SPAQA GLP Monitoring Authority Roundtable 2017

General Questions

1. Information flow

Would it be possible for the GLP notification office to inform SPAQA (vorstand@spaqa.ch) of changes to the Swiss Monitoring Authorities website (e.g. new OECD guidelines, AGIT guidelines etc.) so that SPAQA can better inform its membership of these changes?

Yes, SPAQA will be included in the mailing list of the Notification Authority for Chemicals

Study Plan and Amendments

2. Study Plan: Title change

How should changes to the Study Plan title be actioned?

Is a deviation adequate for a minor change or must a Study Plan Amendment be produced? (For example, the SP title included a trade name that the sponsor requested to be removed; a typing error of no significance)

Changes to the study plan should be done by Amendment to the study plan. The study title should be the same on the study plan and on the final report.

3. Superseding Documents

In some Test Facilities it is their practice to amend the study plan with study plan amendments which supersede the previous document. e.g. study plan amendment No. 1 is reflecting the complete amendment (study plan?), including the changes and the reason for changing and supersedes the study plan; Amendment No. 2 is then created the same way and supersedes Amendment No.1.

GLP Principles leave it quite open how study plan amendments shall be handled, and traceability ensured.

However, in the case of pre-clinical multi-site studies, this practice is used as well, and by the fact that the last amendment is for the study director considered the "governing document", test sites and PIs allocated to the study after study initiation, receive only the last amendment, where they are announced as a test site.

According to OECD Document No. 13, the test sites should receive the study plan and all amendments thereof. This is not done with the practice creating superseding documents.

a) What is the position of the Swiss GLP Authorities concerning the issuance of amendments superseding the previous document?

Amendments including the complete information from the previous document(s) are acceptable, if:
- the document is identified as "Amendment No..."
- changes and reason for changes are clearly indicated

However, the original version of the study plan remains in force regarding the signatures and study initiation dates since an amendment is not required to be signed by the test facility management.

b) What is their position regarding multi-site studies, when only the last study plan amendment is provided to the test site, and the recommendation of OECD Document No.13 is not being followed?

In case of amendments superseding previous documents, the last amendment should contain all the previous information such as study initiation date. It can be considered as "the study plan and all amendments thereof" according to OECD document No. 13.

4. Timing and consequence of signatures on Study Plans and consequences for appointment of PIs

When is the official start date of a GLP study if the SD and TFM signatures are not on the same day? Since TFM management must appoint the SD, is the date of the last signature the governing date?

According to the OGLP the study plan should be approved by dated signature of the Study Director and approved by the test facility management. The study initiation date means the date the Study Director signs the study plan. Therefore, the date of the SD's signature would allow a study to be started.

According to OECD Doc. No. 8 management should maintain a policy document defining the procedures adopted for selection and appointment of Study Directors [...]. The OGLP requires the dated signature of the TFM, a policy document might not be necessary; however, in this case the TFM should sign the study plan before the study director.

What needs to be documented during the appointment of a PI? When and how must TSM document this appointment? Must TSM sign the Study Plan/Study Plan Amendment or is it sufficient to have a PI appointment sheet signed by TSM?

According to OECD Doc. Nr. 13 the appointment of Principal Investigators should be described in SOPs. There should be documented agreement that the Principal

Investigator will conduct the delegated phase in accordance with the study plan and the Principles of GLP. Signature of the study plan/study plan amendment by the Principal Investigator would constitute acceptable documentation. The TSM is not required to sign a study plan.

Please address the following scenarios

- Scenario 1: PI and TSM signatures before SD and TFM

  PI-Nomination: Signed by PI, Test Site QA und Test Site-Management: 4. August 2016

  Study Plan: Signed by Study Director and Lead QA: 21. September 2016; Signed by Test Facility Management: 27. September 2016.

  When has the PI officially been nominated and when can the PI officially perform GLP work? *Nomination: 4.8.16, start: 21.9.16*

  When did the study start? *21.9.16*

  When is the PI Phase initiation date? *21.9.16*

As indicated earlier, a study can start after the SD's approval of the study plan. Since the Principal Investigator acts on behalf of the Study Director for the delegated phase, this phase is considered to be part of study which is initiated after the SD's approval of the study plan.

- Scenario 2: PI and TSM signatures after SD and TFM
  In this case the PI and Test site are included in the Study plan signed by SD and TFM
  Study Plan: Signed by Study Director and TFM: 21. September 2016;
  PI-Acknowledgement: PI signed 30 October 2016; TSM signed on 3 November 2016

  When is the PI phase initiation date? *30.10.2016*

  Can the Study Director send samples to the PI prior to TSM signature date? *Yes, if the PI acknowledgement was already signed. The TSM is not required to sign the study plan/study plan amendments, however, SOPs for PI appointment should be considered.*

  Are PI activities prior to TSM signature date under GLP (e.g. making of study specific test standards or reagents)? *Yes, see above.*

- Scenario 3: Study Director has neglected/forgotten to write an amendment but has sent samples to an external colleague (PI) for assessment. The work is performed prior to any amendment being signed. If an amendment announcing the PI is then signed, can the work be considered to have been performed according to GLP?
  An amendment should be finalized before any GLP activities at the test site start. This phase should be excluded from the Statement of Compliance.

5. Computerized Systems

OECD 17

The Application of GLP Principles to Computerised Systems, OECD Advisory Document No. 17 became effective on 22 April 2016. This document includes a number of new requirements particularly concerning TFM and QA involvement in key CSV and post system release activities. Please could Swissmedic advise on their expectations regarding timing for implementation of these various new requirements?

The requirements are more detailed in OECD Doc. 17, but the level of responsibility did not change. The current procedures should be checked and revised if necessary in the normal cycle of SOP revisions.

How much time does the test facility have to comply with the requirements of newly issued OECD documents? What are the expectations from authorities? Could you please confirm that we do not have to comply with them retroactively?

The current procedures should be checked and revised if necessary in the normal cycle of SOP revisions.

In general new requirements should be applied in due time for new studies and for systems in use, but not retroactively. If a system had been validated and operated according AGIT guidelines before April 2016, no immediate or retroactive action is needed. However, computerised systems should be periodically reviewed to confirm that they remain in a validated state, are compliant with GLP and continue to meet stated performance criteria (e.g. reliability, responsiveness, capacity etc.).

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6. Electronic Record Archival

To ensure long term readability of electronic records (during the mandatory 10-year archiving period and beyond), is it acceptable to archive a flat file (e.g. PDF/PDFA for long term access/readability) and retain the original data capture file in its original format? This would facilitate long term preservation of the complete data set (including all associated metadata) as well as its presentation in human readable form. This approach would result in two sets of electronic records, potentially retained in 2 different systems (an e-archiving system and the original computerized system).

Yes, this procedure is acceptable. The transfer (conversion or "printing") of the original file to the PDF/PDFA copy needs to be validated, and the way of dual archiving should be described in an SOP.

What are Swissmedic expectations regarding maintaining readability of electronic analytical raw data in the event that a software vendor ceases business or a software application is taken out of use? Of particular interest is a situation where even if the software application is retained, the operating system on which it runs will eventually become un-usable. Even if original data capture files are extracted from the original computerised system and transferred to a dedicated e-archiving system, they can be retained unchanged but they are of no practical use without the application and applicable operating system.

There are technical solutions if the application software and the operating system should be preserved in a functional state (e.g. emulation of older OS versions or archiving a system with hard- and software). However, it is not required that applications must be functional during the archiving period as long as raw data are preserved in a human readable form (comparable to a print of acquired raw data and the metadata of the acquisition). OECD Doc. 17 says in para. 117 "Consideration may have to be given to archiving electronic data in an open format that is independent from proprietary file format e.g. from an instrument manufacturer."

7. Use of Microsoft Office

What records are expected for GLP compliance when office PC software is updated (e.g. Windows upgrade; change of Microsoft Office version used for preparation of study plans, study reports etc.)?

Office PCs that are used as text processors are not considered as computerized systems as long as they only are used to produce text documents that are printed and signed. No records on updates are expected.

If "office" PCs are used to capture or process raw data, or if the text documents are valid in their electronic version, the PCs and software are considered to be

computerized systems. In this case, the functions used should be validated and the software update should be handled according change management procedures. (see "Guidelines for change management and risk assessment of validated computerized systems in a GLP environment, AGIT, 2012")

What documentation is necessary if Microsoft Office is being used in spreadsheets? Can one use historical data run with the new system to show that no revalidation is necessary?

Spreadsheets need to be validated. A software update is a change to a validated system and should be handled according change management procedures. A risk assessment should be performed as basis for the re-validation to determine the necessary extent of testing. (see "Guidelines for change management and risk assessment of validated computerized systems in a GLP environment, AGIT, 2012")

8. Pathology Data

Based on the expectations of OECD Advisory Documents no. 16 and 17
a) at which time point should the electronic audit trail be activated during the collection of histopathology findings?
b) depending on answer to a) above, how will changes during peer review be tracked?
c) exactly which records are considered to be the pathologists "notes" and which records are supporting GLP relevant raw data/records?

Ad a.) The audit trail should be activated once the pathologist signs the report.

Ad b.) According to OECD No. 16 in most cases where there are no significant differences of opinion it will not be necessary to report in detail the outcome of the peer review in the pathology report or the final report. A simple statement that it was conducted and that the pathology report presents the agreed findings would usually suffice. Procedures should be in place in case of diverging opinions.

Ad c.) According to interpretation 8.16 the pathologist's interim notes, therefore, which are subject to frequent changes as the pathologist refines the diagnosis, are not raw data because they do not contribute to study reconstruction. Accordingly, only the signed and dated final report of the pathologist comprises raw data with respect to the histopathological evaluation of tissue specimens. Raw data are defined in the OGLP as all original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study. Pathology raw data should be handled in the same way as other raw data. The signed report of the pathologist comprises the raw data.

Based on the expectations of OECD Advisory Documents no. 16 (sections 2.9-2.10), at which time point should the peer review statement be signed?

The statement should be signed after the conduct of the peer review. In case of diverging opinions and the need for panel of experts, this information should be provided additionally.

9. QA Activities

Based on OECD Advisory Document no. 17 (section 1.3.3), could Swissmedic advise on their expectations regarding QA responsibilities during inspection of studies where data are held within a computerized system. What QA actions are expected in relation to scope and level of detail when reviewing the audit trail, data analysis, used techniques and results for a specific study? For example, should QA verify content of the audit trail at each inspection activity such as study-based inspection, data/report audit and prior to report signature etc.?

During study-based inspections the QA should have direct read-only access to the data which should also include information in the audit trail – this scenario is comparable to inspection of raw data on paper including corrections. This is also relevant for the inspection of the study report and should be in-line with the in house SOPs (e.g. 10 % raw data check).

Is it acceptable that inspection reports for short term studies of the same study type with the same SD, which were run at the same time, are combined in one QA inspection report? The archival of the QA documentation is separate for each study; copies are annotated with the location of the original documentation.

Assuming that each individual study was inspected to be reported in the QA statement, this is acceptable. Otherwise process –based inspections could be considered.

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10. Study Reporting

What are the expectations of the GLP monitoring authorities with respect to the writing of final reports when a GLP study is stopped after the signature of the Study Plan?

- In the case that no raw data has been collected?
- In the case that raw data has been collected?

According to interpretation 8.6, a written confirmation of the study's termination must be generated as a Study Plan amendment. The reason for the termination must be given therein. The study plan, amendment and all study documentation/materials should be archived. Therefore, no final report is expected.

In case a final report is expected, can the data only be summarized without QA statement or GLP statement of compliance?

n.a.

11. Timelines for finalization of Study Reports

A sponsor has a complex internal report review procedure and states that study reports should only be signed by the Study Director when this process is complete, but the timeline could be as long as 1 year. The GLP regulations do not specify that reporting timelines are included in the study plan therefore the sponsor sees no reason to clearly define the reporting arrangements. Can Swissmedic clarify their expectations?

According to interpretation 9.3, the time span for receiving the sponsor comments should not exceed six (6) months. Raw data should be stored in a safe place during this time. If the draft report is still with the sponsor after that time, the SD should contact the sponsor and ask for the commented draft report. In case of no answer within two weeks the study should be archived without finalisation. If the sponsor sends the commented draft report at a later date, the study needs to be taken out from the archive.

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12. Study Director Compliance Statement

PI Test Sites may never have been inspected by their local GLP national monitoring authority (e.g. FDA or new to a GLP compliance program).

Does this need to be explicitly stated in the Study Director's Statement of Compliance? (e.g. XYZ test site has not yet been inspected by their GLP monitoring authority but claims compliance to national GLP regulations).

The following answer only applies to countries in the OECD MAD framework.

The claim of GLP compliance is regulated on a national level. If the national legal framework allows a claim without prior inspection the test site must not be excluded from the Study Director's statement; however, the study director should describe the situation. Assessors should be aware of this potential gap and have the right to initiate study audits to verify the claim.

Caveat: Currently under discussion within the EU.

13. Test Item Archival

Could you please confirm that we don't need to archive a test or reference item that is not stable anymore at the time of the archiving of the study? If yes, where would you expect to see the justification that the items are not archived?

Samples of test and reference items and specimens should be retained only as long as the quality of the preparation permits evaluation. When samples of test and reference items and specimens are disposed of before the expiry of the required retention period for any reason, this should be justified and documented e.g. in the test item management documentation or raw data. (OGLP)