FDA Proposes to Modify Good Laboratory Practice Regulations, Broaden Application and Authority

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On August 24, 2016, the US Food and Drug Administration (FDA) issued a Proposed Rule[1] on Good Laboratory Practice for Nonclinical Laboratory Studies (Proposed Rule), which broadens the application and authority of Good Laboratory Practice (GLP) regulations. The Proposed Rule imposes heightened quality requirements for laboratory studies, including safety and toxicity studies, that are intended to support both product applications and other regulatory submissions that are not directly related to product approval. The Proposed Rule also modifies provisions for the care and handling of animals under the so-called Animal Rule and expands requirements to encompass tobacco products. Interested parties have until November 22, 2016, to submit comments, suggestions and feedback.

The Proposed Rule requires the use of a complete quality system approach (GLP Quality System) for nonclinical laboratory studies when such studies support or are intended to support marketing applications or other submissions to FDA.[2] FDA proposes to mandate use of a GLP Quality System that is consistent with International Organization for Standardization (ISO) standard ISO 9001:1994, "Quality Systems—Model for Quality Assurance in Design, Development, Production, Installation and Servicing"; "FDA's Quality System Regulation (QSR)" in 21 CFR Part 820; and wherever possible, Organisation for Economic Co-operation and Development guidance documents for GLP.

Collectively, these standards require tighter controls and procedures for the laboratory Quality Assurance Unit (QAU) and documentation and monitoring of equipment, data and personnel. Among other requirements, FDA proposes to amend provisions related to facility management to specify that the QAU must submit written periodic status reports on GLP Quality System performance for each study to specifically designated management personnel with "executive responsibility" for the facility's operations. The Proposed Rule also imposes new requirements for communication among personnel, internal quality audits, and the creation and documentation of Standard Operating Procedures (SOPs). Notably, FDA proposes to exercise enforcement discretion with respect to the review and evaluation of QAU records by stating that such records will not be subject to routine inspections, but they will be inspected for litigation or during inspections "for cause" under an inspection warrant.

The Proposed Rule also expands the application of Part 58 to efficacy studies conducted on animals under the Animal Rule pathway. Under this pathway, the FDA may grant marketing approval through the use of animal studies to establish the safety and effectiveness of human drugs or biological products when human efficacy studies are unethical or field trials are infeasible (*e.g.*, deliberate exposure of healthy human volunteers to potentially lethal or permanently disabling toxic chemicals). The Proposed Rule differentiates between the types of Animal Rule-specific studies that must adhere to Part

[1] 81 Fed. Reg. 58,342 (Aug. 24, 2016).
[2] According to FDA, other submissions include nutrient content and health claim petitions for food, authorizations to market edible animal products, product development protocols for medical devices and data supporting changes to medical device performance standards. *See* 81 Fed. Reg. 58,367–58,368 (Aug. 24, 2016).

58, noting that the data quality and integrity requirements are not necessarily appropriate for all types of Animal Rule-specific studies (*e.g.*, studies using challenge agents that require high-containment facilities). The proposed "covered Animal Rule studies" include the adequate and well-controlled efficacy studies that serve as substantial evidence of effectiveness necessary for approval or licensure of human drugs or biological products; pharmacokinetic or pharmacodynamics studies in animals used to select a dose and regimen in humans; and natural history studies to support qualification of new animal models under FDA's Animal Model Qualification Program, the model-defining natural history studies. FDA seeks comment on whether current or proposed requirements pose a unique or disproportionate obstacle or burden on the conduct of certain animal studies specific to product development under the Animal Rule.

In recognition of FDA's authority to regulate tobacco products under the Family Smoking Prevention and Tobacco Control Act of 2009, the Proposed Rule addresses requirements for laboratory studies involving tobacco products. FDA proposes to apply the new GLP requirements to studies designed to "provide evidence regarding the relative toxicities of new or modified risk tobacco products," as specified in sections 905, 910 and 911 of the Federal Food, Drug, and Cosmetic Act (FDCA). The Proposed Rule states that the labeling of a tobacco product may not be used to characterize such a product if it is used as a control or reference article in a nonclinical laboratory study, because labeling of currently marketed tobacco products does not provide the information required for full product characterization, *e.g.*, chemical and microbiological composition or design parameters. FDA plans to issue regulations under section 910(g) of the FDCA, providing conditions under which tobacco products intended for investigational use may be exempted from general tobacco product requirements under the FDCA.

The chart below describes these and other revisions to key provisions of the rule in greater detail. The chart compares selected provisions of Part 58 in its current form with the Proposed Rule and describes potential implications of the changes, in the event any or all of the Proposed Rule's sections are implemented in its final iteration.[3]

[3] Note, the chart does not contain every proposed modification. It excludes certain items, deemed minor or described elsewhere in this document.

§	Part 58: Current	Part 58: Proposed Rule	Implications (If Any)
Subpart A – General Provisions			
§ 58.1 – Scope	Prescribes GLPs for conducting nonclinical laboratory studies of safety.	Expands scope of GLP studies to include toxicity studies, or studies of the acute or long-term adverse effects that could result from the use of the FDA-regulated product. Expands language to include tobacco products. Modifies and broadens "medical devices for human use" to "devices," in order to include Center for Veterinary Medicine. Changes "for research and marketing permits" to "applications or submissions." Adds § 58.1(c) to describe "where appropriate."	May need to conduct (additional) toxicity studies if nonclinical laboratory study is done with intent to support application or submission to FDA. Would include tobacco products pursuant to §§ 905, 910 and 911 of the FDCA. Would include devices used in veterinary medicine.
§ 58.3 – Definitions	Definitions in paragraphs (a) through (p).	Adds new definitions, modifies certain current definitions and alphabetizes complete listing of definitions. Includes applications and submissions for tobacco products unless exempted under future FDA regulations under § 910(g) of the FDCA for investigational tobacco products. Adds applications and submissions not specifically included, *e.g.*, Humanitarian Device Exemption applications and device 510(k) submission. Adds and modifies several definitions, notably: • "Attending Veterinarian" • "Contracted Person" • "Contributing Scientist" • "Facility-Based Inspection" • "GLP Quality System" • "Lead Quality Assurance Unit" • "Management with Executive Responsibility" • "Multisite Study" • "Nonclinical Laboratory" (including changing "field trials in animals" to "clinical investigational use in animals") • "Principal Investigator" • "Sponsor"	Would include tobacco products. Would clarify that Humanitarian Device Exemption and 510(k) submissions are included. Would create distinct responsibilities for individuals with specific roles. Would include studies with phases conducted at more than one site under GLP Would add and broaden definitions for "Test Site and "Testing Facility," respectively, to include a "person" responsible for a phase of or responsible for a multisite nonclinical laboratory study, respectively.

		• "Test Article" (to add "tobacco product") • "Testing Facility."	
§ 58.5 – Sponsor Responsibilities		Sponsor is responsible for adequacy and validity of nonclinical laboratory tests, including protocol; use of accredited persons; communication; and use of test, control and reference articles.	Would create obligations for study sponsor, including ultimate responsibility over sponsor responsibilities even when transferred or contracted to another party.
§ 58.10 – Transfer of Responsibilities	Part 58 applies to studies performed under grants and contracts.	Study transfers must be documented, and responsibilities must be performed in compliance with 21 CFR Part 58 and chapter I.	May need to develop SOP for study transfers and verifying compliance by grantee or contractor.
§ 58.15 – Inspection of Any Person Conducting a Phase of a Nonclinical Laboratory Study	Testing facility shall permit inspection by FDA. FDA will not consider a nonclinical laboratory study in support of an application for a research or marketing permit if the testing facility refuses to permit inspection.	Clarifies FDA's inspection authority to include inspecting any person that conducts a phase of a nonclinical laboratory study of an FDA-regulated product.	Expands scope of persons potentially subject to inspection.
Subpart B – Organization and Personnel			
§ 58.29 –Personnel	Personnel must have education, training and experience; have training summarized; take necessary sanitation and health precautions; wear appropriate clothing; and, if ill, be excluded from contact with operations and functions that may be adversely affected.	Personnel must have training and experience with GLP requirements. All study personnel must have access to and comply with study protocol, applicable amendments and SOPs; deviations must be reported to study director.	May require review and updating of training documentation and employee qualification requirements.
§ 58.31 – Test Facility Management with Executive Responsibility	Testing facility management must designate a study director; assure there is a quality assurance unit; assure testing and control; assure adequate resources; assure that personnel understand their functions; and communicate and take corrective actions when deviations occur.	Specifies that upper management at a testing facility or test site is ultimately responsible for GLP compliance by adding "with executive responsibility" to the heading. Various responsibilities related to written GLP Quality System SOPs, management, protocols and periodic reviews.	May need to establish and develop system for periodic review for SOPs and protocols by senior management.
§ 58.32 – Test Site Management with Executive Responsibility		Management has executive responsibility and appropriate SOPs.	May need to establish and develop system for periodic review for SOPs and protocols.
§ 58.33 – Study Director	Study director has overall responsibility for technical conduct of study, including protocol; data; unforeseen circumstances and corrective actions; test systems; all applicable GLP requirements; and archiving raw data,	Study director cannot delegate overall responsibility for a nonclinical laboratory study. Clarified various requirements regarding communication, documentation and archiving study documentation.	

	documentation, protocols, specimens and reports.	Where protocol impacts test animal use, must review and approve and must consult with attending veterinarian.	
§ 58.35 – Quality Assurance Unit (QAU)	QAU has responsibility to monitor to assure conformance with regulations in Part 58. QAU shall maintain master schedule protocol; inspect study; submit written status reports; determine whether deviations from procedures or protocols were made without documentation; and review, prepare and sign the final study report.	QAU function and location. Lead QAU required. QAU must review study protocol before initiating or implementing. QAU must review all SOPs. Various requirements regarding deviations, audits, verifications. Expands QAU inspections recognized to include process- and facility-based. Where problems are identified, written certification of how such problems were addressed is required. QAU requires "access" to master schedule and protocols, including in computerized system.	May require review and updating of current quality assurance functions and SOPs.
§ 58.37 – Contributing Scientist		Individual expert or specialist who is an independently employed contracted person. When responsible for study phase, other specific documentation and report requirements.	
§ 58.39 – Principal Investigator		Designating principal investigator is optional. Specific requirements and responsibilities consistent with ensuring Part 58 compliance.	
Subpart C – Facilities			
§ 58.41 – General	For "each testing facility."	Any person conducting a phase of a nonclinical laboratory study must have facilities of suitable size and construction.	Would include multisite studies
§ 58.43 – Animal Care Facilities	Basic conditions for testing facility, including room, isolation and sanitation requirements.	Includes multisite studies and covers any phase involving use of animals.	
§ 58.47 – Facilities for Handling Test, Control and Reference Articles	Requirements for separate handling and storage areas.	Reference articles.	

Subpart D – Equipment			
§ 58.61 – Equipment Design	Equipment shall be of appropriate design and adequate capacity to function according to the protocol, and shall be suitably located.	Includes computerized systems.	
§ 58.63 – Maintenance and Calibration of Equipment	Equipment shall be adequately inspected, cleaned and maintained pursuant to written SOPs, and written records of maintenance operations shall be maintained.	Maintenance, archiving and retrieval of data.	Would include multisite studies.
Subpart E – Testing Facilities Operation (Changed to "Nonclinical Laboratory Study Operations")			
§ 58.81 – Standard Operating Procedures	All testing facilities shall establish written SOPs pursuant to a non-exhaustive list.	All testing facilities and test sites must establish written SOPs pursuant to a non-exhaustive list for each applicable phase of a study. Certain new SOPs are required, including SOPs that describe (1) the preparation, modification and administration of all SOPs and mandate the development and maintenance of a historical file of SOPs; (2) oversight of quality assurance for multisite studies; and (3) establishment of a GLP Quality System.	May require the addition or modification of existing written SOPs.
§ 58.90 – Animal Care	All newly received animals from outside sources shall be evaluated. Animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study.	Test animals must also be evaluated throughout the study. Animals may be treated for disease or signs of disease as determined necessary by the study's veterinarian.	May require modification of existing animal evaluation procedures.
Subpart F – Test and Control Articles (Changed to "Test, Control, and Reference Articles")			
§ 58.105 – Test, Control and Reference Article Characterization	There are no current requirements for tobacco products or provision of results of analyses to study director. Empty containers from test articles must be retained.	A determination for each batch and documentation of chemical composition, microbiological characterization and design parameters that define the test, control and reference articles for tobacco products is required. Currently marketed tobacco product labeling insufficient in support of product characterization—must be separately determined and documented. All test, control and reference article characterization must be provided to the study director as soon as available (*see also* new	May require modification for inclusion of tobacco products. May require modification of policies and procedures to ensure that the study director is promptly provided with results as well as verification and documentation of the distribution and disposal of articles.

		requirement in § 58.113). Except for tobacco products, marketed products used as control or reference articles may be characterized by their labeling. Empty containers no longer must be retained, but the study director must verify and document the distribution and disposal of the test article.	
Subpart G – Protocol for and Conduct of a Nonclinical Laboratory Study			
§ 58.120 – Protocol	All protocols must contain, where applicable, certain information.	Protocol must also contain contact information for all persons conducting a phase of the study; a description of the analysis and reporting procedures to be followed in the event of peer-review of any phase; identification of which phases will be conducted by which person(s); a list of study-specific records required to be maintained and, in multisite studies, archived; and dated signatures of the sponsor, study director and others that indicate protocol approval. Studies using animals must be reviewed and approved by an animal care and use committee before being initiated or changed. Approval must be documented. Any change, revision or amendment to an approved protocol must be approved with a dated signature by the sponsor, study director and any other affected person(s). The sponsor and testing facility management with executive responsibility must sign and date a statement affirming compliance with Part 58. The statement must be appended to the protocol.	May require modification of existing protocol initiation, review, approval and amendment processes. May require implementation of an animal care and use committee framework.
§ 58.130 – Conduct of a Nonclinical Laboratory Study	The study and test systems shall be conducted in accordance with the protocol. Postmortem observation findings should be available to the pathologist.	The analytical methods for all phases must be sufficiently precise and sensitive enough to result in accurate and reproducible data. Animal welfare, including humane care and ethical treatment, must be considered in advance and upheld in conjunction with achievement of study objectives. The attending	May require modification of existing policies and procedures to ensure veterinarian input on matters of animal welfare and availability of postmortem observations.

		veterinarian must be included and deferred to in animal welfare decisions. Commentary to the Proposed Rule indicates that the FDA may evaluate on a case-by-case basis protocol deviations to prevent a potential hazard to animal welfare or study integrity. Unless specified in the protocol, postmortem observations must be available to the pathologist.	
Subpart J – Records and Reports			
§ 58.180 – Data Quality and Integrity	This Section is not currently present, but the Proposed Rule relocates and revises existing data requirements in § 58.130(e).	Quality data is accurate, legible, contemporaneous, original and attributable (ALCOA), as well as credible, internally consistent and corroborated. Electronic records systems must be compliant with applicable regulations, including 21 CFR Part 11. The final study report must contain all data accrued during the study.	May require modification of existing data-related policies and procedures.
§ 58.185 – Reporting of Nonclinical Laboratory Study Results	A final study report shall include the items described in a non-exhaustive list.	In addition to previous requirements, a final study report must include the names of all attending veterinarians; all health-related issues reported by an attending veterinarian or appropriately designated personnel; and a statement describing the extent of compliance with Part 58 and, when applicable, noting deviations. Study report should not be an integrated final study report in lieu of individual scientists' reports, as it would obscure accountability and accurate reporting. For studies discontinued prior to completion, the study director should write, sign, date and archive a short written summary report.	May require modification of existing final and discontinued study reporting policies and procedures.
§ 58.190 – Storage and Retrieval of Records and Data	All raw data, documentation, protocols, final reports and specimens generated as a result of the study shall be retained. Archiving is required, but timeframes are not currently specified.	Subject to exceptions, reserve samples and specimens generated as a result of the study must also be retained, including correspondence and other documents related to the interpretation and evaluation of data other than those contained in the final study report. Certain study materials must be	May require modification of existing retention and archival policies and procedures.

		archived and indexed no later than two weeks after the study completion date. SOPs outlining specific archival procedures are mandatory. In the event the study sponsor delays finalization of the study report, the final study report and appropriate archiving must occur within six months after completion of the last draft of the final study report. In the event the sponsor stops a study prior to completion of all protocol-required testing, a decision regarding discontinuation must be made no later than six months after stopping the study. For discontinued studies, a summary report and study material must be archived within two weeks of the date of the study director's signature of the summary report. Archiving specifications for multisite studies must also be included in the protocol.	
§ 58.195 – Retention of Records	Certain materials must be archived pursuant to prescribed timeframes. If a facility conducting a study goes out of business, material shall be transferred to the archives of the sponsor of a study, and the FDA shall be notified in writing. No timeframe is specified.	Applies the two-year retention period to applications and submissions to FDA that might not result in an approval, clearance or premarket authorizations—"administratively closed." A change in archival location may be due to a change other than closure of a testing facility (*e.g.*, change in ownership or change in physical location), but material must be transferred to the study sponsor or other appropriate archive facility. The transfer must be reported to FDA, and in some cases to the study sponsor, in writing no later than 10 working days after the transfer occurs.	May require modification of existing retention, transfer and notification policies and procedures.
Subpart K – Disqualification of Testing Facilities (Changed to "Disqualification of Any Person Conducting a Phase of a Nonclinical Laboratory Study[4]")			
§ 500.200 – Purpose	Studies that were conducted by a testing facility.	Studies for which a phase was conducted by any person.	
§ 58.202 – Grounds for Disqualification	The FDA Commissioner (Commissioner) may disqualify	Disqualifies any person conducting a phase of a	May require modification of policies and procedures to avoid

[4] The Proposed Rule generally broadens the authority of the Commissioner of Food and Drugs to include disqualification of *any person* conducting a phase of a study upon a finding of either or both of the conditions for disqualification. Disqualification under the Proposed Rule occurs by person rather than testing facility.

	a testing facility upon finding all of the following: failure to comply with regulations; that the noncompliance adversely affected the validity of the study or studies; and that other lesser regulatory actions are inadequate.	nonclinical laboratory study upon finding that person repeatedly or deliberately failed to comply with regulations or submitted false information required in any report.	submission of false information.
§ 58.204 – Notice of and Opportunity for Hearing on Proposed Disqualification	Commissioner may issue testing facility written notice proposing that the facility be disqualified.	FDA may issue person written notice proposing that person be disqualified.	May require modification of disqualification policies and procedures to reference individual persons as opposed to the testing facility.
§ 58.206 – Final Order on Disqualification	Commissioner issues final order disqualifying testing facility and provides notice of action.	Notice explains that disqualified person is ineligible to receive test article under Part 511 and therefore is ineligible to conduct any nonclinical laboratory study intended to support application for research or marketing permit for new animal drug.	May require modification of Part-511-related policies and procedures. Disqualification under § 58.206 results in ineligibility under Part 511 (see 81 Fed. Reg. 57,812 (Aug. 24, 2016)).
§ 58.210 – Actions upon Disqualification	Describes the circumstances by which a study conducted by a disqualified testing facility will be reviewed and acted upon by the FDA. No nonclinical laboratory study for which any phase was begun by a disqualified testing facility after date of disqualification can be considered in support of any application or submission to FDA unless reinstated.	When a study conducted by a disqualified person is determined to be unacceptable, *data* in support of the application or submission will be eliminated from consideration. No study for which any phase was begun by a disqualified person after date of disqualification can be considered in support of any application or submission to FDA unless reinstated. Such elimination may serve as new information justifying appropriate regulatory action not limited to termination or withdrawal of approval.	May require modification of disqualification policies and procedures.
§ 58.219 – Reinstatement of a Disqualified Person	The Commissioner may require inspection prior to reinstatement.	Prior to consideration of reinstatement, FDA inspection of a disqualified person is required.	May require modification of disqualification policies and procedures to reference mandated inspection.

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