SPAQA Regulatory Round Table
03 December 2013, Basel, CH

Questions

Organization and Personnel

The scope of the US GLP includes medical devices. The Swiss GLP regulation doesn't include this scope and mentions that the compliance monitoring units do not inspect studies that are not subject to GLP regulations.
We are a research institute performing contract research for medical device manufacturers, who want to register their products in the US. We are being asked by our customers to perform GLP compliant studies.

- Is there any intention to include medical devices in the Swiss / European scope of GLP?
- The FDA mentions in a draft guidance document (see attachment page 20 footnote 34), that they want certain studies to be done under GLP for medical device registration. Is something similar foreseeable in Switzerland or Europe?

There is currently no intention to include medical devices in the Swiss / European scope of GLP. Although generally excluded from the scope of GLP in the EU, many EU monitoring authorities will perform GLP inspections in facilities undertaking studies on medical devices for submissions to the US FDA. Therefore, if a TF in Switzerland conducts preclinical studies with medical devices and if for such studies GLP is required for registration in other countries (e.g., US FDA), then the Swiss compliance monitoring units will perform GLP inspections of such a TF.

Follow up to Interpretations 0.5/0.6

Please clarify if a company which performs no GLP Studies (i.e. Staff are never SD) but rather only conduct GLP Phases of non-clinical safety studies (e.g as PI for Bioanalytical analyses, Pathology, Histology, etc) will appear in the official list of GLP TFs on the GLP web-site www.glp.admin.ch?

Would companies which only have PIs be inspected on a regular basis and receive a GLP certificate?

They will be regularly inspected, listed on the official list and receive a GLP certificate if they fulfill the requirements for a test facility.

a) If test sites comply to the requirements for test facilities as outlined in Art.5 OGLP and in the GLP Monitoring Programme they are considered as test facilities.

b) Test sites which do not comply to the requirements for test facilities as outlined in Art.5 OGLP and in the GLP Monitoring Programme are inspected within the framework of the associated TF. They will be mentioned as test site in the official list of GLP test facilities on the GLP web-site www.glp.admin.ch.

Organization and Personnel

c) Activities performed by an organization that is not inspected by the Swiss Monitoring Authorities must be excluded from the GLP statement of the SD/PI.

Follow up to Interpretations 1.8
In number 1.8 of the Swiss Interpretation of the GLP Principles 2013 it is stated that the Study / Phase initiation date is recommended to be in the master schedule. The study initiation date is defined as the day the study director signs the study plan.
What is regarded as the Phase initiation date since according to number 8.4 there are no phase plans?

- *What is the definition/interpretation of "Phase Initiation Date"?*

The test site should define the phase initiation date according to the type of study.

However, the phase initiation date should not be before the study plan has been signed.

Follow up to Interpretations 1.10

In this interpretation you state the following: "The GLP principles do not require signatures by Test Site Management or the Sponsor on Principle Investigator's phase report; the sole requirement is the signature by the Principle Investigator, their signed GLP statement and where appropriate, a QA statement."
If a Phase Report is being written, under what circumstances is a QA statement not required?

If the lead QA of the test facility performed all QA activities for the phase, the content of QA activities will be reflected in the QA statement of the study report. In this case, the phase report should show evidence that appropriate quality assurance monitoring was performed at that test site.

Follow-up question to the Interpretations 1.12

- *A deputy study director has signed a study plan amendment/deviation during an absence of the study director. Is it acceptable when the study director approves the amendment/deviation on a separate form filed in the raw data?*

- *What exactly is the meaning of „countersigned" (new interpretations)? Please define*

It is acknowledged that "countersigning" means that the SD signs onto a document previously signed by the deputy SD. With this the SD confirms upon return that he is aware of the changes initiated by the deputy during his absence. However it is acceptable that the SD acknowledges the amendment/deviation on a separate document filed in the raw data.

Follow up to Interpretations 1.18b
"In case of a collaboration with external co-workers, a Service Level Agreement (SLA) should be available reflecting the processes and responsibilities. The TFM should insure that the co-workers receive adequate GLP training and comply with their SOPs. This should be documented."

In large companies, TFM is rarely involved in the outsourcing to external contractors who maintenance work within the test facility premises (e.g. HVAC maintenance, replacement of light bulbs, emptying of trash from laboratories). How should TFM document that these tasks require no GLP training, nor documentation maintained within the test facility?

TFM should insure that external co-workers who have a direct link with the conduct of studies are mentioned in the GLP personnel, receive adequate GLP training and comply with their SOPs. This should be documented. However, external contractors who do maintenance work within the TF premises, such as Heating, Ventilation and Air Conditioning maintenance, replacement of light bulbs, emptying of trash from laboratories, i.e. tasks without direct link with the conduct of GLP studies, are not comprised in the GLP personnel and thus do not require GLP training nor corresponding documentation.

Follow up to Interpretations 10.4:

Will be discussed directly between the Monitoring Authority and the Test Facility.

TF/TSM responsibilities

- *How should TSM document the appointment of PIs?*

  It is up to the test site management to decide how to document the appointment of the PI.

- *The Swiss GLP ordinance requires the signature of TFM on the Study plan. No signature of TFM is required for Study Plan amendments. TFM is not required to be on the circulation list of amendments. How can it be assured that TFM is aware of and takes responsibility in the circumstance that new PIs are added or additional work at the test facility is to be performed?*

  The Study Director will approve and issue amendments to and acknowledge deviations from the study plan, including those relating to work undertaken at sites. The TFM should approve and sign study plan amendments only if he appoints a new study director. In other cases, he can be informed by inclusion into the distribution list of the amendments to study plan. If it becomes necessary to replace a PI, the test site management will appoint a replacement PI in consultation with the sponsor, the Study Director and TFM where necessary.

The Study Director is the single point of study control and has the responsibility for the overall conduct of the study and for its final report.

- *If study plan amendments are to be treated analogously to study plans (archival, QA review...), then why is TFM signature on these documents not required?*

The signature of the TFM on the study plan is required to nominate the SD. If the SD is to be changed, TFM will sign the corresponding amendment to the study plan. He ensures that for each study a SD with the appropriate qualifications, training, and experience is designated before the study is initiated.

Quality Assurance

Process-Based Inspections: Is it sufficient to inspect Peer Review Pathology (i.e. Pathologist's review of slides) as a Process based inspection only on a quarterly basis? In many OECD countries this is standard practice and is accepted by the respective GLP authorities.

The frequencies for process-based inspections as described in interpretation 2.2 refer to short term studies but not critical phases within a study. Pathology peer review could be considered as critical phase and the frequency of inspection should therefore be defined in the QA programme. However, interpretation 2.2 will be extended to include this aspect.

Quality Assurance Statements:

- *For Lead QA: Should QA reviews of Study Plan Amendments be listed individually or can the phrase (e.g. All study plan amendments were also reviewed) be used?*

The verification of the study plan and its amendments can be listed individually or as a summary in the QA statement but it is not mandatory. The statement has only to specify the types of inspections including the phase(s) of the study inspected.

- *For Test Site QA: Can Test Site QA only list the amendments which pertained to their PI? Can they use the phrase «All study plan amendments pertaining to PI activities were reviewed»?*

The verification of the study plan and its amendments is in the responsibility of the lead QA.

The sentence can be added to the QA Statement of the test site QA; however it is not mandatory.

It is important to document that the relevant parts of the study plan or amendments (for the conduct of the phase at the test site) have been reviewed by the test site QA.

Computerized Systems

Use of SuisseID from Post or QuoVadis (a recognised system for adding a "fully qualified" electronic signature):

- *a) Is the use of the SuisseID system acceptable for GLP documentation if included as part of a validated computer system (e.g. Document Management System for*

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SOPs)?

- *b) Is the use of the SuisseID system acceptable for signature of Study Director and Test Facility Management on Study Plans, Study Reports (there would be no "wet ink" signature but the document would be printed for study records)?*

- *If acceptable, what level of validation would be required?*

a) The use of SuisseID is acceptable
- if it is covered by the validation of the system, and
- if the recommendations of SuisseID on computer security and handling of hardware and PIN are followed (http://www.suisseid.ch/).

b) Yes, this is acceptable. However, keep in mind that the study report will be sent to the sponsor and will finally be submitted to a registration authority. Therefore, we recommend to check with the sponsor whether a wet ink signature on a printed version is required or not. Any document with an electronic signature should be submitted and archived in electronic form, not as printout.

The validation should be focused on the overall performance of the computerized system where the SuisseID is used. It can be assumed that the device itself works correctly and in a secure way, since it has been developed in order to meet to national legislation:

http://www.seco.admin.ch/sas/00229/05092/index.html?lang=en

This register lists the bodies which are entitled to issue and administer qualified electronic certificates in accordance with the "Bundesgesetz vom 19. Dezember 2003 über die elektronische Signatur (ZertES, SR 943.03)", in accordance with the "Verordnung vom 3. Dezember 2004 über die elektronische Signatur (VZertES, SR 943.032)" and the "Technische und administrative Vorschriften des BAKOM vom 6. Dezember 2004 über Zertifizierungsdienste im Bereich der elektronischen Signatur (SR 943.032.1)".

Directory of the certified bodies conform to the Bundesgesetz über die elektronische Signatur (ZertES)

Do Swiss GLP Monitoring Authorities have any experience of inspections involving fully electronic Study Plan/Study Report production and approval?

- *If yes, what are the main challenges in setting up such a system?*

No, there was no inspection of a test facility where study plan and study report were only available in electronic form.

The system would have to comply with the requirements of OECD consensus document

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No.10 and can be established according the AGIT guidelines.

Test and Reference/Control Items

For reference materials we receive certificates of analysis (CoA) from our suppliers. These CoA are archived and are also uploaded in our LIMS system.

Do we have to put the CoA in every study dossier, whenever we use it for a study; or is it sufficient to only mention all the details (supplier, batch no., expiry date, etc.) in the study plan and the report?

According to the OGLP it is sufficient to mention the details regarding the characterization of a reference material (reference item) in the study plan and report. However a reference indicating where the CoA is kept should be documented with the study raw data (in a study folder).

For certain reference materials we do not get an expiry date or only a retest date in a maximum of 1 year for example. Sometimes there is no CoA. Since these materials are often stable for ages (such as 3,5-Dichlorophenol, atrazine, phenanthrene, phenol, etc.) we apply an expert judgment and define an expiry date.

- *Which requirements have to be fulfilled in this expert judgment?*
- *Who can make an expert judgment (the Study Director? Someone else?)*

If possible, the expiry date should be provided by the supplier of the material on a CoA or similar document. If it is necessary that the test facility defines the expiry date, the following requirements should be fulfilled:

- The decision should be scientifically justified, preferably by analysis.
- Storage conditions must be considered when defining the date.
- The expiry date should be defined by a qualified person of the test facility having experience with chemicals. The name of the person should be documented.

Study Plan

If validated Excel Spreadsheets (according AGIT Guideline) are used for calculations/ evaluations during a study, how do they need to be reflected in the study plan and in the report? Which details are needed?

The spreadsheet should be identified clearly in the study plan and in the report, e. g. with an individual name or number and version number or date.

The traceability to the validation documents of the spreadsheet and to any referring SOP must be ensured.

A French Test Facility informed us that for the French GLP Authority it is not necessary to

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incorporate phase related information into the study plan or study plan amendment. According to this information they regard the link to the phase as sufficient. For this reason, the test facility refused to add the phase description into the study plan, and issued a separate document which describes the phase, even after we informed them about the position of the Swiss GLP Authorities' Interpretation.

- *How can such a situation be handled by a test site, since the test facility and lead QA are the leading parties?*

We recommend to inform the test facility about the requirement as indicated in OGLP 8.2.e.5. The study plan should contain at least the following information:

> "Detailed information on the experimental design, including a description of the chronological procedure of the study, all methods, materials and conditions, type and frequency of analysis, measurements, observations and examinations to be performed, and statistical methods to be used (if any)."

According to this, the document describing the delegated phase ("phase plan") should be included into the study plan. If some of the requested information is missing at the time of experimental start, the information can be added to the study plan as study plan amendment.

In the case that is described above, the requirements of the French GLP authority have to be respected since the test facility is subjected to French GLP regulations. Therefore, this practice can be considered as compliant if the principal requirements are fulfilled:

- The test site should contribute to the content of the study plan and its amendments or the documents describing the phase that will be conducted
- Copies of the documents are available in the test site.
- The traceability from the study documents to the phase plan and in the opposite direction must be ensured.

Study Conduct

Facility Documentation:

Temperature is monitored in all incubation rooms and cupboards. The temperature data loggers are regularly checked with a certified thermometer and the temperatures are logged out and archived at regular intervals

- *Do we have to print out the temperatures and file in every study dossier or is it sufficient to store all the temperature data in the archive?*

The full records have to be archived. If temperature is a critical parameter for the study, the full records or a final assessment of the temperature during the study - including mean and max/ min values, impact of eventual deviations to specified values - must be performed and archived with the study raw data, together with an indication where the full records are archived.

Study Reporting

Two phases of one Study are placed to the same Test Site (i.e. histotechnique and pathology evaluation) They have separate Phase numbers (XXXXXXA and XXXXXXB) and Principal Investigators A and B respectively.

- *Is it acceptable to have a combined Phase Report XXXXXX describing the performance and results of both phases, with separate compliance statements from the PIs and with a QA statement reflecting both phases?*

In general, we do not recommend to split the responsibilities between two PIs for phases such as preparation of slides and pathology evaluation.

However, a PI can also deliver raw data, *i.e.* histopathology slides, of his phase including GLP and QA statements, instead of a phase report to the study director or to the pathology PI. In the latter the second PI will be responsible for the phase report including the contribution of the first PI. This should be described in the study plan.

A final report was finalized with the QA-Statement and GLP-Compliance Statement being issued on the same day (01 May 2013). In error however, the study director signed the GLP Compliance Statement with the date 01. June 2013. This mistake was only realized on May 2nd, 2013.

- *Is it permitted that the SD makes a handwritten correction on the original signature page to document this?*

As the report was finalised with the dated signature of the study director any correction should be done in form of an amendment to the final report.

Study Director Signature on the Final Report:
Some companies have all authors including the Study Director sign an Authors signature page, and have an additional signature by the SD on a compliance statement. The authors signature page is given to QA for their final report check.

- *Can the SD signature on the report and compliance statement be signed on different dates?*
- *Which date serves as the study completion date?*

The principles of GLP mention that the study director has to "sign and date the final report to indicate acceptance of responsibility for the validity of the data and to indicate the extent to which the study complies with these Principles of Good Laboratory Practice"

Only one dated signature is required. If the test facility decides to provide two signatures, which is accepted, both should be done on the same day.

Pathologist's Report Follow-up to Interpretation 2.15 of the GLP Principles:
The pathology report is based on the slides (raw data). The pathology report itself is defined as raw data after the finalization (Answer of the authorities to 8.16 of Swiss Interpretation of the GLP Principles).

- *What raw data do the authorities expect QA to use as the basis for their QA Audit?*
- *Is it sufficient to check against "pathologist interim notes as described in the Pathology Position Paper "Society of Toxicologic Pathology Position on Histopathology Data Collection and Audit Trail: Compliance with 21 CFR Parts 58 and 11"*

If understood correctly from Interpretations 2.15 and 8.16, the pathologists must finalize their pathology report so that it can be provided to QA for review.
Thus if there are discrepancies between the Pathology tables and the written summary (e.g. Reference to incorrect group names or incorrect numbers of animals with a given finding), then the Pathologists must amend their report.

- *Is this really the process that is intended?*

Pathology raw data are considered to be the original observations from slide evaluation. The notes taken by a pathologist during histopathological examination are the result of original observations, but are not necessary for the reconstruction and evaluation of the final report and therefore not considered raw data. The QA should therefore use the raw data mentioned above for their inspection. If a pathologist as a PI prepares a phase report, that report should comply with the same requirements that apply to the final study report. In case changes needed to be done in a signed phase report, this should be made by an amendment to report and audited by QA. (see also interpretation 9.2)

The last sentence in interpretation 8.16 should read: The signed report of the pathologist comprises the raw data. The interpretation will be revised accordingly.

Amended Final Report

Would the GLP monitoring authorities please provide the process flow for the following situations:

New experimental work to be performed within a finalized study:
The Sponsor of a study receives additional information regarding compound X, e.g. that compound X causes histopathological changes on organ Y. The Sponsor wishes to have finalized studies «reopened» to examine this more fully, using new staining procedures of slides of organ Y. Thus, histotechnique and pathology require additional work to be performed by Test facility staff and external PIs.

Please address the following specific points:

- *Acknowledgement that TFM is even aware that additional work is to be performed (impacts MSS, workload etc) if final report amendments only signed by the SD?*
- *Approval by TFM that sufficient qualified staff, facilities etc. are available to perform the work?*
- *How is the liaison between TFM and TSM assured?*
- *How is the information (the details) of what should be done communicated to all concerned (could/should this be documented in a Study plan amendment?) with distribution to internal staff, Lead QA, PI, TS-QA as was done for Study Plan)*
- *How should the Amendment to Final Report be documented in the Master schedule of the TF?*
- *Is a new compliance statement added only for the modifications, or does the SD compliance statement reflect the entire study?*
- *Can the QA statements of the amended report only reflect the changes with reference to the previous QA statement?*
- *Does the added work that was performed reset the clock regarding retention time for study materials?*

In general there should be procedures in place to ensure, that the TFM is informed about new activities to ensure appropriate staffing. Amendments to the final report can only be produced by the Study Director.
If a specific phase is concerned, the same requirements apply as for a multisite study with regard to the information loop and responsibilities.
An amendment to report should contain all relevant information to proceed with the experimental work (comparable to a study plan) and should be mentioned in the master schedule. The result of the additional work will be reported in another amendment to report. This amendment should contain a compliance statement of the SD and a QA statement, both applying to the additional work conducted and reported. The retention time of the material is consequently re-set. (see also interpretation 9.7)

If no new experimental work is performed, but information has come to light that changes the interpretation of the findings by the Study Director, then what is the process? Please note: In this scenario, no raw data has changed, only the Study Directors interpretation has changed due to additional information from other studies.

- *If an Amendment to the Final Report is written to reflect the new information, then is a new compliance statement and QA Statement necessary?*

If the interpretation of the findings has to be modified, the amendment to the final report should clearly specify which part of the report is replaced by the amendment. The reasons of change have to be given in the amendment.
According to consensus document no 4 "Quality assurance and GLP:

Any correction of or addition to a completed final report must be audited by QA. A revised or additional QA statement would then need to be provided.
The amendment to a final report should be done according to a GLP procedure. *See also interpretation 9.7*

SOPs

Signature of multilingual SOPs:
A Facility implements multilingual SOPs as a single document; for this reason, the SOP including the title page bearing the signatures was translated.

Is it sufficient to sign only on the first title page? This process is described in an SOP. The translated title pages have a comment included to this effect.

If the multilingual SOP is a single document it is sufficient to sign only the first title page.

In the study plan it is stated that all phase raw data and the final phase report of a study phase performed by a Test Site will be retained with the original study documents at the Test Facilities Archive. However, the Test facility is not required by their local GLP authority to maintain documents for 10 years (Netherlands)

- *We maintain copies of the phase raw data and final phase report at the Test Site for a minimum of 3 years. Is it sufficient for the Swiss authorities if these copies will be retained for 3 years in the case that these docs are no longer available at the TF (unknown final disposition (e.g. returned to Sponsor)) or should the Test Site keep the copies for ten years if the archiving period of the TF is shorter than 10 years?*

In this specific case, it is acceptable to maintain the copies 3 years only.