Chapter 4. Quality Program

Specifications for the Conduct of Toxicity Studies by the Division of Translational Toxicology at the National Institute of Environmental Health Sciences

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4. Quality Program

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4.1. Quality Management Plan

The contractor shall establish and maintain a quality management plan (QMP). A QMP governs quality aspects of all work performed. The QMP shall follow the requirements set forth in the U.S. Environmental Protection Agency (EPA) Requirements for Quality Management Plans (EPA QA/R-2).[1] QMPs shall be submitted before performance of work under the contract and updated versions submitted at regular intervals (e.g., biannually), or if the plan has been updated substantively.

4.2. Quality Assurance Unit

The contractor shall establish an effective and independent quality assurance unit (QAU).

The purpose of quality assurance (QA) is to provide assurance that studies are conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice (GLP) regulations. National Institute of Environmental Health Sciences (NIEHS) toxicology studies shall be conducted in compliance with FDA GLP regulations as specified in Part 58 of "Good Laboratory Practices for Nonclinical Laboratory Studies" (21 CFR Part 58[2]), in addition to these DTT specifications, unless otherwise specified in the work assignment and the resulting laboratory study protocol. On occasion, NIEHS might require that a study be conducted in compliance with EPA regulations ("Toxic Substances Control; Good Laboratory Practice Standards; Final Rule," Federal Register, Tuesday, November 29, 1983, Part III) in addition to FDA GLP regulations, or, conversely, not in compliance with either FDA or EPA regulations (i.e., non-GLP). The quality standard for a particular project will be clearly communicated in writing upon assignment of the project. For non-GLP studies, all quality aspects of the studies shall occur with the exception of those specifically related to the QAU.

For testing facilities that conduct studies in compliance with FDA GLP regulations, the facility shall have a QAU, which shall be responsible for monitoring each study to provide assurance that the facilities, equipment, personnel, methods, practices, records, and controls are in compliance with the regulations. For any given study, the QAU shall be entirely separate from and independent of the personnel engaged in the direction and conduct of that study (FDA GLP 58.35).

The conduct of QA audits and inspections is the responsibility of the testing facility/test site laboratory QAU. Aspects of the studies are to be inspected and resulting data audited according to the frequency of the data collected, the extent of quality control (QC) review, and the potential

[1]https://www.epa.gov/quality/epa-qar-2-epa-requirements-quality-management-plans
[2]https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-58

relevance of errors. These factors and the monitoring frequency are to be considered and established in concert with the study director/test site principal investigator (PI), discipline leaders, contract PI, and the laboratory's management. The schedule of inspections and audits reflects a dynamic process and will be influenced by a variety of factors such as previous findings, follow-up activities, workload and quality issues expressed by management, and inspectional findings from outside reviewers.

Audits and inspections by the QAU shall encompass all aspects of the studies performed under the purview of the laboratory's QAU, from prestart chemistry and inhalation through the final report and archiving of data/specimens (where applicable). The study protocol and amendments shall be reviewed by the testing facility's QAU for compliance with GLP regulations, with signed and dated documentation of this review before the initiation of the study, or before the amended change effective date. Those phases of a study that occur only once and include procedures or conditions that can be directly observed shall be inspected at the time they occur and resulting data audited. If a once-only phase undergoes a formal and documented QC review by technical staff, the QAU might limit its responsibility to inspecting the procedures of the QC review for that phase. Repetitive or routine procedures that affect the generation, collection, and handling of study data need to be subjected to inspection and audit on a periodic basis for each study. All data and statements of fact included in study reports submitted shall be audited by the testing facility's QAU. In addition, the QAU shall prepare and sign a statement that will be included with the final study report that specifies dates of inspections and dates of reports provided to management, the contract PI, and the study director (FDA GLPs). If a laboratory or testing facility has one or more test sites, each test site QAU shall be responsible for the critical phase inspections and data and report audits occurring at its site and shall prepare and sign the QAU statement. Ultimately, it is the study director's responsibility to determine the overall effect of the audit findings on the study.

4.3. Quality Control

The contractor shall establish policies and procedures that ensure QC at all levels, including development of a QC program. The purpose of QC is to ensure that all information generated by the study-conduct staff (e.g., data, records, and reports) are accurate, consistent, and complete. The laboratory shall have a robust and comprehensive QC program in place to accomplish this. This program shall be in operation for all projects, regardless of whether they are to be performed under FDA GLP regulations. This program shall be separate from and subject to periodic assessment by the QAU. Ensuring that the procedures, studies, data, and reports reflect contractual standards, including these specifications, is a QC function and shall be the responsibility of study management.

NIEHS's independent quality assessment support contractor performs retrospective assessments of NIEHS studies, data, and reports. The project officer will provide the results of the assessments to the study laboratory. It is expected that the study laboratory will review these reports and, if required, use the findings to inform improvements to the quality program. On occasion, NIEHS might determine that a finding(s) is sufficient to require a revision to a report. In this case, the study laboratory shall submit a revised report and respond to the assessment.

4.4. On-site Inspection

At its discretion, NIEHS may perform on-site inspection with prior notification, by the contracting officer's representative (COR) or his/her designee, of equipment, facilities, records, and procedures, including those of the QAU periodic site visits to the laboratory. These visits may include technical discussions, reviews of schedules, audits and inspections of studies, procedures, data, records, and reports for projects in progress. In addition, the visits may include evaluation of the organization and function of the laboratory's QAU, with evaluations to include the organization and function of the laboratory's QAU as well as audit/inspection of various aspects of ongoing studies.

The laboratory shall maintain a file of QAU reports (inspections, audits, master schedule entries) and responses to them in connection with NIEHS studies. As the sponsor for the studies, NIEHS management, QA personnel, and the program COR shall have access to the file for review purposes. The confidential, proprietary, and predecisional information contained in this file shall not be divulged by NIEHS reviewers. The file shall not be revealed to any outside parties, including QA support contractors for the NIEHS or GLP compliance inspectors for the FDA or EPA. When a study is completed, the QAU reports file shall not be part of the study record and shall not be submitted to the NTP Archives.

4.5. Standard Operating Procedures

The contractor shall develop and maintain standard operating procedures (SOPs) for all contract operations, procedures, assignments, and tasks that describe how each activity is to be performed. In addition to the study protocol, laboratory SOPs are considered essential to the successful conduct, documentation, inspection, and auditing of a study. The review and revision of existing SOPs, the creation of new SOPs, or the retirement of outdated SOPs shall be a continuing process. For this reason, all new SOPs shall be reviewed by the laboratory's QAU at a frequency documented in the laboratory's QMP (e.g., biannually). New or revised SOPs shall be prepared, reviewed, and approved by appropriate study facility personnel, including the QAU, before implementation. The decision to develop and implement program-specific SOPs shall be that of study laboratory management. All SOPs used in connection with each study shall be maintained as records in the study file and submitted to the NTP Archives. These SOPs are subject to review by NIEHS personnel upon request, as they document how work is performed.

4.6. Subcontractors

The contractor shall establish procedures to ensure that work performed by subcontractors meets the same quality requirements as work performed by the prime contractor. Testing facility management, the contract PI, and the study director shall assume responsibility for all the work assigned to the testing facility. For multisite studies, in which aspects of the studies conducted under GLPs are delegated to independent subcontractors (test sites), the delegated phases of the study performed by an independent subcontractor are audited by the test site QAU according to its SOPs. Before the initiation of this subcontract work, the testing facility's QAU shall assess the subcontractor's quality system. The appropriate staff, including discipline leaders or the study director, the contract PI, and testing facility management, as appropriate, shall review data and reports submitted by a subcontractor and determine their acceptability.

4.7. Peer Review

The Division of Translational Toxicology (DTT) conducted a peer review of chapters 1, 2, 3, 4, 11, and 12 within the draft *Specifications for the Conduct of Toxicity Studies by the Division of Translational Toxicology at the National Institute of Environmental Health Sciences* by letter in February 2022 by the expert listed below. Reviewer selection and document review followed established DTT practices. The reviewer was charged to:

1. Peer review the following chapters within the draft Specifications for the Conduct of Toxicity Studies by the Division of Translational Toxicology at the National Institute of Environmental Health Sciences.
    - Chapter 1: General Personnel Requirements
    - Chapter 2: Facilities
    - Chapter 3: Health and Safety
    - Chapter 4: Quality Program
    - Chapter 11: Data Collection and Submission
    - Chapter 12: Report Formats and Guidance
2. Comment on the completeness of each chapter.

DTT carefully considered reviewer comments in finalizing this document.

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