PROPOSED GLP QUALITY SYSTEM QUALITY ASSURANCE UNIT PART 1 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. 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

§ 58.35 Quality assurance unit (QAU)
...
(b) QAUs must:

...
(3) Review all protocols before study initiation, and all protocol amendments before implementation, to ensure that they can be conducted in compliance with this part. This review must be documented.

(4) Review all SOPs to be used for the conduct of all phases of a nonclinical laboratory study to assess their clarity and compliance with this part. This review must be documented.

(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.

(6) Maintain written and properly signed records of all inspections that include the date of the inspection, the individual performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for reinspection. For study-specific inspections, reports must also include the identity of the study and the phase of the study inspected.

(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).

...
(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.
(d) A designated representative of FDA must, upon request, be given access to the written SOPs established for QAU inspections. If requested by FDA, the person inspected must certify that inspections are being implemented, performed, documented, and followed up according to this part.
(e) If a person conducting a phase of a nonclinical laboratory study chooses to conduct process-based inspections, that person must prepare a written certification, as specified in SOPs as required in § 58.81(b)(21), whenever a process-based inspection reveals problems. This certification must document actions taken to properly inform and, when applicable, modify reports for all studies impacted by the results of the process or procedure in question.

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

“In new § 58.35(b)(3), we propose requiring the QAU to review the study protocol before initiating the study and all protocol amendments before implementing them, along with documenting this review. In new § 58.35(b)(4), we propose requiring the QAU to review all SOPs applicable to a given nonclinical laboratory study along with documenting this review.

Current regulations state the QAU is “responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance” with GLPs (current § 58.35(a)). Our proposed initial review by the QAU of the study protocol and applicable facility SOPs will help ensure compliance with part 58 from the start of the study. Otherwise, when the study is underway, amendments to the study protocol and SOPs might be needed if QAU inspections reveal compliance deficiencies.

We propose in § 58.35(b)(5) expanding the types of QAU inspections recognized by FDA by adding process-based and facility-based inspections. Many comments to the December 2010 ANPRM request this change consistent with QAU inspections described in the OECD consensus document, Quality Assurance and GLP (Ref. 7), specifically supporting an appropriate mix of study-specific and process-based inspections. However, many comments to the December 2010 ANPRM express concern about how process-based inspection results will be appropriately considered for all relevant studies, particularly when an inspection reveals problems. This concern is especially relevant to any phase involving a short-term study, as we propose to define this term. Process-based inspections are conducted on a prearranged schedule, which is not connected to the timing of any particular nonclinical laboratory study. Therefore, a facility utilizing process-based inspections might conduct a short-term study that is not inspected during its in-life period (that is, during the time data are collected). This concern also is addressed in the OECD consensus document, The Application of the GLP Principles to Short Term Studies (Ref. 15).

To ensure that any problem revealed during a process-based inspection is properly captured in the reports of all relevant studies, we propose adding § 58.35(e). This provision requires preparation of a written certification, by the person conducting a phase of the study, whenever a process-based inspection reveals problems. As proposed, this certification requires documenting actions taken to properly inform, and modify (when applicable), reports for all studies impacted by the results of that process or procedure. While a management responsibility, we propose adding this requirement in § 58.35 because of its similarity to the existing requirement in current § 58.35(d) for management to provide an FDA representative, upon request, a certification regarding the implementation of required QAU inspections.”

…
“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.**"

POTENTIAL IMPACT OF THE PROPOSED CHANGE

Section 58.35 of the proposed FDA GLP regulations contains significant changes with regards to the quality system. With the additional review of the protocol, amendments, and SOPs, as well as the changes in inspections performed, the day to day operation of the QAU can be expected to change. Study timelines and QA resources may also need to be considered if these changes are accepted.

Additional QAU responsibilities are outlined in Part 58.35(b)(3) and (4) of the proposed regulations, where it states that QA should review protocols, amendments, and SOPs. The benefit of reviewing these, as stated in the preamble, is to "ensure compliance with part 58 from the start of the study." When making changes, a QA review can also help to account for any potential issues or conflicts before they arise. It is already common practice for some companies to have the protocol reviewed by test facility QA but not necessarily the amendments or SOPs. A main concern about this change has to do with study timelines. The time taken for review when a study is starting or when a change needs to be made ASAP may significantly delay study start dates or changes and therefore compromise study integrity. Also related to this addition, the QAU review of SOPs is unclear. Some question when the SOP review is to happen and if they are to be re-reviewed for each study. Additionally, it is not stated which QAU is to perform all of these reviews, nor does it state what the review entails (e.g. compliance with GLPs). All this being said, **it is reasonable to expect that this proposed change, combined with the other responsibilities outlined in the proposed regulations, may require additional QAU resources**. These additional reviews would put a significant strain on smaller companies and those that contract out QA services.

In the proposed regulations, definitions for facility, process, and study based inspections have also been added and are proposed as options for use as part of QA's responsibility to "ensure the integrity of the specific study." This is mostly viewed as a positive change and promotes flexibility in company procedures. Currently, the same critical phase, such as sample preparation, may be audited every day on different studies. This type of process can quickly lose value and limit perspective. With the proposed changes, a process audit may be done at adequate intervals (as defined in SOPs) to identify any problems which would allow for focus on other areas of risk that can be identified. In association with this flexibility, details have been proposed in the regulations to make certain any issues noted are appropriately taken care of for all applicable studies. With this change, it is also possible that a study may not technically have any audits performed. Therefore, justification will be important and time frames for which process audits are considered applicable should be well thought out and documented in SOPs.

One item in question is found in Part 58.35 (b)(11)(ii) where it states that the QA statement is to include "Findings reported to management with executive responsibility and to the study director." Before and after this text, parts (i) and (iii) of this section start with "The dates of …" however, part (ii) does not. It is questioned whether this was written in error or if it is the intention to include findings in the QA statement of reports. The current regulations are similarly worded but not divided into separate bullet points. Through comments submitted to the FDA, we hope to gain clarity on this issue and the impact it could have on reporting.

In the preamble to the proposed changes, the FDA is specifically requesting "feedback about the use and relevance of periodic status reports." This topic was previously discussed in the preamble of 1987 and the current regulations are not very specific on this topic. Therefore, the opinions regarding status reports as well as how they are handled differ widely between companies. The idea that upper management would get status reports on burning issues on a regular basis has obvious benefits however this leaves the questions of how often and who determines what is important enough to include. Because these questions are not defined in the regulations, some companies see no value in status reports since information regarding findings is already reported to study directors and management in study audits. One area that status reports include that is not already covered through study audits is studies that have no current audits being performed, such as the terminated studies that have not been finalized. Status reports are a beneficial way to track such studies. One other way status reports could help to close gaps is if they were to include facility issues as well. There are instances in various audits where facility issues are noticed but the study audit may not be the applicable place to address such findings. Expanding the scope of status reports, would allow for a place to address these with management. Though there is no specific proposed change that may impact businesses, now is the time to send comments to the FDA to suggest modifications that will benefit the industry as a whole.

Though these particular proposed changes to the FDA GLPs may look like more work, it is important to remember the end goal which is creating studies with higher integrity. The review of protocols, amendments, and SOPs as well as the different types of inspections suggested both lend toward a proactive rather than reactive process to determine any areas of deficiency. Now is the time to think about how these changes will impact your company and, if you have suggestions or concerns, share them with the FDA by submitting your comments.

NEED HELP ENSURING THAT YOUR COMPANY IS READY TO COMPLY WITH THE FDA'S LATEST RULES AND REGULATIONS? REQUEST A CONSULTATION FROM QA COMPLIANT BY CONTACTING JAYME GIBSON AT (913) 850-5150 OR JAYME@QACOMPLIANT.COM.
