effective quality assurance than does a more superficial observation of the conduct of the same study phase in a series of studies.

The agency has concluded that the QAU's inspection schedule should take into account the need for inspection of each study on a schedule adequate to assure the integrity of the study being monitored. The change in § 58.35(b)(3) permits the QAU to exercise reasonable flexibility and judgment so that inspections can be scheduled to best achieve the goal of assuring that studies are properly conducted. The agency advises, however, that each study, no matter how short, needs to be inspected in-process at least once. Further, across a series of studies all phases should be inspected in order to assure the integrity of the studies. For these reasons, FDA does not believe that the regulation as

revised will result in decreased compliance with the GLP regulations or that the term "critical phase" needs to be defined.

19. Eight comments addressed FDA's proposal to delete § 58.35(b)(4), which currently requires the QAU to submit periodic written status reports to management and to the study director. One of the comments supported the proposal on the basis that the provisions of § 58.35(b)(3), which require reports to management on problems likely to affect study integrity, are adequate to assure study quality. Several comments questioned whether deleting § 58.35(b)(4) would provide any practical benefit to testing facilities, noting that management is likely to continue to expect periodic reports. One comment noted that elimination of the requirement for status reports could allow management to disregard quality assurance problems if management is only marginally supportive of good laboratory practice and quality assurance. Three comments argued that, by deleting the provision, FDA would inappropriately place on the QAU rather than on the study director the obligation of determining what constitutes a problem likely to affect the integrity of a study. One comment argued that, because management is required to be involved in corrective actions under the provisions of §§ 58.31(g) and 58.35(b)(3), management must be kept informed respecting the status and the progress of any study inspected by the QAU. Another comment suggested that FDA delete the requirement that status reports be provided to the study director but retain the requirement that management receive such reports.

After careful consideration of these comments, FDA has concluded that § 58.35(b)(4) should be retained in its current form. The agency proposed to delete the paragraph based on its tentative conclusion that routine reports of unremarkable findings by the QAU are not essential to study quality. The comments, however, are persuasive in that such reports are necessary to demonstrate to management that the QAU is functioning properly. It is also necessary that the study director continue to receive such reports because that individual is responsible for all aspects of any study being conducted by a facility, including GLP compliance.

20. One comment suggested that, in lieu of deleting the entire paragraph, § 58.35(b)(4) be modified by removing the requirement for status reports on each study, thereby reducing paperwork.

In accord with the conclusions stated in paragraph 19 of this preamble, FDA

believes that it is inappropriate to eliminate the requirement for status reports for each study. Without status reports on each study, there would not be adequate assurances concerning the quality of the ongoing studies.

21. One comment urged FDA to revise current § 58.35(b)(5) to hold the QAU responsible only to (1) determine that known deviations from approved protocols or standard operating procedures were not made without proper documentation, and (2) require authorization for anticipated deviations. The comment argued that the current wording of the regulation implies that the QAU shall have prior knowledge of any deviations and shall approve such deviations, which is not the case in most instances.

FDA would not consider a laboratory to have violated § 58.35(b)(5) if a deviation was not authorized in advance because it was unanticipated. For example, as recognized in the preamble to the final rule (43 FR 59998), a fire in the facility would necessitate immediate action. Also, as discussed at length at 43 FR 59998, FDA does not intend that the QAU is responsible for authorizing any deviations from the protocol or standard operating procedures, rather it is responsible for detecting any such deviations by its inspection and audit procedures. The revision suggested by the comment would remove the accountability of the QAU for detecting deviations and would undermine the requirements for quality assurance.

22. FDA proposed to revise current § 58.35(b)(7) to provide that the statement which the QAU prepares to accompany the final report would be required to identify the phases of the study inspected and the number of inspections conducted. Eleven comments objected to the proposed change to the regulation, which currently requires only that the statement by the QAU specify the dates that inspections of the study were made and the dates that findings were reported to management and to the study director. Most of the comments were concerned with the additional reporting burden imposed by the proposed revision. Some of the comments argued that the information sought by FDA through the proposed revision in § 58.35(b)(7) is currently required under the provisions of § 58.35(b)(3) and (c). These comments pointed out that requiring additional documentation would be duplicative and contrary to the stated purposes of the proposed revisions to the GLP regulations.

FDA has carefully reevaluated its proposal to require that the QAU

statement identify the phases of a study inspected and the number of inspections conducted. The agency is persuaded that the proposal would have provided information redundant to that which is available under other provisions of the GLP regulations. Accordingly, FDA has decided not to change § 58.35(b)(7) and is retaining this provision in its current form. Proposed § 58.35(b)(6) (as § 58.35(b)(7) would have been renumbered) is not being adopted.

#### *Animal Care Facilities*

23. One comment objected to the proposed modification to § 58.43(c), which would delete the current requirement that all laboratory facilities include separate areas for the diagnosis, treatment, and control of laboratory animal diseases. The comment noted that animal health is a major problem in toxicology testing. For this reason, the comment argued that any relaxation of the current requirements in the GLP regulations for animal care is ill-advised and contradictory to FDA's responsibility for the welfare of animals.

As discussed in the preamble to the proposed amendments to the GLP regulations (49 FR 43532), a laboratory may elect to dispose of diseased animals, thereby obviating the need for dedicated areas for such animals. FDA believes that it is not cost-effective to require separate areas in every case and has concluded that the decision concerning appropriate separation of animals should be made by the study director in consultation with other scientific personnel. The agency does not believe that providing for dedicated laboratory areas as appropriate compromises FDA's continuing commitment to animal welfare, which is specifically dealt with in § 58.90. Indeed, FDA believes that the GLP regulations foster quality animal testing under defined conditions so that fewer animals are required to establish product safety.

#### *Animal Supply Facilities*

24. FDA proposed to revise § 58.45 to permit laboratories to store perishable supplies or feed by methods most appropriate to the characteristics of the materials. One comment urged FDA to amend § 58.45 further to permit storage of animal feed in rooms housing small animals or small groups of animals that are isolated from other studies.

FDA declines to amend § 58.45 as recommended by the comment. In developing the current GLP regulations, the agency carefully considered whether animal feed or bedding might be stored within any test areas. FDA concluded at that time that storage areas needed for feed and bedding should be separate

from the areas housing the test system to preclude mixups and contamination of test article-carrier mixtures and inadvertent exposure of the test system to potentially interfering contaminants. FDA continues to believe that separate storage areas for feed and animal bedding should be required and the comment did not provide any data to counter this belief. FDA advises, however, that § 58.45 does not preclude holding of limited quantities of test or control article-feed mixtures for short periods of time in properly constructed and labeled containers in the animal rooms.

25. One comment objected to the proposed changes to § 58.47, arguing that it believed the current requirements respecting facilities for handling test and control articles have resulted in fewer mixups.

Based on the comment, FDA has reconsidered the proposed revision of § 58.47. The agency agrees with the comment, in principle. Indeed, the agency intended the revision to be only editorial to simplify and to make clear that laboratories shall provide separate areas for receipt, mixing, and storage of test and control articles and their mixtures as necessary to prevent contamination or mixups. Inadvertently, however, the proposed revision would have deleted an essential requirement of good laboratory practice, i.e., the need to provide storage areas for test and control article mixtures adequate to preserve the identity, strength, purity, and stability of the mixtures. For this reason, the agency has concluded that the regulation is appropriate as currently stated and existing § 58.47 is retained.

#### *Maintenance and Calibration of Equipment*

26. FDA proposed to revise § 58.63(b) to provide that written standard operating procedures respecting maintenance and calibration of equipment would allow laboratories to discard faulty equipment as an alternative to the current provisions of § 58.63(b), which provide only for the repair of equipment that fails or malfunctions. Under FDA's proposal, a testing facility would need to specify remedial action in the event of equipment failure or malfunction only when remedial action is "appropriate" to the particular piece of equipment. Three comments recommended that FDA amend § 58.63(a) to require testing, calibration, and/or standardization of equipment in accord with written standard operating procedures. The comments argued that by changing

current § 58.63(a) in this fashion, FDA might delete § 58.63(b) in its entirety without substantively affecting the requirements of the GLP regulations applicable to laboratory equipment.

FDA advises that § 58.63(b) concerns not only setting forth in standard operating procedures the details of routine inspection, cleaning, maintenance, testing, calibration, and/or standardization of equipment, but it also concerns describing remedial actions to be taken when appropriate if the equipment fails or malfunctions. In promulgating existing § 58.63(b), FDA concluded that the specific features set forth in the regulations need to be included in equipment standard operating procedures because of the crucial role that properly used equipment plays in study conduct; a role which pervades every phase of a study and is vital to study quality and final report integrity. The comments did not provide any data that negate FDA's original determination. The agency continues to believe that specification of these features provides useful guidance to persons subject to the GLP regulations and concludes, therefore, that it would be inappropriate to delete § 58.63(b) from the regulations.

27. Section 58.63(b) requires in part that written standard operating procedures designate the person responsible for certain operations respecting equipment, i.e., routine inspection, cleaning, maintenance, testing, calibration, and/or standardization. Although FDA did not propose to revise these requirements of § 58.63(b), three comments stated that by requiring that standard operating procedures designate an individual responsible for performing each operation, FDA obligates testing facilities to change their standard operating procedures frequently. The comments further argued that the requirement to make a copy of the standard operating procedures available to laboratory personnel is redundant to the requirements set forth in § 58.81(c) and should be deleted.

The comments misconstrue the meaning of the word "person" as it is used in § 58.63(b). The second sentence of § 58.63(b) requires, in pertinent part, that "the written standard operating procedures shall designate the person responsible for the performance of each operation \* \* \*." As explained in paragraph 120 of the preamble to the final rule (43 FR 60001), FDA adopted the term "person" as defined in § 58.3(h) rather than the originally proposed term "individual" to allow the standard

operating procedures to designate an organizational unit.

The agency agrees with the comment that § 58.63(b) is redundant to § 58.81(c) insofar as it provides for standard operating procedure availability. Accordingly, FDA is removing the phrase "and copies of the standard operating procedures shall be made available to laboratory personnel" from § 58.63(b).

28. Section 58.63(c) requires that a testing facility maintain written records of all equipment inspection, maintenance, testing, calibration, and/or standardizing operations. Two comments recommended that FDA delete § 58.63(c) in its entirety, arguing that if management is satisfied that the standard operating procedures are adequate, further requirements are unnecessary.

FDA does not agree with the comments. FDA carefully considered the necessity for maintaining the records specified in § 58.63(b) when the agency developed the current GLP regulations. FDA concluded that such records are necessary to reconstruct a study and to ensure the validity and integrity of the data that are obtained from a study (see paragraph 26 of this preamble and 43 FR 60001). The purpose of the record retention requirement is to provide documentation throughout the study of equipment function in accord with design specifications for the equipment, and equipment use in accord with standard operating procedures for maintenance and calibration of the equipment. FDA'S experience in administering the GLP regulations has shown the benefit of maintaining such records. For example, through FDA's laboratory inspection program, the agency has been able to identify the precise period of time of equipment malfunction by an examination of the equipment records. Thus, § 58.63(c) has made it possible to disregard the data collected by a single defective piece of equipment without having to disregard all the data obtained from a specific study.

#### *Standard Operating Procedures*

29. Two comments on the requirements for standard operating procedures suggested that § 58.81(a) be amended to permit appropriate supervisory personnel to authorize deviations from the written standard operating procedures, arguing that the study director may not have the technical expertise to evaluate such deviations. One of the comments further argued for the change on the ground that the principles of good laboratory practice established by the Organization

for Economic Cooperation and Development of the World Health Organization do not require study director approval of all standard operating procedure deviations.

FDA does not accept the suggestion. As discussed in paragraph 9 of this preamble, it is not necessary for the study director to be technically competent in all aspects of a study to assure that appropriate action is taken in response to any circumstances that may affect the quality and integrity of a study. The study director, however, has to be aware of and authorize any deviations that could have an impact on the study. FDA does not agree that the responsibility of the study director, as set forth in § 58.81(a), is inconsistent with the Organization for Economic Cooperation and Development principles of GLP. Chapter 2, section 2.3 (Ref. 1, p. 27) of the Organization for Economic Cooperation and Development document defines the responsibilities of the study director, in part, as "ensur[ing] that the procedures specified in the study plan are followed, and that authorization for any modification is obtained and documented together with the reasons for them \* \* \*." Accordingly, both the GLP regulations and the Organization for Economic Cooperation and Development principles of GLP require that the study director make certain that specified procedures are followed and that all modifications to the procedures in the approved study plan (i.e., standard operating procedures) are documented and approved.

30. One comment recommended that FDA amend § 58.81(b) to delete all examples of standard operating procedures that FDA requires a testing facility to establish on the ground that the list is not all-inclusive and may lead to misinterpretation.

FDA disagrees with the recommendation. The examples listed in § 58.81(b) are those minimal laboratory procedures which the agency believes are essential to assuring the quality and integrity of the data generated in the course of any study (see 41 FR 51213). FDA recognizes that circumstances may necessitate establishment of additional standard operating procedures. The list is not intended to be all-inclusive and should not be interpreted as such.

31. Three comments objected to the proposed deletion of examples of laboratory manuals and standard operating procedures required to be in the laboratory under § 58.81(c). The comments argued that the listing of examples serves to spell out the agency's intent, helps laboratories



decide which areas to cover, and that without such guidance a potential exists for misinterpretation of FDA's intent.

FDA does not agree. Section 58.81(c) requires that each laboratory area have immediately available standard operating procedures relative to the laboratory procedures being performed. Unlike the list in § 58.81(b), which represents specific minimal requirements, the examples listed in § 58.81(c) encompass very broad areas. Each of the areas presented would require the preparation of a group of standard operating procedures to cover adequately the operations within that area. Consequently, the agency concludes that the list in § 58.81(c) is too broad to serve as useful guidance.

#### *Reagents and Solutions*

32. FDA received five comments that recommended that the agency amend § 58.83. Four comments stated that only those reagents and solutions used in the conduct of nonclinical laboratory studies need to be labeled in accord with the requirements of § 58.83, i.e., "to indicate identity, titer or concentration, storage requirements, and expiration date" of the material. These comments argued that such a modification would allow the laboratory flexibility in designing the most suitable system to assure that deteriorated or outdated reagents and solutions are not used. The fifth comment recommended that FDA insert into the first sentence of § 58.83 the phrase "as appropriate" to make the provision read "all reagents and solutions in the laboratory areas shall be labeled to indicate identity, titer or concentration, storage requirements, and, as appropriate, expiration date." This comment argued that it was not necessary to have expiration dates on certain stable reagents and solutions such as water and saline.

FDA declines to amend § 58.83. The agency continues to believe, as discussed in paragraph 148 of the preamble to the final rule (43 FR 60003), that all reagents and solutions maintained in the laboratory area for use in the conduct of nonclinical laboratory studies should be labeled as required by § 58.83. Accordingly, the label should include the identity, titer or concentration, storage requirements, and expiration date. This label information is the minimum information necessary to make clear to the laboratory personnel that the reagents and solutions are suitable for use in the procedures specified in the protocol and to protect against inadvertent mixups of reagents and solutions that are used in nonclinical laboratory studies with those that are not intended for such use.

Further, FDA disagrees with the comment that suggested that expiration dating is not necessary for some reagents and solutions. FDA believes that expiration dates should be required on all reagents and solutions, without regard to their stability so that there is no doubt about the suitability of the materials for use in nonclinical laboratory studies.

#### *Animal Care*

33. One comment recommended that FDA delete § 58.90(a) on the basis that requiring standard operating procedures for housing, feeding, handling, and care of animals is redundant to other provisions of the GLP regulations.

FDA recognizes that § 58.81(b)(2) requires testing facilities to establish standard operating procedures for animal care. Section 58.90(a), however, expressly specifies that standard operating procedures shall also cover animal housing, feeding, and handling. The agency believes that these items are essential features for providing adequate humane treatment of animals and, therefore, is retaining § 58.90(a).

34. Two comments objected to the proposed amendment of the requirements under §§ 58.90 (b) and (c) to provide that animals may be isolated rather than quarantined. The comments argued that allowing laboratories to develop isolation and health status evaluation procedures in lieu of quarantine may not provide adequate assurance of test animal health because such evaluations are done only on a small randomly selected number of animals and are not as reliable as an adequate quarantine period. One comment suggested that the term "segregated" or the term "separated" may more accurately reflect FDA's intent in amending §§ 58.90 (b) and (c) than does the term "isolated."

As discussed in the preamble to the proposed amendments (49 FR 43533), substitution of a requirement for isolation and health status evaluations in lieu of quarantine of newly received animals will 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. As used in current § 58.90(b), the term "quarantine" connotes a rigid set of prestudy procedures which a facility is obligated to follow, including a mandatory holding period, specified diagnostic procedures, and the use of specialized facilities and animal care practices. The agency has concluded that isolation and health status evaluations should provide adequate precautions against entry of unhealthy

animals into a study. Health status evaluations may be performed during the prestudy acclimation period. Under § 58.90(b), the health status of each animal is to be evaluated soon after receipt. Section 58.90(c) prohibits the entry of any diseased animal into the study.

The agency has also concluded that a devoted area equipped to provide isolation of diseased animals is not necessary in all cases. As discussed in the preamble to the proposal (49 FR 43533), FDA believes that it should allow certain options for handling diseased animals, thereby permitting increased flexibility in laboratory operation. FDA agrees that the term "segregate" or the term "separate" rather than the term "isolate" could be used in as much as each term connotes "to set apart." Because "isolate" is a term commonly used and understood in contemporary veterinary medical practice, however, FDA will continue to use that term in these regulations.

35. One comment recommended that FDA amend § 58.90(d) to permit procedural means to provide "appropriate identification" of individual animals in a study.

FDA does not accept the recommendation. The agency notes that proper animal identification throughout a study is essential to study integrity. When animals are housed individually in cages, procedural means can be used to identify each individual animal, i.e., a cage card may be used if it provides all the information necessary to identify the animal specifically, and the animal handling standard operating procedures specify detailed procedures for preventing animal mixups. The agency is not aware, however, of any procedural means that could be used to identify adequately individual animals that are housed within a group in a cage. FDA advises that § 58.90(d) does not preclude identification by means other than the examples enumerated in that section provided that individual identification can be maintained and documented throughout a study.

#### *Test and Control Article Characterization*

36. One comment urged the agency to delete the requirement in § 58.105(b) for stability determination of test and control articles before initiation of the study. The comment argued that changing § 58.105(b) as recommended would make it consistent with FDA's proposed changes to § 58.105(a), which would allow test and control article characterization after completion of the study.

FDA disagrees with the recommendation. As discussed in the preamble to the proposal (49 FR 43533), FDA has concluded that characterization of test and control articles need not be performed until initial toxicology studies with the test article show reasonable promise of the article's reaching the marketplace. In arriving at this conclusion, the agency considered that prior knowledge of the precise molecular structure of a test article is not vital to the conduct of a valid toxicology test. It is important, however, to know the strength, purity, and stability of a test or control article that is used in a nonclinical laboratory study.

A stability determination of a test or control article conducted after completion of the nonclinical laboratory test with the article does not provide any information about the continued strength of either the test or control article previously given to the test system. Determining that the test and control articles are stable for the duration of the study is fundamental to interpreting the results of the study. For this reason, it would be inappropriate to allow for stability determinations only after-the-fact.

The agency does believe, however, that the continued strength of the test or control article may adequately be determined either by stability testing before initiation of the study or through appropriate periodic analysis of each batch. Section 58.105(b) currently allows stability testing of the test and control articles through periodic analysis only if it is not possible to determine their stability before study initiation. Because experience has shown that it is adequate either to determine stability of the test and control articles before initiation of a study or by periodic analysis of the articles while the study is in progress, the agency on its own initiative is revising § 58.105(b) to provide facilities and sponsors the flexibility to use either approach. Therefore, § 58.105(b) has been revised to provide for determination of the stability of the test or control article either before study initiation or through periodic analysis of each batch according to established standard operating procedures.

37. One comment observed that § 58.105(a) provides that testing facilities may rely on the labeling of marketed products for purposes of characterizing such products used as control articles in a study. The comment recommended that the agency also revise § 58.105(b) to allow product labeling to serve as documentation of

stability for marketed products used as control articles.

FDA declines to adopt this recommendation. The only stability information typically included on the labeling of marketed products is the expiration date. The manufacturer's expiration dating on a marketed product is not adequately precise to provide data on the strength of the control article used throughout a nonclinical laboratory study. Lacking precise stability information respecting the control article could raise doubts concerning whether the test and control articles are comparable. Furthermore, mixing the marketed product with a carrier or use of the product in a manner not in accord with its labeling could alter the stability characteristics of the product. For these reasons, FDA concludes that determination of the stability in accordance with the procedures in § 58.105(b) still is appropriate for any products used as control articles.

38. Several comments recommended that FDA revise § 58.105(c) to remove the current requirement that storage containers be assigned to a test article for the duration of a nonclinical laboratory study. The comments argued that the requirement is unnecessary and is inconsistent with the Organization for Economic Cooperation and Development principles of GLP. One comment alleged that the statement is vague and questioned whether the provision would permit a storage container that a laboratory emptied during the conduct of, but before completion of, a study to be destroyed or reused. The same comment also questioned whether, as the test article is depleted during the conduct of a study, the provision would permit a laboratory to transfer the test article into a container smaller than that originally assigned to the article.

FDA does not believe that it would be appropriate to eliminate the storage container provision in § 58.105(c). FDA advises that the provision simply requires that each test article storage container be assigned to a test article at the beginning of a study and remain so assigned until the study is completed, terminated, or discontinued. The test article may not be transferred to different sized storage containers as a study progresses, nor may assigned storage containers be destroyed while a study is in progress.

The agency recognizes that it may be inconvenient for laboratories, especially small laboratories, to devote space to a test article container which is emptied before a study is completely terminated,

or discontinued, or which might be replaced by progressively smaller containers while a study is in progress. Destroying or reusing or otherwise substituting for originally assigned, identified test article storage containers, however, could adversely affect the integrity of the study. FDA established the current provision because the agency observed a lack of accountability for test materials, ostensibly due to the very acts proscribed by the regulation, i.e., transfer of test articles to different sized containers and destruction of empty containers during the progress of nonclinical laboratory studies.

FDA continues to believe that the requirement concerning assignment of storage containers is necessary to ensure the integrity of a study. For example, the mere act of transferring a test article from one storage container to another introduces the opportunity for contamination of the test article by other laboratory materials or for mix-ups with other laboratory materials. In addition, during a transfer the test article would be exposed to air-borne contaminants as well as to moisture, either of which may compromise the integrity of the test article.

FDA also believes that requiring that containers be assigned to a test article for the duration of a study is fully consistent with the Organization for Economic Cooperation and Development principles of GLP. Chapter 2, section 2.3 (Ref. 1, p. 31) of the Organization for Economic Cooperation and Development document states that "storage container(s) should carry identification information, earliest expiration date, and specific storage instructions." Although the Organization for Economic Cooperation and Development document does not further characterize storage instructions that the Organization for Economic Cooperation and Development would recommend be included on containers, FDA concludes that its regulation identifies a "specific" storage instruction that is necessary to assure the integrity of the test article.

#### *Mixtures of Articles with Carriers*

39. Two comments argued that the requirements in § 58.113(a) to determine the uniformity, concentration, and stability of test and control articles in mixtures is unnecessarily burdensome for short-term studies. One comment stated that such tests are not necessary for test articles that are prepared and dispensed on the same day as used in single-dose acute toxicity tests. The comments suggested that the agency

revise § 58.113(a) to require that tests of mixtures of test and control articles need be conducted only "for studies other than short-term."

Section 58.113(a) requires, for all test or control articles mixed with a carrier, a determination of the uniformity of the mixture and a periodic analysis of the concentration of the test or control article in the mixture. In addition, § 58.113(a)(2), as amended, requires a determination of the stability of the test or control article in the mixture adequate to support time of use. Each of these analyses is necessary to assure that the test system is exposed to the test or to the control article in the amounts specifically designated in the protocol for a study. Determination of the uniformity of a mixture assures that each member of the test system receives the intended dose of test or control article. Periodic analysis of the concentration of the test or control article serves as a spot check to assure that the test or control article mixture has been prepared properly and in accord with the protocol and with applicable standard operating procedures. Determining the stability of the test or control article in the mixture helps to determine the period of time during which the test or control article mixture may be suitable for administration to the test system. FDA believes that knowledge of the dose of test or control article used in any test is essential for the proper evaluation of the results of that test. For these reasons, FDA has concluded that the requirements of § 58.113(a) should continue to apply to short-term tests as well as to studies other than short term.

As discussed in paragraph 36 of this preamble, however, FDA has decided to allow facilities and sponsors the flexibility to determine the stability of test and control articles either before study initiation or through periodic analysis of each batch according to established standard operating procedures. The agency believes that it is appropriate to allow similar flexibility with respect to determining the stability of mixtures of articles with carriers. For this reason, on its own initiative, FDA has revised § 58.113(a)(2) to allow determination of the stability of test and control articles in the mixture either before study initiation or through periodic analysis of the mixture according to established standard operating procedures.

40. One comment recommended that FDA delete § 58.113(a)(1), alleging that periodic determinations of the test or control article in mixtures is routine and provisions respecting such

determination would more appropriately be included in § 58.35(b)(3).

The comment misconstrues the function of the QAU (see especially paragraphs 12 and 18 of this preamble). Current § 58.35(b)(3), as well as § 58.35(b)(3) as revised by this final rule assigns responsibility for periodic inspection of laboratory operations to the QAU. The QAU does not, indeed, under § 58.35(a), the QAU may not conduct any portion of a study. Rather, it is responsible for assuring that a study is conducted according to the protocol, the standard operating procedures, and the GLP regulations.

#### *Protocol*

41. A comment urged the agency to delete the provision in current § 58.120(a)(14) (final § 58.120(a)(10)) that requires that the protocol for each study identify the records for the study to be maintained. The comment argued that the requirement in renumbered § 58.120(a)(10) is redundant to the same requirements in §§ 58.33(f), 58.190(a), and 58.195(b).

FDA recognizes that §§ 58.33(f), 58.190(a), and 58.195(b) address records that the GLP regulations require a testing facility to retain in all events. As the authorized master plan for a study, however, the protocol should identify all records of the study to be maintained by the testing facility to inform all study participants fully of recordkeeping obligations. The agency believes that inclusion of this information in the protocol is essential to ensure adequate documentation of the conduct of the study.

For these reasons, FDA declines to remove § 58.120(a)(10) from the GLP regulations.

42. One comment recommended that FDA delete the provision in current § 58.120(a)(16) (final § 58.120(a)(12)) that requires that the protocol for each study include a statement of the proposed statistical methods to be used in the study. The comment argued that a determination of the statistical methods used to evaluate data can, in many cases, be made only after data have been reviewed.

FDA recognizes that circumstances occasionally require a testing facility to modify the proposed statistical methods for analysis of the data in a given study. Good scientific practice, however, requires consideration of the statistical analysis of a study as part of the design of the study to assess whether the objectives of the study can be met. FDA concludes that the requirement is appropriate.

#### *Conduct of a Nonclinical Laboratory Study*

43. Section 58.130(c) provides that materials derived from a test system for examination or analysis (specimens) are to be identified by test system, study, nature, and the date of collection, and requires that such identification is to be located on the specimen container or is to accompany the specimen in a manner that precludes error in the recording and storage of data. Five comments argued that the requirements under § 58.130(c) for specimen identification are overly restrictive and suggested that management should be responsible for determining methods for identifying specimens.

The identification requirements specified in § 58.130(c) are designed to preclude error during the conduct of a nonclinical laboratory study. FDA has reviewed the requirements and has concluded that the identifying information specified in the regulation is the minimum information needed to distinguish each specimen from all others that have been collected in the facility thereby protecting against mixups and permitting orderly storage of specimens. Such information also shows whether the data collected on each specimen are assigned to the correct component of the test system.

FDA has always provided flexibility in the methods to be used for identifying the specimens in that the identifying information can be encoded through, for example, the use of accession numbers affixed to the specimen with the numbers decoded in accompanying information (see, e.g., paragraph 205 of the preamble to the final rule (43 FR 60008)). The agency believes that the requirements with respect to specimen identification are the minimum requirements necessary to prevent mixup of specimens or lost specimen identity.

44. Two comments disagreed with FDA's proposal to revise § 58.130(d), which currently requires that records of gross findings for a specimen from postmortem (necropsy) observations shall, in all cases, be provided to a pathologist during study of the specimen. The proposed revision provides only that such records "should" be made available to the pathologist. Four comments supported the proposed change on the ground that the resulting flexibility allows "blinding" of the pathologist. One comment suggested that § 58.130(d) be deleted in its entirety or, alternatively, modified by specifying that the records

are to be provided to the pathologist "if required by the protocol."

FDA established § 58.130(d) in the belief that the provision would increase the pathologist's ability to describe correctly microscopic findings and to relate such findings properly with the gross postmortem observations (41 FR 51214). FDA continues to believe that for most studies it is important for the pathologist to have available the records of gross findings when examining a specimen histopathologically. The agency recognizes, however, that for certain nonclinical laboratory studies it may be appropriate for pathologists to evaluate the histopathological specimens without being informed of the necropsy findings. The change made in the regulation will permit the study director, in concert with management, to determine the need for "blinding" in relation to the specific objectives of the study.

FDA advises that it continues to believe that for most studies it is a preferred practice not to use "blinding" in histopathological evaluation. For this reason, the agency is not deleting § 58.130(d) as suggested by one comment. The alternative phrase "if required by the protocol" suggested by the comment would serve the same purpose as the modification proposed by the agency. Therefore, the agency is adopting § 58.130(d) as proposed.

45. One comment on § 58.130(e) requested that FDA clarify the meaning of the term "automated data collection systems," stating that it is unclear whether § 58.130(e) applies to tabulation of source data from "hard" copy by automated systems.

As discussed in paragraph 7a. of this preamble, hand-recorded data collected during a study are "raw data." The subsequent entry of these hand-recorded data into a computer system, for example, by data processing clerks or through the use of optical readers, does not alter the status of the hand-recorded data as "raw data." The processing of these data by the computer, e.g., tabulation, is not "direct data input" and is, therefore, not encompassed by the requirements of § 58.130(e).

#### *Reporting of Nonclinical Laboratory Study Results*

46. Section 58.185(a) requires that a final report be prepared for each nonclinical laboratory study conducted and specifies the minimum information that shall be included in a final report. One comment urged that § 58.185(a) should be modified to require final reports to include the specified information only "where appropriate" to

make the requirements respecting final reports consistent with FDA's proposal to change § 58.120(a) respecting protocols. Alternatively, the comment urged that, at the least, § 58.185(a)(8), which requires that any final report shall include a description of the dosage, dosage regimen, route of administration, and duration, should be so modified. The comment argued that some of the information required under this paragraph is not applicable to certain studies involving medical devices.

FDA proposed to change § 58.120(a) in recognition of the fact that certain of the enumerated items are not necessary for the protocols for all studies. FDA has carefully reviewed each of the items listed in § 58.185(a) and has concluded that the information required by this section to be included in a final report for a nonclinical laboratory study is necessary to evaluate any such study. FDA notes that § 58.185 currently allows certain appropriate flexibilities where specified information is determined by the laboratory not to be relevant to a study. For example, § 58.185(a)(4) provides that test and control articles may be identified by "other appropriate characteristics" and § 58.185(a)(7) includes the term "where applicable." The agency believes that the information required by § 58.185(a)(8) is applicable to studies involving medical devices. For example, "dosage" and "dosage regimen" for devices may be expressed in units used per animal at a designated frequency of use. "Route of administration" may describe the means by which the device is used in relation to the animal. "Duration" would pertain to the period of time the device was tested in the animal. These clarifications should permit nonclinical laboratory studies on medical devices to be reported properly.

47. Section 58.185(a)(10) requires that each final report of a nonclinical laboratory study include the name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel involved in the study. One comment recommended that FDA revise § 58.185(a)(10) to require identification only of the study director and of the principal scientists involved in the study.

FDA disagrees with this suggestion. Supervisors play an important role in the data collection process. They supervise those who perform the procedures, may recommend or actually provide training, and assure that data collection is carried out in accordance with the protocol, the standard operating procedures, and the GLP regulations. The names of all scientists,

professionals, and supervisors are needed to assure the accountability of all of those individuals responsible for the integrity of the study. The comment did not provide any data or information to support its recommendation to revise § 58.185(a)(10) and the agency concludes that it should retain the current requirement.

48a. Section 58.185(a)(12) requires that the final report of a nonclinical laboratory study include the signed and dated reports of each of the individual scientists or other professionals who were involved in the study. Two comments recommended that FDA revise § 58.185(a)(12) to allow for combined reports signed by the principal scientists. According to the comments, allowing for such combined reports would be consistent with the Organization for Economic Cooperation and Development principles of GLP.

The agency does not believe that a combined report from scientists of different disciplines would be appropriate. Each individual scientist involved in a study has to be accountable for reporting data, information, and views within his or her designated area of responsibility. Reports which combine the data, information, and views of more than one such person would obscure the individual's accountability for accurate reporting. Furthermore, FDA believes that the comment has misinterpreted the standard that the Organization for Economic Cooperation and Development established respecting reports of persons involved in a nonclinical laboratory study. Chapter 2, section 2.3 (Ref. 1, p. 36) of the Organization for Economic Cooperation and Development document provides that "if reports of principal scientists from co-operating disciplines are included in the final report, they should sign and date them." It provides further that the final report should contain the "names of other principal personnel having contributed reports to the final report." These provisions do not imply that combined reports would be appropriate. Rather, they support the need for individual accountability. The Organization for Economic Cooperation and Development provisions are entirely consistent with the provisions of § 58.185(a)(12).

48b. On its own initiative, FDA is amending § 58.185(b) to provide that the final report shall contain the dated signature of the study director to conform the provision to the definition of "study completion date" being added by this final rule (see paragraph 6 of this preamble).

### Storage and Retrieval of Records and Data

49. FDA proposed to revise § 58.190(a) to allow wet specimens and specimens from mutagenicity tests to be discarded after evaluation and recording. The agency's proposal was supported by several comments. One comment, however, requested that the agency clarify the meaning of "mutagenicity tests" as the term is used in § 58.190(a). The comment asked whether, for example, *in vitro* cell transformation is interpreted to be a mutagenicity test under this provision.

FDA advises that, for the purpose of § 58.190(a), the agency considers mutagenicity tests to be those tests designed to assess the capacity of a test or control article to induce heritable changes in a test system. Accordingly, FDA considers *in vitro* cell transformation to be a mutagenicity test as the term is used in the GLP regulations.

50. One comment recommended that FDA further revise § 58.190(a) to assure that the regulation makes clear that final reports must be retained.

As discussed at length in the preamble to the proposal (49 FR 43534), FDA intended to exclude from the retention requirements of the GLP regulations specimens that are relatively fragile or contribute only in a minor way to safety evaluation. FDA did not intend to change the current requirement that final reports of any nonclinical laboratory study are to be retained in accordance with § 58.195. To preclude any possible confusion regarding the requirement that final reports must be retained, FDA is rewording § 58.190(a) to read "all raw data, documentation, protocols, final reports, and specimens (except those specimens obtained from mutagenicity tests and wet specimens of blood, urine, feces, and biological fluids) generated as a result of a nonclinical laboratory study shall be retained."

### Retention of Records

51. FDA proposed to delete from current § 58.195(c) the listed examples of materials that the agency believes need to be retained only so long as the quality of the preparation affords evaluation. One comment noted that § 58.195(c) should be further revised to delete wet specimens to be consistent with the proposed revisions in § 58.190(a) (see paragraph 50 of this preamble).

FDA agrees with the comment and in this final rule is conforming § 58.195(c) to revised § 58.190(a). In pertinent part, § 58.195(c) now reads "Wet specimens (except those specimens obtained from mutagenicity tests and wet specimens of

blood, urine, feces, and biological fluids), samples of test or control articles, and specially prepared material \* \* \*"

52. Two comments suggested that FDA should specifically provide in new § 58.195(g) that records to be retained under the GLP regulations may be retained as magnetic media.

Section 58.195(g), which is being added to Part 58 by this final rule, provides that records respecting a nonclinical laboratory study may be retained as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Magnetic media could qualify as either "original records" or "accurate reproductions of the original records." This conclusion is consistent with § 58.3(k), which includes "magnetic media" within the meaning of "raw data." Consequently, the agency does not believe that it is necessary to change new § 58.195(g) in order to achieve the result desired by the comments.

### Reference

The following reference has been placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, and may be seen in that office between 9 a.m. and 4 p.m., Monday through Friday.

1. "Good Laboratory Practice in the Testing of Chemicals," Organization for Economic Cooperation and Development Publications, Paris, France, 1982.

### Economic Assessment

As announced in the proposal, FDA has examined the economic consequences of this final rule in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354). At that time, the agency concluded that the changes would not constitute a major rule as defined in the Order and that no regulatory flexibility analysis would be required. The agency also certified that the revisions would not have a significant impact on a substantial number of small entities. The agency has not received any new information or comments that would alter its previous determination.

### Environmental Impact

The agency has determined under 21 CFR 25.24(a)(10) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

### Paperwork Reduction Act of 1980

Sections 58.35(b) (1), (3), and (6), 58.63(b), 58.90(c), 58.105(a), 58.120(a), 58.130(e), and 58.190 (a) and (e) of this final rule contain collection of information requirements. FDA submitted a copy of the proposed rule containing the same requirements to the Office of Management and Budget (OMB). These collection of information requirements were approved under OMB Control No. 0910-0203.

### List of Subjects in 21 CFR Part 58

Laboratories.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under 21 CFR 5.11, Part 58 is amended as follows:

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

1. The authority citation for 21 CFR Part 58 is revised to read as follows:

Authority: Secs. 306, 402(a), 406, 408, 409, 502, 503, 505, 506, 507, 510, 512-516, 518-520, 701(a), 706, 801, Pub. L. 717, 52 Stat. 1045-1046 as amended, 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. 336, 342(a), 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360b-360f, 360f, 360h-360j, 371(a), 376, 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); 21 CFR 5.11.

2. 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.

3. In § 58.3 by removing the phrase "of this chapter" wherever it appears; by revising paragraphs (c), (d), and (e)(8); by removing and reserving paragraph (e)(12); by replacing "in section 513 of the act" with "in Part 860" in paragraph (e)(17); by replacing "section 514 of the act" with "in Part 861" in paragraph (e)(18); and by adding new paragraphs (o) and (p), to read 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]

(o) "Study initiation date" means the date the protocol is signed by the study director.

(p) "Study completion date" means the date the final report is signed by the study director.

4. 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.

5. In § 58.35 by removing paragraph (e), by revising paragraphs (a) and (b) introductory text, (1) and (3), and by adding an OMB number at the end of the section 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 study.

(b) The quality assurance unit shall: (1) Maintain a copy of a master schedule sheet of all nonclinical laboratory studies conducted at the testing facility indexed by test article and containing the test system, nature of study, date study was initiated, current status of

each study, identity of the sponsor, and name of the study director.

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

(Collection of information requirements approved by the Office of Management and Budget under number 0910-0203.)

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 removing paragraph (e) and by revising the first sentence of paragraph (c) to read 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 § 58.49, 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]

10. By removing § 58.53 Administrative and personnel facilities.

11. 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.

12. In § 58.63 by revising paragraph (b) and by adding an OMB number at the end of the section, 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. The written standard operating procedures shall designate the person responsible for the performance of each operation.

(Collection of information requirements approved by the Office of Management and Budget under number 0910-0203.)

13. In § 58.81 by revising the first sentence of paragraph (c), 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.

14. In § 58.90 by revising paragraphs (b) and (c) and by adding an OMB number at the end of the section, to read as follows:

§ 58.90 Animal care.

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

(c) At the initiation of a nonclinical laboratory study, animals shall be free of any disease or condition that might interfere with the purpose or conduct of the study. If, during the course of the study, the animals contract such a disease or condition, the diseased animals shall be isolated, if necessary. These animals may be treated for disease or signs of disease provided that

such treatment does not interfere with the study. The diagnosis, authorizations of treatment, description of treatment, and each date of treatment shall be documented and shall be retained.

\* \* \* \* \*

(Collection of information requirements approved by the Office of Management and Budget under number 0910-0203.)

15. In § 58.105 by revising the first sentence of paragraph (a), by revising paragraph (b), and by adding an OMB number at the end of the section, to read as follows:

**§ 58.105 Test and control article characterization.**

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

(b) The stability of each test or control article shall be determined by the testing facility or by the sponsor either: (1) Before study initiation, or (2) concomitantly according to written standard operating procedures, which provide for periodic analysis of each batch.

\* \* \* \* \*

(Collection of information requirements approved by the Office of Management and Budget under number 0910-0203.)

16. In § 58.113 by revising paragraph (a)(2), to read as follows:

**§ 58.113 Mixtures of articles with carriers.**

(a) \* \* \*  
(2) To determine the stability of the test and control articles in the mixture as required by the conditions of the study either (i) before study initiation, or (ii) concomitantly according to written standard operating procedures which provide for periodic analysis of the test and control articles in the mixture.

\* \* \* \* \*

17. In § 58.120 by revising paragraph (a) and by adding an OMB number at the end of the section, 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 reasonably expected to be present in the dietary materials and are known to be capable of interfering with the purpose or conduct of the study if present at levels greater than established by the specifications.

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

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

(10) The records to be maintained.

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

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

\* \* \* \* \*

(Collection of information requirements approved by the Office of Management and Budget under number 0910-0203.)

18. In § 58.130 by revising paragraphs (d) and (e) and by adding an OMB number at the end of the section, 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 initialed by the person entering the data. Any change in entries shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change. In automated data collection systems, the individual responsible for direct data

input shall be identified at the time of data input. Any change in automated data entries shall be made so as not to obscure the original entry, shall indicate the reason for change, shall be dated, and the responsible individual shall be identified.

(Collection of information requirements approved by the Office of Management and Budget under number 0910-0203.)

19. In § 58.185 by revising paragraph (b), to read as follows:

**§ 58.185 Reporting of nonclinical laboratory study results.**

\* \* \* \* \*

(b) The final report shall be signed and dated by the study director.

20. In § 58.190 by revising paragraphs (a) and (e) and by adding an OMB number at the end of the section, to read as follows:

**§ 58.190 Storage and retrieval of records and data.**

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

\* \* \* \* \*

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

(Collection of information requirements approved by the Office of Management and Budget under number 0910-0203.)

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

\* \* \* \* \*

(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]

22. In § 58.204 *Notice of and opportunity for hearing on proposed disqualification* in paragraph (b) by removing "of this chapter"

§ 58.213 [Amended]

23. In § 58.213 *Public disclosure of information regarding disqualification* in paragraph (b) by removing "of this chapter."

§ 58.219 [Amended]

24. In § 58.219 *Reinstatement of a disqualified testing facility* by removing "of this chapter."

Frank E. Young,

*Commissioner of Food and Drugs.*

Otis R. Bowen,

*Secretary of Health and Human Services.*

Dated: August 10, 1987.

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