



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 16 and 58

[Docket No. FDA-2010-N-0548]

Good Laboratory Practice for Nonclinical Laboratory Studies

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the regulations for good laboratory practice (GLP) for nonclinical laboratory studies to require a complete quality system approach, referred to as a GLP Quality System, when safety and toxicity studies support or are intended to support applications or submissions for products regulated by FDA.

We are proposing additional management responsibilities and standard operating procedures (SOPs) consistent with the proposed requirement for a GLP Quality System. We also propose to revise the testing facility definition to reflect current practices for the conduct of nonclinical laboratory studies, particularly multisite studies. These proposals are intended to build quality into planning, conducting, and reporting a nonclinical laboratory study and to help ensure data quality and integrity.

DATES: Submit either electronic or written comments on the proposed rule by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL

REGISTER] see section IX). See section VII for the proposed effective date of a final rule based on this proposed rule.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <http://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2010-N-0548 for “Good Laboratory Practice for Nonclinical Laboratory Studies.” Received comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <http://www.regulations.gov> or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <http://www.regulations.gov>. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public docket, see 80 FR

56469, September 18, 2015, or access the information at:

<http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Submit comments on information collection issues to the Office of Management and Budget (OMB) in the following ways:

Fax to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202-395-7285, or email to oir_submission@omb.eop.gov. All comments should be identified with the title, “Reporting and Recordkeeping Requirements for Good Laboratory Practice for Nonclinical Laboratory Studies.”

FOR FURTHER INFORMATION CONTACT: Vernon Toelle, Office of Surveillance and Compliance, Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Pl., MPN4-142, Rockville, MD 20855, 240-402-5637; or Kristin Webster Maloney, Office of Policy and Risk Management, Office of Regulatory Affairs, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, rm. 4373, Silver Spring, MD 20993, 240-402-4993.

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I. Executive Summary

A. Purpose of the Proposed Rule

Nonclinical laboratory studies, often referred to as preclinical studies when conducted before first-in-human clinical studies, provide safety or toxicity information, or both, that is essential for the development of FDA-regulated products and help determine the safety of new food ingredients. For drugs administered to animals whose products will be consumed by humans, nonclinical laboratory studies are critical for determining safe levels of residual drug product. For tobacco products, nonclinical laboratory studies may provide evidence regarding the relative toxicities of new or modified risk tobacco products. FDA's regulation of the conduct of nonclinical laboratory studies is important to help ensure the quality and integrity of data derived from those studies, the protection of human subjects, and that marketing decisions are based on accurate and reliable data.

Therefore, FDA proposes to amend the GLP regulations to require the use of a complete quality system approach (proposed GLP Quality System) when a nonclinical laboratory study supports or is intended to support an application or submission to FDA. Part 58 (21 CFR part 58) presently includes many aspects of a quality system approach. However, certain fundamentals of a fully implemented GLP Quality System considered essential to a quality system, such as certain SOPs and adequate management roles, responsibilities, and accountability, are not presently required. We therefore propose a fully implemented GLP

Quality System as the proper framework for building quality into planning, conducting, and reporting a nonclinical laboratory study to help ensure the quality and integrity of the resulting data used to support FDA regulatory decisions.

We also propose to amend the GLP regulations to reflect current practices for the conduct of nonclinical laboratory studies, particularly multisite studies, while allowing industry flexibility to meet the proposed requirements.

B. Summary of the Major Provisions of the Proposed Rule

Under the proposed GLP Quality System, FDA intends to enhance the current quality system approach for nonclinical laboratory studies. The GLP Quality System will provide additional responsibilities for testing facility management and new responsibilities for maintaining SOPs. We propose modifications to the definition of a testing facility to be applicable to all nonclinical laboratory studies, whether they are conducted at a single facility or at multiple sites. We propose amending roles and functions consistent with the revised testing facility definition. FDA expects that a GLP Quality System will provide the appropriate framework for building quality into a nonclinical laboratory study and will result in more reliable data for FDA to consider when making regulatory decisions.

C. Legal Authority

FDA proposes to issue this rule under the authority of the provisions in sections 351 and 354-360F of the Public Health Service Act (PHS Act) and the provisions in the Federal Food, Drug, and Cosmetic Act (the FD&C Act) applicable to the conduct of nonclinical laboratory studies, specifically under section 701(a) of the FD&C Act (21 U.S.C 371(a)), as essential to enforcement of the Agency's responsibilities under sections 402, 406, 408, 409, 501, 502, 503, 505, 510, 512-516, 518-520, 571, 721, 801, 905, 910, and 911 of the FD&C Act (21 U.S.C. 342,

346, 348, 349, 351, 352, 353, 355, 360, 360b-360f, 360h-360j, 360ccc, 379, 381, 387e, 387j, and 387k).

D. Costs and Benefits

Costs estimates of the rule include annual costs from the additional reporting and recordkeeping responsibilities required under the proposed GLP Quality System. One-time costs include reading and understanding the rule, updating existing SOPs, writing new SOPs, and training. We estimate annualized costs, over a 10-year period, at a 7-percent discount rate would average \$51.9 million, or \$51.5 million with a 3-percent discount rate. We lack sufficient information to quantify the benefits of the proposed rule, but we anticipate that it would result in better quality and more reliable data to support applications and submissions to us. The table summarizes these estimates along with their ranges.

Summary of Benefits, Costs and Distributional Effects of Proposed Rule

| Category | | Primary Estimate | Low Estimate | High Estimate | Units | | | Notes |
|-----------|--|--|--------------|---------------|--------------|---------------|----------------|-------|
| | | | | | Year Dollars | Discount Rate | Period Covered | |
| Benefits | Annualized Monetized \$millions/year | | | | 2014 | 7% | 10 years | |
| | | | | | 2014 | 3% | 10 years | |
| | Annualized Quantified | | | | 2014 | 7% | 10 years | |
| | | | | | 2014 | 3% | 10 years | |
| | Qualitative | The proposed rule would clarify GLP standards to facilitate a more consistent approach and provide greater international consistency. As a result, we anticipate improvements in the integrity and quality of data submitted for FDA review decisions. | | | | | | |
| Costs | Annualized Monetized \$millions/year | \$51.9 | \$34.4 | \$69.3 | 2014 | 7% | 10 years | |
| | | \$51.5 | \$34.2 | \$68.9 | 2014 | 3% | 10 years | |
| | Annualized Quantified | | | | 2014 | 7% | 10 years | |
| | | | | | 2014 | 3% | 10 years | |
| | Qualitative | | | | | | | |
| Transfers | Federal Annualized Monetized \$millions/year | | | | 2014 | 7% | 10 years | |
| | | | | | 2014 | 3% | 10 years | |
| | | From: | | | To: | | | |
| | Other Annualized | | | | 2014 | 7% | 10 years | |
| | | | | | 2014 | 3% | 10 years | |

| Category | Primary Estimate | Low Estimate | High Estimate | Units | | | Notes |
|---------------------------|--|--------------|---------------|--------------|---------------|----------------|-------|
| | | | | Year Dollars | Discount Rate | Period Covered | |
| Monetized \$millions/year | From: | | | To: | | | |
| Effects | <p>State, Local or Tribal Government: None estimated.</p> <p>Small Business: The proposed requirements would likely impose a significant burden on small entities employing fewer than 10 workers in “Dental Equipment and Supplies” (between 1.87 and 8.94 percent of average annual sales). However, we do not have data on how many of these dental-equipment small entities perform nonclinical laboratory studies to support, or intended to support, an application or submission regulated by us; only such entities would be affected by the rule.</p> <p>Wages: None estimated.</p> | | | | | | |

II. Introduction

FDA is proposing to amend the GLP regulations in part 58 to require the use of a complete quality system approach, referred to as a GLP Quality System, for the conduct of nonclinical laboratory studies when safety or toxicity studies, or both, support or are intended to support applications or submissions to FDA. FDA proposes to define a GLP Quality System as the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management in the conduct of nonclinical laboratory studies.

While many aspects of a quality system approach are presently included in part 58, we expect that implementation of a GLP Quality System will provide an improved framework that is more flexible and will help ensure quality in planning, conducting, and reporting nonclinical laboratory studies. Consistent with the proposed requirement for a GLP Quality System, we propose additional management responsibilities, with accompanying SOPs, to ensure management’s responsibility for establishing and maintaining the quality system. We also propose to revise the definition of a testing facility to reflect current practices for the conduct of nonclinical laboratory studies, particularly the conduct of multisite studies. Conforming modifications are proposed for consistency with the proposed GLP Quality System and today’s prevalence of multisite studies.

FDA is proposing these changes to help ensure the quality and integrity of data from nonclinical laboratory studies conducted in support of applications and submissions to FDA. We also are modernizing the regulations to further the Agency's efforts to encourage the implementation of the principles of the "3Rs," to reduce, refine, and replace animal use in testing. This approach seeks to minimize the use of animals in such testing and promote more humane, appropriate, and specific test methods for evaluating product safety. These proposed changes will clarify and update the regulations. In particular, we are proposing changes recognizing the current prevalence of multisite studies while adding flexibility consistent with current practices and the use of ever-changing technology.

A. What is the Background for This Rule?

On December 21, 2010, FDA published an advanced notice of proposed rulemaking (ANPRM), "Good Laboratory Practice for Nonclinical Laboratory Studies" (December 2010 ANPRM) (75 FR 80011), to solicit stakeholder input regarding FDA's intention to modify the GLP regulations in part 58. As stated in the December 2010 ANPRM, FDA is proposing to require that all facilities conduct nonclinical laboratory studies under a GLP Quality System when those studies support or are intended to support an application or submission to FDA.

The December 2010 ANPRM addressed nine specific areas to consider for amending part 58. Those nine areas are: (1) The GLP Quality System, (2) Multisite Studies, (3) Electronic/Computerized Systems, (4) Sponsor Responsibilities, (5) Animal Welfare, (6) Information on Quality Assurance Inspection Findings, (7) Process-Based Systems Inspections, (8) Test and Control Article Information, and (9) Sample Storage Container Retention.

FDA received about 90 comments to the December 2010 ANPRM. Most of the comments address the nine specific areas; however, a number of the comments include

additional areas for FDA's consideration. All comments were reviewed and considered by a working group with representatives from all FDA Centers, along with representatives from the U.S. Environmental Protection Agency (EPA), the Animal and Plant Health Inspection Service of the U.S. Department of Agriculture (USDA/APHIS), and the Office of Laboratory Animal Welfare at the National Institutes of Health (NIH/OLAW).

In addition to the December 2010 ANPRM comments, we reviewed and considered the documents of the working group on GLP of the Organisation for Economic Co-operation and Development (OECD), including the general principles of GLP and consensus and advisory documents (Ref. 1). The United States is a signatory to OECD's GLP Mutual Acceptance of Data agreement (Ref. 2) and, as an OECD member country, FDA participated in the development of OECD's GLP documents. For this proposal, we strive for consistency with the relevant OECD documents whenever possible.

B. Why is FDA Proposing This Rule?

The proposed GLP Quality System would help to provide a flexible framework for building quality into planning, conducting, and reporting a nonclinical laboratory study, and would help ensure the integrity of data submitted to FDA to support FDA regulatory decisions. The present regulations do not require certain fundamentals considered essential to a complete quality system. For example, the present regulations do not specifically require SOPs for developing and maintaining SOPs, or SOPs for developing and periodically assessing a quality system, nor do they provide for adequate management roles, responsibilities, and accountability. We note that a major principle of a complete quality system is management's ultimate responsibility for establishing and maintaining the quality system.

This proposal also is intended to update the regulations to reflect today's conduct of nonclinical laboratory studies, particularly the conduct of multisite studies. For multisite studies that may have multiple contracts and subcontracts for various study phases, effective communication is essential, especially considering the proposed requirement for a single final study report. We agree with the numerous comments to the December 2010 ANPRM that support a clear delineation of study responsibilities and effective communication among all parties involved in multisite studies.

Some stakeholders suggest that certain provisions in part 58 are outdated and hamper efficient use of present technology (for example, requiring hard copies of records and documentation instead of allowing computerized options). Several industry organizations approached FDA after the announcement of the Bioresearch Monitoring (BIMO) Modernization Initiative in 2006 (Ref. 3), requesting that we modernize the GLP regulations. One request, among others, was to remove the requirement that the quality assurance unit (QAU) must maintain the master schedule and copies of protocols. These requests were echoed in several comments to the December 2010 ANPRM. FDA agrees with those comments and proposes to update part 58 to help address the use of present technology.

Because the number of FDA inspections is limited by competing priorities and limited resources, we look to sponsors and nonclinical laboratory management to help ensure that data submitted to FDA in support of applications and submissions are reliable. For those nonclinical laboratory studies that are the bases for allowing a new medical product into first-in-human clinical studies, the quality and integrity of the data are crucial to human subject protection.

This proposal complements the intent of the original GLP proposed rule to ensure the quality and integrity of the resulting data (41 FR 51206 at 51210, November 19, 1976) (Ref. 4).

FDA expects that requiring a GLP Quality System will help ensure data quality and integrity. The proposed GLP Quality System also will allow the flexibility to develop site-specific procedures for related SOPs. Because of the great diversity in institutions, research activities, and organizational structures covered by these regulations, it is important to have sufficient flexibility in the regulations to allow the regulated parties to meet these requirements in a manner that best suits their organizational needs.

III. Description of the Part 58 Proposal

A. What Did FDA Consider When Drafting This Rule?

1. Animal Rule

Several comments to the December 2010 ANPRM requested that FDA modify part 58 to accommodate studies conducted in animals to support the effectiveness of human drugs or biological products when human efficacy studies are not ethical or feasible. Those comments refer to the “Animal Rule” (21 CFR parts 314 and 601) (67 FR 37988, May 31, 2002).

The Animal Rule provides a pathway for FDA to grant marketing approval based on adequate and well-controlled animal efficacy studies when the results of those studies establish that the drugs or biological products are reasonably likely to produce clinical benefit in humans. Products evaluated for efficacy under the Animal Rule should be evaluated for safety under the existing requirements for establishing the safety of new drugs and biological products. The provisions in part 314, subpart I for drugs and part 601, subpart H for biological products apply only to situations when adequate and well-controlled human efficacy studies cannot ethically be conducted because they would involve deliberate exposure of healthy human volunteers to a potentially lethal or permanently disabling toxic chemical, biological, radiological, or nuclear

substance, and field trials to study the product's effectiveness after an accidental or hostile exposure have not been feasible.

In the past, FDA has said that "All studies subject to this rule must be conducted in accordance with preexisting requirements under the good laboratory practices (21 CFR part 58) regulations" (67 FR 37988 at 37989, May 31, 2002). FDA made this statement because part 58 includes requirements for a quality system structure to ensure the quality and integrity of animal study data. These studies are intended to generate data that are essential for the approval or licensure of products intended for human use. Thus, ensuring the quality and integrity of data from these studies is critical as they serve as substantial evidence of effectiveness of the product.

Part 58 was issued to ensure the quality and integrity of nonclinical laboratory studies conducted to assess the safety of FDA-regulated products. In response to comments made to the ANPRM, FDA questions whether any requirement presently in part 58 or in this proposal poses a unique or disproportionate obstacle or burden on the conduct of certain animal studies specific to product development under the Animal Rule.

FDA, however, tentatively concludes there may be justifiable limitations to applying GLP regulations when conducting Animal Rule-specific studies, especially for studies using challenge agents that require high-containment facilities (for example, biosafety level 4 (BSL-4)¹ laboratory environments). Therefore, although part 58 embodies critical elements of a quality system to ensure data quality and integrity, FDA also recognizes that some current part 58 requirements may not be appropriate, or may require modification to address adequately data quality practices for the Animal Rule-specific studies.

¹ BSL-4 refers to the practices, safety equipment, and safeguards required for laboratories that work with highly infectious and lethal pathogenic microbes which cause, for example, such lethal diseases in humans as smallpox, Ebola, or Marburg virus hemorrhagic fever. BSL-4 is the highest biosafety level designation possible and means that the most stringent safeguards are in place to protect researchers, non-laboratory building occupants, the general public, and the environment from exposure to exotic or lethal agents.

Accordingly, although not included in the regulatory text portion of this proposal, FDA is considering expanding part 58 to include the conduct of certain Animal Rule studies that support approval or licensure of products for human use under the established data quality and integrity standards. We seek comment on this proposal. In particular, we invite comment on the possibility of amending the scope of the regulation in § 58.1(a) to encompass not only nonclinical laboratory studies, but also to include certain Animal Rule-specific studies. Correspondingly, we are considering adding a definition in § 58.3 for “Animal Rule-specific studies subject to GLP” (for purposes of this document, “Animal Rule-specific studies subject to GLP” are referred to as “covered Animal Rule studies”).

Specifically, FDA is considering including within the definition of covered Animal Rule studies only the following types of studies to support product approval under the Animal Rule: (1) The adequate and well-controlled animal efficacy studies that serve as substantial evidence of the effectiveness necessary for approval or licensure of human drugs or biological products, respectively; (2) pharmacokinetic and/or pharmacodynamic studies in animals used to select a dose and regimen in humans; and (3) if seeking qualification through FDA’s Animal Model Qualification Program,² the model-defining natural history studies.^{3,4}

² The Animal Model Qualification Program is part of FDA’s Drug Development Tool (DDT) Qualification Program. The DDT Program provides a framework for development and regulatory acceptance of scientific tools for use in drug development programs. Qualification of an animal model is not required for the approval of drugs or licensure of biologics under the Animal Rule. For more information about this program, see FDA’s guidance for industry and FDA staff [Qualification Process for Drug Development Tools](#) (January 2014) (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm230597.pdf>), and the Animal Model Qualification Program Web site: <http://inside.fda.gov:9003/CDER/OfficeofTranslationalSciences/BiomarkerQualifications/ucm271856.htm>.

³ In the context of animal model qualification, the model-defining natural history studies are the animal studies that establish the ranges of values of key parameters of the disease or condition that will be specified in the context of use statement for the qualified model and that will be used as measures of quality control and quality assurance when the model is replicated.

⁴ Natural history studies that will not be used to support the qualification of an animal model, as defined in footnote 2, would not be subject to GLP regulations.

FDA seeks comment on the impact of expanding part 58 to include these covered Animal Rule studies. We also request comment on what other changes to the regulations, beyond amending the scope and definitions, are needed to address issues unique to covered Animal Rule studies. FDA specifically requests comments in response to the following questions:

1. Would amending part 58 to expand the scope to include covered Animal Rule studies establish an appropriate quality system approach to the conduct of such studies to ensure data quality and integrity? If not, what gaps or shortcomings would remain, and how should they be addressed?
2. Would such an amendment provide sufficient clarity and flexibility to sponsors and investigators? If not, what alternatives or changes to this approach are needed?
3. FDA is considering adding a definition in part 58 for “Animal Rule-specific studies subject to GLP” (referred to as “covered Animal Rule studies”). As discussed in section III.A.1., the proposed definition contains three specific types of studies that would be subject to part 58. Is the term “Animal Rule-specific studies subject to GLP,” as defined in § 58.3, clear and appropriately inclusive?
4. What are the benefits, challenges, and burdens of amending part 58 to include covered Animal Rule studies?
 - a. Would this proposed expansion of the scope in § 58.1(a) impact entities conducting covered Animal Rule studies?
 - b. Would the proposed expansion of the scope in § 58.1(a) impact those entities engaged in conducting nonclinical laboratory studies to assess product safety?
 - c. What could be done to minimize burdens or costs, including costs or burdens on small entities, associated with part 58 compliance for covered Animal Rule studies?

5. Are there any challenges or differences involved in the conduct of covered Animal Rule studies (versus nonclinical laboratory studies) that merit different standards or establishment of a separate regulation? If so, what are those challenges or differences, and what alternative(s) would be preferable?
6. Based on possible differences identified in question 5, are there any particular aspects in the current or proposed part 58 that would be unduly difficult to meet? What changes to current part 58, or the proposed amendments, could be made to address or accommodate these issues? For example:
 - a. Would it be satisfactory to include a provision to allow on a case-by-case basis a covered Animal Rule study sponsor to seek FDA agreement on deviations from certain part 58 requirements that may not be practicable to meet as follows: “When the study is an Animal Rule-specific study subject to GLP, FDA may agree to deviations from any requirement of this part that it finds unnecessary to ensure the quality and integrity of the study by written agreement with the sponsor before the conduct of the study. In such cases, FDA’s acceptance of deviations from the requirements will be contingent upon compliance with any alternative requirements included in that agreement.”
 - b. Would it be workable or appropriate to entirely exempt covered Animal Rule studies from certain requirements of part 58? If so, what exemption(s) would be necessary or appropriate?

As discussed in section III.A.1., FDA considers GLP regulations to be a well-established and relevant system for ensuring data quality and integrity for covered Animal Rule studies.

Therefore, until a final rule is published, FDA recommends the use of the current GLP

framework (for example, definitions, procedures, roles and responsibilities, and controls) for covered Animal Rule studies to the extent practicable, and intends to provide more information about FDA's expectations for adapting a GLP framework to these studies.

Before initiating covered Animal Rule studies, sponsors should identify aspects of the studies anticipated to be challenging with regard to GLP and propose methods for adapting the studies to ensure the quality and integrity of the resulting data. Sponsors should submit this information to FDA for concurrence on the data quality and integrity plan before the studies are initiated. A guidance document is available regarding the essential elements necessary to address efficacy under the Animal Rule.⁵

2. ISO 9001 and GLP Quality System

Many comments to the December 2010 ANPRM note that the International Organization for Standardization (ISO) 9001 is very general and not all aspects outlined in ISO 9001 are applicable to GLPs. FDA acknowledges this. However, ISO 9001 is an internationally recognized standard for quality systems. Also, FDA's Quality System Regulation (QSR) in part 820 (21 CFR part 820) for current good manufacturing practice requirements for medical devices was harmonized, to the extent possible, with the ISO 9001: 1994 "Quality Systems--Model for Quality Assurance in Design, Development, Production, Installation and Servicing."

Some comments to the December 2010 ANPRM state that consistency with the ISO 9001 standard would be acceptable if we retained what they perceived as the present flexibility of the regulations. A number of comments state that it would be beneficial to borrow elements of a quality system from the QSR requirements in part 820 rather than reference ISO 9001:1994.

⁵ See FDA's guidance for industry Product Development Under the Animal Rule (October 2015), at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM399217.pdf>.

Many comments also request that we define the operational areas necessary for broader adoption of a quality system approach.

In this proposal, we incorporate aspects of ISO 9001:1994 that are consistent with part 820 and our desire to propose a complete quality system approach. For example, we propose to address establishing and maintaining a GLP quality system by adding to part 58 certain definitions, relevant SOPs, and management roles and responsibilities modeled after the part 820 requirements. Our proposed additions to more fully enable a GLP quality system will help expand the present flexibility in part 58. Our proposals also are consistent with OECD guidance documents for GLP wherever possible and, at the very least, do not conflict with them.

3. Animal Welfare

Many comments to the December 2010 ANPRM note that § 58.90 covers animal care and thus, FDA investigators review documentation of animal care during GLP inspections. This is true. If animal care is not compliant with appropriate standards, there is a high likelihood that such noncompliance could confound the results of affected studies. Since the good laboratory practice regulations were published, the Animal Welfare Act has been amended and the public's perception of animal welfare has changed. Therefore, we propose specific responsibilities regarding animal welfare because the humane treatment of animals in research settings is essential to the quality and integrity of GLP studies.

Many comments to the December 2010 ANPRM state that addressing animal welfare in part 58 would be a duplication of USDA/APHIS or the NIH regulations. That is not our intention. FDA has a Memorandum of Understanding (MOU) (Ref. 5) with USDA/APHIS and NIH/OLAW regarding animal welfare oversight. FDA forwards to the relevant regulatory agency any concerns regarding animal welfare observed during FDA inspections for their

followup. Those animal welfare observations are not included on a Form FDA 483 (Inspectional Observations) that may be issued at the close of an FDA inspection, unless the observations also show noncompliance with § 58.90.

While this proposal addresses animal welfare concerns, FDA supports the use of non-animal testing methods when scientifically valid alternatives are available. We encourage sponsors with questions about non-animal testing methods to approach FDA early in the development process for consultation on the suitability and acceptability of non-animal tests for their particular product. This approach reflects FDA's position in its May 20, 2010, citizen petition response to the Mandatory Alternatives Petition Coalition and subsequent Agency statements. That petition requested that FDA require only non-animal test methods instead of corresponding animal test methods whenever such scientifically satisfactory methods are available. (See Docket No. FDA-2007-P-0109.)

4. Multisite Studies

As stated in the December 2010 ANPRM, FDA's intent was simply to add new definitions relevant to roles and responsibilities specific to multisite studies. Many comments to the December 2010 ANPRM state that the present regulations are basically adequate and suggested only minimal modifications.

Since publication of the December 2010 ANPRM, we have changed our thinking concerning regulatory changes needed to address multisite studies. For example, we have determined that amending the definition of a testing facility will help address the current conduct of multisite studies. We discuss in section III.B.2. our proposed changes to that definition.

Many comments to the December 2010 ANPRM suggest that we align our requirements regarding multisite studies with the OECD consensus document entitled, The Application of the

OECD Principles of GLP to the Organisation and Management of Multi-Site Studies (Ref. 6).

The comments also requested that we not be as prescriptive as those OECD directives. We agree with those comments. We reviewed and considered this OECD consensus document and incorporated into our proposal the same general concepts, where applicable.

5. GLP Roles and Responsibilities

We propose to maintain the current GLP roles for management, study director, and QAU. We propose that the overarching responsibilities of those who fulfill these roles remain as follows: Management is responsible for establishing and maintaining conditions and procedures necessary for the conduct of nonclinical laboratory studies compliant with GLPs; the study director, as the sole point of study control, is responsible for implementing those procedures in specific studies; and the QAU is responsible for inspecting and general oversight of studies, verifying that they are GLP compliant or recommending changes needed for bringing them into compliance.

These responsibilities complement each other and sometimes overlap in multiple areas, providing for a system of checks and balances. We intend for this proposal to maintain the authority necessary for fulfilling each of these roles while allowing maximum flexibility for the conduct of a GLP-compliant nonclinical laboratory study.

We are interested in feedback about whether this proposal will accomplish our goal of maintaining the necessary interrelationships among these roles, and whether our proposal undermines any one of these roles or fails to provide adequate flexibility.

B. Part 58, Subpart A--General Provisions

1. 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 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 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.

2. 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 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 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 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 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 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 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 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 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, 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 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 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.

3. 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 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 animals⁶ (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,

⁶ The document, "International Guiding Principles for Biomedical Research Involving Animals," last revised in December 2012, advocates among other principles, the "Three Rs" of the ethical use of animals--replacement, refinement, and reduction (Ref. 10). Additionally, the protocol must meet the requirements in § 58.90 for animal care. USDA's Animal Welfare Act regulations (Code of Federal Regulations, Title 9, Chapter 1, Subchapter A, Parts 1-4) and the Institute for Laboratory Animal Research's Guide for the Care and Use of Laboratory Animals (Ref. 11), provide specifics regarding the veterinary care expected when animals are used for research.

regulations, policies, and guidelines. This information must be included in the compliance 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.

4. 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.

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) 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.

5. 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 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”.

C. Part 58, Subpart B--Organization and Personnel

1. 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 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.

2. 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 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 § 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 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 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.

3. 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.

4. 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).

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 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 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.

5. Quality Assurance Unit (QAU) (§ 58.35)

In § 58.35, we propose keeping the QAU functions currently in 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 testing 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 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 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

⁷ The term “study-based inspection” is not used in current FDA regulations; however, this type of inspection is equivalent to the QAU inspection currently required in part 58.

conduct a short-term study that 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 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 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.

6. 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 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 (3)).

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.

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.

7. 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 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.

D. Part 58, Subpart C--Facilities

1. 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.

2. 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 all nonclinical laboratory studies, including multisite studies.

3. 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.

E. Part 58, Subpart D--Equipment

1. 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.

2. 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.

F. Part 58, Subpart E--Nonclinical Laboratory Study Operations

Consistent with our proposals in part 58 to address multisite 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.

1. 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.

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.

2. 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.

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.

G. Part 58, Subpart F--Test, Control, and Reference Articles

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.⁸

1. 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

⁸ There is a draft guidance document regarding bioanalytical method validation, “Bioanalytical Method Validation Draft Guidance” (Ref. 16). When final, this guidance will provide FDA’s current thinking. We consider many of the general principles in this draft guidance document applicable to method validation in nonclinical laboratory studies.

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 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.

2. 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.

3. 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.

H. 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 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 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.).

2. 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 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.

I. 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 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.

2. 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 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 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.⁹ 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 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.

3. 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.

⁹ A link to those templates is provided in the Pesticide Registration Notice 2011-3 "Standard Format for Data Submitted Under the Federal Insecticide, Fungicide, and Rodenticide Act and Certain Provisions of the Federal Food, Drug, and Cosmetic Act" (Ref.17).

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 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 without compromising the integrity of study material.

4. 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 our proposals throughout this document and to update the regulations consistent with current practices.

J. 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 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, 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 that supports an application for a research 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.

IV. Regulatory Hearing Before FDA

We propose to add to 21 CFR 16.1(b)(2) a new provision for 21 CFR part 58, subpart K relating to disqualifying any person that conducts a phase of nonclinical laboratory studies of FDA-regulated products.

V. Analysis of Environmental Impact

The Agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Legal Authority

Legal authority to issue good laboratory practice regulations exists under section 701(a) of the FD&C Act, as essential to enforcement of the Agency’s responsibilities under sections 402, 406, 408, 409, 501, 502, 503, 505, 510, 512-516, 518-520, 571, 721, 801, 905, 910, and 911 of the FD&C Act; and, sections 351 and 354-360F of the PHS Act.

VII. Proposed Implementation Plan

FDA proposes that any final rule that may issue based on this proposal become effective 1 year after the date of publication of the final rule in the Federal Register.

VIII. Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the proposed rule. We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed requirements are likely to impose a significant burden on small entities employing fewer than 10 workers in “Dental Equipment and Supplies” (between 1.87 and 8.94 percent of average annual sales), we find that the proposed rule would have a significant economic impact on a substantial number of small entities, but the impacts are uncertain.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$146 million, using the most current (2015) Implicit Price

Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary

This proposed rule would amend the regulations regarding GLPs and would require that nonclinical laboratory studies (sometimes referred to as preclinical studies) follow a complete quality system approach, referred to as a GLP Quality System, when safety and toxicity studies support or are intended to support applications and submissions to FDA. The proposed rule would expand the scope to include all products for which nonclinical laboratory studies are currently conducted that are not explicitly discussed in the current regulations, specifically tobacco products. The proposed expanded scope also includes all applications and submissions under the FD&C Act that can be supported by the results of nonclinical laboratory studies. In addition, the proposed rule would introduce and modify definitions, terms, and organizational and personnel roles and responsibilities consistent with the implementation of the proposed GLP Quality System and the prevalence of multisite studies. Finally, the proposed rule would incorporate wording consistent with some of the existing domestic and international guidelines, rules or regulations covering good laboratory practices such as those established by the OECD.

Costs of the rule, when final, would include annual and one-time costs. Annual costs would include the additional reporting and recordkeeping responsibilities required under the proposed GLP Quality System. One-time costs include reading and understanding the rule, updating existing SOPs, writing new SOPs, and training. Combined, all costs annualized over a ten-year period at a 7-percent discount rate are estimated to range between \$34.4 million and \$69.3 million, with an average annualized cost of \$51.9 million. By contrast, with a 3 percent

discount rate, annualized cost would range from \$34.2 million to \$68.9 million, with an average annualized cost of \$51.5 million.

Conducting nonclinical laboratory studies under the proposed GLP Quality System is expected to improve the reliability and quality of the data that support applications and submissions to us, including those applications and submissions that lead to the use of new medical products in first-in-human clinical studies. In addition, the proposed system is conducive to improving compliance and accountability by all involved in the conduct of nonclinical laboratory studies.

As described, we understand the potential effects on small entities. We therefore seek comment, particularly from small entities, about the proposed effective date of 1 year after the date of publication of any final rule that may issue (see section VII. Proposed Implementation Plan).

The full discussion of economic impacts is available in docket FDA-2010-N-0548 at <http://www.regulations.gov> and at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm> (Ref. 18).

Table 1 summarizes the costs and benefits.

Table 1.--Summary of Benefits, Costs and Distributional Effects of Proposed Rule¹

| Category | | Primary Estimate | Low Estimate | High Estimate | Units | | | Notes |
|----------|--------------------------------------|--|--------------|---------------|--------------|---------------|----------------|-------|
| | | | | | Year Dollars | Discount Rate | Period Covered | |
| Benefits | Annualized Monetized \$millions/year | | | | 2014 | 7% | 10 years | |
| | | | | | 2014 | 3% | 10 years | |
| | Annualized Quantified | | | | 2014 | 7% | 10 years | |
| | | | | | 2014 | 3% | 10 years | |
| | Qualitative | The proposed rule would clarify GLP standards to facilitate a more consistent approach and provide greater international consistency. As a result, we anticipate improvements in the | | | | | | |

| Category | Primary Estimate | Low Estimate | High Estimate | Units | | | Notes | |
|-----------|--|---|---------------|--------------|---------------|----------------|----------|--|
| | | | | Year Dollars | Discount Rate | Period Covered | | |
| | | integrity and quality of data submitted for FDA review decisions. | | | | | | |
| Costs | Annualized Monetized \$millions/year | \$51.9 | \$34.4 | \$69.3 | 2014 | 7% | 10 years | |
| | | \$51.5 | \$34.2 | \$68.9 | 2014 | 3% | 10 years | |
| | Annualized Quantified | | | | 2014 | 7% | 10 years | |
| | | | | | 2014 | 3% | 10 years | |
| | Qualitative | | | | | | | |
| Transfers | Federal Annualized Monetized \$millions/year | | | | 2014 | 7% | 10 years | |
| | | | | | 2014 | 3% | 10 years | |
| | | From: | | | To: | | | |
| | Other Annualized Monetized \$millions/year | | | | 2014 | 7% | 10 years | |
| | | | | 2014 | 3% | 10 years | | |
| | | From: | | | To: | | | |
| Effects | <p>State, Local or Tribal Government: None estimated.</p> <p>Small Business: The proposed requirements would likely impose a significant burden on small entities employing fewer than 10 workers in “Dental Equipment and Supplies” (between 1.87 and 8.94 percent of average annual sales). However, we do not have data on how many of these dental-equipment small entities perform nonclinical laboratory studies to support, or intended to support, an application or submission regulated by us; only such entities would be affected by the rule.</p> <p>Wages: None estimated.</p> | | | | | | | |

¹ Full Disclosure Preliminary Impact Analysis of the proposed rule “Good Laboratory Practice for Nonclinical Laboratory Studies,” Docket No. FDA-2010-N-0548. (Available at: <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.)

IX. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). A description of these provisions is given in the Description section of this document with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection

of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Reporting and Recordkeeping Requirements for Good Laboratory Practice for Nonclinical Laboratory Studies--OMB Control Number 0910-0119--Revision

Description: This proposed rule would revise the existing information collection requirements in the GLP regulations to provide for the development and implementation of a GLP Quality System and to reflect current procedures for the conduct of nonclinical laboratory studies, particularly multisite studies.

Description of respondents: Respondents to the information collection are persons conducting a phase of a nonclinical laboratory study that is within the proposed expanded scope of part 58, including their personnel, independent contributing scientists, and study sponsors as the latter two terms are defined in this proposed rule; universities; or government agencies.

Reporting: Currently, the GLP regulations include requirements to: (1) Report the results of QAU inspections; (2) submit periodic QAU study reports; (3) provide a QAU statement as part of the final study report; (4) provide the results of test and control article characterization and the testing of mixtures of test and control articles with carriers; (5) report a change in archive location; and (6) prepare in writing a final study report containing an overall interpretation of nonclinical laboratory studies.

The proposed rule will revise these requirements to include: (1) A final study report incorporating additional information about all persons conducting one or more nonclinical

laboratory study phases and a study director's compliance statement; (2) QAU reports on facility-based inspections and process-based inspections, where conducted; (3) written certification whenever a process-based QAU inspection reveals problems, with documentation that records the actions taken; (4) summaries of the closeout of discontinued studies; (5) notification of the change of archival site within a specified timeframe; (6) reports by the study sponsor to the study director of known risks of the test article and necessary measures to protect study personnel; and (7) reports by the study sponsor to the study director of the results of characterization of any reference articles that may be employed in a study as well of mixtures of such reference articles with carriers. Finally, for sponsors who submit the results of nonclinical laboratory studies in support of applications or submissions to FDA that are proposed additions to the scope of part 58 and that lack enacting regulations, (8) submission of the final study report and a GLP compliance statement.

QAU inspection reports provide the study director and management with executive responsibility information about the progress of a study and its compliance with GLP regulations so they can take any corrective actions required to ensure the quality and integrity of the data. Test, control, and reference article information helps ensure proper dosing of the test system(s) and allows interpretation of study results in the final study report. The study sponsor receives the final study report and commonly submits the report in support of an application or submission to FDA. The information in the final study report gives FDA's scientific review experts the information needed to help determine the safety or toxicity of the test article or both. FDA needs such safety and toxicity information to make regulatory decisions regarding the test article, including permitting the conduct of clinical studies on human subjects, determining safe levels of residual drug for drugs administered to animals whose products will be consumed by

humans, and marketing new products for both human and non-human animal use. Since a number of the additional applications and submissions proposed for the scope expansion do not have enacting regulations, inclusion in part 58 is necessary.

We estimate the reporting burden of this collection of information as follows:

Table 2.--Estimated One-Time Reporting Burden¹

| Activity | No. of Respondents | No. of Responses per Respondent | Total Annual Responses | Average Burden per Response | Total Hours |
|---|--------------------|---------------------------------|------------------------|-----------------------------|-------------|
| Read and Understand the Proposed Rule: Sponsors of Nonclinical Laboratory Studies | 2,193 | 1 | 2,193 | 7.2 | 15,790 |
| Read and Understand the Proposed Rule: Testing Facilities of Nonclinical Laboratory Studies | 300 | 1 | 300 | 18 | 5,400 |
| Total | | | 2,493 | | 21,190 |

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 2 shows the estimated one-time burden associated with the new reporting provisions of the proposed rule. We expect that persons conducting a phase of a nonclinical laboratory study that is within the proposed expanded scope of part 58 will need to read and understand the proposed rule. We expect that some entities would face lower complexity from reading the proposed rule and some entities would face higher complexity. In the Preliminary Regulatory Impact Analysis (PRIA), we calculated lower and upper estimates of time to read and understand the proposed rule under a low-complexity scenario for sponsors of nonclinical laboratory studies who would face fewer provisions. Our estimates under a high-complexity scenario apply to testing facilities of nonclinical laboratory studies that would have to read and understand more provisions in the rule. As stated in the PRIA, we estimate that there are 2193 sponsors of nonclinical laboratory studies and 300 testing facilities of nonclinical laboratory studies. We estimate that the 2193 sponsors of nonclinical laboratory studies will take from 4.8 to 9.6 hours, for an average of 7.2 hours, to read and understand the proposed rule. We expect

that the 300 testing facilities of nonclinical laboratory studies will take from 12 to 24 hours, for an average of 18 hours, to read and understand the proposed rule.

Table 3:--Estimated Recurring Reporting Burden¹

| 21 CFR Section | No. of Respondents | No. of Responses per Respondent | Total Annual Responses | Average Burden per Response | Total Hours |
|---|--------------------|---------------------------------|------------------------|-----------------------------|-------------|
| Sponsor provides test, control, and reference article characterization and risk information (§ 58.5(g) & (h)) | 1,316 | 5 | 6,580 | 1 | 6,580 |
| Sponsor provides nonclinical laboratory study report in support of applications and submissions (§ 58.5(k)) | 10 | 1 | 10 | 15 | 150 |
| Expanded content of QAU statement in final study report (§ 58.35(b)(11)) | 300 | 60.25 | 18,075 | .25 (15 minutes) | 4,518.75 |
| Management report of actions taken when a process-based inspection reveals problems (§ 58.35(e)) | 10 | 2 | 20 | 5 | 100 |
| Expanded contents of final study report (§ 58.185(a)) | 300 | 60.25 | 18,075 | 2 | 36,150 |
| Compliance statement by study director appended to final study report (§ 58.185(a)(16)) | 300 | 60.25 | 18,075 | .5 (30 minutes) | 9,037.5 |
| Summary report of close-out for discontinued studies (§ 58.185(d)) | 300 | 2 | 600 | 2 | 1,200 |
| Reports by independent contributing scientists (§58.37(a)(2)) | 30 | 1 | 30 | 5 | 150 |
| Principal Investigator (PI) reports of deviations (§ 58.39(c)) | 200 | 10 | 2,000 | 1 | 2,000 |
| PI study report & compliance statement (§ 58.39 (d)) | 200 | 5 | 1,000 | 8 | 8,000 |
| Management report of personnel deviations from protocol (§ 58.29(b)) | 300 | 10 | 3,000 | .5 (30 minutes) | 1,500 |
| Total..... | | | 67,465 | | 69,386.25 |

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 3 shows the estimated recurring reporting burden associated with the proposed rule. Together, this results in a total of 90,576.25 hours and 69,958 responses.

Recordkeeping: Currently, the GLP regulations include requirements that respondents must record: (1) Personnel job descriptions and summaries of training and experience; (2) master schedules, protocols, and protocol amendments; (3) equipment inspection, maintenance, calibration, and testing records; (4) SOPs; (5) documentation of feed and water analyses and

animal treatments; (6) test article accountability records; and (7) study documentation, including raw data.

This proposed rule will add to the existing requirements with regard to initial changes and additions to SOPs for both testing facilities and test sites to develop, implement, and maintain a GLP Quality System and to expand many SOPs to specifically include multisite studies.

This proposed rule would also expand personnel record maintenance to require records of training and experience on GLP requirements and species-specific animal care. In addition, this proposed rule includes revisions to the required content of study protocols as part of a GLP Quality System and for multisite study specifics.

The additional documentation by management with executive responsibility and study directors is for the implementation of a GLP Quality System and the resulting additional burden is nominal. Documentation by independent contributing scientists, as defined in this proposed rule, includes records these individuals would usually retain, so a nominal added burden is predicted.

To implement the proposed checks and balances discussed previously in the preamble, proposed revisions will require that added documentation be made by the study director and the QAU to ensure the viability of the proposed GLP Quality System (see Table 5).

This proposed rule also adds requirements for the study sponsor to maintain records of: (1) Protocol and protocol amendment approval; (2) the accreditation status of a contracted person (as defined in this proposed rule) that conducts a phase of the study that involves the use of animals; (3) test, control, and reference article characterization; and (4) the qualifications of all contracted persons.

In addition, the proposed rule includes recordkeeping requirements for nonclinical laboratory studies that choose to utilize the option of having a principal investigator, particularly for multisite studies. These individuals will have recordkeeping responsibilities comparable to those of the study director for the nonclinical laboratory study phases for which they are responsible.

The persons potentially retaining nonclinical laboratory study documents are persons conducting a phase of a nonclinical laboratory study that is within the proposed expanded scope of part 58, including independent contributing scientists, and study sponsors as defined in this proposed rule. Results of nonclinical laboratory studies may be used by firms in support of applications and submissions to FDA, including applications and submissions for research and marketing of new products. The additional documentation of the conduct and data collection of nonclinical laboratory studies of FDA-regulated products will help ensure the quality and integrity of final study reports. FDA conducts on-site reviews of records and study reports during inspections of persons conducting one or more nonclinical laboratory study phases to verify the reliability of results submitted in support of applications and submissions to FDA.

We estimate the recordkeeping burden of this collection of information as follows:

Table 4.--Estimated One-Time Recordkeeping Burden¹

| Activity | No. of Recordkeepers | No. of Records per Recordkeeper | Total Annual Records | Average Burden per Recordkeeping | Total Hours |
|----------------------|----------------------|---------------------------------|----------------------|----------------------------------|-------------|
| Update Existing SOPs | 300 | 12 | 3,600 | 7.5 | 27,000 |
| Write New SOPs | 300 | 10 | 3,000 | 24 | 72,000 |
| Training | 300 | 2 | 600 | 14 | 8,400 |
| Total | | | 7,200 | | 107,400 |

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 4 shows the estimated one-time burden associated with the revised recordkeeping provisions of the proposed rule. We expect that the 300 testing facilities of nonclinical laboratory studies will need to update existing SOPs and to write new SOPs. In the PRIA, we estimated that each facility would need to update 12 existing SOPs and write 10 new SOPs. We

calculated lower and upper estimates of time to update existing SOPs and to write new SOPs. We estimate that it will take from 4 to 11 hours, for an average of 7.5 hours, to update 12 existing SOPs. We estimate that it will take from 15 to 33 hours, for an average of 24 hours, to write 10 new SOPs. We also expect that the 300 testing facilities of nonclinical laboratory studies will need to conduct training. In the PRIA, we estimated that for the low estimate one person would be doing the training and one person would be trained. By contrast, for the high estimate, we estimated that also one person would be doing the training and potentially three people would receive such training, for an average of two employees for each facility. We calculated lower and upper estimates of time to train, estimating that it will take from 5 to 23 hours, for an average of 14 hours, to train.

Table 5.--Estimated Recurring Recordkeeping Burden¹

| | Number of Respondents | Number of Records per Recordkeeper | Total Annual Records | Average Burden per Recordkeeping | Total Hours |
|--|-----------------------|------------------------------------|----------------------|----------------------------------|-------------|
| Sponsor documentation (§ 58.5): | | | | | |
| - (c) protocol approval and (i) all amendments | 2,193 | 100 | 219,300 | 1 | 219,300 |
| - (b) animal welfare | 1,316 | 5 | 6,580 | 2 | 13,160 |
| - (d) accreditation status of testing facility | 1,316 | 5 | 6,580 | .5 (30 minutes) | 3,290 |
| - (g) test, control, and reference article parameters | 1,316 | 5 | 6,580 | .5 (30 minutes) | 3,290 |
| - (j) archival locations | 2,193 | 62.25 | 136,514 | .25 (15 minutes) | 34,128.5 |
| - (e) qualifications of contracted persons | 1,316 | 5 | 6,580 | 2 | 13,160 |
| Documentation by management with executive responsibility: | | | | | |
| - GLP training and experience (§ 58.29(a) & (d)) | 300 | 500 | 150,000 | .25 (15 minutes) | 37,500 |
| - Animal care training and experience (§ 58.29(a) & (d)) | 300 | 5 | 1,500 | .25 (15 minutes) | 375 |
| - all persons are qualified for multisite studies (§ 58.31(i)) | 300 | 500 | 150,000 | .25 (15 minutes) | 37,500 |
| - Periodic review of GLP Quality System (§ 58.31(b)) | 300 | .25 | 75 | .5 (30 minutes) | 37.5 |
| - Periodic review of QAU (§ 58.31(r)) | 300 | 1 | 300 | .5 (30 minutes) | 150 |

| | | | | | |
|--|-----|-----|---------|---------------------|--------|
| -Appointment of management representative (§ 58.31(e)) | 300 | .1 | 30 | .25 (15 minutes) | 7.5 |
| -all test sites have master schedule (§ 58.31(j)) | 300 | 15 | 4,500 | .25 (15 minutes) | 1,125 |
| -appointment of person to manage master schedule (§ 58.31(k)) | 300 | 0.1 | 30 | .25 (15 minutes) | 7.5 |
| -selection of lead QAU for multisite studies (§ 58.31(p)) | 300 | 5 | 1,500 | .25 (15 minutes) | 375 |
| -QAU review of protocols, SOPs, & their amendments (§ 58.31(q)) | 300 | 5 | 1,500 | .25 (15 minutes) | 375 |
| QAU | | | | | |
| -review of study protocols + amendments (§ 58.35(b)3)) | 300 | 17 | 5,100 | 1.5 | 7,650 |
| -SOPs review + amendments (§ 58.35(b)4)) | 300 | 17 | 5,100 | 1.5 | 7,650 |
| -facility and process-based inspections (§ 58.35(b)5)) | 150 | 5 | 750 | .25 (15 minutes) | 187.5 |
| -audits of final reports of contributing scientists (§ 58.35(b)9)) | 300 | 600 | 180,000 | .5 (30 minutes) | 90,000 |
| -audits of principal investigator reports (§ 58.35(b)9)) | 300 | 120 | 36,000 | .5 (30 minutes) | 18,000 |
| -audits of final study reports for multisite studies (§ 58.35(b)10)) | 300 | 60 | 18,000 | .5 (30 minutes) | 9,000 |
| Study Director | | | | | |
| -Multisite study need for PIs (§ 58.33(b)7(ii)) | 300 | 180 | 54,000 | 1 | 54,000 |
| -communications (§ 58.33(b)12)) | 300 | 180 | 54,000 | .25 (15 minutes) | 13,500 |
| -protocol followed (§ 58.33(b)1)) | 300 | 60 | 18,000 | 1 | 18,000 |
| -QAU review of protocol & SOPs (§ 58.33(b)2)) | 300 | 17 | 5,100 | .25 (15 minutes) | 1,275 |
| -management provided adequate resources (§ 58.33(b)3)) | 300 | 5 | 1,500 | .5 (30 minutes) | 750 |
| -computerized systems validated (§ 58.33(b)4)) | 300 | 5 | 1,500 | .25 (15 minutes) | 375 |
| -Committee review 58.33(b)5) | 300 | 17 | 5,100 | .25 (15 minutes) | 1,275 |
| -multisite study personnel qualified (§ 58.33(b)7(i)) | 300 | 15 | 4,500 | 1 | 4,500 |
| -test system as required (§ 58.33(b)10)) | 300 | 5 | 1,500 | .25 (15 minutes) | 375 |
| -GLP compliance (§ 58.33(b)11)) | 300 | 60 | 18,000 | 1 | 18,000 |
| -test article accountability when containers disposed of (§ 58.105(d)) | 300 | 6 | 1,800 | .25 (15 minutes) | 450 |

| | | | | | |
|--|-------|-------|-----------|---------------------|-----------|
| Independent contributing scientists: | | | | | |
| -Education, training, and experience (§ 58.37(b)(2)) | 30 | 1 | 30 | .25 (15 minutes) | 7.5 |
| -Archive location (§ 58.37(b)(4)) | 30 | 1 | 30 | .25 (15 minutes) | 7.5 |
| -Appropriate animal care (§ 58.37(b)(3)) | 2 | 1 | 2 | .5 (30 minutes) | 1 |
| PIs | | | | | |
| -Protocol + amendment acceptance (§ 58.39(a)) | 200 | 5 | 1,000 | .25 (15 minutes) | 250 |
| -Study deviations (§ 58.39(c)) | 200 | 10 | 2,000 | .5 (30 minutes) | 1,000 |
| -Archive location (§ 58.39(e)) | 200 | 40 | 8,000 | .25 (15 minutes) | 2,000 |
| Recordkeeping (§ 58.195) | 300 | 251.5 | 75,450 | 3.9 | 294,255 |
| Total..... | | | 1,188,031 | | 906,289.5 |

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 5 shows the estimated recurring recordkeeping burden associated with the proposed rule. Together, this results in a total of 1,013,689.5 hours and 1,195,231 records.

To ensure that comments on information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB (see ADDRESSES). All comments should be identified with the title of the information collection.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3407(d)), the Agency has submitted the information collection provisions of this proposed rule to OMB for review. These requirements will not be effective until FDA obtains OMB approval. FDA will publish a notice concerning OMB approval of these requirements in the Federal Register.

X. Federalism

FDA has analyzed this proposed rule according to the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized, would not contain policies that would have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency tentatively concludes that the

proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XI. References

The following references are on display in the Division of Dockets Management (see ADDRESSES and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <http://www.regulations.gov>. FDA has verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. “OECD Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring,” (the link provided is to an index of all OECD documents related to GLPs, with links to each of the individual documents) (<http://www.oecd.org/chemicalsafety/testingofchemicals/oecdseriesonprinciplesofgoodlaboratorypracticeglpandcompliancemonitoring.htm>).
2. “Mutual Acceptance of Data (MAD),” (<http://www.oecd.org/env/ehs/mutualacceptanceofdatamad.htm>).
3. FDA, “FDA Announces New Initiative to Modernize the Regulation of Clinical Trials and Bioresearch Monitoring,” FDA News Release, June 26, 2006 (<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108677.htm>).
4. FDA, “Nonclinical Laboratory Studies; Proposed Regulations for Good Laboratory Practice Regulations” 41 FR 51206 (November 19, 1976).
5. MOU 225-06-4000. “Memorandum of Understanding Among the Animal and Plant Health Inspection Service, U.S. Department of Agriculture, and the Food and Drug

Administration, U.S. Department of Health and Human Services, and the National Institutes of Health, U.S. Department of Health and Human Services, Concerning Laboratory Animal Welfare,”

(<http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm247294.htm>).

6. “OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring Number 13,” The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies; Consensus Document of the Working Group on Good Laboratory Practice

([http://search.oecd.org/officialdocuments/displaydocumentpdf/?doclanguage=en&cote=en/jm/mono\(2002\)9](http://search.oecd.org/officialdocuments/displaydocumentpdf/?doclanguage=en&cote=en/jm/mono(2002)9)).

7. “OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring Number 4 (Revised),” Consensus Document; Quality Assurance and GLP

([http://search.oecd.org/officialdocuments/displaydocumentpdf/?doclanguage=en&cote=en/jm/mono\(99\)20](http://search.oecd.org/officialdocuments/displaydocumentpdf/?doclanguage=en&cote=en/jm/mono(99)20)).

8. “OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring Number 1,” The OECD Principles on Good Laboratory Practice

([http://search.oecd.org/officialdocuments/displaydocumentpdf/?doclanguage=en&cote=en/mc/chem\(98\)17](http://search.oecd.org/officialdocuments/displaydocumentpdf/?doclanguage=en&cote=en/mc/chem(98)17)).

9. “OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring Number 11,” Advisory Document of the Panel on Good Laboratory Practices, The Role and Responsibilities of the Sponsor in the Application of the Principles of GLP

([http://search.oecd.org/officialdocuments/displaydocumentpdf/?doclanguage=en&cote=en/mc/chem\(98\)16](http://search.oecd.org/officialdocuments/displaydocumentpdf/?doclanguage=en&cote=en/mc/chem(98)16)).

10. Council for International Organization of Medical Sciences and The International Council for Laboratory Animal Science, International Guiding Principles for Biomedical Research Involving Animals, December 2012 (revised) (<http://www.cioms.ch/images/stories/CIOMS/IGP2012.pdf>).

11. Institute for Laboratory Animal Research, Guide for the Care and Use of Laboratory Animals, Eighth Edition, 2011 (<http://grants.nih.gov/grants/olaw/Guide-for-the-Care-and-Use-of-Laboratory-Animals.pdf>).

12. FDA, “Nonclinical Laboratory Studies, Good Laboratory Practice Regulations,” Final Rule, 43 FR 59986 (December 22, 1978).

13. Compliance Policy Guide (CPG 7151.02), Sec. 130.300--FDA Access to Results of Quality Assurance Program Audits and Inspections (<http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm073841.htm>).

14. “OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring Number 8 (Revised),” Consensus Document, The Role and Responsibilities of the Study Director in GLP Studies ([http://search.oecd.org/officialdocuments/displaydocumentpdf/?doclanguage=en&cote=en/nv/jm/mono\(99\)24](http://search.oecd.org/officialdocuments/displaydocumentpdf/?doclanguage=en&cote=en/nv/jm/mono(99)24)).

15. “OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring Number 7 (Revised),” Consensus Document, The Application of the GLP Principles to Short Term Studies

([http://search.oecd.org/officialdocuments/displaydocumentpdf/?doclanguage=en&cote=en/jm/mono\(99\)23](http://search.oecd.org/officialdocuments/displaydocumentpdf/?doclanguage=en&cote=en/jm/mono(99)23)).

16. Bioanalytical Method Validation Draft Guidance for Industry

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>).

17. Pesticide Registration Notice 2011-3 “Standard Format for Data Submitted Under the Federal Insecticide, Fungicide, and Rodenticide Act and Certain Provisions of the Federal Food, Drug, and Cosmetic Act”

(<https://www.epa.gov/sites/production/files/2014-04/documents/pr2011-3.pdf>) (Study profile templates available at <https://www.epa.gov/pesticide-registration/study-profile-templates>).

18. Full Analysis of Economic Impacts (Docket Number FDA-2010-N-0548).

Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, and Unfunded Mandates Reform Act Analysis for Good Laboratory Practice for Nonclinical Laboratory Studies; Proposed Rule, available at

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

List of Subjects

21 CFR Part 16

Administrative practice and procedure.

21 CFR Part 58

Laboratories, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 16 and 58 be amended as follows:

PART 16--REGULATORY HEARING BEFORE THE FOOD AND DRUG
ADMINISTRATION

1. The authority citation for part 16 continues to read as follows:

Authority: 15 U.S.C. 1451-1461; 21 U.S.C. 141-149, 321-394, 467f, 679, 821, 1034; 28 U.S.C. 2112; 42 U.S.C. 201-262, 263b, 364.

2. In § 16.1, amend paragraph (b)(2) by removing the entry for § 58.204(b) and adding an entry for §§ 58.200 through 58.219 to read as follows:

§ 16.1 Scope.

* * * * *

(b) * * *

(2) * * *

§§ 58.200 through 58.219 (see part 58, subpart K of this chapter), relating to disqualifying any person conducting a phase of a nonclinical laboratory study of FDA-regulated products.

* * * * *

PART 58--GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY
STUDIES

3. The authority citation for part 58 is revised to read as follows:

Authority: 21 U.S.C. 342, 346, 346a, 348, 351, 352, 353, 355, 360, 360b-360f, 360h-360j, 360ccc, 371, 379e, 381, 387e, 387j, 387k; 42 U.S.C. 216, 262, 263b-263n.

4. In § 58.1, revise paragraph (a) and add paragraph (c) to read as follows:

§ 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 in a nonclinical laboratory study whose results lack the required reliability.

5. Revise § 58.3 to read as follows:

§ 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.

(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 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 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.

(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 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.

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.

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 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 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 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.

6. 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 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.

7. Revise § 58.10 to read as follows:

§ 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.

(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.

8. Revise § 58.15 to read as follows:

§ 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 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.

9. Revise § 58.29 to read as follows:

§ 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 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.

10. Revise § 58.31 to read as follows:

§ 58.31 Testing facility management with executive responsibility.

Management with executive responsibility is ultimately responsible for the GLP Quality 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)), 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 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 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).

11. 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.

12. Revise § 58.33 to read as follows:

§ 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;

(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.

(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.

13. Revise § 58.35 to read as follows:

§ 58.35 Quality assurance unit (QAU).

(a)(1) Function. A QAU must monitor 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 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 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 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 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 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.

14. Add § 58.37 to subpart B to read as follows:

§ 58.37 Contributing scientist.

(a) Each contributing scientist must:

(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.

15. 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 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.

16. Revise § 58.41 to read as follows:

§ 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.

17. 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:

- (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.

18. Revise § 58.47 to read as follows:

§ 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.

19. Revise § 58.61 to read as follows:

§ 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.

20. 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.

* * * * *

21. Revise the heading of subpart E to read as follows:

Subpart E--Nonclinical Laboratory Study Operations

22. Revise § 58.81 to read as follows:

§ 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.
- (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.

23. 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 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.

* * * * *

24. Revise the heading of subpart F to read as follows:

Subpart F--Test, Control, and Reference Articles

25. Revise § 58.105 to read as follows:

§ 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.

(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.

26. 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:

* * * * *

27. Revise § 58.113 to read as follows:

§ 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.

28. Revise § 58.120 to read as follows:

§ 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 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.

(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.

29. Revise § 58.130 to read as follows:

§ 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 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.

30. 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.

(c) All data accrued as required in paragraphs (a) and (b) of this section must be included in the final study report.

31. Revise § 58.185 to read as follows:

§ 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, 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 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).

(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.

32. Revise § 58.190 to read as follows:

§ 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. 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 the archives, including maximum timeframes material can remain outside of the archives.

33. Revise § 58.195 to read as follows:

§ 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 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.

(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.

34. Revise the heading of subpart K to read as follows:

Subpart K--Disqualification of Any Person Conducting a Phase of a Nonclinical Laboratory Study

35. Revise § 58.200 to read as follows:

§ 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; and

(2) To exclude from consideration all studies completed after the 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.

36. Revise § 58.202 to read as follows:

§ 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 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.

37. 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.

* * * * *

38. Revise § 58.206 to read as follows:

§ 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 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.

39. Revise § 58.210 to read as follows:

§ 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 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.

40. Revise § 58.213 to read as follows:

§ 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 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.

41. Revise § 58.215 to read as follows:

§ 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 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.

42. Revise § 58.217 to read as follows:

§ 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 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.

43. Revise § 58.219 to read as follows:

§ 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 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.

Dated: August 16, 2016.

Peter Lurie,

Associate Commissioner for Public Health Strategy and Analysis.

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