Comparison of 2016 Proposed GLP Quality System

Part 58-explanation of changes	PART 58—GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES	PART 58—GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES (Proposed)
Scope (§ 58.1) We propose to expand the scope of FDA-regulated nonclinical laboratory studies to specifically include toxicity studies. For purposes of this proposal, toxicity means the acute or long-term adverse effects that could result from use of the FDA-regulated product. While some nonclinical laboratory studies of FDA-regulated products evaluate a product's safety, including toxicity, most are conducted solely to determine a product's toxicity. For example, when combined with the results of clinical trials, determination of toxicity at various doses can inform an appropriate risk-to-benefit analysis when relevant to FDA's consideration of a product's marketing application or submission. For drugs administered to animals whose products will be consumed by humans, toxicity studies are critical for determining safe levels of residual drug product. Nonclinical laboratory studies of food ingredients and food contact substances provide the basis for establishing levels at which a substance will not, with reasonable certainty, be harmful under its intended conditions of use. In the evaluation of tobacco products, FDA could use the data derived from nonclinical	Subpart A—General Provisions **§ 58.1 Scope.** (a) This part prescribes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, animal food additives, human and animal drugs, medical devices for human use, biological products, and electronic products. Compliance with this part is intended to assure the quality and integrity of the safety data filed pursuant to sections 406, 408, 409, 502, 503, 505, 506, 510, 512-516, 518-520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.	**§ 58.1 Scope.** (a) This part prescribes good laboratory practices (GLPs) for conducting nonclinical laboratory studies of safety or toxicity or both that support or are intended to support an application or submission for products regulated by the Food and Drug Administration (FDA), including food and color additives, animal food additives, human and animal drugs, devices, biological products, electronic products, and tobacco products. Applications and submissions to FDA affected by these regulations include those listed in § 58.3. Compliance with this part is intended to assure the quality and integrity of data from nonclinical laboratory studies filed or submitted pursuant to sections 402, 406, 408, 409, 501, 502, 503, 505, 510, 512-516, 518-520, 571, 701, 721, 801, 905, 910, and 911 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act. * * * * * (c) In this part the term “where appropriate” is used several times. When a requirement is qualified by “where appropriate,” it is deemed to be “appropriate” unless justification can be otherwise documented. A requirement is “appropriate” if non-implementation could reasonably be expected to result

Red = Proposed GLP revision

laboratory studies to evaluate relative toxicity as opposed to evaluating safety. Additional proposed modifications to the scope in § 58.1 expand the language to include FDA jurisdictional oversight of tobacco products as specified in the FD&C Act, sections 905, 910, and 911. We also propose to modify and broaden "medical devices for human use" to "devices" to include FDA's Center for Veterinary Medicine (CVM), which has jurisdiction over devices used in veterinary medicine. In addition, we propose changing the provision "for research and marketing permits" to "applications or submissions" for FDA-regulated products. This proposed change will include the applications and submissions to FDA listed in the definitions section of this proposal. As stated in both the preamble to the original proposed regulations (original GLP proposed rule) (41 FR 51206 at 51210) and the preamble to the original GLP final rule (43 FR 59986 at 59988), the GLP "regulations are intended to ensure, as far as possible, the quality and integrity of test data that are submitted to FDA and become the basis for regulatory decisions made by the Agency." Therefore, the phrase "intended to support" in present and proposed § 58.1(a) means that any nonclinical laboratory study included within the proposed expanded scope of Part 58 that is conducted with the intent that it may support an application or submission to FDA should be conducted in compliance with the GLP regulations. Also, we propose adding § 58.1(c) to describe what we mean by "where appropriate" when used in the part 58		in a nonclinical laboratory study whose results lack the required reliability.

regulatory text. This proposal addresses studies conducted at a single testing facility as well as at multiple sites. We propose using "where appropriate" in many of the revised or added provisions because not all requirements are applicable to all studies. For example, a test site tasked only with interpreting a study's histopathology would not require all of the SOPs required for a test site responsible for multiple phases.		
Definitions (§ 58.3) The current § 58.3 *Definitions*, is not alphabetized and includes paragraphs (a) through (p). We propose to remove the paragraph designations, add new definitions, modify certain current definitions, and alphabetize the complete listing of definitions. We propose modifying current § 58.3(e) to change the defined term from "Application for research or marketing permit" to "Applications and Submissions to FDA". We propose this change because nonclinical laboratory studies can support applications and submissions to FDA other than those for research and marketing. Also, in the definition for "Applications and Submissions to FDA" proposed paragraphs (1) through (35), we add certain relevant statutory or regulatory citations for consistency. We propose including applications and submissions for tobacco products described in the FD&C Act. We note that FDA plans to issue regulations under section 910(g), providing conditions under which tobacco products intended for investigational use may be exempted from the requirements of chapter IX of the FD&C Act. It is our intent that applications for such investigational tobacco	**§ 58.3 Definitions**. As used in this part, the following terms shall have the meanings specified: (a) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 *et seq.,* as amended (21 U.S.C. 321-392)). (b) *Test article* means any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act. (c) *Control article* means any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any article other than a test article, feed, or water that is administered to the test system in the course of a nonclinical laboratory study for the purpose of establishing a basis for comparison with the test article. (d) *Nonclinical laboratory study* means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in	**§ 58.3 Definitions.** As used in this part, the following terms have the meanings specified: *Applications and Submissions to FDA* include: (1) A color additive petition, described in section 721 of the Federal Food, Drug, and Cosmetic Act, and as described in part 71 of this chapter. (2) A food additive petition, described in section 409 of the Federal Food, Drug and Cosmetic Act, and as described in parts 171 and 571 of this chapter. (3) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for use, which use results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §§ 170.35 and 570.25 of this chapter. (4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in § 180.1 of this chapter.

products will be included within the scope of § 58.3. We also propose adding those applications and submissions for FDA-regulated products that include nonclinical laboratory study results but are not currently specifically included. For example, Humanitarian Device Exemption applications are new since publishing in 1987 the last final rule modifying part 58. We also propose expressly adding the medical device Premarket Notification (also known as a "510(k)" submission). *Attending Veterinarian:* We propose adding a definition for an attending veterinarian. Our proposed definition is the same as the definition in USDA's Animal Welfare Regulations (9 CFR 1.1) but without specifics about educational requirements. We propose defining an attending veterinarian as a veterinarian with training, experience, or both in the care and management of the species being attended, with direct or delegated authority for activities involving animals. We propose this definition because we propose in part 58 certain provisions about animal welfare. For example, we propose that the study director must defer to the attending veterinarian when decisions regarding animal welfare arise, particularly when animals are in pain or distress. *Batch:* We propose changing the definition of batch currently in § 58.3(n) to reference the relevant provisions in § 58.105 (Test, control, and reference article characterization) and § 58.107 (Test, control, and reference article handling). We also add that batch means a specific quantity or lot of a reference article (see section	animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article. (e) *Application for research or marketing permit* includes: (1) A color additive petition, described in part 71. (2) A food additive petition, described in parts 171 and 571. (3) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for use, which use results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §§ 170.35 and 570.35. (4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in § 180.1. (5) An *investigational new drug application,* described in part 312 of this chapter. (6) A *new drug application,* described in part 314. (7) Data and information regarding an over-the-counter drug for human use, submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in part 330. (8) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and	(5) A petition for a nutrient content claim, described in section 403 of the Federal Food, Drug, and Cosmetic Act, and as described in subpart D of part 101 of this chapter. (6) A petition for a health claim, described in section 403 of the Federal Food, Drug, and Cosmetic Act, and as described in subpart E of part 101 of this chapter. (7) An *investigational new drug application,* described in section 505(i) of the Federal Food, Drug, and Cosmetic Act, and as described in part 312 of this chapter. (8) *Applications for FDA approval to market a new drug,* described in section 505 of the Federal Food, Drug, and Cosmetic Act, and as described in part 314 of this chapter. (9) Data and information regarding an over-the-counter drug for human use, submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in part 330 of this chapter. (10) 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 sections 406, 408, and 409 of the Federal Food, Drug, and Cosmetic Act, and as described in parts 109 and 509 of this chapter. (11) A *notice of claimed investigational exemption for a new animal drug,* section 512(j) of the Federal Food, Drug, and Cosmetic Act, and as described in described in part 511 of this chapter. (12) *New animal drug applications,* described in section

III.B.2.), we discuss the addition of a reference article definition. *Contracted Person:* We propose adding a definition for contracted person to mean a person that assumes, either directly or indirectly as an independent contractor, one or more of the responsibilities for conducting a nonclinical laboratory study. Several comments to the December 2010 ANPRM state that the responsibilities of all persons (any legal entity) involved in multisite studies need to be addressed in the regulations. We propose the use of this term to allow us to address the comments without specifically identifying all possible contracted entities. The comments also request that FDA include specifics for multisite studies as to how responsibilities are to be met and by whom. In response to these comments, we intend that a contracted person includes any person (for example, testing facility or individual) that the sponsor contracts with to conduct a phase (defined activity or set of activities) of a nonclinical laboratory study. Also, the term contracted person includes any person that is under a subcontract to conduct a phase of a nonclinical laboratory study. *Contributing Scientist:* We propose adding and defining the term contributing scientist. A contributing scientist is an individual responsible for conducting, interpreting, analyzing, or performing any service for a phase of a nonclinical laboratory study. The current regulation in § 58.185 for reporting study results refers to "individual scientists or other professionals involved in the study" (see § 58.185(a)(12)). Our	food-packaging materials, described in parts 109 and 509. (9) Data and information regarding an antibiotic drug submitted as part of the procedures for issuing, amending, or repealing regulations for such drugs, described in § 314.300 of this chapter. (10) A *Notice of Claimed Investigational Exemption for a New Animal Drug,* described in part 511. (11) A *new animal drug application,* described in part 514. (12) [Reserved] (13) An *application for a biological product license,* described in part 601. (14) An *application for an investigational device exemption,* described in part 812. (15) An *Application for Premarket Approval of a Medical Device,* described in section 515 of the act. (16) A *Product Development Protocol for a Medical Device,* described in section 515 of the act. (17) Data and information regarding a medical device submitted as part of the procedures for classifying such devices, described in part 860. (18) Data and information regarding a medical device submitted as part of the procedures for establishing, amending, or repealing a performance standard for such devices, described in part 861. (19) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard,	512 of the Federal Food, Drug, and Cosmetic Act, and as described in part 514 of this chapter. (13) An *abbreviated application for a new animal drug,* described in section 512(b) of the Federal Food, Drug, and Cosmetic Act. (14) An *application for conditional approval of new animal drugs for minor use and minor species,* described in section 571(a)(2) of the Federal Food, Drug, and Cosmetic Act, and as described in part 516 of this chapter. (15) *Authorization to market edible products from experimental animals* as described in parts 170 and 570 of this chapter. (16) A request to establish or amend an import tolerance described in section 512 of the Federal Food, Drug, and Cosmetic Act. (17) [Reserved] (18) An *application for a biologics license,* described in section 351 of the Public Health Service Act, and as described in part 601 of this chapter. (19) An *application for an investigational device exemption,* described in section 520(g) of the Federal Food, Drug, and Cosmetic Act, and as described in part 812 of this chapter. (20) An *application for premarket approval of a medical device,* described in section 515 of the Federal Food, Drug, and Cosmetic Act, and as described in part 814 of this chapter. (21) An *application for humanitarian device exemption,* authorized under section 520(m) of the Federal Food, Drug, and Cosmetic Act, and as described in part 814, subpart H of this chapter. (22) A *product development protocol for a medical device,* described in section 515 of the

proposal replaces these scientists or other professionals with the term contributing scientist. In addition, when a contributing scientist is a contracted independent expert or specialist, we use the term independent contributing scientist. See, also, section III.C.6. where we discuss § 58.37 (Contributing scientist). *Control Article:* We propose modifying the definition of control article currently in § 58.3(c) by changing "medical device for human use" to "device" to expand the regulations to include devices used in veterinary medicine. Also, the revised definition proposes to include a "tobacco product". *Establish:* For this part 58 proposal, the meaning of establish is to define, document (in writing or electronically), and implement. We propose adding a definition for establish to help eliminate repeating in the applicable regulatory text the words that define establish. Our proposed definition is identical to the definition of establish in the part 820 quality system regulation in § 820.3(k). *Facility-Based Inspection:* We propose introducing the term facility-based inspection to mean a QAU inspection that covers the general facilities and activities; for example, installations, support systems, computer systems, training, environmental monitoring, and equipment maintenance and calibration. This addition, along with the definition of process-based inspection (see section III.B.2.) would allow for greater efficiency instead of duplicating, for each study, inspection of those general facilities and activities. Our proposed definition also is consistent with the definition for	described in subpart D of part 1003. (20) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such product, described in section 358 of the Public Health Service Act. (21) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard as described in § 1010.4. (22) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from any electronic product performance standard, as described in § 1010.5. (f) *Sponsor* means: (1) A person who initiates and supports, by provision of financial or other resources, a nonclinical laboratory study; (2) A person who submits a nonclinical study to the Food and Drug Administration in support of an application for a research or marketing permit; or (3) A testing facility, if it both initiates and actually conducts the study. (g) *Testing facility* means a person who actually conducts a nonclinical laboratory study, i.e., actually uses the test article in a test system. *Testing facility* includes any establishment required to register under section 510 of the act that conducts nonclinical laboratory studies and any consulting laboratory described in section 704 of the act that conducts such studies. *Testing facility* encompasses only those operational units that are being or have been used to	Federal Food, Drug, and Cosmetic Act, and as described in part 814 of this chapter. (23) A *premarket notification submission* for a medical device as authorized under section 510(k) of the Federal Food, Drug, and Cosmetic Act, and as described in part 807, subpart E of this chapter. (24) Data and information regarding a medical device submitted as part of the procedures for classifying such devices described in part 860, subpart B of this chapter, reclassification petitions described in part 860, subpart C of this chapter, and requests associated with the evaluation of automatic class III designations, authorized under section 513(f)(2) of the Federal Food, Drug, and Cosmetic Act. (25) Data and information regarding a medical device submitted as part of the procedures for establishing, amending, or revoking a performance standard for such devices, described in section 514 of the Federal Food, Drug, and Cosmetic Act, and as described in part 861 of this chapter. (26) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in subpart D of part 1003 of this chapter. (27) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such product, described in section 358 of the Public Health Service Act.

facility-based inspection in the OECD document, *Quality Assurance and GLP* (Ref. 7). *GLP Quality System:* We propose adding a definition for GLP Quality System to mean the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management in the conduct of nonclinical laboratory studies. As discussed in section II.B., we consider a fully implemented GLP Quality System the proper framework for building quality into planning, conducting, and reporting a nonclinical laboratory study while allowing flexibility for site-specific procedures. *Lead Quality Assurance Unit:* We propose adding a definition for a lead quality assurance unit (lead QAU) meaning the QAU responsible for quality assurance (QA) in a multisite nonclinical laboratory study. We propose that testing facility management with executive responsibility selects the lead QAU. The location of the lead QAU may be at the testing facility, with another person conducting a phase of the study, or provided through a contractual relationship. This definition is consistent with the definition for lead QAU in the OECD consensus document, *The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies* (Ref. 6). *Management with Executive Responsibility:* We propose adding a definition for management with executive responsibility to mean senior employees of the testing facility or test site who have the authority to establish or make changes to the quality policy and GLP Quality System at their testing facility or test site. We	conduct nonclinical laboratory studies. (h) *Person* includes an individual, partnership, corporation, association, scientific or academic establishment, government agency, or organizational unit thereof, and any other legal entity. (i) *Test system* means any animal, plant, microorganism, or subparts thereof to which the test or control article is administered or added for study. *Test system* also includes appropriate groups or components of the system not treated with the test or control articles. (j) *Specimen* means any material derived from a test system for examination or analysis. (k) *Raw data* means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data. *Raw data* may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments (l) *Quality assurance unit* means any person or organizational element, except the study director, designated by testing facility management to perform the duties relating to quality assurance of nonclinical laboratory studies.	(28) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard as described in § 1010.4 of this chapter. (29) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from any electronic product performance standard, as described in § 1010.5 of this chapter. (30) A *premarket notification for a food contact substance,* described in section 409 of the Federal Food, Drug, and Cosmetic Act, and as described in part 170, subpart D of this chapter. (31) [Reserved] (32) A *premarket application for a new tobacco product,* as described in section 910(b)(1) of the Federal Food, Drug, and Cosmetic Act. (33) A *substantial equivalence report* as described in section 905(j) of the Federal Food, Drug, and Cosmetic Act. (34) A *request for exemption* under section 905(j)(3) of the Federal Food, Drug, and Cosmetic Act, and as described in part 1107 of this chapter. (35) An *application or submission related to a modified risk tobacco product,* as described in section 911 of the Federal Food, Drug, and Cosmetic Act. *Attending veterinarian* means a veterinarian who has training or experience or both in the care and management of the species being attended and who has direct or delegated authority for activities involving animals. *Batch* means a specific quantity or lot of a test, control, or

note that part 820 (see § 820.3(n)) adopted this term describing senior management to be consistent with the quality system specifications in ISO 9001:1994 (61 FR 52602 at 52609, October 7, 1996). *Master Schedule:* We propose adding a definition for master schedule that means a compilation of information used for assessment of workload and the tracking of nonclinical laboratory studies. The master schedule will include information about all nonclinical laboratory studies conducted. For multisite studies, the master schedule also will include the phases conducted (see proposed 58.31(k)). Our proposed definition of master schedule is consistent with the definition in the OECD GLP document, *OECD Principles on Good Laboratory Practice* (Ref. 8). When we discuss § 58.31 (Management with executive responsibility, section III.C.2.), we elaborate on requirements concerning the master schedule. *Multisite Study:* We propose adding a definition for multisite study to mean any study that has phases (defined in section III.B.2.) conducted at more than one site. Our proposed definition of multisite study is consistent with the definition in the OECD consensus document, *The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies* (Ref. 6). *Nonclinical Laboratory Study:* We propose modifying the current definition in § 58.3(d) for a nonclinical laboratory study to add after "under laboratory conditions" the phrase "or in the applicable environment". This addition recognizes that the conduct of a nonclinical	(m) *Study director* means the individual responsible for the overall conduct of a nonclinical laboratory study. (n) *Batch* means a specific quantity or lot of a test or control article that has been characterized according to § 58.105(a). (o) *Study initiation date* means the date the protocol is signed by the study director. (p) *Study completion date* means the date the final report is signed by the study director.	reference article that has been characterized according to § 58.105 and handled according to § 58.107. *Contracted person* means a person who assumes, either directly or indirectly as an independent contractor, one or more responsibilities for the conduct of a nonclinical laboratory study. *Contributing scientist* means an individual responsible for the conduct, interpretation, analysis, or any other service for a phase of a nonclinical laboratory study. An individual expert or specialist who is an independently employed contracted person, as defined in this section, is an independent contributing scientist. *Control article* means any food additive, color additive, drug, biological product, electronic product, device, tobacco product, or any article other than a test article, reference 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. *Establish* means define, document (in writing or electronically), and implement. *Facility-based inspection* means an inspection which is not based on specific studies but covers general facilities and activities, for example, installations, support systems, computer systems, training, environmental monitoring, and equipment maintenance and calibration. *GLP Quality System* means the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management in the conduct of a nonclinical laboratory study.

laboratory study is not limited to a traditional laboratory environment. We propose to make clear that the purpose for conducting nonclinical laboratory studies may be to determine relative toxicity. For example, because tobacco products are not safe, nonclinical laboratory studies help FDA evaluate the relative toxicities of those products. We also propose to update the regulations by changing "field trials in animals" to "clinical investigational use in animals", which more accurately describes our intent. We propose a sentence structure change in the last sentence in this definition to clarify our intent, which is often misinterpreted due to the current sentence structure. *Phase:* We propose adding a definition for phase to mean a defined activity or set of activities in the conduct of a nonclinical laboratory study. We propose this new definition to aid in understanding the new proposed definition of multisite study, which is any study that has phases conducted at more than one site. Our proposed definition is consistent with the definition of phase in the OECD consensus document, *The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies* (Ref. 6). *Principal Investigator:* We propose adding a definition for principal investigator to mean an individual with specific responsibilities delegated by the study director for a phase of a nonclinical laboratory study. We propose defining principal investigator in general terms rather than specifying the principal investigator's single role in a multisite study as defined in the OECD document, OECD Principles on Good Laboratory		*Lead quality assurance unit* (lead QAU) means the QAU responsible for quality assurance (QA) in a multisite nonclinical laboratory study. Testing facility management with executive responsibility selects the lead QAU. *Management with executive responsibility* means those senior employees of a testing facility or test site who have the authority to establish or make changes to the quality policy and GLP Quality System at the testing facility and test site, respectively. *Master schedule* means a compilation of information used for assessment of workload and the tracking of nonclinical laboratory studies. *Multisite study* means any study that has phases conducted at more than one site. *Nonclinical laboratory study* means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions or in the applicable environment to determine their safety or toxicity or both. The term does not include studies involving human subjects, clinical studies, or clinical investigational use in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or basic exploratory studies to determine the physical or chemical characteristics of a test article. *Person* includes an individual, partnership, corporation, association, scientific or academic establishment, government agency, or organizational unit thereof, and any other legal entity. *Phase* means a defined activity or set of activities in the conduct of a nonclinical laboratory study.

Practice (Ref. 8). However, we propose that principal investigator responsibilities are those delegated by the study director, which is consistent with OECD principles. See, also, section III.C.7. where we discuss § 58.39 (Principal investigator). *Process-based Inspection:* We propose adding a definition for process-based inspection to mean inspecting repetitive, frequently performed procedures and processes (for example, certain mutagenicity studies). This definition recognizes present practice and allows for greater efficiency, as noted elsewhere (section III.B.2.). Our proposed definition is consistent with the definition for process-based inspection in the OECD document, *Quality Assurance and GLP* (Ref. 7). *Quality:* We propose adding a definition for quality, meaning the totality of features and characteristics bearing on the ability of a nonclinical laboratory study to provide reliable data. *Quality Assurance Unit (QAU):* We propose modifying the current definition in § 58.3(*l*) to remove "except the study director" and "designation by testing facility management". Also, we propose adding a sentence "The QAU must be entirely separate from and independent of the personnel engaged in the direction and conduct of the particular study." We propose these changes for clarity and to be consistent with our inclusion of multisite studies and with the statement currently in § 58.35. *Quality Policy:* We propose adding a definition for quality policy that is identical to the definition in § 820.3(u), meaning "the overall intentions and direction of an organization with respect to quality, as established		*Principal investigator* means an individual who has specific responsibilities for one or more phases of a nonclinical laboratory study as delegated by the study director. *Process-based inspection* means an inspection conducted to monitor procedures or processes of a repetitive nature that are very frequently performed. Process-based inspections are conducted on a prearranged schedule, which is not connected to the timing of any particular nonclinical laboratory study. Performance of process-based inspections covering processes or procedures that occur with a very high frequency (for example, certain mutagenicity studies) may cause some studies to be uninspected during the in-life period of the study, as defined in this section within the definition of *Short-term study*. *Quality* means the totality of features and characteristics that bear on the ability of a nonclinical laboratory study to provide data that can be relied upon. *Quality assurance unit* (QAU) means any person or organizational element designated to perform the duties relating to quality assurance (QA) of nonclinical laboratory studies. For any given study, the QAU must be entirely separate from and independent of the personnel engaged in the direction and conduct of the study. *Quality policy* means the overall intentions and direction of an organization with respect to quality, as established by management with executive responsibility. *Raw data* means all original nonclinical laboratory study records and documentation or exact copies that maintain the

by management with executive responsibility." *Raw Data:* We propose modifying the current definition in § 58.3(k) to update the regulations to address copying requirements and computerized systems, and to specifically include the pathology report. We propose adding to the definition that raw data means "all nonclinical laboratory study records and documentation or exact copies that maintain the original intent and meaning and are made according to the person's certified copy procedures." This additional regulatory text eliminates the need to provide examples of what we consider a copy. We also propose adding "correspondence" and "other documentation (regardless of capture medium)" to the examples of raw data. The addition of "regardless of capture medium" eliminates the need to provide examples of possible capture media. Also, we propose including as raw data "the signed and dated pathology report" to clarify what we consider as raw data. *Reference Article:* We propose adding a definition for reference article consistent with EPA's GLP regulations in 40 CFR 160.3 and 792.3 for defining a "reference substance" to mean an article used to establish a basis for comparison of the test article for known chemical or biological measurements. We propose this addition to acknowledge the use of reference articles in certain studies. *Short-Term Study:* We propose adding a definition for short-term study to mean when the in-life period (study period during which data are collected) is completed within several days or, at most, a week. Since the pre-specified,		original intent and meaning and are made according to the person's certified copy procedures. *Raw data* includes any laboratory worksheets, correspondence, notes, and other documentation (regardless of capture medium) that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. *Raw data* also includes the signed and dated pathology report. *Reference article* means any chemical substance or mixture, or analytical standard, or material other than a test article, control article, feed, or water that is administered to or used in analyzing the test system in the course of a study for the purposes of establishing the basis for comparison with the test article for known chemical or biological measurements. *Short-term study* means a study for which the in-life period is completed within several days or a week at most. The in-life period of a study is that period during which data are collected. *Specimen* means any material derived from a test system for examination, analysis, or retention. *Sponsor* means: (1) A person that initiates and supports, by provision of financial or other resources, a nonclinical laboratory study; or (2) A person that submits a nonclinical laboratory study in support of an application or submission to FDA; or (3) A person that initiates a nonclinical laboratory study and functions as, and has the same responsibilities as, a testing facility, test site, or contributing

periodic timing of process-based inspections can result in the lack of an inspection of a short-term study, this definition is necessary to address our proposed addition of process-based inspections (see also the discussion of the definition of process-based inspection in section III.B.2.). *Specimen:* We propose adding "or retention" to the end of the current definition of specimen in § 58.3(j) to read, "Specimen means any material derived from a test system for examination, analysis, or retention." We propose this change because a specimen may be collected solely for retention purposes. Also, this proposed change is consistent with the definition in the OECD GLP document, *OECD Principles on Good Laboratory Practice* (Ref. 8). *Sponsor:* We propose modifying the current definition of sponsor in § 58.3(f) consistent with our proposal to expand the scope of part 58, and to address possible roles of the sponsor in multisite studies. We propose revising the current definition in § 58.3(f)(3) to include the possible roles a sponsor could play in a multisite study in addition to initiating and supporting the study. Those roles and applicable requirements are the same as those for a testing facility, test site, or contributing scientist as we propose to define those terms. See, also, section III.B.3. where we discuss § 58.5 (Sponsor responsibilities). *Standard Operating Procedures (SOPs):* We propose adding a definition for SOPs to mean documented procedures describing how to perform tests or activities normally not specified in detail in study protocols. We propose this addition because many proposed		scientist, as those terms are defined in this section. *Standard operating procedures* (SOPs) means documented procedures which describe how to perform tests or activities normally not specified in detail in study protocols. *Study-based inspection* means an inspection of a critical operation of the study which is scheduled according to the chronology of the given study. Management with executive responsibility at the testing facility and/or test site identifies which operations are critical before initiation of the study. *Study completion date* means the date the final report is signed by the study director. *Study director* means the individual responsible for the overall conduct of a nonclinical laboratory study. *Study initiation date* means the date the protocol is signed by the study director. *Test article* means any food additive, color additive, drug, biological product, electronic product, device, tobacco product, or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act or under sections 351 and 354-360F of the Public Health Service Act. *Test site* means a person who is responsible for one or more phases of a multisite nonclinical laboratory study. A test site includes management with executive responsibility and supporting SOPs relevant to the conduct of nonclinical laboratory studies. *Test system* means any animal, plant, microorganism, or subparts thereof to which the test, control, or reference article is administered or added for study. *Test system* also includes

modifications in § 58.31 refer to required SOPs. This definition is consistent with the OECD GLP document, *OECD Principles on Good Laboratory Practice* (Ref. 8). *Study-based Inspection:* We propose adding a definition for study-based inspection to mean the same QAU inspection specified currently in § 58.35(b)(3) for inspecting a critical operation of the study that is scheduled according to the study's chronology or sequence of events. Our proposed definition is consistent with the definition for study-based inspection in the OECD consensus document, *Quality Assurance and GLP* (Ref. 7). *Test Article:* We propose modifying the current definition of test article in § 58.3(b) to change "medical device for human use" to "device" and to add "tobacco product". As discussed in section III.B.1. concerning the scope of part 58, we propose these changes to broaden devices to include FDA's CVM and to include FDA's jurisdiction of tobacco products. *Test Site:* We propose adding a definition for test site to mean a "person" (currently defined in § 58.3(h)) responsible for a phase of a multisite nonclinical laboratory study. We propose that a test site includes management with executive responsibility and supporting SOPs for the conduct of a nonclinical laboratory study. For a different nonclinical laboratory study, a test site could function as a testing facility. *Test System:* We propose modifying the current definition of test system in § 58.3(i) to add "reference" article consistent with our other proposed changes. See elsewhere in section III.B.2. for		appropriate groups or components of the system not treated with the test, control, or reference articles. *Testing facility* means the person responsible for coordinating, conducting, or completing a nonclinical laboratory study, or any combination thereof. The testing facility designates the study director. *Validation* means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled. *Vehicle* means any agent which serves as a carrier and is used to mix, disperse, or solubilize the test, control, or reference article for administration or application to the test system.

our proposed definition and explanation for adding a definition of reference article. *Testing Facility:* We propose removing and replacing most of the current definition of testing facility in current § 58.3(g) to update the regulations consistent with the conduct of multisite nonclinical laboratory studies. Our proposed definition is as follows: "Testing facility means a person responsible for conducting, coordinating, or completing a nonclinical laboratory study, or any combination thereof. The testing facility designates the study director." We propose this change because, in a multisite study, the testing facility might not be the person treating the test system with the test article as specified in the current definition. Rather, the person treating the test system with the test article might be a contracted or subcontracted person. Therefore, this general definition of a testing facility is necessary to capture all possible contractual relationships in a multisite study. *Validation:* We propose adding a definition for validation to mean confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use of a system or process can be consistently fulfilled. This proposed definition is similar to the definition in § 820.3(z), and addresses comments to the December 2010 ANPRM requesting a definition for validation of a system or process *Vehicle:* We propose adding a definition for vehicle to mean any agent that serves as a carrier and is used to mix, disperse, or solubilize the test, control, or reference article for		

administration or application to the test system. This proposal recognizes the use of vehicles in the conduct of nonclinical laboratory studies. Our proposed definition is consistent with the definition of vehicle in the OECD GLP document, *OECD Principles on Good Laboratory Practice* (Ref. 8), for describing a carrier for test, control, or reference articles.		
Sponsor Responsibilities (§ 58.5) The present regulations in § 58.10 cover only a sponsor's responsibilities to notify a consulting laboratory, contractor, or grantee that their service "is part of a nonclinical laboratory study that must be conducted in compliance with the provisions of this part [part 58]". FDA received many comments to the December 2010 ANPRM noting that there are other sponsor responsibilities implicit throughout the present regulations, and stating that the study sponsor must share in the responsibility for complying with part 58. We agree with those comments. Therefore, we propose adding § 58.5 *Sponsor responsibilities,* that provides explicit provisions for the presently implied sponsor responsibilities and adds new sponsor responsibilities. Our proposed sponsor responsibilities are consistent with the preamble to the original GLP proposed rule stating that the adequacy and validity of nonclinical laboratory tests remain the responsibility of the sponsor of the product as part of establishing the marketability of the product (41 FR 51206 at 51206) (Ref. 4). In addition, we propose adding provisions consistent with the OECD		Add § 58.5 to subpart A to read as follows: **§ 58.5 Sponsor responsibilities.** For each nonclinical laboratory study, the sponsor must: (a) Ensure the nonclinical laboratory study protocol (the study protocol) meets the requirements in § 58.120. (b) Ensure that the study protocol provides for humane care and ethical treatment of animals. (c) Sign and date the study protocol to indicate approval. (d) Contract with persons accredited as following appropriate animal welfare procedures for phases of a nonclinical laboratory study that include the use of animals. If these contracted persons are not accredited, document this fact, the reason for using a non-accredited person, and the qualifications of the non-accredited person. This information must be included in the compliance statement required in paragraph (k) in this section. (e) Document that any contracted person conducting a phase of a nonclinical laboratory study is qualified according to the provisions in this part. (f) Ensure that appropriate lines of communication are established among all persons conducting a phase of the

advisory document, *The Role and Responsibilities of the Sponsor in the Application of the Principles of GLP* (Ref. 9). For each nonclinical laboratory study, we propose that the sponsor must ensure the study protocol meets the requirements specified in § 58.120 (*Protocol* (see proposed § 58.5(a) regulatory text, elsewhere in this document). Also, we propose that the sponsor must ensure the study protocol provides for the humane care of animals (see proposed § 58.5(b)). We propose these additions because the sponsor is responsible for developing the study protocol, either directly or through a contracted person. To indicate the sponsor's approval of the study protocol, we propose that the sponsor must sign and date the study protocol (see proposed § 58.5(c)). For any phase of a nonclinical laboratory study that includes the use of animals, we propose that the sponsor contract with persons accredited as following appropriate animal welfare procedures. If, for any reason, the sponsor does not use an accredited person for a phase that includes the use of animals, we propose that the sponsor must document the reason for using the non-accredited person. (See proposed § 58.5(d).) If the study supports an application or submission to FDA, we propose requiring in the application or submission the reason for using a non-accredited person, along with supporting information to show the qualifications of that person, such as a copy of SOPs showing the application of current animal welfare laws, regulations, policies, and guidelines. This information must be included in the compliance		nonclinical laboratory study and document all study-related communications that involve the sponsor. (g) Document that test, control, and reference articles are prepared, characterized, and labeled according to subpart F of this part, and are appropriately shipped. Obtain, and provide to the study director as soon as available, information regarding test, control, and reference article characterization as specified in § 58.105. (h) Inform the study director of any known potential risks of the test article to human health or the environment and any measures necessary to protect study personnel and the environment. (i) Review, approve, sign, and date each protocol amendment before implementation. (j) Document and update as necessary the archive location of all raw data and records as described in §§ 58.190 and 58.195. (k) Include, in any application or submission to FDA that includes the results of a nonclinical laboratory study, the final study report and all amendments. If a summary report of the nonclinical laboratory study is included in such applications or submissions, a copy of the final study report, as described in § 58.185, must be appended or provided elsewhere within the application or submission. Also, include either a statement that the study was conducted in compliance with the requirements set forth in this part, or, if the study was not conducted in compliance with these regulations, a brief statement of the reason for the noncompliance.

statement. (See proposed § 58.5(d) and (k).) We are proposing these requirements to help ensure animal welfare concerns are adequately addressed, and to help safeguard the reliability of study results. A sponsor may transfer to another party responsibility for any or all of the obligations set forth in this part. A party that assumes any obligation of a sponsor must comply with the specific regulations in this chapter applicable to this obligation and must be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Although a sponsor might transfer certain responsibilities, the sponsor is still ultimately responsible for compliance with all sponsor responsibilities provided in this chapter. When referring to the sponsor throughout this proposal, we also mean any person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor. We propose that the sponsor must document that the contracted person conducting a phase of the nonclinical laboratory study is qualified according to the provisions in part 58 applicable for the phase or phases that person is contracted to perform. (See proposed § 58.5(e).) Using qualified contracted persons is essential for ensuring GLP compliance and the quality and integrity of the resulting data. We propose adding communication requirements to sponsor responsibilities. The OECD consensus document, *The Application of the OECD Principles of GLP to the Organisation and Management of*		

Multi-Site Studies (Ref. 6), states that many problems associated with the conduct of multisite studies "can be prevented by clear allocation of responsibilities and effective communication among all parties involved in the conduct of the study." This includes the sponsor, study director, management, principal investigators, QAU, and all other study personnel. Many comments to the December 2010 ANPRM repeat this opinion. We agree and propose that the sponsor must ensure appropriate lines of communication are established (defined, documented in writing or electronically, and implemented) among all persons conducting any phase of the nonclinical laboratory study. We also propose that communications established among persons conducting a phase of the study that involve the sponsor must be documented by the sponsor. (See proposed § 58.5(f).) We propose that the sponsor must document that test, control, and reference articles are prepared, characterized, and labeled according to part 58, subpart F, and are appropriately shipped. In addition, the sponsor must obtain, and provide to the study director as soon as available, information about test, control, and reference article characterization as specified in § 58.105. (See proposed § 58.5(g).) We propose this requirement in § 58.5(g), because the study director must have characterization information to help ensure appropriate dosing of the test article and to interpret study results in the final study report. We propose that the sponsor inform the study director of any known potential risks of the test		

article to human health or to the environment, and any measures necessary to protect study personnel. (See proposed § 58.5(h).) Since the sponsor is most familiar with test article characteristics because of either direct testing or receiving results from a contracted person that characterized the test article, we propose this requirement as a sponsor responsibility. If there are known or suspected risks to human health or the environment, it is essential that the study director, as the single point of study control, is aware of the risks and the measures necessary to protect study personnel and the environment. This is consistent with OECD's advisory document, *The Role and Responsibilities of the Sponsor in the Application of the Principles of GLP* (Ref. 9). We propose that the sponsor must review, approve, sign, and date each protocol amendment before implementation. (See proposed § 58.5(i).) Many comments to the December 2010 ANPRM recommend this requirement and we agree. After initiating the study, the sponsor must be aware of proposed study protocol changes and why the changes are proposed. This requirement is part of our proposed checks and balances in part 58 and will help ensure that the amended protocol complies with GLP. We propose that the sponsor must document and update, as necessary, the archive location of all raw data and records described in proposed §§ 58.190 and 58.195. When we conduct BIMO GLP inspections as a result of an application or submission to FDA, we rely on the sponsor to provide the		

location of the study archives. (See proposed § 58.5(j).) We propose that the sponsor must include, in any application or submission to FDA that contains the results of a nonclinical laboratory study, the final study report of the nonclinical laboratory study and all amendments to the final report described in proposed § 58.185. Also, we propose that the sponsor must include either a statement that the study was conducted in compliance with the requirements in part 58 or, if not conducted in compliance with part 58, a brief statement of the reason for noncompliance. (See proposed § 58.5(k)). We propose this requirement, consistent with the proposed expansion of the scope, to include all applications and submissions to FDA supported by data from nonclinical laboratory studies.		
Transfer of Responsibilities (§ 58.10) We propose significant changes to current § 58.10 to help address the possibility of multiple contractual relationships, including subcontracting, in multisite nonclinical laboratory studies, and to conform as much as possible to the regulations in 21 CFR 312.52, Transfer of obligations to a contract research organization, and 21 CFR 511.1(f), Contract research organizations. Many comments to the December 2010 ANPRM suggest that we specify in part 58 the parties responsible in a multisite study and how any transfer of responsibilities is accomplished. We agree with those suggestions. We also propose the changes because the current regulations address explicitly only testing facilities.	**58.10 Applicability to studies performed under grants and contracts.** When a sponsor conducting a nonclinical laboratory study intended to be submitted to or reviewed by the Food and Drug Administration utilizes the services of a consulting laboratory, contractor, or grantee to perform an analysis or other service, it shall notify the consulting laboratory, contractor, or grantee that the service is part of a nonclinical laboratory study that must be conducted in compliance with the provisions of this part.	**§ 58.10 Transfer of responsibilities.** (a) Any person utilizing the services of a contracted person (as defined in § 58.3) to perform a phase (as defined in § 58.3) of a nonclinical laboratory study may transfer to the contracted person any regulatory responsibility in this chapter, unless delegation of such responsibility is expressly prohibited. Any such transfer must be described in writing. Any responsibility not covered by the written description is deemed not transferred. (b) Any person transferring to a contracted person any responsibility for a phase of a nonclinical laboratory study must inform that contracted person that the transferred responsibility must be performed in compliance with the provisions in this part.

We propose changing the title of § 58.10 from "Applicability to studies performed under grants and contracts" to "Transfer of responsibilities" to reflect the proposed changes to this section. We also propose adding paragraph designations (a), (b), and (c). In § 58.10(a), we propose to require written documentation of any transfer of responsibilities to a "contracted person", as that term is proposed in § 58.3, referring to any person a sponsor utilizes to provide a service for the conduct of a nonclinical laboratory study. Contracted persons may, for example, serve as the study director, management with executive responsibility, the QAU, a testing facility, a test site, or an independent contributing scientist. These contracted persons may further contract with other individuals or entities. Specifically, we propose that any responsibility required by the regulations that is transferred must be described in writing, and that any responsibility not covered by the written description is considered not transferred. We propose to add in § 58.10(b) that any person transferring to a contracted person any regulatory responsibility for a phase of a nonclinical laboratory study must inform that contracted person that the transferred responsibility is required to be performed in compliance with the provisions in part 58. Proposed paragraph (b) therefore includes what is currently in § 58.10. In § 58.10(c), we propose adding that a contracted person assuming any regulatory responsibility for a phase of a nonclinical laboratory study must comply with the regulations in chapter I (21 CFR chapter I)		(c) A contracted person assuming any responsibility for a phase of a nonclinical laboratory study must comply with the regulations in this chapter applicable to the transferred responsibility and is subject to the same regulatory actions as those transferring the responsibility.

applicable to the transferred responsibility. That contracted person will be subject to the same regulatory requirements as those regulated persons transferring the responsibility. We propose these requirements for transfer of responsibilities in a nonclinical laboratory study to help ensure contracted persons perform any transferred responsibilities in compliance with part 58 and to help ensure the quality and integrity of data supporting applications and submissions to FDA. Also, our proposal is consistent with industry's desire for flexible relationships among persons conducting phases of a nonclinical laboratory study.		
Inspection of Any Person Conducting a Phase of a Nonclinical Laboratory Study (§ 58.15) We propose revising § 58.15 to clarify FDA's inspection authority to include inspecting any person that conducts a phase of a nonclinical laboratory study of an FDA-regulated product. This includes all contracted and subcontracted persons that agree to assume one or more regulatory responsibilities. We propose revising the heading of § 58.15 to be consistent with these proposed changes. Also, we propose modifying the provision about FDA inspection of QAU records. In the preamble to the original GLP final rule (43 FR 59986 at 59998, December 22, 1978) (Ref. 12) and repeated in FDA's compliance policy guide (CPG 7151.02) (Ref. 13), we state our policy that FDA investigators will not routinely inspect QAU records. Exceptions when FDA will inspect QAU records include "for cause" FDA inspections, or inspections conducted under an inspection warrant, or when	**§ 58.15 Inspection of a testing facility.** (a) A testing facility shall permit an authorized employee of the Food and Drug Administration, at reasonable times and in a reasonable manner, to inspect the facility and to inspect (and in the case of records also to copy) all records and specimens required to be maintained regarding studies within the scope of this part. The records inspection and copying requirements shall not apply to quality assurance unit records of findings and problems, or to actions recommended and taken. (b) The Food and Drug Administration will not consider a nonclinical laboratory study in support of an application for a research or marketing permit if the testing facility refuses to permit inspection. The determination that a nonclinical laboratory study will not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation	**§ 58.15 Inspection of any person conducting a phase of a nonclinical laboratory study.** (a) Any person conducting a phase of a nonclinical laboratory study must permit, at reasonable times and in a reasonable manner, an authorized employee of FDA to inspect and copy all records and inspect all specimens required to be maintained for nonclinical laboratory studies within the scope of this part and, where applicable, to collect reserve samples for such studies. The records inspection and copying requirements do not routinely apply to QAU records of findings and problems or to actions recommended and taken. However, FDA retains the authority to inspect all QAU records when necessary to ensure compliance with this part. (b) FDA will not consider a nonclinical laboratory study submitted in support of an application or submission to FDA if any person conducting a phase of the nonclinical laboratory study refuses to permit

necessary for litigation purposes. Therefore, we propose modifying § 58.15(a) to specifically state that the "records inspection and copying requirements do not routinely apply to QAU records of findings and problems, or to actions recommended and taken". We propose adding for clarity, that "FDA retains the authority to inspect all QAU records when necessary to ensure compliance with this part [part 58]". In § 58.15(b), we propose changing certain terms for consistency within this proposal. For example, we propose changing "the testing facility" to "any person conducting a phase of the nonclinical laboratory study".	under any applicable statute or regulation to submit the results of the study to the Food and Drug Administration.	inspection. The determination that a nonclinical laboratory study will not be considered in support of an application or submission to FDA does not, however, relieve the applicant of any obligation under any other applicable statute or regulation to submit the results of the study to FDA.
Personnel (§ 58.29) We propose no changes to the intent of current § 58.29(a). However, we propose adding to the end of this provision clarifying sentences, "This must include training and experience with GLP requirements. Personnel who work with animals must have both general and species specific training and experience." Several comments to the December 2010 ANPRM state that training on GLP requirements is essential for all personnel in a nonclinical laboratory study. This proposed training requirement also is consistent with the personnel requirements in the OECD Principles on Good Laboratory Practice (Ref. 8). Therefore, we propose requiring GLP training to ensure all personnel in a nonclinical laboratory study understand how to comply with GLP and all aspects of a nonclinical laboratory study are GLP compliant. As we state elsewhere in section III.A.3., we propose specific	Subpart B—Organization and Personnel **§ 58.29 Personnel.** (a) Each individual engaged in the conduct of or responsible for the supervision of a nonclinical laboratory study shall have education, training, and experience, or combination thereof, to enable that individual to perform the assigned functions. (b) Each testing facility shall maintain a current summary of training and experience and job description for each individual engaged in or supervising the conduct of a nonclinical laboratory study. (c) There shall be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol. (d) Personnel shall take necessary personal sanitation and health precautions designed to avoid contamination of test and control articles and test systems. (e) Personnel engaged in a nonclinical laboratory study shall	**58.29 Personnel.** (a) Each individual engaged in the conduct of, or responsible for the supervision of, a nonclinical laboratory study must have education, training, and experience, or a combination thereof, to enable that individual to perform the assigned functions. This must include training and experience with GLP requirements. Personnel who work with animals must have both general and species-specific training and experience. (b) All study personnel must have access to and comply with the protocol and all applicable protocol amendments and SOPs. Any deviation must be reported to the study director. (c) All study personnel must record raw data, as defined in § 58.3, promptly and accurately as required by § 58.180. (d) Any person conducting a phase of a nonclinical laboratory study must maintain a current summary of training and experience and a job description

responsibilities regarding animal welfare because compliance with animal care requirements helps ensure the quality and integrity of study data. Therefore, we propose that all personnel involved with animal treatment and care must have relevant training and experience, including species-specific training when applicable. In § 58.29(b), we propose adding a requirement that all study personnel must have access to and comply with the study protocol and applicable protocol amendments and SOPs, and any protocol deviation must be reported to the study director. In § 58.29(c), we propose adding a requirement that all study personnel must record raw data promptly and accurately as required by a new regulatory provision in § 58.180 Data quality and integrity. We propose these new provisions to help ensure compliance with GLPs and to update the regulations consistent with current practices and the prevalence of multisite studies. This proposal also is consistent with personnel responsibilities in the OECD Principles on Good Laboratory Practice (Ref. 8). In proposed § 58.29(d) (currently, § 58.29(b)), we replace "Each testing facility" with "Any person conducting a phase of a nonclinical laboratory study". We propose this and other conforming changes in § 58.29 to address the occurrence of contracting and subcontracting in multisite studies, to update the regulations, and for consistency with our proposals in part 58.	wear clothing appropriate for the duties they perform. Such clothing shall be changed as often as necessary to prevent microbiological, radiological, or chemical contamination of test systems and test and control articles. (f) Any individual found at any time to have an illness that may adversely affect the quality and integrity of the nonclinical laboratory study shall be excluded from direct contact with test systems, test and control articles and any other operation or function that may adversely affect the study until the condition is corrected. All personnel shall be instructed to report to their immediate supervisors any health or medical conditions that may reasonably be considered to have an adverse effect on a nonclinical laboratory study	for each individual in the person's employment engaged in or supervising the phase of the study for which the person is responsible. (e) There must be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol. (f) Personnel must take necessary personal sanitation and health precautions designed to avoid contamination of test, control, and reference articles and test systems. (g) Personnel engaged in a nonclinical laboratory study must wear clothing appropriate for the duties they perform. Such clothing must be changed as often as necessary to prevent microbiological, radiological, or chemical contamination of test systems and test, control, and reference articles. (h) Any individual found at any time to have an illness that may adversely affect the quality and integrity of the nonclinical laboratory study must be excluded from direct contact with test systems; test, control, and reference articles; and any other operation or function that may adversely affect the study until the condition is corrected. All personnel must be instructed to report to their immediate supervisors any health or medical conditions that may reasonably be considered to have an adverse effect on a nonclinical laboratory study.
Testing Facility Management with Executive Responsibility (§ 58.31) We propose significant changes in § 58.31 consistent with our proposal requiring a GLP Quality System. To clarify who is	**§ 58.31 Testing facility management.** For each nonclinical laboratory study, testing facility management shall:	**§ 58.31 Testing facility management with executive responsibility.** Management with executive responsibility is ultimately responsible for the GLP Quality

responsible for the proposed requirements in § 58.31, we propose adding "with executive responsibility" to the current heading of "Testing facility management." We propose this change to specify that upper management at a testing facility or test site is ultimately responsible for GLP compliance. We also propose summarizing in the introductory paragraph the expanded responsibilities of management consistent with the regulatory text in part 820 (see § 820.20). The current provisions in § 58.31(c) through (g) require only assurances that certain activities are available, performed, understood, or communicated. For those responsibilities currently in § 58.31, we propose clarifying and expanding them, requiring actions and referencing specific SOPs (where applicable). We also propose adding new responsibilities consistent with a GLP Quality System and the conduct of multisite studies. We propose a new § 58.31(a) requiring testing facility management with executive responsibility to establish and update written GLP Quality System SOPs. For continuing oversight of the GLP Quality System, in new § 58.31(b), we propose requiring testing facility management with executive responsibility to review at specified and sufficient intervals and document that the GLP Quality System meets the requirements in proposed part 58. We propose that testing facility management with executive responsibility is responsible for overseeing the implementation of the requirements in proposed § 58.31(b), according to established procedures to be included in proposed §	(a) Designate a study director as described in § 58.33, before the study is initiated. (b) Replace the study director promptly if it becomes necessary to do so during the conduct of a study. (c) Assure that there is a quality assurance unit as described in § 58.35. (d) Assure that test and control articles or mixtures have been appropriately tested for identity, strength, purity, stability, and uniformity, as applicable. (e) Assure that personnel, resources, facilities, equipment, materials, and methodologies are available as scheduled. (f) Assure that personnel clearly understand the functions they are to perform. (g) Assure that any deviations from these regulations reported by the quality assurance unit are communicated to the study director and corrective actions are taken and documented.	System and must establish policy and objectives for a GLP Quality System and a commitment to quality, as defined in § 58.3. Management with executive responsibility must ensure that the quality policy, as defined in § 58.3, is implemented and maintained at all levels of the organization. Management with executive responsibility must: (a) Establish and update written SOPs, as required in § 58.81(b)(2) for a GLP Quality System. (b) Review the suitability and effectiveness of the GLP Quality System at defined intervals and with sufficient frequency according to established procedures, to be included in SOPs for the GLP Quality System (§ 58.81(b)(2)), to ensure that the GLP Quality System satisfies the established quality policy and objectives and the requirements of this part. The dates and results of these reviews must be documented. (c) Establish and maintain an adequate organizational structure (personnel, resources, facilities, equipment, materials, and methodologies) to ensure that all testing complies with the established GLP Quality System, according to the requirements of this part. (d) Establish procedures, to be included in SOPs for the GLP Quality System (§ 58.81(b)(2)), for the appropriate responsibility, authority, and interrelationship among all personnel who manage, perform, and assess work affecting quality, and provide the independence and authority necessary to perform these tasks. (e) Appoint and document the appointment of, according to procedures to be included in SOPs for the GLP Quality System

58.81(b)(2) (establishment and periodic review of a GLP Quality System) In § 58.31(e), we propose that testing facility management with executive responsibility appoint and document the appointment of a management representative who is a member of the testing facility management with authority over and responsibility for documenting that GLP Quality System requirements are effectively established and maintained. We also propose that this appointed member reports to management with executive responsibility about the performance of the GLP Quality System, which includes reports from the QAU. Appointment of this individual is an organizational responsibility of the testing facility management with executive responsibility such as in part 820, Quality System Regulation, the model for the GLP Quality System. In § 58.31(f), we propose that testing facility management with executive responsibility is responsible for documenting that all persons in a multisite study follow adequate equipment related SOPs. In § 58.31(h), we propose this same management is responsible for documenting that all study personnel are trained to perform their assigned functions. In § 58.31(k), we propose this same management is responsible for appointing a person to maintain the master schedule along with other requirements concerning the master schedule, such as requiring in a master schedule the core information presently specified under QAU responsibilities in § 58.35(b)(1). This core information is essential on each master schedule to ensure consistent identification		(§ 58.81(b)(2)), a management representative who is a member of the testing facility management with authority over and responsibility for: (1) Documenting that GLP Quality System requirements are effectively established and effectively maintained; and (2) Reporting on the performance of the GLP Quality System to management with executive responsibility for review, including all reports from the QAU. (f) Establish SOPs for equipment, as required in § 58.81(b)(14), including standards for appropriate documentation of equipment validation, as defined in § 58.3. For multisite studies, document that any person conducting a phase of the nonclinical laboratory study follows adequate equipment-related SOPs. (g) Establish SOPs to ensure that computerized systems are suitable for their intended purposes and are appropriately validated, operated, and maintained as required in § 58.81(b)(15). (h) Document that all study personnel are trained to perform their assigned functions. (i) Establish SOPs, as required in § 58.81(b)(18), for ensuring and documenting the qualifications of any person conducting a phase of a nonclinical laboratory study. (j) Establish SOPs for the development and maintenance of the master schedule as required in § 58.81(b)(13). (k) Appoint and document the appointment of a person to maintain the master schedule. The master schedule must be indexed by test article and contain the identification of the test system, the nature of the study, the date the study was

across all persons (individuals or entities) in a multisite study. We propose adding § 58.31(m), requiring testing facility management with executive responsibility to review all protocols to ensure that environmental, animal welfare, or work resource issues or issues with scientific methodology do not affect or bias any phase of the study's conduct. We propose adding § 58.31(r) to require testing facility management with executive responsibility to review the suitability and effectiveness of the QAU or lead QAU, as applicable, at defined intervals and with sufficient frequency, according to established SOPs as required in proposed § 58.81(b)(17). Periodic review of the QAU's capability to fulfill their responsibilities helps to ensure the quality and integrity of study data and is also consistent with a quality system. We propose adding § 58.31(u), requiring testing facility management with executive responsibility to establish SOPs for archiving records and materials generated during the course of a nonclinical laboratory study, including the designation and replacement of the archivist and any supporting staff. This archiving process is an essential aspect of compliance with GLPs because maintenance of raw data and specimens from a specific study enables reconstruction of that study for verification of the information in the final study report and confirmation of the study's compliance with part 58. These and other proposals in § 58.31 are consistent with the preamble to the original GLP final rule that states, "A determination of the adequacy of each standard		initiated, the current status of each study, the identity of the sponsor, and the name of the study director. For multisite studies, the master schedule of each person conducting a phase of a nonclinical laboratory study must also include the specific phases that person conducts. (l) Establish procedures, to be included in SOPs for multisite studies required in § 58.81(b)(18), for the transfer of data, specimens, and samples among all persons conducting phases of the nonclinical laboratory study; verification of the accuracy and completeness of any translations of SOPs and protocols, when applicable; and storage, return, or disposal of test, control, and reference articles, as applicable. (m) Review all protocols to determine that there are no environmental, animal welfare, or work resource issues or issues with scientific methodology that might affect or bias any phase of the conduct of the proposed study. Document the review and acceptance of each protocol. (n) Establish SOPs, as required in § 58.81(b)(3), for designation of a study director, as described in § 58.33, before the study is initiated and prompt replacement of the study director if it becomes necessary to do so during the conduct of a study. (o) Establish procedures, to be included in SOPs for the GLP Quality System (§ 58.81(b)(2)), to ensure a clear line of communication among the study director, principal investigator(s), QAU(s), the sponsor, and all study personnel, as applicable. (p) Provide for a QAU as described in § 58.35. Before initiating a multisite study, as defined in § 58.3, designate and document the designation of the

operating procedure is the responsibility of the management" (43 FR 59986 at 60002) (Ref. 12). Also, our proposals are responsive to many comments to the December 2010 ANPRM asking that we define operational areas necessary for broader adoption of a quality system approach to the conduct of nonclinical laboratory studies. Rather than specifying how essential activities of a GLP Quality System must be conducted, we propose requiring management with executive responsibility at testing facilities and test sites to establish essential SOPs. This flexible approach would allow testing facilities and test sites to establish SOPs best suited to their specific organizational structure.		lead QAU with overall responsibility for the entire study. Provide the information described in § 58.35(a) of the lead QAU to all persons involved in the conduct of the study and all QAUs serving those persons. (q) Establish procedures, to be included in SOPs for the GLP Quality System (§ 58.81(b)(2)), to ensure QAU review of SOPs and study protocols to verify that they meet GLP requirements. This review must be documented. (r) *Review the suitability and effectiveness of the QAU or lead QAU, as applicable, at defined intervals and with sufficient frequency, according to established SOPs as required in § 58.81(b)(17),* to ensure that the QAU satisfies established quality policy and objectives and the requirements of this part. For multisite studies, testing facility management with executive responsibility must periodically review the suitability and effectiveness of the lead QAU. The dates and results of reviews of the QAU must be documented. (s) Establish SOPs, as required in § 58.81(b)(6), for the receipt of information regarding the characterization of all test, control, and reference articles or mixtures, including data on their identity, strength, purity, stability, and uniformity, as applicable. (t) Establish SOPs, with appropriate timeframes, for the conduct of QAU inspections and for the receipt, review, and followup of all concerns, problems, and regulatory deviations reported by the QAU. These SOPs must include procedures for correcting reported problems and, as necessary, for modification of relevant SOPs to prevent a recurrence of any problems, as

		required in § 58.81(b)(20) and (21). (u) Establish SOPs, as required in § 58.81(b)(13), for the development and maintenance of an archive system, including the designation and replacement of the archivist and any supporting staff. (v) Establish procedures to ensure maintenance of a historical file of all SOPs as required in § 58.81(b)(1).
Test Site Management with Executive Responsibility (§ 58.32) We propose updating the regulations by adding § 58.32. This new provision would address the current prevalence of multisite studies and require test site management with executive responsibility to comply with relevant requirements in proposed § 58.31 and develop and maintain SOPs described in § 58.81, "where appropriate", as that term is proposed in § 58.1(c). We expect that a test site, like a testing facility, has management with executive responsibility and appropriate SOPs. Therefore, while a test site might be conducting a phase of a particular multisite study, for a different study the same test site could function as a testing facility by coordinating, conducting, or completing the entire study.		Add § 58.32 to subpart B to read as follows: **§ 58.32 Test site management with executive responsibility.** For multisite studies, each test site participating in the study must have management with executive responsibility for the test site who must: (a) Comply with responsibilities delineated for testing facility management with executive responsibility, as described in section § 58.31, where appropriate. (b) Develop and maintain SOPs as specified in § 58.81, where appropriate.
Study Director (§ 58.33) In § 58.33, we propose modifying and adding study director requirements to update the regulations and to address the prevalence of multisite studies. We propose certain study director requirements for consistency with our other proposals in part 58 (for example, our proposals for a GLP Quality System and for checks and balances to help ensure data quality and integrity).	**§ 58.33 Study director.** For each nonclinical laboratory study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, shall be identified as the study director. The study director has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of results, and represents the single point of	**§ 58.33 Study director.** (a) For each nonclinical laboratory study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, must be identified as the study director. The study director represents the single point of study control and has overall responsibility, which cannot be delegated, for: (1) The technical conduct of the entire study;

In § 58.33(a), we propose keeping the current requirement that the study director is the single point of study control. We propose adding that the study director cannot delegate overall responsibility for a nonclinical laboratory study. This proposed addition clarifies and emphasizes that a study director cannot delegate oversight of an entire nonclinical laboratory study, even though a study director may delegate to a principal investigator certain responsibilities. This proposed change is consistent with FDA's longstanding interpretation of a study director's responsibilities and consistent with present FDA and EPA GLP regulations. This proposed addition also is consistent with the OECD consensus document, The Role and Responsibilities of the Study Director in GLP Studies (Ref. 14). Many comments to the December 2010 ANPRM stress the importance of the study director remaining the single point of study control. We propose in § 58.33(a)(2) the study director's responsibility for implementing procedures that ensure adequate communication among all study personnel and with the sponsor, as applicable, because communication is essential in a nonclinical laboratory study. In § 58.33(b), we propose new requirements for the study director for documenting, consulting, signing, and archiving (see proposed §§ 58.33(b)(2) through (7) and (12) through (14)). In § 58.33(b)(13), we propose that the study director must sign and date the final study report. FDA agrees with OECD's discussion in this regard in both the OECD Principles on Good Laboratory Practice (Ref. 8) and the	study control. The study director shall assure that: (a) The protocol, including any change, is approved as provided by § 58.120 and is followed. (b) All experimental data, including observations of unanticipated responses of the test system are accurately recorded and verified. (c) Unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study are noted when they occur, and corrective action is taken and documented. (d) Test systems are as specified in the protocol. (e) All applicable good laboratory practice regulations are followed. (f) All raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study.	(2) The implementation of procedures to ensure adequate communication among all study personnel and with the study sponsor, as applicable; and (3) The interpretation, analysis, documentation, and reporting of results and study compliance. (b) The study director must: (1) Approve the protocol, including any changes, as provided by § 58.120, and document that it is followed. (2) Document that the QAU has reviewed the protocol and all applicable SOPs, and any amendments, before study initiation and implementation of applicable amendments to ensure that they are compliant with GLP requirements. (3) Document that testing facility management with executive responsibility has committed adequate resources for the conduct of the specific study. (4) Document that computerized systems are validated and fit for use in the specific study. (5) For studies requiring the use of animals, document that the initial protocol and any amendments that impact the use of animals are reviewed and approved, as required in § 58.120(b) and (e), by a committee whose function is to ensure that the care and use of animals in studies is appropriate and humane, before study initiation and the implementation of applicable amendments. (6) Consult with the attending veterinarian, as defined in § 58.3, during review of proposed study protocols to determine potential animal welfare concerns and appropriate responses to likely contingencies. Defer to the attending veterinarian when decisions regarding animal welfare arise, particularly when animals are in pain or distress.

consensus document, The Role and Responsibilities of the Study Director in GLP Studies (Ref. 14). The study director's signature on the final study report indicates acceptance of responsibility for the validity of the data and the extent to which the study complies with GLP principles. We also recognize that we use the terms retain and archive interchangeably throughout this proposal (see, for example, proposed § 58.33(b)(14)), and we seek comment on which term is preferred by industry. We propose adding in § 58.33(b)(5) and (6) new study director responsibilities affecting the welfare of test animals. When a protocol and its amendments impact test animal use, we propose the study director must document that a committee whose function is ensuring the appropriate and humane care of animals must first review and approve the protocol and applicable amendments before initiating the study or implementing the amendments. The study director also must document that such a committee has reviewed and approved general procedures for commonly conducted animal tests. Any protocol requiring only those tests, with their approved parameters, would not require additional review before study initiation. However, if a protocol increases the numbers of animals to be used or alters any of the approved testing parameters, specific review and approval of that protocol would be required before study initiation. We propose in 58.35(b)(6), that the study director must consult with the attending veterinarian during review of proposed study protocols to determine potential animal welfare concerns and		(7) For multisite studies: (i) Document the qualifications of any person conducting a phase of the nonclinical laboratory study. (ii) Determine and document the need for principal investigators. (8) Document that all experimental data, including observations of unanticipated responses of the test system, are accurately recorded and verified. (9) Document unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study when they occur and the corrective action taken. (10) Document that test systems are as specified in the approved study protocol. (11) Document that all applicable GLP regulations are followed and include a study compliance statement in the final study report. (12) Document all communications with all persons conducting a phase of the nonclinical laboratory study and with the sponsor, as applicable. (13) Sign and date the final study report. (14) Archive all raw data, documentation, protocols, specimens, reserve samples, and final reports no later than 2 weeks after the study completion date.

appropriate responses to likely contingencies. Early identification of potential animal welfare concerns benefits the test animals because they will receive prompt care, which improves the quality of the data collected. In 58.33(b)(11), we propose adding that the study director must document that all applicable GLP regulations are followed and include a study compliance statement in the final study report. FDA agrees with the statement in the OECD consensus document, The Role and Responsibilities of the Study Director in GLP Studies (Ref. 14) that the study director should ascertain that GLP requirements are fully complied with in every phase of a study, that the study protocol is faithfully followed, and that all observations, including any deviations from the protocol, are fully documented. In § 58.33(b)(14), we propose adding a timeframe for archiving of no later than 2 weeks after the study completion date. We think that timely archiving of raw data, documents, protocols, specimens, and final reports will help prevent their loss or destruction. Stakeholders requesting modernizing part 58 asked specifically for a reasonable time period after the study completion date to complete study archiving. Numerous comments to the December 2010 ANPRM agree, particularly with regard to archiving computerized systems. We propose the 2-week timeframe to allow flexibility for archiving material without jeopardizing study material integrity.		
Quality Assurance Unit (QAU) (§ 58.35) In § 58.35, we propose keeping the QAU functions currently in	**§ 58.35 Quality assurance unit.** (a) A testing facility shall have a quality assurance unit which shall be responsible for monitoring	**§ 58.35 Quality assurance unit (QAU).** (a)(1) *Function.* A QAU must monitor each study to assure

the regulations. We propose modifying § 58.35(a) by separating it into paragraph (1) QAU function and paragraph (2) QAU location. We propose this change for consistency with our other proposals in part 58 (for example, to address the location of the lead QAU for multisite studies), and in response to comments to the December 2010 ANPRM requesting a clear description of the relationship between the QAU and test facility management. We propose in § 58.35(a)(2)(ii) that, for multisite studies, testing facility management with executive responsibility must designate a lead QAU. The concept of a lead QAU is consistent with the discussion in the preamble of the original GLP final rule stating that when portions of a study must be contracted to a site that lacks a QAU "the person letting the contract, and not the contract facility, is responsible for the performance of the quality assurance functions" (43 FR 59986 at 59997) (Ref. 12). This change also is consistent with the OECD consensus document, Quality Assurance and GLP (Ref. 7). Several comments to the December 2010 ANPRM specifically note the need for a lead QAU in multisite studies. We propose several modifications to current § 58.35(b). We propose changing the present QAU requirement to maintain a copy of the master schedule and all protocols to require that the QAU maintain "access" to them. For example, if the QAU is a contracted person, then the QAU might not have overall knowledge about the person (i.e., testing facility) to which they are providing QA services. However, the QAU	each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the regulations in this part. For any given study, the quality assurance unit shall be entirely separate from and independent of the personnel engaged in the direction and conduct of that study. (b) The quality assurance unit shall: (1) Maintain a copy of a master schedule sheet of all nonclinical laboratory studies conducted at the testing facility indexed by test article and containing the test system, nature of study, date study was initiated, current status of each study, identity of the sponsor, and name of the study director. (2) Maintain copies of all protocols pertaining to all nonclinical laboratory studies for which the unit is responsible. (3) Inspect each nonclinical laboratory study at intervals adequate to assure the integrity of the study and maintain written and properly signed records of each periodic inspection showing the date of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for reinspection. Any problems found during the course of an inspection which are likely to affect study integrity shall be brought to the attention of the study director and management immediately. (4) Periodically submit to management and the study director written status reports on	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 QAU must be entirely separate from and independent of the personnel engaged in the direction and conduct of the study. (2) *Location and identity.* (i) For studies conducted entirely at the testing facility, the QAU can consist of personnel at the facility itself or be a separately contracted unit. (ii) For multisite studies, a lead QAU must be designated by testing facility management with executive responsibility and must have responsibility for the QA of the entire study. The lead QAU can consist of personnel at the testing facility, be a QAU for another person conducting a phase of the study, or be a separately contracted unit. QAUs for persons conducting a phase of the study must coordinate with the lead QAU as specified in SOPs as described in § 58.81(b)(17) and (20). The lead QAU has direct QA responsibility for any person lacking a QAU. (b) QAUs must: (1) Maintain access to the master schedule (defined in § 58.3) of all nonclinical laboratory studies conducted by the person employing the QAU or contracting for QA services. For multisite studies, the lead QAU must maintain access to the master schedule of any person lacking a QAU. (2) Maintain access to copies of all protocols pertaining to all nonclinical laboratory studies for which the QAU is responsible. (3) Review all protocols before study initiation, and all protocol amendments before implementation, to ensure that

requires “access” to the master schedule and protocols to ensure GLP compliance. We recognize that many sites have a central computerized system for maintenance of essential documents. Our proposed change about QAU access to the master schedule responds to stakeholder requests to modernize part 58 and also to comments to the December 2010 ANPRM. This change also is consistent with our proposal in § 58.195(d) that management with executive responsibility must ensure “maintenance” of the master schedule and copies of study protocols. Because the lead QAU is responsible for ensuring GLP compliance of all phases of a multisite study, we propose that the lead QAU must maintain access to the master schedule of any person that lacks a QAU. We consider the master schedule an important tool for determining whether a person is capable of conducting a GLP compliant study. For example, a person with numerous scheduled studies still in progress may lack sufficient resources to begin the conduct of a GLP compliant study. Also, as many comments to the December 2010 ANPRM suggest, we propose removing the word “sheet” from the term “master schedule sheet”. We propose removing “sheet” because we do not want to imply that a paper copy is required for electronic systems. In new § 58.35(b)(3), we propose requiring the QAU to review the study protocol before initiating the study and all protocol amendments before implementing them, along with documenting this review. In new § 58.35(b)(4), we propose requiring the QAU to review all SOPs applicable to a given	each study, noting any problems and the corrective actions taken. (5) Determine that no deviations from approved protocols or standard operating procedures were made without proper authorization and documentation. (6) Review the final study report to assure that such report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the nonclinical laboratory study. (7) Prepare and sign a statement to be included with the final study report which shall specify the dates inspections were made and findings reported to management and to the study director. (c) The responsibilities and procedures applicable to the quality assurance unit, the records maintained by the quality assurance unit, and the method of indexing such records shall be in writing and shall be maintained. These items including inspection dates, the study inspected, the phase or segment of the study inspected, and the name of the individual performing the inspection shall be made available for inspection to authorized employees of the Food and Drug Administration. (d) A designated representative of the Food and Drug Administration shall have access to the written procedures established for the inspection and may request testing facility management to certify that inspections are being implemented, performed, documented, and followed-up in accordance with this paragraph.	they can be conducted in compliance with this part. This review must be documented. (4) Review all SOPs to be used for the conduct of all phases of a nonclinical laboratory study to assess their clarity and compliance with this part. This review must be documented. (5) Inspect each nonclinical laboratory study for which the QAU is responsible at intervals adequate to ensure the integrity of the specific study. Inspections must determine compliance with the protocol, applicable SOPs, and the requirements of this part. These can include study-based, process-based, and facility-based inspections as defined in § 58.3 and as specified in SOPs as required in § 58.81(b)(20). For multisite studies, the lead QAU must coordinate the conduct of study inspections with any other existing QAUs, as specified in SOPs as required in § 58.81(b)(20). Upon discovery, any problems found during an inspection which are likely to affect study integrity must be reported to the study director and management with executive responsibility for the study or studies affected. (6) Maintain written and properly signed records of all inspections that include the date of the inspection, the individual performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for reinspection. For study-specific inspections, reports must also include the identity of the study and the phase of the study inspected. (7) Periodically submit to management with executive responsibility and the study

nonclinical laboratory study along with documenting this review. Current regulations state the QAU is "responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance" with GLPs (current § 58.35(a)). Our proposed initial review by the QAU of the study protocol and applicable facility SOPs will help ensure compliance with part 58 from the start of the study. Otherwise, when the study is underway, amendments to the study protocol and SOPs might be needed if QAU inspections reveal compliance deficiencies. We propose in § 58.35(b)(5) expanding the types of QAU inspections recognized by FDA by adding process-based and facility-based inspections.7 Many comments to the December 2010 ANPRM request this change consistent with QAU inspections described in the OECD consensus document, Quality Assurance and GLP (Ref. 7), specifically supporting an appropriate mix of study-specific and process-based inspections. However, many comments to the December 2010 ANPRM express concern about how process-based inspection results will be appropriately considered for all relevant studies, particularly when an inspection reveals problems. This concern is especially relevant to any phase involving a short-term study, as we propose to define this term. Process-based inspections are conducted on a prearranged schedule, which is not connected to the timing of any particular nonclinical laboratory study. Therefore, a facility utilizing process-based inspections might conduct a short-term study that		director written status reports on each study that discuss the overall progress and compliance status of the study and that include any problems observed and the corrective actions taken. The content and frequency of these reports must be specified in SOPs, as described in § 58.81(b)(21). (8) Determine that no deviations from approved protocols or SOPs were made without proper authorization and documentation. For multisite studies, the lead QAU is responsible for identifying all deviations that occur across the entire study, including deviations identified by all other QAUs participating in the study, as described in SOPs in § 58.81(b)(17). (9) Audit the reports of all contributing scientists, and any amendments to such reports, to ensure such reports reflect the protocol and all amendments, accurately describe the methods and SOPs, and report all of the raw data of the specific phases covered by each report. For multisite studies, QAUs for persons conducting a phase of the study must audit the reports of any principal investigators and all contributing scientists for whom they are responsible, and any amendments to such reports, as specified in SOPs as described in § 58.81(b)(17). The lead QAU must audit the reports, and any amendments to such reports, of any principal investigators and all contributing scientists for any person lacking a QAU and of any independent contributing scientists. (10) Audit the final study report, and any amendments to this report, to ensure that such report accurately describes the methods and SOPs, all raw data of the nonclinical laboratory

is not inspected during its in-life period (that is, during the time data are collected). This concern also is addressed in the OECD consensus document, The Application of the GLP Principles to Short Term Studies (Ref. 15). To ensure that any problem revealed during a process-based inspection is properly captured in the reports of all relevant studies, we propose adding § 58.35(e). This provision requires preparation of a written certification, by the person conducting a phase of the study, whenever a process-based inspection reveals problems. As proposed, this certification requires documenting actions taken to properly inform, and modify (when applicable), reports for all studies impacted by the results of that process or procedure. While a management responsibility, we propose adding this requirement in § 58.35 because of its similarity to the existing requirement in current § 58.35(d) for management to provide an FDA representative, upon request, a certification regarding the implementation of required QAU inspections. In § 58.35(b)(7) (a redesignation and revision of current § 58.35(b)(4)), we propose expanding the requirement that the QAU must submit to management with executive responsibility and the study director a periodic written status report on each study. We propose that these periodic reports "discuss the overall progress and compliance status of the study and include any problems observed and the corrective actions taken." In conjunction with this requirement, we propose that the content and frequency of these reports be specified in SOPs as		study are reported, and that all original and amended signed and dated reports from all contributing scientists are appended. For multisite studies, this is the responsibility of the lead QAU. (11) Prepare, sign, and date a statement to be included with the final study report that specifies: (i) The dates of study-specific inspections, process-based inspections if applicable, and facility-based inspections; (ii) Findings reported to management with executive responsibility and to the study director; and (iii) The dates of QAU audits of the reports of all contributing scientists (including any independent contributing scientists), any principal investigators, and of the final study report and all amendments to such. For multisite studies, this is the responsibility of the lead QAU. When other persons conducting a phase of the study have QAUs, those QAUs must provide to the lead QAU such statements regarding the audits they conducted, for appending to the final study report. (c) The responsibilities and procedures applicable to the QAU, the records maintained by the QAU, and the method of indexing such records must be in writing and must be maintained as specified in SOPs as required in § 58.81(b)(17). For multisite studies, the lead QAU and all other QAUs participating in the study must maintain those documents relevant to their oversight. These SOPs as well as documentation of the dates of all QAU inspections, the study or process or procedure, or facility inspected as applicable, the phase or segment of the study inspected for study-specific

required in proposed § 58.81(b)(21). We propose this revision in § 58.35(b)(7) because feedback to management with executive responsibility and the study director about the overall progress and compliance status of the study is essential to ensure study compliance. We intend these periodic reports to give a general overview of the study. We expect these periodic reports to complement any inspection reports for the study, which only provide a snapshot in time. We are interested in receiving feedback about the use and relevance of periodic status reports. Specifically, we are seeking comment about whether QAUs regularly provide such reports and whether they are useful to the study director and management when provided. Consistent with our proposals addressing multisite studies, we propose adding in new § 58.35(b)(8) (revision of current § 58.35(b)(5)) that the lead QAU must identify all deviations occurring in the entire study, including deviations identified by any other existing QAUs participating in the study. We expect this requirement may be facilitated by principal investigator reports to the study director, documentation by other existing QAUs, and direct oversight by the lead QAU of independent contributing scientists and any persons conducting a phase of the study lacking either a principal investigator or a QAU or both. We propose this requirement to ensure the lead QAU is made aware of protocol deviations in a timely manner. This awareness will help alert the lead QAU to the need to correct or modify relevant SOPs and the study protocol when necessary to		inspections, and the name of the individual performing the inspection must be made available for inspection to authorized employees of FDA. (d) A designated representative of FDA must, upon request, be given access to the written SOPs established for QAU inspections. If requested by FDA, the person inspected must certify that inspections are being implemented, performed, documented, and followed up according to this part. (e) If a person conducting a phase of a nonclinical laboratory study chooses to conduct process-based inspections, that person must prepare a written certification, as specified in SOPs as required in § 58.81(b)(21), whenever a process-based inspection reveals problems. This certification must document actions taken to properly inform and, when applicable, modify reports for all studies impacted by the results of the process or procedure in question.

maintain data integrity. The remaining additions we propose in § 58.35 relate to QAU oversight of the integrity of data in the final study report. Current responsibilities in § 58.35(b)(6) (revised and redesignated as § 58.35(b)(10)) are to ensure the quality and integrity of the final study report. Therefore, we propose in § 58.35(b)(9)that the QAU must audit the reports of all contributing scientists and all existing principal investigators. Currently § 58.35(b)(6) requires the QAU to assure that the "reported results accurately reflect the raw data of the nonclinical laboratory study." However, QAU members might not have the scientific judgment needed for evaluating the scientific merits of the final report and determining whether the results accurately reflect the data. In the preamble to the original GLP final rule (43 FR 59986 at 59998, comment 90) (Ref. 12), we agreed that "the QAU should not attempt to evaluate the scientific merits of the final report." Therefore, in § 58.35(b)(9) and (10), we propose clarifying our intent. Specifically, we propose that the QAU must audit all contributing scientists' reports and any report amendments to ensure they include a report of all data and reflect the protocol, and amendments, and applicable SOPs. This requires that all data generated during the study are included and discussed, which is essential for the full transparency necessary for reconstruction of the study. For multisite studies, we propose that other QAUs participating in the study must audit the reports and report amendments of any principal investigators and all contributing scientists for whom		

they are responsible. We also propose in § 58.35(b)(9), for any person that lacks a QAU, that the lead QAU audits the reports and amendments of all contributing scientists and any principal investigators. This includes audits of any independent contributing scientist. This proposed requirement will ensure all data from a nonclinical laboratory study will receive QAU review, thus improving the quality and integrity of the final study report. In § 58.35(b)(10), we propose that the QAU must verify that all original and amended signed and dated reports from contributing scientists are appended to the final study report. For multisite studies, we propose that the lead QAU is responsible for this requirement. Under existing regulations that require providing the final study report and any amendments, we expect that both original and amended versions of reports from all contributing scientists be appended to the final study report. The proposed changes make this expectation a specific requirement. This requirement will allow the study sponsor and FDA reviewers to have access to the original conclusions for each phase and any modifications made as a result of interactions among those involved with the study. We propose this requirement to address the potential inadvertent or intentional introduction of bias that may result when only the final amended version of contributing scientists' reports are included.		
Contributing Scientist (§ 58.37) As discussed in section III.B.2., we propose adding a definition for a contributing scientist. In that definition, we include an		Add § 58.37 to subpart B to read as follows: **§ 58.37 Contributing scientist.** (a) Each contributing scientist must:

independent contributing scientist as an individual expert or specialist who is an independently employed contracted person. We propose adding responsibilities for contributing and independent contributing scientists to help facilitate the development of a GLP Quality System. To describe the responsibilities of these positions, we propose adding § 58.37(a) and (b), respectively. When a contributing scientist is responsible for a phase, we propose in § 58.37(a) that the contributing scientist must comply with part 58; provide a signed and dated report for inclusion in the final study report; and permit oversight by the designated QAU. (See proposed § 58.37(a)(1) through (In § 58.37(b), we propose requirements for an independent contributing scientist in addition to those requirements in § 58.37(a). The proposed requirements in § 58.37(b) include, among others, that independent contributing scientists must document, maintain, and update information about their education, training, and experience related to their responsibilities for a particular phase. Also, we propose they must archive all materials as required by the protocol and by proposed § 58.195.3)). Our proposal for adding § 58.37 is consistent with the expectations in the present regulations for individual scientists and professionals. We propose these requirements in part to help clarify the regulations.		(1) Conduct, oversee, analyze, and provide any other service for the conduct of all phases of the nonclinical laboratory study for which the contributing scientist is responsible according to the requirements of this part. (2) Provide a signed and dated report of all phases for which the contributing scientist is responsible, to be included in the final study report. When there are amendments to the original report, provide a signed and dated copy of the amended report, to be included in the final study report along with the original report. Provide the report, and all amendments, to the study director or, when a multisite study employs principal investigators, through the principal investigator. (3) Permit oversight by the designated QAU. (b) In addition to the requirements in paragraphs (a)(1) through (3) of this section, an independent contributing scientist must: (1) Date and sign the study protocol to indicate agreement to comply with protocol requirements for all phases of the nonclinical laboratory study the independent contributing scientist will conduct and the applicable requirements of this part. Date and sign any protocol amendments applicable to the phases of the nonclinical laboratory study conducted by the independent contributing scientist to indicate agreement. (2) Maintain and update documentation of education, training, and experience pertinent to those phases of the nonclinical laboratory studies for which the independent contributing scientist is responsible.

		(3) If conducting phases of a nonclinical laboratory study that include the use of animals: (i) Document that housing, feeding, handling, and care of the animals as specified in § 58.90 are available. (ii) Document that an attending veterinarian is available for consult and deferred to as necessary, particularly when animals are in pain or distress. (iii) Document corrective actions required to assure the humane care and ethical treatment of animals. (4) Archive all materials pertinent to all phases of the nonclinical laboratory the independent contributing scientist conducted, as required by the protocol and § 58.195; document when and where archiving was completed.
Principal Investigator (§ 58.39) We propose adding § 58.39 to include principal investigator requirements related to a principal investigator's responsibilities for a phase of a nonclinical laboratory study. We propose that designating a principal investigator is optional. The OECD Principles on Good Laboratory Practice (Ref. 8) includes the term principal investigator solely in reference to multisite studies. We recognize, however, the possibility of a testing facility employing a principal investigator for a single-site study. For example, a single site study conducted in a facility situated on a large campus with multiple buildings might have one or more principal investigators. We also recognize that a testing facility may conduct a multisite study where, at all sites, only the study director oversees the study. Several comments to the December 2010		Add § 58.39 to subpart B to read as follows: **§ 58.39 Principal investigator.** The study director can delegate to principal investigators responsibility for phases of a nonclinical laboratory study but not responsibility for an entire study. For all phases of the nonclinical laboratory study for which the principal investigator is responsible, a principal investigator must: (a) Sign and date the study protocol, and any applicable amendments, to document agreement to comply with the protocol requirements and the applicable requirements of this part. (b) Verify that the study is conducted according to the requirements of this part. (c) Document all deviations noted during the conduct of the study, report those deviations to the study director as soon as possible after discovery, and document that the information

ANPRM note these various practices. We therefore propose in § 58.39 principal investigator requirements for specific responsibilities in one or more phases as delegated to the principal investigator by the study director. We propose principal investigator responsibilities consistent with a principal investigator's role of ensuring compliance with part 58 for a specific phase. For example, we propose the principal investigator must document and report to the study director all deviations the principal investigator observes during the conduct of the study. These requirements also are consistent with the responsibilities of a principal investigator in The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies (Ref. 6), and with a GLP Quality System.		was forwarded to the study director. (d) Submit to the study director either: (1) The signed and dated reports from all contributing scientists for whom the principal investigator is responsible and any amendments to such reports, any raw data not covered by such reports, and a signed compliance statement indicating any areas of noncompliance; or (2) Signed and dated report of all phases for inclusion in the final study report. The signed report must include the original principal investigator's report and any amendments, reports of all contributing scientists for whom the principal investigator is responsible and any amendments to such reports, and a signed compliance statement indicating any areas of noncompliance. (e) Document that all materials and records are appropriately archived, as required by the protocol and § 58.195.
General (§ 58.41) In § 58.41, we propose changing "Each testing facility shall be" to "Any person conducting a phase of a nonclinical laboratory study must have facilities" of suitable size and construction to facilitate the proper conduct of nonclinical laboratory studies. We propose this change to include multisite studies.	Subpart C—Facilities **§ 58.41 General.** Each testing facility shall be of suitable size and construction to facilitate the proper conduct of nonclinical laboratory studies. It shall be designed so that there is a degree of separation that will prevent any function or activity from having an adverse effect on the study.	**§ 58.41 General.** Any person conducting a phase of a nonclinical laboratory study must have facilities of suitable size and construction to facilitate the proper conduct of nonclinical laboratory studies. Facilities must 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.
Animal Care Facilities (§ 58.43) In § 58.43, we propose changes to include multisite studies and to cover any phase involving the use of animals. We propose these changes consistent with our proposal revising the testing facility definition and our goal of applying the GLP regulations to	**§ 58.43 Animal care facilities.** (a) A testing facility shall have a sufficient number of animal rooms or areas, as needed, to assure proper: (1) Separation of species or test systems, (2) isolation of individual projects, (3) quarantine of animals, and	In § 58.43, revise paragraphs (a), (b), and (d) to read as follows: **§ 58.43 Animal care facilities.** (a) Any person conducting a phase of a nonclinical laboratory study that utilizes animals must have a sufficient number of animal rooms or areas, as needed, to assure proper:

all nonclinical laboratory studies, including multisite studies.	(4) routine or specialized housing of animals. (b) A testing facility shall have a number of animal rooms or areas separate from those described in paragraph (a) of this section to ensure isolation of studies being done with test systems or test and control articles known to be biohazardous, including volatile substances, aerosols, radioactive materials, and infectious agents. (c) Separate areas shall be provided, as appropriate, for the diagnosis, treatment, and control of laboratory animal diseases. These areas shall provide effective isolation for the housing of animals either known or suspected of being diseased, or of being carriers of disease, from other animals. (d) When animals are housed, facilities shall exist for the collection and disposal of all animal waste and refuse or for safe sanitary storage of waste before removal from the testing facility. Disposal facilities shall be so provided and operated as to minimize vermin infestation, odors, disease hazards, and environmental contamination.	(1) Separation of species or test systems, (2) Isolation of individual projects, (3) Quarantine of animals, and (4) Routine or specialized housing of animals. (b) Any person conducting a phase of a nonclinical laboratory study that utilizes animals must have a number of animal rooms or areas separate from those described in paragraph (a) of this section to ensure isolation of studies being done with test systems or test, control, or reference articles known to be biohazardous, including volatile substances, aerosols, radioactive materials, and infectious agents. * * * * * (d) When animals are housed, facilities must exist for the collection and disposal of all animal waste and refuse or for safe sanitary storage of waste before removal from any facility at which a phase of a nonclinical laboratory study that utilizes animals is conducted. Disposal facilities must be so provided and operated as to minimize vermin infestation, odors, disease hazards, and environmental contamination.
	§ 58.45 Animal supply facilities There shall be storage areas, as needed, for feed, bedding, supplies, and equipment. Storage areas for feed and bedding shall be separated from areas housing the test systems and shall be protected against infestation or contamination. Perishable supplies shall be preserved by appropriate means.	

Facilities for Handling Test, Control, and Reference Articles (§ 58.47) In § 58.47 we propose adding "reference" to refer to "reference articles" for consistency with our other proposals	**§ 58.47 Facilities for handling test and control articles.** (a) As necessary to prevent contamination or mixups, there shall be separate areas for: (1) Receipt and storage of the test and control articles. (2) Mixing of the test and control articles with a carrier, e.g., feed. (3) Storage of the test and control article mixtures. (b) Storage areas for the test and/or control article and test and control mixtures shall be separate from areas housing the test systems and shall be adequate to preserve the identity, strength, purity, and stability of the articles and mixtures.	**§ 58.47 Facilities for handling test, control, and reference articles.** (a) As necessary to prevent contamination or mixups, there must be separate areas for: (1) Receipt and storage of the test, control, and reference articles. (2) Mixing of the test, control, and reference articles with a carrier, *e.g.,* feed. (3) Storage of the test, control, and reference article mixtures. (b) Storage areas for the test, control, and reference articles and test, control, and reference article mixtures must be separate from areas housing the test systems and must be adequate to preserve the characteristics of the articles and mixtures, including their identity, strength, purity, and stability, as applicable.
	§ 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.	
	§ 58.51 Specimen and data storage facilities. Space shall be provided for archives, limited to access by authorized personnel only, for the storage and retrieval of all raw data and specimens from completed studies.	
Equipment Design (§ 58.61) In § 58.61, we propose adding that equipment includes computerized systems. We also propose adding in § 58.61, equipment used for maintenance, archiving, and retrieval of data. We propose these additions to update and clarify the regulations.	**§ 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.	**§ 58.61 Equipment design.** Equipment, including computerized systems, used in the generation, measurement, maintenance, archiving, retrieval, or assessment of data (or any combination thereof) and equipment used for facility environmental control must be of appropriate design and adequate capacity to function according to the protocol and must be suitably

		located for operation, inspection, cleaning, and maintenance.
Maintenance and Calibration of Equipment (§ 58.63) In § 58.63, we propose adding to paragraph (a) maintenance, archiving, and retrieval of data. In paragraph (b), we propose changing the citation reference from § 58.81(b)(11) to (14) and adding a reference to the written SOP requirement in § 58.81(b)(15). Also, in paragraph (b), we propose adding "as applicable" to address the possibility of a multisite study. We propose these changes for consistency with our other proposed changes in part 58 and to update the regulations to address multisite studies.	**§ 58.63 Maintenance and calibration of equipment.** (a) Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized. (b) The written standard operating procedures required under § 58.81(b)(11) shall set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration, and/or standardization of equipment, and shall specify, when appropriate, remedial action to be taken in the event of failure or malfunction of equipment. The written standard operating procedures shall designate the person responsible for the performance of each operation. (c) Written records shall be maintained of all inspection, maintenance, testing, calibrating and/or standardizing operations. These records, containing the date of the operation, shall describe whether the maintenance operations were routine and followed the written standard operating procedures. Written records shall be kept of nonroutine repairs performed on equipment as a result of failure and malfunction. Such records shall document the nature of the defect, how and when the defect was discovered, and any remedial action taken in response to the defect.	In § 58.63, revise paragraphs (a) and (b) to read as follows: **§ 58.63 Maintenance and calibration of equipment.** (a) Equipment must be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, maintenance, archiving, retrieval, or assessment of data (or any combination thereof) must be adequately tested, calibrated, and standardized, as applicable. (b) The written SOPs required under § 58.81(b)(14) and (15) must set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration, and standardization of equipment, as applicable, and must specify, when appropriate, remedial action to be taken in the event of failure or malfunction of equipment. The written SOPs must designate the person responsible for the performance of each operation. * * * * *
Part 58, Subpart E--Nonclinical Laboratory Study Operations Consistent with our proposals in part 58 to address multisite	Subpart E—Testing Facilities Operation	Revise the heading of subpart E to read as follows: Subpart E—Nonclinical Laboratory Study Operations

studies, we propose revising the heading of subpart E from "Testing Facilities Operation" to "Nonclinical Laboratory Study Operations". Also, accordingly, we propose modifying the sections in subpart E.		
Standard Operating Procedures (SOPs) (§ 58.81) We propose modifying § 58.81 Standard operating procedures (SOPs), consistent with our proposals for a GLP Quality System and to address multisite studies. In § 58.81(a), we propose adding to the current requirement that a testing facility must have written SOPs, that all test sites, too, must have written SOPs. Also, in § 58.81(a), we propose changing "management" to "management with executive responsibility". In § 58.81(b), consistent with our proposal in § 58.81(a), we propose adding that the testing facility and all test sites must establish SOPs for an applicable phase of a nonclinical laboratory study. As discussed in section III.B.1., we use the terms "applicable phases" and "where appropriate" because in a multisite study no one person will conduct all phases of the study. Therefore, each person requires SOPs only for those phases which that person conducts. We propose adding to the current list of SOPs in § 58.81(b) numerous topics that require SOPs. For example, we propose adding that SOPs must include an SOP for preparing, modifying, and administering all SOPs. We propose these additional SOP requirements because they are essential components of a complete quality system approach (i.e., the proposed GLP Quality System) and also address the current prevalence of multisite studies.	**§ 58.81 Standard operating procedures.** (a) A testing facility shall have standard operating procedures in writing setting forth nonclinical laboratory study methods that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study. All deviations in a study from standard operating procedures shall be authorized by the study director and shall be documented in the raw data. Significant changes in established standard operating procedures shall be properly authorized in writing by management. (b) Standard operating procedures shall be established for, but not limited to, the following: (1) Animal room preparation. (2) Animal care. (3) Receipt, identification, storage, handling, mixing, and method of sampling of the test and control articles. (4) Test system observations. (5) Laboratory tests. (6) Handling of animals found moribund or dead during study. (7) Necropsy of animals or postmortem examination of animals. (8) Collection and identification of specimens. (9) Histopathology. (10) Data handling, storage, and retrieval. (11) Maintenance and calibration of equipment. (12) Transfer, proper placement, and identification of animals.	**58.81 Standard operating procedures (SOPs).** (a) The testing facility and all test sites must have SOPs in writing setting forth nonclinical laboratory study procedures that management with executive responsibility is satisfied are adequate to ensure the quality and integrity of the data generated in the course of a study. All deviations from SOPs in a study must be authorized by the study director and must be documented in the raw data. Significant changes in established SOPs must be properly authorized in writing by management with executive responsibility. (b) The testing facility and all test sites must establish SOPs for all applicable phases of a nonclinical laboratory study. Where appropriate, SOPs must include the following: (1) Preparation, modification, and administration of all SOPs. These must include procedures for developing and maintaining a historical file of SOPs and all revisions, including the dates of such revisions. (2) Establishment and periodic review of a GLP Quality System. (3) Designation and replacement of the study director. (4) Animal room preparation. (5) Animal care. (6) Receipt, identification, storage, handling, mixing, and method of sampling of the test, control, and reference articles. (7) Test system observations for in vivo and in vitro testing, as applicable.

Our proposal in § 58.81 will require initial efforts by testing facilities and test sites to modify or add SOPs as needed for a GLP Quality System. However, once established, the GLP Quality System will facilitate greater flexibility and efficiency for the conduct of nonclinical laboratory studies and, over time, will help reduce costs.	(c) Each laboratory area shall have immediately available laboratory manuals and standard operating procedures relative to the laboratory procedures being performed. Published literature may be used as a supplement to standard operating procedures. (d) A historical file of standard operating procedures, and all revisions thereof, including the dates of such revisions, shall be maintained.	(8) Laboratory tests. (9) Handling of animals found moribund or dead during study. (10) Necropsy of animals or post mortem examination of animals. (11) Collection and identification of specimens. (12) Histopathology. (13) Data handling, storage, and retrieval, including maintenance of the master schedule and all study protocols, and the establishment and maintenance of an archive system. (14) Validation, maintenance, and calibration of equipment. (15) Ensuring computerized systems are suitable for their intended purpose and are appropriately validated, operated, and maintained and that electronic records from computerized systems are readily available for review and assessment. (16) Transfer, proper placement, and identification of animals. (17) QAU functions, including QA oversight for multisite studies. (18) Multisite studies. (19) Designation and replacement of a principal investigator. (20) Planning, performing, documenting, and reporting inspections conducted by the QAU. (21) Receipt, review, and followup of all concerns, problems, and regulatory deviations reported by the QAU, including the frequency and content of periodic study reports required by § 58.35(b)(7), and for modifying relevant SOPs when necessary to prevent recurrence. (22) Certifying copies of study records as true copies of the original that maintain the original intent and meaning. (c) Each laboratory area must have immediately available laboratory manuals and SOPs relative to the laboratory

		procedures being performed. Published literature may be used as a supplement to SOPs.
	58.83 Reagents and solutions. All reagents and solutions in the laboratory areas shall be labeled to indicate identity, titer or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions shall not be used.	
Animal Care (§ 58.90) In § 58.90, we propose modifying paragraph (b) to require, throughout the study, evaluation of the health status of test animals according to acceptable veterinary medical practices for the care of test animals. We propose this change because proper animal care is essential during the entire study to ensure the welfare of test animals and the integrity of test results. However, test animal evaluations can be performed by the attending veterinarian or appropriately-trained personnel who are delegated this responsibility by the attending veterinarian. In § 58.90(c), we propose removing from the third sentence the phrase "provided that such treatment does not interfere with the study", and replacing this phrase with "as deemed necessary by the study's attending veterinarian." We propose few changes in § 58.90(d) and (e). In the first sentence of current § 58.90(d), we propose replacing "excluding suckling rodents" with "except nursing neonates" to update the regulation to be more inclusive and appropriate. In§ 58.90(e), we propose adding the word "reference" to conform to changes proposed elsewhere in this document.	**58.90 Animal care**. (a) There shall be standard operating procedures for the housing, feeding, handling, and care of animals. (b) All newly received animals from outside sources shall be isolated and their health status shall be evaluated in accordance with acceptable veterinary medical practice. (c) At the initiation of a nonclinical laboratory study, animals shall be free of any disease or condition that might interfere with the purpose or conduct of the study. If, during the course of the study, the animals contract such a disease or condition, the diseased animals shall be isolated, if necessary. These animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study. The diagnosis, authorizations of treatment, description of treatment, and each date of treatment shall be documented and shall be retained. (d) Warm-blooded animals, excluding suckling rodents, used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that require the animals to be removed from and returned to their home cages for any reason	In § 58.90, revise paragraphs (b) through (e) to read as follows: **§ 58.90 Animal care.** * * * * * (b) All newly received animals from outside sources must be isolated and their health status must be evaluated according to acceptable veterinary medical practices. Also, throughout the study, all test animals must be evaluated for their health status according to acceptable veterinary medical practices. (c) At the initiation of a nonclinical laboratory study, animals must 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 must be isolated, if necessary. These animals may be treated for disease or signs of disease as deemed necessary by the study's attending veterinarian. The diagnosis, treatment authorizations, treatment description, and each treatment date must be documented and must be retained as part of the study raw data. (d) Warm-blooded animals, except nursing neonates, used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that

We propose these changes in § 58.90 to update and clarify the regulations, and because test animal welfare concerns are an essential part of a GLP Quality System.	(e.g., cage cleaning, treatment, etc.), shall receive appropriate identification. All information needed to specifically identify each animal within an animal-housing unit shall appear on the outside of that unit. (e) Animals of different species shall be housed in separate rooms when necessary. Animals of the same species, but used in different studies, should not ordinarily be housed in the same room when inadvertent exposure to control or test articles or animal mixup could affect the outcome of either study. If such mixed housing is necessary, adequate differentiation by space and identification shall be made. (f) Animal cages, racks and accessory equipment shall be cleaned and sanitized at appropriate intervals.(g) Feed and water used for the animals shall be analyzed periodically to ensure that contaminants known to be capable of interfering with the study and reasonably expected to be present in such feed or water are not present at levels above those specified in the protocol. Documentation of such analyses shall be maintained as raw data. (h) Bedding used in animal cages or pens shall not interfere with the purpose or conduct of the study and shall be changed as often as necessary to keep the animals dry and clean. (i) If any pest control materials are used, the use shall be documented. Cleaning and pest control materials that interfere with the study shall not be used.	require the animals to be removed from and returned to their home cages for any reason (*e.g.,* cage cleaning, treatment, etc.), must receive appropriate identification. All information needed to specifically identify each animal within an animal-housing unit must appear on the outside of that unit. (e) Animals of different species must be housed in separate rooms when necessary. Animals of the same species, but used in different studies, should not ordinarily be housed in the same room when inadvertent exposure to control, reference, or test articles or animal mixup could affect the outcome of either study. If such mixed housing is necessary, adequate differentiation by space and identification must be made. * * * * *
G. Part 58, Subpart F—Test, Control,and Reference Articles	Subpart F—Test and Control Articles	Revise the heading of subpart F to read as follows:

We propose adding the term ''Reference'' to the heading in subpart F, and in certain applicable provisions in subpart F. We also propose adding in subpart F specifics concerning tobacco products, and a reference to method validation.		Subpart F—Test, Control, and Reference Articles
Test, Control, and Reference Article Characterization (§ 58.105) We propose modifying § 58.105 to require that all information about test, control, and reference article characterization be provided to the study director as soon as available. This information is necessary for determining appropriate dosing and drafting conclusions in the final study report. The lack of this information limits the important test result discussion in the final study report. Reports submitted to FDA must provide study information based on the characteristics of the product (test article) studied. We expect a test article to be characterized to the extent required to interpret the study properly. For nonclinical laboratory studies conducted in support of initiating clinical ''first-in-human'' studies, this characterization information is particularly important for human subject protection. We propose modification of § 58.105(a) to exclude the use of a marketed tobacco product's labeling to characterize such a product if it is used as a control or reference article in a nonclinical laboratory study. The labeling of currently marketed tobacco products does not provide the information required for full product characterization. That is, the chemical composition (including mainstream smoke composition), microbiological composition, and design parameters of the product are	**§ 58.105 Test and control article characterization.** (a) The identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article shall be determined for each batch and shall be documented. Methods of synthesis, fabrication, or derivation of the test and control articles shall be documented by the sponsor or the testing facility. In those cases where marketed products are used as control articles, such products will be characterized by their labeling. (b) The stability of each test or control article shall be determined by the testing facility or by the sponsor either: (1) Before study initiation, or (2) concomitantly according to written standard operating procedures, which provide for periodic analysis of each batch. (c) Each storage container for a test or control article shall be labeled by name, chemical abstract number or code number, batch number, expiration date, if any, and, where appropriate, storage conditions necessary to maintain the identity, strength, purity, and composition of the test or control article. Storage containers shall be assigned to a particular test article for the duration of the study. (d) For studies of more than 4 weeks' duration, reserve samples from each batch of test and control articles shall be retained for the period of time provided by § 58.195.	**§ 58.105 Test, control, and reference article characterization.** (a) For all test, control, and reference articles other than tobacco products, the identity, strength, purity, and composition or other characteristics which will appropriately define the test, control, or reference article must be determined for each batch and must be documented. For test, control, and reference articles for tobacco products, the chemical composition (including mainstream or aerosol smoke composition, when applicable), microbiological characterization (fermented tobacco products), and design parameters which will appropriately define the test, control, or reference article must be determined for each batch and must be documented. These analyses must be performed by the sponsor or by a contracted person either: (1) Before study initiation, or (2) Concomitantly according to written SOPs as required in § 58.81(b)(6). The results of such analyses must be provided to the study director as soon as available. In those cases where marketed products are used as control or reference articles, with the exception of tobacco products, such products can be characterized by their labeling. (b) Methods of synthesis, fabrication, or derivation of the test, control, and reference articles must be documented by the person who conducts the analyses.

not fully described in tobacco product labels. Thus, the composition and toxicant deliveries of currently marketed tobacco products are less well defined in tobacco product labeling than the safety and efficacy information described in the labels of marketed drug products. Therefore, FDA notes that when using a marketed tobacco product as a control or reference article, the marketed tobacco product's characteristics must be determined and documented as required in this part. We propose revising and redesignating the current provisions in § 58.105(b), (c), and (d). These proposed changes are necessary for consistency with our other proposals in part 58, such as the addition of reference articles. The current regulations imply that empty containers from test articles must be retained. Comments to the December 2010 ANPRM did not see the need to retain the empty containers provided appropriate product information is maintained and test article accountability is fully documented. We agree with those comments and propose to remove this implied requirement. To provide for adequate test article accountability, in lieu of retaining empty test article containers, we propose requiring in § 58.105(d) that the study director verify and document by dated signature the distribution and final disposition of the test article		(c) The stability of each test, control, and reference article must be determined as required by the conditions of the study either: (1) Before study initiation, or (2) Concomitantly according to written SOPs, as required in § 58.81(b)(6), which provide for periodic analysis of each batch. The results of such testing must be provided to the study director as soon as available. (d) Each storage container for a test, control, or reference article must be labeled by name; Chemical Abstract Service (CAS) number or code number, where such identification exists; batch number; expiration date, if any; and, where applicable, storage conditions necessary to maintain the identity, strength, purity, and composition of the test, control, or reference article, other than tobacco products. For tobacco product test, control, and reference articles, labeling must include storage conditions necessary to maintain the chemical composition (including mainstream smoke composition), microbiological composition, and design parameters, where applicable. Storage containers must be assigned to a particular test article for the duration of the study. Empty test article containers may be disposed of once the study director verifies and documents the distribution and final disposition of the test article. Approval for the disposal of empty containers must be in writing and signed and dated by the study director. (e) For studies of more than 4 weeks duration, reserve samples from each batch of test, control, and reference article must be retained for the period of time provided by § 58.195.

Test, Control, and Reference Article Handling (§ 58.107) We propose minimal conforming changes in § 58.107, such as adding ''reference'' to the section heading and first sentence.	**58.107 Test and control article handling.** Procedures shall be established for a system for the handling of the test and control articles to ensure that: (a) There is proper storage. (b) Distribution is made in a manner designed to preclude the possibility of contamination, deterioration, or damage. (c) Proper identification is maintained throughout the distribution process. (d) The receipt and distribution of each batch is documented. Such documentation shall include the date and quantity of each batch distributed or returned.	In § 58.107, revise the heading and introductory text to read as follows: **§ 58.107 Test, control, and reference article handling.** Procedures must be established, as required in § 58.81(b)(6), for a system for the handling of the test, control, and reference articles to ensure that: * * * * *
Mixtures of Articles with Carriers (§ 58.113) We propose modifying § 58.113 by adding ''reference'' to the provisions proposed in § 58.113(a), (a)(1), (a)(2), (b)(2), and (d). Also, we propose requiring that the results from the determination of the uniformity, concentration, and stability of mixtures of test articles with carriers are provided to the study director as soon as available. We propose these changes in § 58.113 for the same reasons we propose changes in § 58.105.	**§ 58.113 Mixtures of articles with carriers.** (a) For each test or control article that is mixed with a carrier, tests by appropriate analytical methods shall be conducted: (1) To determine the uniformity of the mixture and to determine, periodically, the concentration of the test or control article in the mixture. (2) To determine the stability of the test and control articles in the mixture as required by the conditions of the study either: (i) Before study initiation, or (ii) Concomitantly according to written standard operating procedures which provide for periodic analysis of the test and control articles in the mixture. (b) [Reserved] (c) Where any of the components of the test or control article carrier mixture has an expiration date, that date shall be clearly shown on the container. If more than one component has an expiration date, the earliest date shall be shown.	**§ 58.113 Mixtures of articles with carriers.** (a) For each test, control, and reference article that is mixed with a carrier, tests by appropriate analytical methods must be conducted: (1) To determine the uniformity of the mixture and to determine, periodically, the concentration of the test, control, or reference article in the mixture; and (2) To determine the stability of the test, control, and reference articles in the mixture as required by the conditions of the study. (b) Determination of uniformity, concentration, and stability must be conducted either: (1) Before study initiation; or (2) Concomitantly according to written SOPs, as required by § 58.81(b)(6), which provide for periodic analysis of the test, control, or reference articles in the mixture. (c) The results of such testing, performed by the sponsor or by a contracted person, must be provided to the study director as soon as available. (d) Where any of the components of the test, control, or reference article carrier mixture has an

		expiration date, that date must be clearly shown on the container. If more than one component has an expiration date, the earliest expiration date must be shown.
Part 58, Subpart G—Protocol for and Conduct of a Nonclinical Laboratory Study 1. Protocol (§ 58.120) We propose modifying § 58.120 to address multisite studies more specifically, and to provide consistency with our other proposed changes discussed elsewhere. Many comments to the December 2010 ANPRM suggest that the study protocol identify all sites participating in a multisite study. We agree, and propose adding in § 58.120(a)(3) that the protocol contain contact information for all persons conducting a phase of the nonclinical laboratory study. Current § 58.120(a)(6) includes in the protocol the methods for controlling bias. We propose adding to this provision the analysis and reporting of study test results and procedures to be followed if a study includes a peer review of any phase. Also, for multisite studies, we propose adding a requirement that the protocol identify the person(s) conducting the phases of the nonclinical laboratory study. We propose expanding current § 58.120(a)(10) to clarify that the protocol must include a listing of the study-specific records that are required to be maintained. We think this clarification will help assure that study specific records are maintained. Current § 58.120(a)(11) requires the date of protocol approval by the sponsor, and the dated signature of the study director. We propose expanding this provision to indicate study	Subpart G—Protocol for and Conduct of a Nonclinical Laboratory Study **§ 58.120 Protocol.** (a) Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study. The protocol shall contain, as applicable, the following information: (1) A descriptive title and statement of the purpose of the study. (2) Identification of the test and control articles by name, chemical abstract number, or code number. (3) The name of the sponsor and the name and address of the testing facility at which the study is being conducted. (4) The number, body weight range, sex, source of supply, species, strain, substrain, and age of the test system. (5) The procedure for identification of the test system. (6) A description of the experimental design, including the methods for the control of bias. (7) A description and/or identification of the diet used in the study as well as solvents, emulsifiers, and/or other materials used to solubilize or suspend the test or control articles before mixing with the carrier. The description shall include specifications for acceptable levels of contaminants that are reasonably expected to be present in the dietary materials and are known to be capable of interfering with	**§ 58.120 Protocol.** (a) Each study must have an approved written protocol that clearly indicates the specific objectives and all methods for the conduct of the study. The protocol must contain, where appropriate, the following information: (1) A descriptive title and statement of the purpose of the study. (2) Identification of test, control, and reference articles by: (i) Name; (ii) Chemical Abstract Service (CAS) number or code number, where such identification exists; (iii) The name and address of the manufacturer(s); and (iv) The person(s) determining their characteristics, as applicable. (3) The name and contact information (including address, phone number, email address, and facsimile number) for the sponsor and the testing facility and the name and affiliation of the study director. Also, for multisite studies, the contact information for all persons conducting a phase of the nonclinical laboratory study, including all principal investigators and independent contributing scientists. (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

protocol approval by the dated signature of the study sponsor, the study director, independent contributing scientists, principal investigators, and any other person conducting a phase of the nonclinical laboratory study, as applicable. We propose redesignating and modifying § 58.120(b) as § 58.120(d). In § 58.120(d), we propose requiring, before implementing any change or revision to an approved protocol, that the study sponsor and the study director document their approval of the change or revision. For a multisite study, any person affected by the proposed changes (for example, the principal investigator or independent contributing scientist) also must document approval. We consider a person's dated signature on the protocol revision to be acceptable documentation indicating approval. We propose that these signed and dated protocol amendments must be maintained with the protocol. Before initiating any study using animals, we propose requiring in new § 58.120(b) protocol review and approval by ''a committee whose function is to ensure that the care and use of animals in studies is appropriate and humane''. In new § 58.120(e), we propose the same review and approval by this committee before implementing any protocol changes that affect animal welfare. These additions are consistent with the proposal in § 58.33(b)(5) that the study director must ensure that all studies that include the use of animals are approved by such a committee. In new § 58.120(c), we propose requiring that the study sponsor and testing facility management with	the purpose or conduct of the study if present at levels greater than established by the specifications. (8) Each dosage level, expressed in milligrams per kilogram of body weight or other appropriate units, of the test or control article to be administered and the method and frequency of administration. (9) The type and frequency of tests, analyses, and measurements to be made. (10) The records to be maintained. (11) The date of approval of the protocol by the sponsor and the dated signature of the study director. (12) A statement of the proposed statistical methods to be used. (b) All changes in or revisions of an approved protocol and the reasons therefor shall be documented, signed by the study director, dated, and maintained with the protocol.	bias in the conduct of the study and the analysis and reporting of study test results and procedures to be followed when a study includes a peer review of any phase. For multisite studies, identification of which phases of the nonclinical laboratory study will be conducted by which person or persons. (7) A description or identification, as applicable, of the diet used in the study as well as solvents, emulsifiers, and/or other materials used to solubilize or suspend the test, control, or reference articles, as applicable, before mixing with the carrier. The description must 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, control, or reference article to be administered and the method and frequency of administration. For each test, control, or reference article that is mixed with a carrier for administration, limits for the results of concentration, uniformity, and stability testing and the name and address of the person conducting the testing. (9) The type and frequency of tests, analyses, and measurements to be made. (10) A list or description of the records to be maintained for the specific study. For multisite studies, the archive location(s) of study materials and records from all phases of the nonclinical laboratory study.

executive responsibility sign and date a statement that the study will be conducted in compliance with part 58. We propose appending this statement to the protocol. This proposal is consistent with the requirement in § 58.10(b) that a sponsor must inform a contracted person that the study must be conducted in compliance with chapter I. This proposal also is consistent with the requirements discussed elsewhere in this document that the study director documents applicable GLP regulations are followed (section III.C.4.), and that the QAU ensures studies conform to the regulations in part 58 (section III.C.5.).		(11) The dated signature of the study sponsor, the study director, independent contributing scientists, principal investigators, and any other person conducting a phase of the nonclinical laboratory study, as applicable. (12) A statement of the proposed statistical methods to be used. (b) For studies that include the use of animals, a committee whose function is to ensure that the care and use of animals is appropriate and humane must review and approve the study before initiation of the study and approval must be documented. (c) A statement that the study must be conducted in compliance with the provisions of this part, to be signed and dated by the study sponsor and testing facility management with executive responsibility, must be appended to the protocol. (d) All changes in or revisions of an approved protocol and the reasons for the changes must be documented. These amendments to the protocol must be signed and dated by the study sponsor and the study director. For multisite studies, these amendments must also be signed and dated by all independent contributing scientists, principal investigators, and any other person conducting a phase of the nonclinical laboratory study affected by the amendment. Signed and dated amendments must be maintained with the protocol. (e) A committee whose function is to ensure that the care and use of animals in studies is appropriate and humane must review and approve any protocol changes that would impact animal welfare before implementation and approval must be documented.

Conduct of a Nonclinical Laboratory Study (§ 58.130) We propose redesignating current § 58.130(a) through (c), as (d), (f), and (g) respectively. In new proposed § 58.130(a), we require demonstration that all analytical methods are accurate, sufficiently precise, and sensitive enough to result in accurate and reproducible data. We expect this requirement will help ensure data quality and integrity as its intent is to produce accurate and reproducible data. This requirement also is consistent with requirements in part 320 (21 CFR part 320), ''Bioavailability and Bioequivalence Requirements'' (see § 320.29(a)). In new § 58.130(b), we propose conducting test, control, and reference article characterization as specified in part 58, subpart F. We propose this requirement to clarify our current and future expectations regarding test, control, and reference article characterization. In new § 58.130(c), we propose that ''humane care and ethical treatment of test animals must be considered in advance and upheld in conjunction with achieving study objectives.'' We propose this provision is consistent with our other proposals addressing animal welfare discussed elsewhere in section III.A.3. In new § 58.130(e), we propose that any change to the protocol must be approved as an amendment. We propose this requirement consistent with the proposed requirement in § 58.120(d) for approval of protocol amendments. However, we understand the importance of test animal welfare along with maintaining the integrity of the study. Therefore, FDA intends to	**§ 58.130 Conduct of a nonclinical laboratory study.** (a) The nonclinical laboratory study shall be conducted in accordance with the protocol. (b) The test systems shall be monitored in conformity with the protocol. (c) Specimens shall be identified by test system, study, nature, and date of collection. This information shall be located on the specimen container or shall accompany the specimen in a manner that precludes error in the recording and storage of data. (d) Records of gross findings for a specimen from postmortem observations should be available to a pathologist when examining that specimen histopathologically. (e) All data generated during the conduct of a nonclinical laboratory study, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and legibly in ink. All data entries shall be dated on the date of entry and signed or initialed by the person entering the data. Any change in entries shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change. In automated data collection systems, the individual responsible for direct data input shall be identified at the time of data input. Any change in automated data entries shall be made so as not to obscure the original entry, shall indicate the reason for change, shall be dated, and the responsible individual shall be identified.	**§ 58.130 Conduct of a nonclinical laboratory study.** (a) The analytical methods used for all phases of a nonclinical laboratory study must be demonstrated to be accurate and of sufficient sensitivity to measure, with appropriate precision, the analytes in question. (b) Test, control, and reference article characterization testing must be conducted as described in subpart F of this part. (c) Humane care and ethical treatment of test animals must be considered in advance and upheld in conjunction with achieving study objectives. The attending veterinarian must be included in consultations regarding the impact of a given protocol on the welfare of test animals, in particular the recognition and alleviation of species-specific pain or distress and methods of euthanasia. The attending veterinarian must be deferred to when decisions regarding animal welfare arise, particularly when animals are in pain or distress. (d) The nonclinical laboratory study must be conducted according to the protocol. The person responsible for a given phase of a nonclinical laboratory study must sign and date the protocol, as required in § 58.120(a)(11), before initiation of that phase of the study. (e) Any change to the protocol must be approved as an amendment, as required in § 58.120(d), before implementation. (f) The test systems must be monitored in conformity with the protocol. (g) Specimens must be identified by test system, study, nature, and date of collection. This information must be located on

evaluate on a case-by-case basis certain circumstances when a protocol deviation is necessary to prevent a potential hazard to animal welfare or study integrity. In proposed § 58.130(h) (revised and redesignated current § 58.130(d)), postmortem observations must be available to the pathologist unless specified otherwise in the study protocol. We understand that some study protocols might blind the pathologist to postmortem observations. We expect, however, in most cases the pathologist will not need to be blinded to postmortem observations.		the specimen container or must accompany the specimen in a manner that precludes error in the recording and storage of data (h) Records of gross findings for a specimen from post mortem observations must be available to a pathologist when examining that specimen histopathologically, unless specified otherwise in the study protocol.
	Subparts H-I[Reserved]	
Part 58, Subpart J—Records and Reports 1. Data Quality and Integrity (§ 58.180) We propose adding a new § 58.180 for data quality and integrity. Ensuring data quality and integrity in a nonclinical laboratory study is one of our critical goals in this part 58 proposal. Therefore, we propose adding this separate § 58.180 to clearly identify requirements for data quality and integrity. We propose this new section in subpart J because data are part of study records and reports. We propose moving to this new section, and revising, the requirements in current § 58.130(e). In § 58.180(a), we propose creating the acronym ''ALCOA''. This is a mnemonic that signifies quality data to stakeholders that conduct clinical and nonclinical studies. We propose therefore that all nonclinical laboratory study data are ''accurate, legible, contemporaneous, original, and attributable''. In § 58.180(b), we propose modifying and updating the		Add § 58.180 to subpart J to read as follows: **§ 58.180 Data quality and integrity.** (a) All data generated during the conduct of a nonclinical laboratory study must be accurate, legible, contemporaneous, original, and attributable (ALCOA). Also, data must be credible, internally consistent, and corroborated. (b) All data must be recorded indelibly, directly, and promptly to a permanent medium at the time of observation and must identify unambiguously the person entering the data. Any change to any entry must be made so as not to obscure the original entry, must indicate the reason for such change, must indicate when the change was made, and must identify who made the change. When data are either captured or maintained, or both captured and maintained electronically, these requirements are fulfilled by the use of an electronic records system fully compliant with applicable regulations.

provisions currently in § 58.130(e) to address electronic data capture and maintenance. Numerous comments to the December 2010 ANPRM note that part 11 (21 CFR part 11, ''Electronic Records; Electronic Signatures'') is applicable to part 58 and therefore parts 11 and 58 should be consistent. We agree, and do not intend to duplicate in part 58 the requirements in part 11. As a result, we propose that electronic records systems need to be compliant with applicable regulations. In § 58.180(c), we propose adding that the final study report must contain all data accrued during the study. This proposed requirement is consistent with our proposal in § 58.120(b)(6) requiring that the protocol describe methods for controlling bias. We propose this requirement because selective data inclusion in the study analysis could introduce bias into the final study report.		(c) All data accrued as required in paragraphs (a) and (b) of this section must be included in the final study report.
Reporting of Nonclinical Laboratory Study Results (§ 58.185) Study data must be maintained in a manner that allows for ''reconstruction of the study for the purpose of assessing the quality and integrity of the results or the reinterpretation of the data in the light of later findings'' (41 FR 51206 at 51215) (Ref. 4). Study records and reports required in part 58, subpart J, are acceptable in electronic or paper medium, or a combination of both. In § 58.185, we propose eliminating any current requirements that might impede a fully computerized facility. Many comments to the December 2010 ANPRM suggest we allow testing facilities to develop an integrated final study report. This integrated final study report would be in lieu of	Subpart J—Records and Reports **§ 58.185 Reporting of nonclinical laboratory study results.** (a) A final report shall be prepared for each nonclinical laboratory study and shall include, but not necessarily be limited to, the following: (1) Name and address of the facility performing the study and the dates on which the study was initiated and completed. (2) Objectives and procedures stated in the approved protocol, including any changes in the original protocol. (3) Statistical methods employed for analyzing the data. (4) The test and control articles identified by name, chemical abstracts number or code number, strength, purity, and composition or other appropriate characteristics.	**§ 58.185 Reporting of nonclinical laboratory study results.** (a) A final study report must be prepared for each nonclinical laboratory study and must include the following: (1) Name and address of the testing facility and the dates on which the study was initiated and completed. For multisite studies, additionally the name and address of any person conducting a phase of the nonclinical laboratory study, including the location of all independent contributing scientists. (2) Names of the attending veterinarians for all phases of the nonclinical laboratory study that included the use of animals. (3) Objectives and procedures stated in the approved protocol,

individual scientists' reports, which the study director must then compile and discuss in an integrated final study report. The preamble to the original GLP final rule states that individual reports are required as part of the final report to ensure the findings of the individual scientists are accurately reflected (43 FR 59986 at 60009) (Ref. 12). Also, in the preamble to the 1987 final rule amending part 58, FDA thought that reports combining data, information, and views from scientists of different disciplines would obscure the individual scientist's accountability for accurate reporting (see 52 FR 33768 at 33778) We continue to affirm these statements. However, we support processes used for the efficient review of the draft study report to facilitate completion of the final study report. In § 58.185, we propose adding general statements for consistency with our other part 58 proposals. We propose adding two provisions specific to animal welfare. In § 58.185(a)(2), we propose requiring that final study reports contain the names of all study attending veterinarians. We propose redesignating and modifying § 58.185(a)(9) as (a)(10) to add the example of ''all health-related issues reported by an attending veterinarian or appropriately designated personnel during the course of the study''. This provision recognizes that circumstances affecting the quality and integrity of the data could include health-related issues noted and reported by the attending veterinarian or appropriately designated personnel. We propose this addition to help ensure that all untoward health related	(5) Stability of the test and control articles under the conditions of administration. (6) A description of the methods used. (7) A description of the test system used. Where applicable, the final report shall include the number of animals used, sex, body weight range, source of supply, species, strain and substrain, age, and procedure used for identification. (8) A description of the dosage, dosage regimen, route of administration, and duration. (9) A description of all circumstances that may have affected the quality or integrity of the data. (10) The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study. (11) A description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis. (12) The signed and dated reports of each of the individual scientists or other professionals involved in the study. (13) The locations where all specimens, raw data, and the final report are to be stored. (14) The statement prepared and signed by the quality assurance unit as described in § 58.35(b)(7). (b) The final report shall be signed and dated by the study director. (c) Corrections or additions to a final report shall be in the form of an amendment by the study director. The amendment shall clearly identify that part of the final report that is being added to or corrected and the reasons for the correction or addition, and	including any changes in the original protocol. (4) Statistical methods employed for analyzing the data. (5) Test, control, and reference articles identified by: (i) Name; (ii) Chemical Abstract Service (CAS) number or code number, where such identification exists; (iii) Strength, purity, and composition or other appropriate characteristics, and for tobacco products as described in § 58.105(a); (iv) The name and address of the manufacturer(s); and (v) The name and address of the person(s) conducting the testing to define their characteristics, as applicable. (6) Stability of test, control, and reference articles under the conditions of administration, including the name and address of the person(s) conducting the testing. (7) A description of the methods used, including methods for the control of bias in the conduct of the study and the analysis and reporting of test results. (8) A description of the test system used. Where applicable, the final study report must include the number of animals used, sex, body weight range, source of supply, species, strain and substrain, age, and procedure used for identification. (9) A description of the dosage, dosage regimen, route of administration, and duration, including the results of testing conducted to determine the concentration, uniformity, and stability of mixtures of articles with carriers, as applicable, and the name and address of the person conducting the testing. (10) A description of all circumstances that may have affected the quality or integrity of

observations of test animals are captured and reported so that FDA reviewers can consider their possible effect on study results. We propose redesignating and modifying § 58.185(a)(12) as (a)(13) to be consistent with the EPA's GLP regulations (see 40 CFR 160.185(a)(12) and 792.185(a)(12)). That is, we propose requiring a signed and dated report from each person conducting an analysis or evaluation of study data or specimens after data generation was completed. We propose this addition to provide transparency regarding the review of study findings and the development of conclusions submitted in the final study report. In new § 58.185(a)(16), we propose that the study director provide with the final study report a statement about the study's extent of compliance with part 58, including any study deviations. This requirement is consistent with OECD's consensus document *The Role and Responsibilities of the Study Director in GLP Studies* (Ref. 14) and addresses a recommendation from stakeholders who requested that FDA modernize part 58. Many testing facilities provide services internationally and therefore, this statement is commonly seen in final study reports submitted to FDA. Such a statement also is included in EPA's study profile templates, which outline the necessary documents for submission of supporting data. FDA presently requires such a compliance statement from the applicant for applications and submissions for research and marketing and frequently receives the study director's statement in fulfillment of, or at least as the primary basis for, the	shall be signed and dated by the person responsible.	the data, including those documented by the study director as described in § 58.33(b)(9) and all health-related issues reported by an attending veterinarian or appropriately designated personnel during the course of the study as described in § 58.90(b) and (c). (11) The name and affiliation of the study director, the names of all contributing scientists, principal investigators, and other professionals, the sponsor, and all supervisory personnel who were involved in the study or in the preparation or review of the final study report. (12) A description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis. (13) The original, and any amended, signed and dated reports of each of the contributing scientists, principal investigators, or any other person involved in the study, including each person who conducted an analysis or evaluation of data or specimens from the study after data generation was completed. These reports must contain all data generated. (14) The locations where all specimens, reserve samples, raw data, and the final study report are to be stored. (15) The statement prepared and signed by the responsible QAU as described in § 58.35(b)(11). (16) A statement by the study director of the study's extent of compliance with this part, including a discussion of any study deviations found to impact the integrity of the study as described in § 58.185(a)(10).

required statement. Several comments to the December 2010 ANPRM suggest modifying part 58 to include requirements for studies discontinued before completion. In response to this suggestion, we propose new § 58.185(d) requiring the study director to write, sign, and date a short written summary report closing the study and discussing why the study was discontinued. This report and study material must be archived as required in § 58.190 in case of future study review or study completion		(b) The final report must be signed and dated by the study director. (c) Corrections or additions to a final report must be in the form of an amendment by the study director. The amendment must clearly identify that part of the final report that is being added to or corrected and the reasons for the correction or addition, and must be signed and dated by the person responsible. (d) If for any reason a study is discontinued before completion, the study director must write, sign, and date a short summary report closing the study. This report must discuss the reasons for closure and must be archived, along with all study material, as described in § 58.190.
Storage and Retrieval of Records and Data (§ 58.190) We propose modifying § 58.190(a) to add reserve samples to those items generated as a result of a nonclinical laboratory study that must be retained. We also propose adding a requirement for retention of ''Correspondence and other documents relating to interpretation and evaluation of data, other than those documents contained in the final study report.'' We propose this addition to harmonize with the EPA GLP regulations (see 40 CFR 160.190(a) and 792.190(a)) and to clarify our requirement for retaining these documents. Our other proposed modifications in § 58.190 provide timeframes for archiving required study material and requirements for the SOPs about archiving to include procedures specific to removing study material from the archives. Stakeholders who asked that we modernize part 58 requested a reasonable timeframe after the	**§ 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. (b) There shall be archives for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports. Conditions of storage shall minimize deterioration of the documents or specimens in accordance with the requirements for the time period of their retention and the nature of the documents or specimens. A testing facility may contract with commercial archives to provide a repository for all material to be retained. Raw data and specimens may be retained elsewhere provided that the	**§ 58.190 Storage and retrieval of records and data.** (a) All raw data, documentation, protocols, final reports, reserve samples, 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 must be retained. Correspondence and other documents relating to interpretation and evaluation of data, other than those documents contained in the final study report, must also be retained. (b) There must be archives for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports. Conditions of storage must minimize deterioration of the documents or specimens in accordance with the requirements for the time period of their retention and the nature of the documents or specimens.

study completion date to complete study archiving. Comments to the December 2010 ANPRM also made this request. The SOP requirement for procedures specific to removing study material from the archives is to address concerns that material in the archives could be lost or destroyed if removed without having in place adequate and specific procedures. We propose that archiving occur no later than 2 weeks after the study completion date (see study completion date defined in § 58.3). We propose this 2-week timeframe to prevent required material from being inadvertently misplaced, lost, or destroyed over the long term. We understand that certain situations may prevent archiving study material during, or at the completion of, a nonclinical laboratory study as currently required of the study director in § 58.33(f). We also propose, when the study sponsor delays finalizing the final study report, that the study director must complete, sign, and date the final study report and archive all study material no later than 6 months after completion of the last draft of the final study report. Additionally, if the study sponsor stops a nonclinical laboratory study before all protocol requirements are complete, a decision about discontinuing the study must be made no later than 6 months after stopping the study. For discontinued studies, a summary report and study material must be archived within 2 weeks of the study director signing the summary report. We propose these timeframes to provide the requested flexibility	archives have specific reference to those other locations. (c) An individual shall be identified as responsible for the archives. (d) Only authorized personnel shall enter the archives. (e) Material retained or referred to in the archives shall be indexed to permit expedient retrieval.	A testing facility may contract with commercial archives to provide a repository for all material to be retained. Raw data and specimens may be retained elsewhere provided that the archives have specific reference to those other locations. (c) Material retained or referred to in the archives must be indexed to permit expedient retrieval. (d) All study material described in paragraph (a) of this section must be archived no later than 2 weeks after the study completion date (as defined in § 58.3). (e) If a sponsor delays completion of the final study report, the study director must complete, sign, and date the final study report and archive all study material no later than 6 months after completion of the last draft of the final study report. (f) If a study sponsor halts a nonclinical laboratory study before all protocol-required testing is completed, a decision that the study is discontinued must be made no later than 6 months after the study was stopped. Once the study has been determined to be discontinued, the study director must prepare a summary report, as required by § 58.185(d). The summary report and all study material must be archived no later than 2 weeks after the study director signs the summary report. (g) An individual must be identified as responsible for the archives. Archiving specifications for multisite studies must also be included in the approved study protocol. (h) Only authorized personnel can have access to the archives. (i) SOPs regarding archiving, required in § 58.81(b)(13), must include specific procedures for removal of study materials from

without compromising the integrity of study material.		the archives, including maximum timeframes material can remain outside of the archives.
Retention of Records (§ 58.195) We propose modifying § 58.195(b) to conform with§ 58.190(a) for the listing arrangement. We also propose modifying § 58.195(b)(1) to address those applications and submissions to FDA that might not result in an approval, clearance, or a premarket authorization. We therefore propose adding an additional required retention period from the date an application or submission is administratively closed by FDA. ''Administratively closed'' includes those applications and submissions closed administratively with or without a decision. In § 58.195(h), we propose adding a statement recognizing that a change of archive location may be due to reasons other than closure of a testing facility. For example, changes in ownership as well as changes in physical location would change the archive location. We also propose including a timeframe of ''no later than 10 working days after the transfer occurs" for reporting to FDA and the study sponsor a change in archive location. We propose this timeframe to ensure that FDA is informed of the location of study materials if a GLP BIMO inspection of the study is warranted. This requirement is necessary to prevent waste of inspectional resources and delay in receiving FDA inspectional findings, which provide FDA reviewers information about data quality and integrity. Other proposed changes to § 58.195 are for consistency with	**§ 58.195 Retention of records.** (a) Record retention requirements set forth in this section do not supersede the record retention requirements of any other regulations in this chapter. (b) Except as provided in paragraph (c) of this section, documentation records, raw data and specimens pertaining to a nonclinical laboratory study and required to be made by this part shall be retained in the archive(s) for whichever of the following periods is shortest: (1) A period of at least 2 years following the date on which an application for a research or marketing permit, in support of which the results of the nonclinical laboratory study were submitted, is approved by the Food and Drug Administration. This requirement does not apply to studies supporting investigational new drug applications (IND's) or applications for investigational device exemptions (IDE's), records of which shall be governed by the provisions of paragraph (b)(2) of this section. (2) A period of at least 5 years following the date on which the results of the nonclinical laboratory study are submitted to the Food and Drug Administration in support of an application for a research or marketing permit. (3) In other situations (e.g., where the nonclinical laboratory study does not result in the submission of the study in support of an application for a research or marketing permit), a period of at least 2 years following the date on which the study is completed, terminated, or discontinued.	**§ 58.195 Retention of records.** (a) Record retention requirements set forth in this section do not supersede the record retention requirements of any other regulations in this chapter nor do they supersede any other legal requirements elsewhere in applicable statutes or regulations. (b) Except as provided in paragraph (c) of this section, all raw data, documentation, protocols, final study reports, reserve samples, and specimens pertaining to a nonclinical laboratory study and required to be made by this part must be retained in the archive(s) for whichever of the following periods is shortest: (1) A period of at least 2 years following the date on which an application or submission to FDA, in support of which the results of the nonclinical laboratory study were submitted, is approved or cleared by FDA, a premarket authorization is issued, or the application or submission is administratively closed. This requirement does not apply to studies supporting investigational new drug applications (INDs) or applications for investigational device exemptions (IDEs), records of which are governed by the provisions of paragraph (b)(2) of this section. (2) A period of at least 5 years following the date on which the results of the nonclinical laboratory study are submitted to FDA in support of an application or submission. (3) In other situations (*e.g.,* where the nonclinical laboratory study does not result in the submission

our proposals throughout this document and to update the regulations consistent with current practices.	(c) Wet specimens (except those specimens obtained from mutagenicity tests and wet specimens of blood, urine, feces, and biological fluids), samples of test or control articles, and specially prepared material, which are relatively fragile and differ markedly in stability and quality during storage, shall be retained only as long as the quality of the preparation affords evaluation. In no case shall retention be required for longer periods than those set forth in paragraphs (a) and (b) of this section. (d) The master schedule sheet, copies of protocols, and records of quality assurance inspections, as required by § 58.35(c) shall be maintained by the quality assurance unit as an easily accessible system of records for the period of time specified in paragraphs (a) and (b) of this section. (e) Summaries of training and experience and job descriptions required to be maintained by § 58.29(b) may be retained along with all other testing facility employment records for the length of time specified in paragraphs (a) and (b) of this section. (f) Records and reports of the maintenance and calibration and inspection of equipment, as required by § 58.63(b) and (c), shall be retained for the length of time specified in paragraph (b) of this section. (g) Records required by this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. (h) If a facility conducting nonclinical testing goes out of business, all raw data,	of the study in support of an application or submission to FDA), a period of at least 2 years following the study completion date or the date on which the study is terminated or discontinued. (c) Wet specimens (except those specimens obtained from mutagenicity tests and wet specimens of blood, urine, feces, and biological fluids), samples of test, control, and reference articles, and specially prepared material, which are relatively fragile and differ markedly in stability and quality during storage, must be retained only as long as the quality of the preparation affords evaluation. In no case is retention required for longer periods than those set forth in paragraphs (a) and (b) of this section. (d) Management with executive responsibility must ensure maintenance of the master schedule and copies of study protocols, as specified in SOPs as described in § 58.81(b)(13) and as specified in paragraphs (a) and (b) of this section. QAUs must maintain records of QAU inspections, as required by § 58.35(c) for the period of time specified in paragraphs (a) and (b) of this section. (e) Summaries of training and experience and job descriptions required to be maintained by § 58.29(d) may be retained along with all other employment records for the length of time specified in paragraphs (a) and (b) of this section. (f) Records and reports of the maintenance and calibration and inspection of equipment, as required by § 58.63(b) and (c), must be retained for the length of time specified in paragraph (b) of this section.

	documentation, and other material specified in this section shall be transferred to the archives of the sponsor of the study. The Food and Drug Administration shall be notified in writing of such a transfer.	(g) Records required by this part may be retained either as original records or as true copies that maintain the original intent and meaning and are made according to the person's SOPs as described in § 58.81(b)(22). (h) If a facility conducting nonclinical laboratory testing goes out of business or for any reason can no longer serve as the archive site for a particular study, all raw data, documentation, and other material specified in this section must be transferred to the archives of the sponsor of the study or to another appropriate archive facility. The facility must notify FDA in writing (and the study sponsor if not the recipient of the study material) of the transfer no later than 10 working days after the transfer occurs. (i) A copy of the notification of change of archive site, as required by paragraph (h) of this section, can serve as the amendment to the final study report required in § 58.185(c) when appended to that report.
	Subpart K—Disqualification of Testing Facilities	Revise the heading of subpart K to read as follows: Subpart K—Disqualification of Any Person Conducting a Phase of a Nonclinical Laboratory Study
Part 58, Subpart K—Disqualification of Any Person Conducting a Phase of a Nonclinical Laboratory Study We propose modifying subpart K to extend the authority of the Commissioner of Food and Drugs to disqualify any person conducting a phase of a nonclinical laboratory study upon finding either or both of the conditions for disqualification in the proposed revisions in § 58.202. We propose adding any person conducting a phase of a	**§ 58.200 Purpose.** (a) The purposes of disqualification are: (1) To permit the exclusion from consideration of completed studies that were conducted by a testing facility which has failed to comply with the requirements of the good laboratory practice regulations until it can be adequately demonstrated that such noncompliance did not occur during, or did not affect the validity or acceptability of data generated by, a particular study; and	**§ 58.200 Purpose.** (a) The purposes of disqualification are: (1) To permit the exclusion from consideration of completed studies for which a phase was conducted by any person failing to comply with the requirements of the GLP regulations until it can be adequately demonstrated that such noncompliance did not occur during, or did not affect the validity or acceptability of data generated by, a particular study; (2) To exclude from consideration all studies completed after the

nonclinical laboratory study for consistency with other modifications throughout this proposal. We propose modifying § 58.202 to clarify the conditions for disqualification. To help provide uniformity in FDA regulations, we propose adding as a basis for initiating disqualification proceedings the repeated or deliberate submission of false information in any required report. FDA intends to reserve disqualification for the rare case when the rejection of a particular study is an inadequate regulatory response (see 43 FR 59986 at 60011) (Ref. 12). In addition, we propose to amend the current provision in § 58.206(a) so that a person disqualified under part 58 would no longer be eligible to receive a test article under part 511, New Animal Drugs For Investigational Use. A clinical investigator who is ineligible to receive a test article under part 511 also would be ineligible to conduct any nonclinical laboratory study that is intended to support an application for a research or marketing permit. For certain FDA-regulated products, such as new animal drugs, the study subjects are animals in both ''nonclinical laboratory studies'' and ''clinical investigations.'' In the new animal drug approval process, nonclinical laboratory studies, such as those that target animal safety and human food safety, may be essential in determining whether to approve an application for a research or marketing permit for a new animal drug. For new animal drugs, the same clinical investigator could conduct both nonclinical laboratory studies and clinical investigations. Therefore,	(2) To exclude from consideration all studies completed after the date of disqualification until the facility can satisfy the Commissioner that it will conduct studies in compliance with such regulations. (b) The determination that a nonclinical laboratory study may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.	date of disqualification until the disqualified person can satisfy the Commissioner that it will conduct studies in compliance with such regulations. (b) The determination that a nonclinical laboratory study may not be considered in support of an application or submission to FDA does not, however, relieve the applicant of any obligation under any other applicable regulation to submit the results of the study to FDA.

we propose this action to help protect the safety and welfare of animal research subjects involved in FDA-regulated nonclinical laboratory studies and clinical investigations, and to help ensure the reliability and integrity of the data submitted to FDA to support FDA decisions concerning new animal drugs. Concurrent with this proposal, FDA is publishing elsewhere in this issue of the Federal Register a proposal to amend § 511.1(c), to expand the scope of clinical investigator disqualification under part 511. Under the current regulations, a clinical investigator disqualified by the Commissioner is ineligible to receive the particular type of test article regulated under that part (*e.g.* new animal drugs in § 511.1(c)) and is ineligible to conduct any clinical investigation the research *that supports an application for* or marketing permit for products regulated by FDA. Under the proposed amendment to part 511, a clinical investigator disqualified under part 511 also would be ineligible to conduct any nonclinical laboratory study intended to support an application for a research or marketing permit for a new animal drug. When a clinical investigator is disqualified pursuant to part 511, the basis for that disqualification typically is the repeated or deliberate submission of false information to FDA or a sponsor in any required report. For new animal drugs, the same investigator could conduct both nonclinical laboratory studies and clinical investigations. The proposed amendment to part 511 would make a clinical investigator disqualified under part 511 ineligible to conduct any		

nonclinical laboratory study intended to support an application for a research or marketing permit for a new animal drug. In addition, the proposed amendment to part 511 would help to provide consistency for disqualification proceedings in parts 58 and 511.8. Other proposed provisions in §§ 58.200, 58.202, 58.204, 58.206, 58.210, 58.213, 58.215, and 58.217 are for clarity and consistency with our proposals throughout this document. In § 58.210, when a study is determined to be unacceptable, we propose to eliminate from consideration data in support of the application or submission to FDA, as defined in proposed § 58.3. We also propose to add that such elimination may serve as new information justifying appropriate regulatory action not limited to termination or withdrawal of approval. We propose modifying § 58.219 to reference § 58.210(b) and to require an FDA inspection of a disqualified person before reinstatement can be considered. Presently, § 58.219 states that the Commissioner ''may'' require such an inspection. Before a request for reinstatement can be appropriately considered by FDA, we propose requiring an inspection. This inspection would help provide additional information about the disqualified person that may be relevant to the consideration for reinstatement.		
	§ 58.202 Grounds for disqualification. The Commissioner may disqualify a testing facility upon finding all of the following: (a) The testing facility failed to comply with one or more of the	**§ 58.202 Grounds for disqualification.** FDA may disqualify any person conducting a phase of a nonclinical laboratory study upon finding that person repeatedly or deliberately failed to comply with

	regulations set forth in this part (or any other regulations regarding such facilities in this chapter); (b) The noncompliance adversely affected the validity of the nonclinical laboratory studies; and (c) Other lesser regulatory actions (e.g., warnings or rejection of individual studies) have not been or will probably not be adequate to achieve compliance with the good laboratory practice regulations.	one or more of the regulations set forth in this part (or any other regulations regarding such facilities in this chapter) or repeatedly or deliberately submitted false information in any required report.
	Section 58.204 Notice of and opportunity for hearing on proposed disqualification. (a)Whenever the Commissioner has information indicating that grounds exist under 58.202 which in his opinion justify disqualification of a testing facility,he may issue to the testing facility a written notice proposing that the facility be disqualified. (b)A hearing on the disqualification shall be conducted in accordance with the requirements for a regulatory hearing set forth in part 16 of this chapter.	In § 58.204, revise paragraph (a) to read as follows: **§ 58.204 Notice of and opportunity for hearing on proposed disqualification.** (a) Whenever FDA has information indicating that grounds exist under § 58.202, which justifies disqualification of any person conducting a phase of a nonclinical laboratory study, FDA may issue to that person a written notice proposing that person be disqualified. * * * * *
	§ 58.206 Final order on disqualification. (a) If the Commissioner, after the regulatory hearing, or after the time for requesting a hearing expires without a request being made, upon an evaulation of the administrative record of the disqualification proceeding, makes the findings required in § 58.202, he shall issue a final order disqualifying the facility. Such order shall include a statement of the basis for that determination. Upon issuing a final order, the Commissioner shall notify (with a copy of the order) the testing facility of the action.(b) If the Commissioner, after a regulatory hearing or after	**§ 58.206 Final order on disqualification.** (a) If the Commissioner, after the regulatory hearing, or after the time for requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification proceeding, makes the findings required in § 58.202, the Commissioner issues a final order disqualifying that person. Such order must include a statement of the basis for that determination. Upon issuing a final order, the Commissioner notifies (with a copy of the order) the disqualified person of the action. The notification also will explain that a

	the time for requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification proceeding, does not make the findings required in § 58.202, he shall issue a final order terminating the disqualification proceeding. Such order shall include a statement of the basis for that determination. Upon issuing a final order the Commissioner shall notify the testing facility and provide a copy of the order.	person who is disqualified under this part will be ineligible to receive a test article under part 511 of this chapter. A clinical investigator ineligible to receive a test article under part 511 of this chapter will be ineligible to conduct any nonclinical laboratory study intended to support an application for a research or marketing permit for a new animal drug. (b) If the Commissioner, after a regulatory hearing or after the time for requesting a hearing expires without a request being made, upon an evaluation of the administrative record of the disqualification proceeding, does not make the findings required in § 58.202, the Commissioner issues a final order terminating the disqualification proceeding. Such order must include a statement of the basis for that determination. Upon issuing a final order the Commissioner notifies that person and provides a copy of the order.
	§ 58.210 Actions upon disqualification. (a) Once a testing facility has been disqualified, each application for a research or marketing permit, whether approved or not, containing or relying upon any nonclinical laboratory study conducted by the disqualified testing facility may be examined to determine whether such study was or would be essential to a decision. If it is determined that a study was or would be essential, the Food and Drug Administration shall also determine whether the study is acceptable, notwithstanding the disqualification of the facility. Any study done by a testing facility	**§ 58.210 Actions upon disqualification.** (a) Once a person has been disqualified, each application and submission to FDA containing or relying upon any nonclinical laboratory study for which a phase was conducted by the disqualified person may be examined to determine whether such study was or would be essential to a decision. If it is determined that a study was or would be essential, FDA must also determine whether the study is acceptable, notwithstanding the disqualification of that person. Any study for which a phase was conducted by the disqualified person before disqualification may be presumed to be unacceptable, and the person relying on the study may

	before or after disqualification may be presumed to be unacceptable, and the person relying on the study may be required to establish that the study was not affected by the circumstances that led to the disqualification, e.g., by submitting validating information. If the study is then determined to be unacceptable, such data will be eliminated from consideration in support of the application; and such elimination may serve as new information justifying the termination or withdrawal of approval of the application. (b) No nonclinical laboratory study begun by a testing facility after the date of the facility's disqualification shall be considered in support of any application for a research or marketing permit, unless the facility has been reinstated under 58.219. The determination that a study may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.	be required to establish that the study was not affected by the circumstances that led to the disqualification, *e.g.,* by submitting validating information. If the study is then determined to be unacceptable, such data will be eliminated from consideration in support of the application or submission to FDA and such elimination may serve as new information justifying appropriate regulatory action. (b) No nonclinical laboratory study for which any phase was begun by a disqualified person after the date of that person's disqualification can be considered in support of any application or submission to FDA, unless the disqualified person has been reinstated under § 58.219. The determination that a study may not be considered in support of an application or submission to FDA does not, however, relieve the applicant of any obligation under any other applicable regulation to submit the results of the study to FDA.
	§ 58.213 Public disclosure of information regarding disqualification. (a) Upon issuance of a final order disqualifying a testing facility under § 58.206(a), the Commissioner may notify all or any interested persons. Such notice may be given at the discretion of the Commissioner whenever he believes that such disclosure would further the public interest or would promote	**58.213 Public disclosure of information regarding disqualification.** (a) Upon issuance of a final order disqualifying a person under § 58.206(a), the Commissioner may notify all or any interested persons. Such notice may be given at the discretion of the Commissioner whenever the Commissioner believes that such disclosure would further the public interest or would promote

	compliance with the good laboratory practice regulations set forth in this part. Such notice, if given, shall include a copy of the final order issued under § 58.206(a) and shall state that the disqualification constitutes a determination by the Food and Drug Administration that nonclinical laboratory studies performed by the facility will not be considered by the Food and Drug Administration in support of any application for a research or marketing permit. If such notice is sent to another Federal Government agency, the Food and Drug Administration will recommend that the agency also consider whether or not it should accept nonclinical laboratory studies performed by the testing facility. If such notice is sent to any other person, it shall state that it is given because of the relationship between the testing facility and the person being notified and that the Food and Drug Administration is not advising or recommending that any action be taken by the person notified. (b) A determination that a testing facility has been disqualified and the administrative record regarding such determination are disclosable to the public under part 20 of this chapter.	compliance with the GLP regulations set forth in this part. Such notice, if given, must include a copy of the final order issued under § 58.206(a) and must state that the disqualification constitutes a determination by FDA that nonclinical laboratory studies for which a phase was performed by the disqualified person will not be considered by FDA in support of any application or submission to FDA. If such notice is sent to another Federal Government agency, FDA will recommend that the agency also consider whether or not it should accept nonclinical laboratory studies for which a phase was performed by the disqualified person. If such notice is sent to any other person, it states that it is given because of the relationship between the disqualified person and the person being notified and that FDA is not advising or recommending that any action be taken by the person notified. (b) A determination that a person has been disqualified and the administrative record regarding such determination are disclosable to the public under part 20 of this chapter.
	§ 58.215 Alternative or additional actions to disqualification. (a) Disqualification of a testing facility under this subpart is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, institute against a testing facility and/or against the sponsor of a nonclinical laboratory study that has been submitted to the Food and Drug	**§ 58.215 Alternative or additional actions to disqualification.** (a) Disqualification of any person under this subpart is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the Federal Food, Drug, and Cosmetic Act. FDA may, at any time, institute against a disqualified person or against the sponsor of a nonclinical laboratory study that has been submitted to FDA, or both, any

	Administration any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and prior to, simultaneously with, or subsequent to, disqualification. The Food and Drug Administration may also refer the matter to another Federal, State, or local government law enforcement or regulatory agency for such action as that agency deems appropriate. (b) The Food and Drug Administration may refuse to consider any particular nonclinical laboratory study in support of an application for a research or marketing permit, if it finds that the study was not conducted in accordance with the good laboratory practice regulations set forth in this part, without disqualifying the testing facility that conducted the study or undertaking other regulatory action.	appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, including civil money penalties, in addition to or in lieu of, and before, simultaneously with, or subsequent to, disqualification. FDA may also refer the matter to another Federal, State, or local government law enforcement or regulatory agency for such action as that agency deems appropriate. (b) FDA may refuse to consider any particular nonclinical laboratory study in support of an application or submission to FDA, if it finds that the study was not conducted according to the GLP regulations set forth in this part, without disqualifying any person that conducted one or more phases of the study or undertaking other regulatory action.
	§ 58.217 Suspension or termination of a testing facility by a sponsor. Termination of a testing facility by a sponsor is independent of, and neither in lieu of nor a precondition to, proceedings or actions authorized by this subpart. If a sponsor terminates or suspends a testing facility from further participation in a nonclinical laboratory study that is being conducted as part of any application for a research or marketing permit that has been submitted to any Center of the Food and Drug Administration (whether approved or not), it shall notify that Center in writing within 15 working days of the action; the notice shall include a statement of the reasons for such action. Suspension or termination of a testing facility by a sponsor does not relieve it of any	**§ 58.217 Suspension or termination of any person conducting a phase of a nonclinical laboratory study by a sponsor.** Termination of any person conducting a phase of a nonclinical laboratory study by a sponsor is independent of, and neither in lieu of nor a precondition to, proceedings or actions authorized by this subpart. If a sponsor terminates or suspends any person conducting a phase of a nonclinical laboratory study from further participation in a study that is being conducted as part of any application or submission to FDA that has been submitted to any Center of FDA (whether approved or cleared, premarket authorization issued, or administratively closed), the sponsor must notify that Center

	obligation under any other applicable regulation to submit the results of the study to the Food and Drug Administration.	in writing within 15 working days of the action; the notice must include a statement of the reasons for such action. Suspension or termination of any person conducting a phase of a nonclinical laboratory study by a sponsor does not relieve the sponsor of any obligation under any other applicable regulation to submit the results of the study to FDA.
	58.219 Reinstatement of a disqualified testing facility. A testing facility that has been disqualified may be reinstated as an acceptable source of nonclinical laboratory studies to be submitted to the Food and Drug Administration if the Commissioner determines, upon an evaluation of the submission of the testing facility, that the facility can adequately assure that it will conduct future nonclinical laboratory studies in compliance with the good laboratory practice regulations set forth in this part and, if any studies are currently being conducted, that the quality and integrity of such studies have not been seriously compromised. A disqualified testing facility that wishes to be so reinstated shall present in writing to the Commissioner reasons why it believes it should be reinstated and a detailed description of the corrective actions it has taken or intends to take to assure that the acts or omissions which led to its disqualification will not recur. The Commissioner may condition reinstatement upon the testing facility being found in compliance with the good laboratory practice regulations upon an inspection. If a testing facility is reinstated, the Commissioner shall so notify the testing facility and all organizations and persons who	**§ 58.219 Reinstatement of a disqualified person.** Any person that has been disqualified may be reinstated as an acceptable source of data for a phase of a nonclinical laboratory study to be submitted to FDA if the Commissioner determines, upon an evaluation of materials submitted by that person, as well as the results from an FDA inspection of that person, that procedures are in place that would allow that person to conduct a phase of future nonclinical laboratory studies in compliance with the GLP regulations set forth in this part. As noted in § 58.210(b), no nonclinical laboratory study for which a phase was begun by a disqualified person after the date of that person's disqualification is considered in support of any application or submission to FDA, unless that person has been reinstated. A disqualified person that wishes to be so reinstated must present in writing to the Commissioner reasons why it believes it should be reinstated and a detailed description of the corrective actions it has taken or intends to take to assure that the acts or omissions which led to its disqualification will not recur. The disqualified person must also state its availability for inspection. If a disqualified person is

	were notified, under § 58.213 of the disqualification of the testing facility. A determination that a testing facility has been reinstated is disclosable to the public under part 20 of this chapter.	reinstated, the Commissioner must so notify that person and all organizations and persons who were notified, under § 58.213 of the disqualification of that person. A determination that a disqualified person has been reinstated is disclosable to the public under part 20 of this chapter.

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