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

Vernessa T. Pollard, Veleka Peeples-Dyer, Shelby Buettner, Anisa Mohanty

On August 24, 2016, the US Food and Drug Administration (FDA) issued a Proposed Rule 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. 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

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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.
<table>
<thead>
<tr>
<th>§</th>
<th>Part 58: Current</th>
<th>Part 58: Proposed Rule</th>
<th>Implications (If Any)</th>
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<tr>
<td><strong>Subpart A – General Provisions</strong></td>
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<tr>
<td>§ 58.1 – Scope</td>
<td>Prescribes GLPs for conducting nonclinical laboratory studies of safety.</td>
<td>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.</td>
<td>May need to conduct (additional) toxicity studies if nonclinical laboratory study is done with intent to support application or submission to FDA.</td>
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<td>Expands language to include tobacco products.</td>
<td>Would include tobacco products pursuant to §§ 905, 910 and 911 of the FDCA.</td>
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<td>Modifies and broadens “medical devices for human use” to “devices,” in order to include Center for Veterinary Medicine.</td>
<td>Would include devices used in veterinary medicine.</td>
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<td>Changes “for research and marketing permits” to “applications or submissions.”</td>
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<td>Adds § 58.1(c) to describe “where appropriate.”</td>
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<tr>
<td>§ 58.3 – Definitions</td>
<td>Definitions in paragraphs (a) through (p).</td>
<td>Adds new definitions, modifies certain current definitions and alphabetizes complete listing of definitions.</td>
<td>Would include tobacco products.</td>
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<td>Includes applications and submissions for tobacco products unless exempted under future FDA regulations under § 910(g) of the FDCA for investigational tobacco products.</td>
<td>Would clarify that Humanitarian Device Exemption and 510(k) submissions are included.</td>
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<td></td>
<td>Adds applications and submissions not specifically included, e.g., Humanitarian Device Exemption applications and device 510(k) submission.</td>
<td>Would create distinct responsibilities for individuals with specific roles.</td>
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</tbody>
</table>
| | | 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”  
<p>| | | “Sponsor” | 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. |</p>
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<th>ON THE SUBJECT</th>
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- “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. |

| § 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. |

<p>| § 58.47 – Facilities for Handling Test, Control and Reference Articles | Requirements for separate handling and storage areas. Reference articles. |</p>
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<tr>
<th>Subpart E – Testing Facilities Operation (Changed to “Nonclinical Laboratory Study Operations”)</th>
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<td>§ 58.81 – Standard Operating Procedures</td>
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<td>§ 58.90 – Animal Care</td>
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<tr>
<th>Subpart F – Test and Control Articles (Changed to “Test, Control, and Reference Articles”)</th>
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<tr>
<td>§ 58.105 – Test, Control and Reference Article Characterization</td>
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**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...
A 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.

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<th>Subpart J – Records and Reports</th>
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<td><strong>§ 58.185 – Reporting of Nonclinical Laboratory Study Results</strong></td>
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<td><strong>§ 58.190 – Storage and Retrieval of Records and Data</strong></td>
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<td>§ 58.195 – Retention of Records</td>
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<tr>
<th>Subpart K – Disqualification of Testing Facilities (Changed to “Disqualification of Any Person Conducting a Phase of a Nonclinical Laboratory Study”*)</th>
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<tr>
<td>§ 500.200 – Purpose</td>
<td>Studies that were conducted by a testing facility.</td>
<td>Studies for which a phase was conducted by any person.</td>
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<tr>
<td>§ 58.202 – Grounds for Disqualification</td>
<td>The FDA Commissioner (Commissioner) may disqualify</td>
<td>Disqualifies any person conducting a phase of a study</td>
<td>May require modification of policies and procedures to avoid</td>
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* 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.
| § 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 eligibility 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. |
Office Locations

**BOSTON**
28 State Street
Boston, MA 02109
USA
Tel: +1 617 535 4000
Fax: +1 617 535 3800

**DALLAS**
3811 Turtle Creek
Boulevard, Suite 500
Dallas, TX 75219
USA
Tel: +1 972 232 3100
Fax: +1 972 232 3098

**HOUSTON**
1000 Louisiana Street, Suite 3900
Houston, TX 77002
USA
Tel: +1 713 653 1700
Fax: +1 713 739 7592

**MIAMI**
333 Avenue of the Americas, Suite 4500
Miami, FL 33131
USA
Tel: +1 305 358 3500
Fax: +1 305 347 6500

**NEW YORK**
340 Madison Avenue
New York, NY 10173
USA
Tel: +1 212 547 5400
Fax: +1 212 547 5444

**ROME**
Via Luisa di Savoia, 18
00196 Rome
Italy
Tel: +39 06 462024 1
Fax: +39 06 489062 85

**SILICON VALLEY**
275 Middlefield Road, Suite 100
Menlo Park, CA 94025
USA
Tel: +1 650 815 7400
Fax: +1 650 815 7401

**BRUSSELS**
Avenue des Nerviens 9-31
1040 Brussels
Belgium
Tel: +32 2 230 50 59
Fax: +32 2 230 57 13

**DÜSSELDORF**
Stadttor 1
40219 Düsseldorf
Germany
Tel: +49 211 30211 0
Fax: +49 211 30211 555

**LONDON**
110 Bishopsgate
London EC2N 4AY
United Kingdom
Tel: +44 20 7577 6900
Fax: +44 20 7577 6950

**MILAN**
Via dei Bossi, 4/6
20121 Milan
Italy
Tel: +39 02 78627300
Fax: +39 02 78627333

**ORANGE COUNTY**
4 Park Plaza, Suite 1700
Irvine, CA 92614
USA
Tel: +1 949 851 0633
Fax: +1 949 851 9348

**SEOUL**
18F West Tower
Mirae Asset Center1
26, Eulji-ro 5-gil, Jung-gu
Seoul 100-210
Korea
Tel: +82 2 6030 3600
Fax: +82 2 6322 9866

**WASHINGTON, D.C.**
The McDermott Building
500 North Capitol Street, N.W.
Washington, D.C. 20001
USA
Tel: +1 202 756 8000
Fax: +1 202 756 8087

**CHICAGO**
227 West Monroe Street
Chicago, IL 60606
USA
Tel: +1 312 372 2000
Fax: +1 312 984 7700

**FRANKFURT**
Feldbergstraße 35
60323 Frankfurt a. M.
Germany
Tel: +49 69 951145 0
Fax: +49 69 271599 633

**LOS ANGELES**
2049 Century Park East, 38th Floor
Los Angeles, CA 90067
USA
Tel: +1 310 277 4110
Fax: +1 310 277 4730

**MUNICH**
Nymphenburger Str. 3
80335 Munich
Germany
Tel: +49 89 12712 0
Fax: +49 89 12712 111

**PARIS**
23 rue de l’Université
75007 Paris
France
Tel: +33 1 81 69 15 00
Fax: +33 1 81 69 15 15

**SHANGHAI**
MWE China Law Offices
Strategic alliance with McDermott Will & Emery
28th Floor Jin Mao Building
88 Century Boulevard
Shanghai Pudong New Area
P.R.China 200121
Tel: +86 21 6105 0500
Fax: +86 21 6105 0501