SPAQA Regulatory Round Table
01 November 2011, Basel, CH

Questions

Open questions from previous Roundtables

Please provide the current status of the OECD working group activities of the Peer Review Paper originally created by the MHRA.

Due to a significant number of comments on the original draft of the peer review guidance document, it was decided that the OECD drafting group would produce a second version of the paper which would aim to take into account the feed back received. This second draft will be discussed at the 2012 OECD GLP Working Group meeting.

Organization and Personnel

In-house GLP studies were performed by Company A to support the non-clinical safety of Compound X. Company A sells Compound X to Company B. All studies/results become the legal property of Company B.

- What records must Company A retain to show to the GLP Monitoring Authorities if any?

Company A should retain a list of the studies and eventually other documents transferred from his GLP archive to another GLP archive (it is assumed company B has a GLP archive). The list should also contain the reason of the transfer and be signed by the archivist of the new archive, to acknowledge the receipt of the documents. Final reports of transferred studies should be amended to document new archiving location. This can be done for each study or as a comprehensive amendment. If it is done as comprehensive amendment, a copy should be sent to the monitoring authorities to document the transfer.

- What is the retention time of the documents which must be retained by Company A?

As long as the documents are expected to be archived (10 years after completion of the study)

- Must Company A make copies of non-study documentation (e.g. personnel records and equipment/facility records) to provide to company B?

As long as the company A maintains a GLP archive, it is not mandatory to make copies of non-study documentation for company B.

Organization and Personnel

Are there restrictions on the Head of the Test Facility (Prüfeinrichtungsleiter (PEL)) with respect to his/her position within the management of a company (e.g., analog to GMP guidelines)?

The test facility manager should ensure that the test facility operates in compliance with GLP. It should ensure that a sufficient number of qualified personnel, appropriate equipments and materials are available. This requirement does not define a specific position within the management of the company; however the test facility manager should have enough competence to discuss the budget of the test facility and to assume his responsibilities (nomination of study director, etc.).

After closing a number of areas within our test facility, only 5% of the Phase work we will perform in the future will be GLP-relevant. The vast majority of the remaining work is exploratory analyses, research, GMP analytics, or non-GLP study related activities. Test Facility Management will prioritize work to ensure that the GLP phases have priority over non-GLP work.

Is it sufficient to include only the "GLP Phases" in the Master Schedule sheet (as is done in the US)?

As answered in previous SPAQA round tables (2004, 2006), the authorities recommend to include all studies, in order to estimate the total workload of the test facility (GLP ordinance Appendix 1, section 1.8).

However if only a low percentage (e.g., 5 %) of GLP vs. non GLP studies is performed, a master schedule only for GLP studies (or in case of multi-site studies: study phases) and validation studies performed according to GLP should be established.

Quality Assurance

In a GLP certified facility, is it acceptable to have consultant QA auditors conduct all the facility and study audits?

Yes, test facility management has to ensure that there is a QA Program with designated personnel in place. There is no requirement that these QA personnel must be internally(Appendix 2, Section 1.1.f).

- In this case should the Head of Facility QA (the person doing the outsourcing) be the responsible person named or registered with the regulatory agency as responsible for the QA program or should it be the Consultant?

  The Test facility Management is responsible for the QA program. The responsibilities for QA need to be defined in the QA program and reflected

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in the contract between the Test facility and the Consultant. The situation has to be shown in the organization chart.

- When a group of consultant auditors conducted study audits during the study phases, can the QA manager who was not involved in the audits sign the QA Statement?

  The OGLPV does not define who from the QA team has to sign the QA Statement (OGLPV Appendix 2, section 2.2.f), therefore the QA manager can sign the QA Statement on behalf of the auditors.

What type of updates must a GLP certified facility communicate to Swissmedic or a Health Authority?

Any update needs to be sent to the notification authority, not to Swissmedic. The obligation regarding information about any changes at the GLP test facility to the notification authority are specified in the OGLP, Art. 12.

Art. 12 Obligation to notify

[1]An establishment must immediately notify the notification authority if:
a. it modifies its name or address;
b. one of its test facilities modifies its name or address;
c. one of its test facilities is no longer willing to comply with GLP principles.
d. there are changes in responsibilities at the level of the management of the test facility or of the quality assurance unit.
e. it intends to extend the area of study

When there is a change of QA responsible person, it is necessary to inform the GLP Monitoring authorities or Health Authorities of this change?

Yes, the notification authority has to be informed.

During a recent GLP Monitoring authority inspection, the GLP Monitoring authorities cited QA for including the check of equipment records within a QA statement. These checks were performed however as part of a study-based inspection and were reported to the SD and TFM.

- Where in the GLP ordinance is it defined which activities may be performed/reported as study-based?

  The content of the QA Statement is clearly defined in OGLP Appendix 2, sections 2.2.f and 9.2.d.
  The check of equipment is not considered to be a "study phase", and should therefore be handled as "facility based" inspection.

Quality Assurance

OECD Consensus Document No 4:

-Study-based inspections: These are scheduled according to the chronology of a given study, usually by first identifying the critical phases of the study.

- Facility-based inspections: These are not based upon specific studies, but cover the general facilities and activities within a laboratory (installations, support services, computer system, training, environmental monitoring, maintenance, calibration, etc.).

In our test site, we provide the original of our inspection report to the PI. A summary of the report findings is given simultaneously to the SD, Lead QA, Test Site Management and Test Facility Management. The PI- commented report is then forwarded to Test Site Management for approval. This procedure was criticized by the GLP Monitoring authorities that the original signed report was not provided simultaneously to all parties.

- Where is this required in the GLP ordinance?

  OGLP Appendix 2, sections 2.2.e:

  promptly report any inspection results in writing to management and to the Study Director, and to the Principal Investigator(s) and the respective management, when applicable

  →The procedure described above is compliant to the requirements if the summary contains all findings and if it is reported promptly.

Is there a prescribed text to be used in a QA statement?

If yes, Where is this text published?

According to the OGLP Appendix 2, sections 2.2.f and 9.2.d. as well as in the OECD Consensus Document No 4, the "QA statement would also serve to confirm that the final report reflects raw data…."

Therefore, the QA Statement should include a sentence like:

"This statement also confirms that this final report reflects the raw data."

Must the QA inspection of **draft Phase** reports be communicated to the SD, Lead QA, and TFM or just to the PI/TSM?

According to OGLP "Appendix 2, sections 2.2.e" all inspection results need promptly to be reported to the Study Director, and to the Principal

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Investigator(s) and the respective management, when applicable;

This corresponds to OECD document No. 13 section "responsibilities of test site QA".

Is it possible to consolidate process-based inspections by grouping similar study types together in the inspection programme? (e.g Test Item Formulation for Fish Tox and Fish ELS study types).

Process based inspections refer to a given study type and should not be further combined with other type of studies. However, experiences from inspection of other study types may influence the selection of critical phases that have to be inspected.

Computerized Systems

At present the quality and reliability of standalone computerized systems which are available on the market is very high. The situation has improved tremendously since CSV guidelines were first released. Only vendors known for high quality products achieve sales figures which are good enough to allow them to stay in the market. The vendor has a quality management system in place and computerised systems are being validated by the vendor before release to the market. Documented IQ, OQ and PQ procedures are standard upon installation at the customer site.

In view of this changed situation, which arguments hinder us from handling standalone computerised systems (e.g. photometers, LC, GC or even LC/MS/MS) like systems of the category "simple" in the future?

Background information: Answer from SPAQA 2006

> *IQ und OQ kann vom Hersteller vor Ort durchgeführt werden, muss jedoch mit einem Bericht bestätigt sein. PQ muss vom Benutzer ggfs unter Mitwirkung des Lieferanten mit dem Gerät vor Ort durchgeführt werden. Dabei sind die Akzeptanzkriterien so zu wählen, dass die kritischen Randbedingungen der in der Prüfeinrichtung durchzuführenden Prüfungen getestet werden. Formulare des Herstellers können verwendet werden, sofern sie die Bedürfnisse der Prüfeinrichtung entsprechen. Die Durchführung kann durch den Hersteller oder/ und Mitarbeiter der Prüfeinrichtung erfolgen. Die Verantwortung für den Validierungsplan, die Durchführung und den Validierungsbericht ist jedoch durch einen Validierungsleiter der Prüfeinrichtung zu übernehmen. Der Prüfeinrichtungsleiter ist für die Validierung der Geräte bzw. des computerisierten Systems verantwortlich.*

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Answer 2011: Whether a computerized system is categorized as "complex" or "simple" does not depend on whether the validation has been delegated to the vendor.

The test facility manager is responsible that the system has been validated before he releases it for GLP studies. From then on, he is responsible that the system remains in a validated status. Therefore, regular function checks and the principles of change management should be applied.

E-Forms: An e-Form (electronic raw data) is completed and approved by more than one individual. Later an editorial correction is required and performed. An editorial correction being e.g. typo or obvious mistake but nothing changing the meaning of the data. Is an additional subsequent approval (by all individuals) necessary or is the entry in the audit trail sufficient?

During the conduct of the study, the entry in the audit trail is sufficient. The situation is comparable to a correction on paper raw data, with justification, date and signature. After the completion of the study, such a change should not be possible anymore.

How should one deal with an Online IT-Service tool for incident management (including account management) for GLP Computerized systems (Server based, global system)?

Does the tool need to be tested to show that it is "fit for purpose", controlled access, etc.) or are only the incident management and account management processes themselves considered to be GLP relevant?

One has to decide whether the system is GLP relevant. See AGIT GUIDELINES FOR THE VALIDATION OF COMPUTERISED SYSTEMS, 14. Dec. 2007, p.5:

The following questions may guide the decision process:

- Will the system be used to produce, process, or maintain data that are intended to be used in regulatory submissions?
- Will the system be involved in the environmental control processes (e.g. temperature, humidity, light) of test systems, test items or specimens used in GLP studies?
- Is the system part of a process liable to inspections by GLP monitoring authorities (e.g. electronic document management system for SOPs or training records)?
- If the answer to any of these questions is yes, the system is GLP relevant

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and should be validated.

According to the description above, incident management and account management might be part of a GLP process that might be inspected. If this is the case, the system should be validated.

The Computerized System is accessed through Internet explorer (Intranet) but running on central Oracle server. Does an installation of security patches, active-X elements, Microsoft service patches on the server and/or the accessed workstation require change controls?

This has to be evaluated based on the nature of the computerized system and its way of interaction with the operating system and the browser software. The basic question is whether these patches and functions are a part of the computerized system or not.

If the additional patches and functions are used during the operation of the computerized system, or if they may influence the operation or the data of the computerized system as specified in the user requirements, they are a part of the computerized system, and change control is required. After any new installation of such elements, the function of the system has to be tested. The automatic installation of such items should be avoided.

Whilst AGIT clearly defines the role of validation director there is no reference to an overall system owner as GAMP 5 does. Do the Swiss authorities recommend/recognize other guidance regarding CS such as GAMP and the DIA publications (Red Apple and Peach)?

The role of the system owner has been defined in AGIT GUIDELINES FOR THE VALIDATION OF COMPUTERISED SYSTEMS, 14. Dec. 2007, p.9: The system owner, if designated by the test facility management, is responsible for ensuring that the computerised system is operated and maintained according to the principles of GLP and maintained in a validated state.

The Swiss authorities recognize other guidance as long as the implementation is compliant with the GLP requirements. The relevant documents are the Swiss Ordinance on GLP, then the OECD consensus and advisory documents, and then the AGIT guidelines.

Are Swiss GLP authorities aware of plans by any organization to issue compliance guidance regarding the use of cloud computing in the GXP environment?

What are Swiss GLP authorities current recommendations regarding this subject?

Computerized Systems

The Swiss GLP authorities have started to discuss the topic within AGIT. A future recommendation – if any – will base on the outcome of this project.

Generally, the critical issues in OECD consensus documents 10 and 15 should be addressed.

Although AGIT recommends executing a validation project in the same way as a GLP study and there are numerous advantages for using this comparison, when documents require revising or amending for any reason, producing an amendment with solely the changes is not as effective as producing an updated version of the complete document especially regarding the impact of this to the traceability matrix and ease of reading by system owner and users. What would be the opinion of Swiss authorities regarding this dilemma?

The recommendation to conduct the validation in analogy to a GLP study was focused on the initial validation. After the system release, changes such as modifications or repairs will lead to complete or partial validation activites that have to be documented.

- These additional documents could be added as amendments (incremental), or
- the complete validation document could be revised, or
- replaced by a new validation study.

The chosen policy should be described in a SOP, and allow the traceability of requirements, changes, tests, results and decisions.

If new versions of documents are created, it has to be clear which versions are valid.

(Eudra Lex) GMP Annex 11 was recently revised and clearly states that IT infrastructure should be qualified. What is the position of the Swiss Authorities regarding this topic?

Out of scope for GLP monitoring unit

OECD Consensus Document Nr. 10:

All computerized systems used for the generation, measurement or assessment of data intended for regulatory submission should be developed, validated, operated and maintained in ways which are compliant with the GLP principles.

The GLP principles require that a test facility has appropriately qualified and experienced personnel and that there are documented training programmes including both on-the-job training and where appropriate, attendance of

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external training courses. Records of all such training should be maintained. These provisions should also apply for all personnel involved with computerized systems.

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a.) What validation activities would Swissmedic expect to see for the introduction of a Digital Signature system for approval of SOPs, Study Plans, CVs, Training Records and other GLP documents?
The package identified is a Commercial Off the Shelf (COTS) product that can either be installed on individual PCs or on a server (in-house or outsourced) and claims to meet e-signature regulatory requirements (e.g. FDA; Sarbanes Oxley).
b.) What other regulatory issues should be considered (e.g. if there is no final printed document)?

Ad a.)
The electronic signature system is part of a process liable to inspections by GLP monitoring authorities, since the documented approval of SOPs, study plans, CVs etc. is a relevant element in GLP.

IQ and/or OQ can be performed and documented by the vendor using his own protocols, procedures and tests. In this case the validation plan refers to these two phases and should be issued and approved prior to starting the PQ. During PQ it should be demonstrated that a computerized system is suitable for its intended purpose in the user's environment as defined in the user requirement specifications. However, the complete validation documentation should be available.

Ad b.) GLP relevant issues:

- Access to documents for the inspectors during GLP inspection must be guaranteed.
- Associated documents e.g. SOPs have to be modified.
- Adequate management of electronic documents should be provided. (see AGIT publications)

Test and Reference/Control Items

Can GLP/GCP compliance be claimed if the device/product has a certificate of Analysis and Qualified Person release (for research purposes only), however the device/product is not fully GMP compliant?

GCP compliance is out of scope

GLP principles require a characterization of the test item. It is not specified whether the characterization should be done under a quality management system. However, it is recommended to perform the characterization according to an established quality management system, and to document the quality system that had been used.

Study Plan

Is it possible to use General Study Plans in conjunction with Study Specific Supplements for studies that are significantly longer than 1 month in duration but that are routine in nature and frequently conducted?

If not, What is considered reasonable as the cut-off point?

If yes, Would such procedures be accepted by other regulatory agencies?

A general study plan and study specific supplement can be used for the conduct of short term studies. Short term study is only defined as "study of short duration, with widely used routine technique", however the OECD consensus document no 7 gives some general aspects to be considered (duration of critical phase, frequency of the studies, complexity of the test system, ..). Generally speaking "one working week, in the same test facility" is a reasonable cut-off point.

An OECD regulatory agency has the possibility to request by the Swiss GLP monitoring authorities the conduct of a study audit, if it has reasons to think that the GLP principles were not respected for that study or if the results of the study are very important for the assessment of the test item. The use of a general study plan in conjunction with a study specific supplement - as far as both documents contain all required information to conduct the study - is certainly not a reason to doubt about the GLP compliance of the study.

Study Conduct

Please define „Pathology raw data". If pathology raw data includes the interpretations of the study pathologist that are found in the Pathology report, when does this „pathology raw data" become final?

(Background information: As per the FDA interpretation given in the Preamble, 58.3(k) defines raw data as laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities and are necessary for the reconstruction and evaluation of the final report. Although the notes taken by a pathologist during histopathological examination of slides are indeed the result of original observations, these notes are not necessary for the reconstruction and evaluation of the final report. The final report is evaluated by an analysis of the pathology syndrome as described in the pathologist's report, which is required under § 58.185(a)(12). Further, because § 58.190(a) requires histopathological blocks, tissues, and slides to be retained as specimens, the final report can be reconstructed by verification of the pathology findings by, e.g., a second pathologist or by a team of pathologists.

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 respecting 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 like other raw data. The signed report of the pathologist are the raw data.

Study Reporting

How does QA review a „draft Pathology" report against raw data if the data themselves are not finalized? (Many companies use e-data capture systems to record histopathology findings. These findings are not audit trailed until the report has been finalized).

A pathology report should be based on raw data, allowing a QA check. Electronic systems should always allow an audit trail, if they are used for raw data.

Would a Peer Review statement need to be signed after the Study Pathologist has signed his report? i.e. that the Peer reviewer shows agreement after the report and data of the Pathologist are finalized?

A peer review can result in changes of the study results, therefore a transparent process has to be implemented. It should already be mentioned in the study plan (see 8.2 Content of study plan; e 5) and the final study report; a signed peer review statement should be available in the pathology raw data.

Must all deviations which occurred during the course of a study (both Study plan and SOP deviations) be reflected in the Final Study Report or is it permissible for the SD to "only" include those deviations in the report which he/she feels may have impacted on the integrity of the study? If this were a Phase report, does the PI choose what goes into the report?

All deviations from study plan and from study related SOPs (OGLP Appendix 2, section 7.3.1) have to be documented in the raw data; however the study director has to mention them in the final (phase) report, including the evaluation of the possible impacts on the results.

OECD

OECD Documents: A number of OECD Documents were issued before the effective date of the current version of document No.1 (OECD Principles on Good Laboratory Practice; ENV/MC/CHEM(98)17).

- Is there any intention that these documents will be revised in the nearer future (specifically document no.10)?

  At the moment there is no intention to revise any of the OECD Consensus or Advisory documents. However, this should be necessary in future.

- Can the Swiss GLP Authorities or even organizations like SPAQA, and industrial parties take any influence on the revision of OECD Documents?

  The Swiss GLP authorities can propose revisions to the OECD Working Group of GLP. In addition, a new discussion forum will be created on OECD level between industry organisations and the Working Group. Switzerland will be represented by SPAQA. The OECD Discussion Group will focus on the harmonisation of GLP standards across the OECD GLP community and address the suitability of current GLP requirements for emerging technologies.

Despite being adherents to the OECD MAD some authorities (e.g Thailand) are still requesting letters of certification for GLP studies to indicate they were conducted at GLP test facilities, these letters contain information already present in study reports. Are the relevant authorities (e.g. Thailand DOA) not obliged to accept GLP reports from OECD MAD adherent states without the need for these? Is any follow up being made with such authorities (e.g. Thailand DOA) to ensure these obligations are met?

Countries that are provisional adherents to the Mutual Acceptance of Data system should accept GLP reports from MAD adherent states. If there are any special request from a provisional adherent country, please inform the Swiss GLP authorities about the case.

Thailand joined the Council Decisions on Mutual Acceptance of Data in the Assessment of Chemicals. The period of provisional adherence, during which time Thailand will accept data from OECD member countries and other adhering

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economies while it establishes its GLP compliance monitoring programme, began in July, 2010.

EMA

Bioanalytical method validation – bioanalytical analysis:
According to the EMA guideline on bioanalytical method validation, section 3 "Legal basis", method validations for non-clinical GLP studies should be carried out according to GLP; method validations for the analysis of clinical trials in humans should be performed according to GCP regulations.

- What is Swissmedic's opinion on this guideline? How far is it valid for Switzerland or does Swissmedic have their own expectations on this topic?

The EMA guidelines are not considered binding for GLP test facilities in Switzerland. However, it is recommended to comply to this guideline, since EMA guidelines in general are considered "state of the art" by the Swiss receiving authority (Swissmedic).

Most of the GLP test facilities conducting bioanalytical sample analysis, carry out bioanalysis for non-clinical, as well as for clinical study samples. Currently it is accepted to conduct both types of method validation (non-clinical and clinical) according to GLP. With the decision by EMA, laboratories are in the dilemma of having to "serve" two standards.

Questions that arise due to the the EMA guideline:

- What is Swissmedic's opinion on this guideline?

→ It is up to the test facility to decide whether analysis of human plasma samples should be conducted under GLP. If yes, the associated guidelines etc. for GLP should also be applied to human plasma samples. However, since GLP only applies to non-clinical studies, at least two to three animal studies have to be conducted to receive a GLP certificate.

- How far is it valid for Switzerland or does Swissmedic have their own expectations on this topic?

→ currently under discussion within Swissmedic

- Will it become necessary to claim GCP compliance to be able to conduct further analysis for both sample matrices (e.g. human/animal sera), and what would the prerequisites be to do so (in a GLP lab)?

→ currently under discussion within Swissmedic

GLP /GxP related

In US GLP, FDA requires study monitoring (audit) of GLP studies by QA unit, whereas in GCP, study monitoring (QC) is performed by non-QA person (study monitor)? Why are the terminologies different?

According to the Swiss Ordinance on GLP, QA verifies the study plan and performs inspections. The study monitor is defined as a sponsor representative monitoring a study.