PROPOSED GLP QUALITY SYSTEM TESTING FACILITY MANAGEMENT WITH EXECUTIVE RESPONSIBILITY

AS THE PROCESS OF REVIEWING THE FDA PROPOSED GLP QUALITY SYSTEM CHANGES CONTINUES, WE WANTED TO BREAK DOWN THE PROPOSED CHANGES, RATIONALE, AND INDUSTRY IMPACTS IN MORE DETAIL.

The Quality Assurance Unit (QAU) is an integral part of any GLP regulated facility and/or study. If the proposed changes are accepted, the way study documents are reviewed and inspections are performed may be impacted. Below are some of the FDA proposed changes, reason for the changes, and potential industry impacts.

THE PROPOSED CHANGE

Transfer of responsibilities:

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 follow up 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).

THE REASON FOR CHANGE AS DISCUSSED IN THE PREAMBLE OF PROPOSED REGULATIONS

"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."

…

"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."

POTENTIAL IMPACT OF THE PROPOSED CHANGE

Test facility management "with executive responsibility" is a key player in the proposed GLP Quality System. They are "ultimately responsible for GLP compliance" at a test facility. This position has the capability of significantly improving overall function of the QAU and quality system as a whole. Though, as with any significant change, there are still some potential concerns.

One newly included aspect of this position is the evaluation of the QAU. The proposed regulations identify ways that checks will be added to ensure the quality system is effective. This includes the creation of additional SOPs, including those defining the intervals at which the quality system will be reviewed. Additionally, the proposed regulations include the appointment of a management representative who will document that the quality system requirements are working and report the performance to the test facility management with executive responsibility. This additional evaluation could prove to be invaluable with regards to process improvements and QAU effectiveness. Some suggest it is unnecessary to have this specifically labeled as a separate member of management and that test facilities should be able to complete this beneficial review as they see fit. There is also additional concern when considering the importance of the independence of the QAU and the potential conflict in being evaluated by and reporting to the management proposed in the changes.
Another responsibility of this position is found in proposed § 58.3 Definitions. In the definition for study-based inspection, it states "Management with executive responsibility at the testing facility and/or test site identifies which operations are critical before initiation of the study." Effectively, this states that the management with executive responsibility would be picking what phases of a study are audited and does not address additional audits deemed necessary during the study. Whether or not this change will be adopted, it is important to create SOPs to detail this process and address any concern of conflict of interest.

Meeting the proposed regulations with regards to this position may be straightforward for some companies but require reorganization or additional personnel in others. This is an important position with a range of responsibilities including, but not limited to, those stated above as well as establishing SOPs for the appointment of the study director, appointing a person to maintain the master schedule, and ensuring "any person conducting a phase of the nonclinical laboratory study follows adequate equipment- related SOPs." The oversight this position allows will hold test facilities accountable and allow for vast process improvements in gaps that are currently not addressed.

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