# PROPOSED GLP QUALITY SYSTEM QUALITY ASSURANCE UNIT PART 2 OF 2

## 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. The proposed changes could impact the way the QAU is organized as well as it's day to day operation and communication with other sites. Below are some of the FDA proposed changes, reason for the changes, and potential industry impacts.

## THE PROPOSED CHANGE

*§58.35 Quality assurance unit (QAU)*

(a)(1) *Function.* A QAU must monitor each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the regulations in this part. For any given study, the QAU must be entirely separate from and independent of the personnel engaged in the direction and conduct of the study.

(2) *Location and identity.* (i) For studies conducted entirely at the testing facility, the QAU can consist of personnel at the facility itself or be a separately contracted unit.
(ii) For multisite studies, a lead QAU must be designated by testing facility management with executive responsibility and must have responsibility for the QA of the entire study. The lead QAU can consist of personnel at the testing facility, be a QAU for another person conducting a phase of the study, or be a separately contracted unit. QAUs for persons conducting a phase of the study must coordinate with the lead QAU as specified in SOPs as described in §58.81(b)(17) and (20). The lead QAU has direct QA responsibility for any person lacking a QAU.

(b) QAUs must:
(1) Maintain access to the master schedule (defined in §58.3) of all nonclinical laboratory studies conducted by the person employing the QAU or contracting for QA services. For multisite studies, the lead QAU must maintain access to the master schedule of any person lacking a QAU.
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(5) Inspect each nonclinical laboratory study for which the QAU is responsible at intervals adequate to ensure the integrity of the specific study. Inspections must determine compliance with the protocol, applicable SOPs, and the requirements of this part. These can include study-based, process-based, and facility-based inspections as defined in §58.3 and as specified in SOPs as required in §58.81(b)(20). For multisite studies, the lead QAU must coordinate the conduct of study inspections with any other existing QAUs, as specified in SOPs as required in §58.81(b)(20). Upon discovery, any problems found during an inspection which are likely to affect study integrity must be reported to the study director and management with executive responsibility for the study or studies affected.
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(7) Periodically submit to management with executive responsibility and the study director written status reports on each study that discuss the overall progress and compliance status of the study and that include any problems observed and the corrective actions taken. The content and frequency of these reports must be specified in SOPs, as described in §58.81(b)(21).

(8) Determine that no deviations from approved protocols or SOPs were made without proper authorization and documentation. For multisite studies, the lead QAU is responsible for identifying all deviations that occur across the entire study, including deviations identified by all other QAUs participating in the study, as described in SOPs in §58.81(b)(17).

(9) Audit the reports of all contributing scientists, and any amendments to such reports, to ensure such reports reflect the protocol and all amendments, accurately describe the methods and SOPs, and report all of the raw data of the specific phases covered by each report. For multisite studies, QAUs for persons conducting a phase of the study must audit the reports of any principal investigators and all contributing scientists for whom they are responsible, and any amendments to such reports, as specified in SOPs as described in §58.81(b)(17). The lead QAU must audit the reports, and any amendments to such reports, of any principal investigators and all contributing scientists for any person lacking a QAU and of any independent contributing scientists.

(10) Audit the final study report, and any amendments to this report, to ensure that such report accurately describes the methods and SOPs, all raw data of the nonclinical laboratory study are reported, and that all original and amended signed and dated reports from all contributing scientists are appended. For multisite studies, this is the responsibility of the lead QAU.

(11) Prepare, sign, and date a statement to be included with the final study report that specifies:
(i) The dates of study-specific inspections, process-based inspections if applicable, and facility-based inspections;
(ii) Findings reported to management with executive responsibility and to the study director; and
(iii) The dates of QAU audits of the reports of all contributing scientists (including any independent contributing scientists), any principal investigators, and of the final study report and all amendments to such. For multisite studies, this is the responsibility of the lead QAU. When other persons conducting a phase of the study have QAUs, those QAUs must provide to the lead QAU such statements regarding the audits they conducted, for appending to the final study report.

(c) The responsibilities and procedures applicable to the QAU, the records maintained by the QAU, and the method of indexing such records must be in writing and must be maintained as specified in SOPs as required in §58.81(b)(17). For multisite studies, the lead QAU and all other QAUs participating in the study must maintain those documents relevant to their oversight. These SOPs as well as documentation of the dates of all QAU inspections, the study or process or procedure, or facility inspected as applicable, the phase or segment of the study inspected for study-specific inspections, and the name of the individual performing the inspection must be made available for inspection to authorized employees of FDA.
…

## Reason for change as discussed in the Preamble of Proposed FDA Regulations

“In § 58.35, we propose keeping the QAU functions currently in the regulations. We propose modifying § 58.35(a) by separating it into paragraph (1) QAU function and paragraph (2) QAU location. We propose this change for consistency with our other proposals in part 58 (for example, to address the location of the lead QAU for multisite studies), and in response to comments to the December 2010 ANPRM requesting a clear description of the relationship between the QAU and test facility management.

We propose in § 58.35(a)(2)(ii) that, for multisite studies, testing facility management with executive responsibility must designate a lead QAU. The concept of a lead QAU is consistent with the discussion in the preamble of the original GLP final rule stating that when portions of a study must be contracted to a site that lacks a QAU “the person letting the contract, and not the contract facility, is responsible for the performance of the quality assurance functions” (43 FR 59986 at 59997) (Ref. 12). This change also is consistent with the OECD consensus document, Quality Assurance and GLP (Ref. 7). Several comments to the December 2010 ANPRM specifically note the need for a lead QAU in multisite studies. We propose several modifications to current § 58.35(b). We propose changing the present QAU requirement to maintain a copy of the master schedule and all protocols to require that the QAU maintain “access” to them. For example, if the QAU is a contracted person, then the QAU might not have overall knowledge about the person (i.e., testing facility) to which

they are providing QA services. However, the QAU requires “access” to the master schedule and protocols to ensure GLP compliance.

We recognize that many sites have a central computerized system for maintenance of essential documents. Our proposed change about QAU access to the master schedule responds to stakeholder requests to modernize part 58 and also to comments to the December 2010 ANPRM. This change also is consistent with our proposal in § 58.195(d) that management with executive responsibility must ensure “maintenance” of the master schedule and copies of study protocols. Because the lead QAU is responsible for ensuring GLP compliance of all phases of a multisite study, we propose that the lead QAU must maintain access to the master schedule of any person that lacks a QAU. We consider the master schedule an important tool for determining whether a person is capable of conducting a GLP compliant study. For example, a person with numerous scheduled studies still in progress may lack sufficient resources to begin the conduct of a GLP compliant study.”

“In § 58.35(b)(7) (a redesignation and revision of current § 58.35(b)(4)), we propose expanding the requirement that the QAU must submit to management with executive responsibility and the study director a periodic written status report on each study. We propose that these periodic reports “discuss the overall progress and compliance status of the study and include any problems observed and the corrective actions taken.” In conjunction with this requirement, we propose that the content and frequency of these reports be specified in SOPs as required in proposed § 58.81(b)(21). We propose this revision in § 58.35(b)(7) because feedback to management with executive responsibility and the study director about the overall progress and compliance status of the study is essential to ensure study compliance. We intend these periodic reports to give a general overview of the study. We expect these periodic reports to complement any inspection reports for the study, which only provide a snapshot in time.

We are interested in receiving feedback about the use and relevance of periodic status reports. Specifically, we are seeking comment about whether QAUs regularly provide such reports and whether they are useful to the study director and management when provided.

Consistent with our proposals addressing multisite studies, we propose adding in new § 58.35(b)(8) (revision of current § 58.35(b)(5)) that the lead QAU must identify all deviations occurring in the entire study, including deviations identified by any other existing QAUs participating in the study. We expect this requirement may be facilitated by principal investigator reports to the study director, documentation by other existing QAUs, and direct oversight by the lead QAU of independent contributing scientists and any persons conducting a phase of the study lacking either a principal investigator or a QAU or both. We propose this requirement to ensure the lead QAU is made aware of protocol deviations in a timely manner. This awareness will help alert the lead QAU to the need to correct or modify relevant SOPs and the study protocol when necessary to maintain data integrity. The remaining additions we propose in § 58.35 relate to QAU oversight of the integrity of data in the final study report.”

“For multisite studies, we propose that other QAUs participating in the study must audit the reports and report amendments of any principal investigators and all contributing scientists for whom they are responsible. We also propose in § 58.35(b)(9), for any person that lacks a QAU, that the lead QAU audits the reports and amendments of all contributing scientists and any principal investigators. This includes audits of any independent contributing scientist. This proposed requirement will ensure all data from a nonclinical laboratory study will receive QAU review, thus improving the quality and integrity of the final study report.

In § 58.35(b)(10), we propose that the QAU must verify that all original and amended signed and dated reports from contributing scientists are appended to the final study report. For multisite studies, we propose that the lead QAU is responsible for this requirement. Under existing regulations that require providing the final study report and any amendments, we expect that both original and amended versions of reports from all contributing scientists be appended to the final study report. The proposed changes make this expectation a specific requirement. This requirement will allow the study sponsor and FDA reviewers to have access to the original conclusions for each phase and any modifications made as a result of interactions among those involved with the study. We propose this requirement to address the potential inadvertent or intentional introduction of bias that may result when only the final amended version of contributing scientists’ reports are included.”

## Potential Impact of the Proposed Change

Section 58.35 of the proposed FDA GLP regulations is lengthy and the suggested changes are extensive. The changes include the addition of test facility management with executive responsibility, specification of lead QA and associated multisite responsibilities, as well as audits being open for FDA investigation. If these proposed changes are accepted, the way the QAU functions may be significantly affected.
Currently the reporting structure of QA supports a high level of independence. In the proposed regulations, the position of test facility management with executive responsibility has been suggested to provide oversight and determine the effectiveness of the QAU. Regarding whether or not this change will promote study integrity, both sides can be argued. This could be a positive change to have someone with the bigger picture in mind assessing QA effectiveness. Their support in upper management could drive more changes and provide QA with additional backing and support. On the other hand, it can be argued that this position carries a risk of influencing QA to be less effective in order to support the business's bottom line and time constraints. Another significant argument is that this additional layer in the organizational structure may prove to make it especially difficult for smaller companies to comply. In addition to this position, in proposed 58.33, the study director will be responsible for ensuring that the QAU has reviewed the protocol and SOPs. These changes will more directly interconnect the QAU with facility and study personnel and have blurred some of the applicable responsibilities.

Also in the new proposed regulations, test facility management with executive responsibility is to designate a lead QAU for a multisite study. This lead QA has "responsibility for the QA of the entire study." This is beneficial to have one point of responsibility, which is not dependent upon location. It covers QA concerns when using test sites that do not have their own QAU including the specification that "the lead QAU must coordinate the conduct of study inspections with any other existing QAUs." With the overall responsibility, the lead QAU must have access to the master schedule of any test site without a QAU. Also, "the lead QAU is responsible for identifying all deviations that occur across the entire study, including deviations identified by other QAUs." This may seem like a duplication of responsibility but should go a long way to ensure the reporting of deviations is not overlooked. If these changes are accepted, it will be essential to make sure SOPs are provided to define roles and detail coordination between the lead QAU and any other QAUs in a study.

An additional hot topic of the overall proposed changes is found in another section (58.15 (a)) where it says "FDA retains the authority to inspect all QAU records when necessary to ensure compliance with this part." From the preamble, this change is suggested in order to reflect current practice of reviewing QAU records only when deemed necessary. Many are concerned however, that FDA will change their inspection processes to more regularly review QAU records. If that were to happen, some believe that this change will weaken the QAUs effectiveness. Some others believe this is a valuable change and will allow FDA to truly assess whether or not the QAU is meeting their regulatory responsibilities- noting that this is similar to other regulatory authorities.

Overall, if these changes are accepted, reorganization and additional QAU responsibilities can be expected. Though the proposed changes with regards to the QAU are considerable, there is still room for flexibility to allow for a customized process for compliance. It will be essential to have a well thought out and detailed plan on how best to move forward.

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