

An Update on FDA's Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies Proposed Rule

SOT: Regulatory and Safety Evaluation Specialty Section Webinar
September 29, 2017

Mark Seaton, Ph.D., DABT, FDA/CDER/OTS/OSIS



Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily reflect the official views of the Food and Drug Administration (FDA)

GLP for Nonclinical Laboratory Studies Proposed Rule

Outline

- A Brief History of GLP Regulations
- Background for Notice of Proposed Rulemaking (NPRM)
- Highlights of Proposed Changes

Good Laboratory Practice (GLP) for
Nonclinical Laboratory Studies
Proposed Rule

A BRIEF HISTORY OF GLP REGULATIONS



GLPs: How did we get here?



Printed in Collier's magazine, 11 articles in 1905, by Samuel Hopkins Adams on fraud in the pharmaceutical industry. The publication so outraged the public that Congress was finally able to enact the first of several pure food and drug laws in 1906. In the 1920's the U.S. Food & Drug Administration was established to regulate the Nation's food and drug industry.



History – 1900's

Pure Food and Drug Act, 1906

- Banned foreign and interstate traffic in adulterated or mislabeled food and drug products.
- Directed the U.S. Bureau of Chemistry to inspect products and refer offenders to prosecutors.
- Required that active ingredients be placed on the label of a drug's packaging and that drugs could not fall below purity levels.
- Drug labels had to list any of 10 ingredients that were deemed "addictive" and/or "dangerous" on the product label if they were present, including alcohol, morphine, opium, cannabis.
- Did not require **safety** or **efficacy** testing.

History – 1930's

Federal Food, Drug & Cosmetic Act, 1938

- Gave FDA authority to oversee the safety of food, drugs and cosmetics.
 - Included cosmetics and medical devices.
 - Required drugs be labeled with adequate directions for safe use.
 - Prohibited false therapeutic claims for drugs.
 - Mandated pre-market approval of all new drugs, **including proving safety.**



History – 1960's

- 1962, “Silent Spring” by Rachel Carson detailed the negative impact on the environment of indiscriminate pesticide use.



- 1970, Formation of EPA
 - Requirement for **more safety testing** studies and **more labs** in which to conduct those studies.

Industrial Bio-Test Laboratories (IBT)

- 1975, FDA received a tip that there were problems with tests submitted to FDA.
- The medical officer found study data was ‘unbelievably clean’, no rats on 2 year study developed cancer.
- The medical officer found enough deficiencies to warrant an inspection.
- Visit to IBT in April 1976: “What we found there is enough to make your hair stand up”.



“Magic Pencil Study”

- Terminal blood and urine samples were not collected.
- Draft data tables for the blood and urine assessments were blank, as expected.
- However, the final report not only had values reported, but had the technical writer’s name written in.
All of those results had been fabricated.



“The Swamp”

- System designed for automatic watering and flushing waste from cages rarely worked properly.
- Faulty nozzles sprayed the room with a continuing mist. The floor was at times submerged under 4 inches of water.
- Technicians only entered the room wearing rubber boots.
- Clogged water nozzles and drain hoses drenched some rats in a cold spray, while others died of thirst.



Regulatory Action

- FDA and EPA reviewed compounds that relied on IBT for data in support of safety.
- Called into question the reviews of more than 200 pesticides, many were retested at manufacturer's expense.
- 618 of 867 (71%) of studies audited by the FDA were invalidated for having "numerous discrepancies between the study conduct and data".



HISTORY -1970's

- Congress proposed and enacted the Good Laboratory Practice Regulations for FDA as part of the Federal Food, Drug, and Cosmetic Act (FD&C).
- 21 CFR Part 58 Good Laboratory Practices For Nonclinical Studies
- The *proposed* regulations for Good Laboratory Practice were published in the Federal Register on November 19, 1976.
- The Good Laboratory Practice Regulations, Final Rule was published in the Federal Register on December 22, 1978.

History – 1980s

- Federal Register of October 29, 1984 (49 FR 43530), FDA published a proposal to amend the agency's regulations in 21 CFR Part 58.
- 33 commenters.
- Revised Good Laboratory Practice Regulations, Final Rule was published in the Federal Register on September 4, 1987.
 - Significant changes in the provisions with respect to quality assurance, protocol preparation, test and control article characterization, and retention of specimens and samples

History – 2000’s

- 2003, Coulston Foundation was disqualified by the FDA
 - TFM and QAU deficiencies
 - Study records deficiencies
- Warning letters December 22, 1999 and October 11, 2001 led to consent agreement
- “Notice of Opportunity for a Hearing” letter March 18, 2003



Primary References

- *Faking It, The Case Against Industrial Bio-Test Laboratories*, The Amicus Journal, Spring 1983
- *Creative Penmanship in Animal Testing Prompts FDA Controls*, Science, 23Dec1977
- *Taste of Raspberries, Taste of Death, the 1937 Elixir Sulfanilamide Incident*, FDA website
- *The Murky World of Toxicity Testing*, Science, 10Jun83
- *The Bressler Report*,
www.mpwhi.com/complete_bressler_report.pdf
- Coulston NOH:
www.fda.gov/downloads/RegulatoryInformation/FOI/ElectronicReadingRoom/UCM144540.pdf]

Good Laboratory Practice (GLP) for
Nonclinical Laboratory Studies
Proposed Rule

BACKGROUND



Background

- GLP Working Group
 - Included all FDA Centers, ORA, OGCP, NCTR, OCC.
 - Included other Federal Agencies.
 - EPA, NIH/OLAW, USDA/APHIS
- Advanced Notice of Proposed Rulemaking (ANPRM)
 - Published in December 2010 (75 FR 80011).
 - Approximately 90 commenters responded.



Background

- ANPRM Areas (request for comments):
 - GLP Quality System
 - Multisite Studies
 - Electronic/Computerized Systems
 - Sponsor Responsibilities
 - Animal Welfare
 - Information on Quality Assurance Inspectional Findings
 - Process-Based Systems Inspections
 - Test and Control Article Information
 - Sample Storage Container Retention



Background

- Notice of Proposed Rulemaking (NPRM)
 - Published on August 24, 2016 (81 FR 58342)
 - Considered ANPRM comments and consistency with relevant OECD documents
 - Comment period closed on January 21, 2017
 - 90 day comment period
 - 60 day extension
 - 78 commenters
 - Multiple comments per submission



Good Laboratory Practice (GLP) for
Nonclinical Laboratory Studies
Proposed Rule

HIGHLIGHTS OF PROPOSED CHANGES



Highlights of Proposed Changes

- Enhance (require) the existing quality system approach.
- Reflect current practices such as multisite studies.
- Incorporate wording consistent with domestic and international (OECD) guidelines or regulations.

Specifically,

- Expand scope
- Add definitions
- Clarify GLP roles and responsibilities
- Add animal welfare provisions
- Request comment on Animal Rule studies

Proposed § 58.1 Scope

- Proposed expansion includes:
 - Toxicity studies
 - Tobacco products
 - Devices (to include veterinary)
- Proposed changes:
 - “Applications and Submissions” – not just for research or marketing
- Animal Rule
 - Requested comment on inclusion of certain Animal Rule studies in GLP scope

Proposed § 58.3 Definitions

- Test Site
- Contracted Person
- Test Facility Management with Executive Responsibility
- Attending Veterinarian
- Contributing Scientist
- Principal Investigator





Proposed § 58.5 Sponsor Responsibilities

- Proposed responsibilities relating to the protocol:
 - Meets requirements in § 58.120
 - Provides for humane care of animals
 - Review, approve, sign, and date each protocol and amendment
- Proposed responsibilities relating to accredited and qualified persons
- Proposed responsibilities relating to study communication:
 - Ensure appropriate lines of communication are established
 - Document communications

Proposed § 58.5 Sponsor Responsibilities

- Proposed responsibilities relating to test, control, and reference articles:
 - Document characterization,
 - Provide characterization information to study director as soon as available,
 - Inform study director of any known potential risks of the test article.
- Proposed responsibilities related to statement of compliance
 - the final study report and amendments to the final report must include a statement of compliance or noncompliance.

Proposed § 58.15 Inspections

- Clarification of FDA's inspection authority to include any person that conducts a phase of a nonclinical laboratory study.
- Includes any contracted or subcontracted person that agrees to assume any regulatory responsibility.

* Person includes an individual, partnership, corporation, association, scientific or academic establishment, government agency, or organizational unit thereof, and any other legal entity.

Proposed § 58.31 Testing Facility Management with Executive Responsibility (TFMWER)

- “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.”



Proposed § 58.31 TFMWER

- Propose new responsibilities related to:
 - GLP Quality System
 - review at specified intervals
 - appoint management representative
 - Multisite studies
 - all persons are trained and follow equipment SOPs
 - Master schedule
 - individual, not necessarily QAU
 - Protocol review

Proposed § 58.31 TFMWER

- Propose new responsibilities related to:
 - QAU review
 - SOPs



Proposed § 58.33 Study Director

- “The study director represents the single point of study control and has overall responsibility, which cannot be delegated, for...
 - ...Implementation of procedures to ensure adequate communication among all study personnel and with the study sponsor, as applicable...”
 - Document communications with all persons conducting a phase of the nonclinical study and with the sponsor.



Proposed § 58.33 Study Director

- Proposed new requirements:
 - Consult with attending veterinarian during review of proposed study protocol,
 - Defer to attending veterinarian on animal welfare decisions.
 - For multisite studies:
 - Document qualifications of any person conducting a phase of the nonclinical study,
 - Determine and document the need for a principal investigator.

Proposed § 58.33 Study Director

- Proposed new requirements:
 - Archive all raw data, documentation, protocols, specimens, reserve samples and final reports no later than 2 weeks after the study completion.



Proposed § 58.35 Quality Assurance Unit (QAU)

- For studies conducted entirely at the testing facility, the QAU can:
 - Consist of personnel at the facility itself; or,
 - Be a separately contracted unit.
- For multisite studies:
 - A Lead QAU must be designated by TFMWER, and
 - Provide QA oversight for the entire study.
- Requirements for Lead QAU included throughout proposed 58.35

Proposed § 58.35 QAU

- QAU inspections can include:
 - Study-based inspections
 - Facility-based inspections
 - Process-based inspections
 - If a person conducting a phase of a nonclinical laboratory study chooses to conduct process-based inspections, that person must prepare a written certification...whenever a process-based inspection reveals problems.

Proposed § 58.37 Contributing Scientist

- Proposed responsibilities:
 - For those phases for which the contributing scientist is responsible:
 - Comply with Part 58,
 - Provide a signed and dated report of all phases to include in final study report,
 - Both original and amended versions of reports from all contributing scientists be appended to the final study report.
 - Permit oversight by the designated QAU.

Proposed § 58.37 Contributing Scientist

- Independent contributing scientist - Proposed responsibilities include:
 - Date and sign the study protocol to indicate agreement to comply with the protocol requirements,
 - Maintain and update documentation of their education, training, and experiences,
 - Archiving responsibilities.

Proposed § 58.39 Principal Investigator (PI)

- The study director can delegate to the PI responsibility for phases of a nonclinical laboratory study but not responsibility for an entire study.
- Proposed responsibilities include:
 - Verify study conducted according to Part 58,
 - Report deviations to study director.



Proposed § 58.105 Test, control, and reference article characterization

- Analyses must be performed by the sponsor or by a contracted person either:
 - Before study initiation; or,
 - Concomitantly according to written SOPs.
- Results must be provided to the study director as soon as available.





Proposed § 58.130 Conduct of a nonclinical laboratory study

Proposed requirements for:

- Demonstration that all analytical methods are accurate, sufficiently precise, and sensitive enough to result in accurate and reproducible data
- Considering the humane care and ethical treatment of animals,
 - Consulting the attending veterinarian regarding the impact of the protocol on the welfare of test animals,
 - Deferring to the attending veterinarian on animal welfare decisions.

Proposed § 58.180 Data quality and integrity

- All data generated during the conduct of a nonclinical laboratory study must be ALCOA
 - Accurate
 - Legible
 - Contemporaneous
 - Original, and
 - Attributable

Proposed § 58.180 Data quality and integrity

- Any change to any entry must:
 - be made so as not to obscure the original entry,
 - indicate the reason for the change,
 - indicate when the change was made,
 - must identify who made the change.
- Use of an electronic records system must be fully compliant with applicable regulations.
- All data accrued as required in this section must be included in the final study report.

Proposed § 58.185 Reporting of Nonclinical Laboratory Study Results

- A signed and dated report from each person conducting an analysis or evaluation of study data or specimens after data generation was completed,
- 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,
- For discontinued studies, the study director to write, sign, and date a short written summary report closing the study and discussing why the study was discontinued

Proposed § 58.190 Storage and retrieval of records and data

- All study material must be archived no later than 2 weeks after the study completion date.
- SOPs regarding archiving, required in 58.81(b)(13), must include specific procedures for the removal of study materials from the archives, including maximum timeframes material can remain outside of the archives.



Proposed § 58.202

- “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 of more of the regulations set forth in this part...or repeatedly or deliberately submitted false information in any required report”

Person includes an individual, partnership, corporation, association, scientific or academic establishment, government agency, or organizational unit thereof, and any other legal entity.



Link to NPRM

www.federalregister.gov/documents/2016/08/24/2016-19875/good-laboratory-practice-for-nonclinical-laboratory-studies

Contact Information

Mark Seaton, Ph.D., DABT

CDER/OTS/Office of Study Integrity & Surveillance

Mark.Seaton@fda.hhs.gov

(301)-796-3408



