SPAQA Regulatory Round Table
November 17 2010, Basel, CH

Questions

Open questions from previous Roundtables

Q: Swiss GLPMA definition of short-term studies with respect to duration: Still pending from last round table in 2009.

A: As already mentioned in 2009, consensus could not be reached in OECD on a precise definition of short-term studies. According to GLP consensus doc. no 7, criteria to consider a study a short-term study include "the duration of critical phases, the frequency with which such studies are conducted and the complexity of the test system as well as the routine of the personnel involved, which will increase with growing frequency of study".

The Swiss GLPMA defined the frequency, in relation to process-based inspections, as a minimum of 10 studies of the same type per year. Duration should be considered together with the complexity of the critical phases (e.g. multi-site, handling), so that a precise answer with respect to the duration can not be given.

Generally speaking we can consider the "one working week (in the same test facility)" as a reasonable limit.

Consequence:

- - A 28 days sub-acute toxicity study is not a short-term study
- - A residue study is not a short-term study

Q: Pathology peer review: status within the OECD GLP Panel on commenting the UK paper and deadlines.

A: OECD-WG panel with participation of F, JP, US/EPA/FDA, SP, CH, and E (lead)

Status:

- Draft paper by panel established, and feedback from large organisations and societies received (eg. the European Society of Toxicologic Pathology (ESTP)
- 2nd consultation round, if needed
- next version to be established by January 2011.
- Submission to the GLP Working Group Secretariat in February 2011
- Presentation and discussion at GLP Working Group Meeting in May, 2011 (Paris, France)

Organization and Personnel

Q: When laboratories of a GLP Test Facility are also used by personnel from a different, non-GLP compliant company, what is the expectation of the authorities to demonstrate that compliance of the Test Facility is not compromised? Is it sufficient to have documentation (e.g. Job description, CV) and a training record to demonstrate relevant training (GLP awareness and use of GLP equipment)?

A: When laboratories of a GLP Test Facility are also used by personnel from a different, non-GLP compliant company or laboratory, their training records should be available, as documentation that they have the knowledge of the applicable requirements of GLP.
Furthermore any measurement on a GLP apparatus should be documented with date/time and visa. The operation and documentation should be performed according the SOP used for GLP work. Any problem or maintenance operation with the apparatus should be recorded. Obviously, the results of the measurements by non-GLP personnel may not be used for GLP studies.

Quality Assurance

Q: GLP Interpretations (SPAQA 1996): Abstracted and translated from the BAG Webpage : (http://www.bag.admin.ch/themen/chemikalien/00253/00539/04399/index.html?lang=de)

How often must a short term study be conducted before it can be inspected with process-based inspections?

Absolute numbers can not be given. The type of inspection (study-based or process-based) is not only dependent on the numbers of studies per week/month/year but rather from the complexity and the duration of the individual studies. As soon as the complexity of a study, even if it is only for a few hours, is high and at the same time the frequency it is conducted is small, then it can no longer be considered a routine activity, and should also be inspected with study-based inspections.

The Swiss GLP monitoring authorities agree that a process-based inspection program within a Test facility should have the following minimum frequencies of Study-based inspections:

1 - 10 Studies/year 100% study-based inspections
11 - 50 Studies/year min. 20% study-based inspections
more than 50 Studies/year min. 10% study-based inspections

A) Could you please clarify whether this means one and the same activity has to be inspected and documented as a process-based inspection and a study based inspection or whether these are two independent inspections?

In case a process based inspection program will be based on the above mentioned Swissmedic GLP interpretation, it is ambiguous why process based inspections have to be additionally documented as study based inspections

If it is not the case (but rather, in addition to the process based inspections the study based inspections have to be performed) shouldn't the critical phases for study based inspections be planned in advance based on the content of the reviewed study plan?

Answer A)

Accordingly to the frequency mentioned above, short term studies have to be inspected during their experimental phase (study based inspection). The studies conducted in-between will not be inspected, they are considered to have been process-based inspected, as a consequence of the study based inspection.

The QA statement of the (study based) inspected study will mention "study based inspection" with the indication of the inspected phase. This inspection date will be used for the QA statement of the next X studies (of the same study type) with the indication "process based study" and the indication of the inspected phase.

For this purpose, the critical phases of the different short term studies should be defined in advance and the QA should make sure that all critical phases are inspected on a regular interval. QA should also maintain documentation showing that the frequency of inspection is respected.

B) Could you please explain the background for this approach?

Answer B)

Please refer to Consensus Document No 7 "

II.2.2.1. [NOTE]: Because of the high frequency and routine nature of some standard short-term studies, it is recognised in the OECD Consensus Document on Quality Assurance and GLP that each study need not be inspected individually by Quality Assurance during the experimental phase of the study. In these circumstances, a process-based inspection programme may cover each study type. The frequency of such inspections should be specified in approved Quality Assurance Standard Operating Procedures, taking into account the numbers, frequency and/or complexity of the studies being conducted in the facility. The frequency of inspections should be specified in the relevant QA Standard Operating Procedures, and there should be SOPs to ensure that all such processes are inspected on regular basis.

C) Are you planning to revise the GLP interpretations from1996?

Answer C)

The interpretations are regularly up-dated and completed. However we think there is no need to review our interpretation concerning the frequency of inspection regarding short term studies.

Computerized Systems

Q: Computer Systems Validation: In the AGIT Guidelines, validation responsibilities are defined for System Owner, Validation Director, Personnel and Management. In a small company, there may not be enough appropriate staff to allocate separate roles.

Can (for example) the System Owner also be Management and Validation Director? If not, which roles can be combined and which must remain as independent functions?

A: The roles of Management, Validation Director and Quality Assurance should be separated under all circumstances. This follows from the view of a validation as being analogous to a GLP study. Other functions can help to allocate responsibilities to suited persons, but they are not mandatory.

It is e.g. possible that the test facility manager is the system owner (no delegation of this function). However, if the validation director is the system owner, there should be no delegation of functions from the Management to the System owner.

See AGIT-paper: Good Laboratory Practice (GLP)–Guidelines for the Validation of Computerised Systems; Esch et al.,Qual Assur J 2007; 11, 208–220

Q: Data validation in Excel spreadsheets is not foolproof and can be circumvented by pasting data into the cells. Will the validation be mandatory for GLP study related activities only or for all GxP and non-GxP?

A: If a Test facility considers Excel spreadsheets not to be secure enough for the intended purpose, they should not use this program. There are ways to circumvent some security measures, but it is possible to reach an acceptable level of security, depending on the purpose and on the efforts.

Under GLP, the validation of any computerized system is required.

See Swiss Ordinance on GLP and OECD Consensus Doc. 10. "The Application of the Principles of GLP to Computerised Systems".

Standard Operating Procedures

Q: What are the authorities expectations regarding attachments to SOPs used for documentation, e.g. forms, regarding the traceability to the "source" SOP, versioning and content of information?

A: Expectations are that the respective version number of the "source SOP" can be readily traced back from the attachments.

Hence, the attachment requires to be

- Identified with the SOP name and version number
- Archived with the respective version o the "source" SOP

The process requires to be described in a SOP.

Alternatively, it may be decided that changes in attachments are directly combined with a change of the SOP.

Q: Who must assess the impact of facility SOP deviations? Who must be informed? (e.g. The master schedule sheet is not appropriately maintained as per internal SOP).

A: Ultimate responsibility lies with the Test Facility Management, who has to sign and enforce the SOP.

Assessments should be conducted by the author of the SOP (in the cited case, the author of the master schedule SOP him-/herself).

Major deviations need to be communicated to the test facility management in a proactive way (eg. via author or study director).

Test and Reference/Control Items

Q: Should a solution of test item be used for GLP purposes if the test item expiry date (of the powder) has already been reached?

Example: Test item expiry 30 April 2010. Test item solution made from this test item was made on 29 April, with the solution expiry set at 1 month: 29 May 2010. The stability data for the test item solution is available but was generated with test item which was not near its expiry date.

Is there a difference to the answer if the term "Retest date" is used instead of expiry? (Roche)

A: The stability of the test item under storage and test conditions should be

known for all studies.

For the cited example, there is in our opinion no difference between „retest date" and „expiry date", and a control measurement need to be conducted anyhow (measuring a sample of the solution at the end of May and comparing it with the measurement performed on 29 April would be sufficient).

Study Plan

Q: In GLP studies, the study plan requires signatures from the Study Director to commence the study. There is nothing in the OECD GLP guideline that QA has to sign the study plan but only to verify that the plan is in compliance with the GLP principles which should be documented (and this is done by means of an audit and an audit report) and to have a copy of the study plan.

Is it mandatory to have QA signature in the study plan? If so, does the signature have to be the same date as the SD signature?

A: No, it is not mandatory to have QA signature in the study plan. QA signature in the study plan can be used as documentation of the verification in replacement of an audit report.

In case QA will sign the study plan, this should be done before, or on the same day of the Study Director's signature, as with the SD signature the study is already initiated.

Q: Once the SD signed the study plan, the study starts. Does it mean that the other signatories (Test Facility Management, Sponsor, Principal Investigator (for multisite studies) are not necessary? or can they sign before or after the SD signature. Their signatures will not all be on the same date since this is quite difficult in practice, especially for multisite sites study. (It only brings doubts if all signatories actually signed the document on the same day).

A: According to the GLP ordinance, a study plan should be signed by the study director and the test facility management, the final report should be signed by the study director and should contain a quality assurance statement signed by a member of the QA unit. Other signatures are not mandatory.

Concerning the sequence of the signatures, the GLPMA consider that in order to assume the overall GLP responsibility on the study, the study director should obtain the mandatory signatures before he signs himself the study plan or the final report. Other signatures can be obtained later on, they are not considered as a modification of the study plan or the final report.

In exceptional cases it can be accepted that the test facility manager or the QA signs the study plan after study director's signature. However this signature should be available before the beginning of the experimental phase.

If requested to be in the study plan, signatures of the PIs should de done before the SD's signature or later in amendments but before the study phase starts. Alternatively the PI could provide his agreement in signing a PI acknowledgement

form.

Q: As per OECD GLP, the PI acts on behalf of the SD for a multi-site study and has defined responsibility for the delegated phase of the study, and a scientist is one who contributed to the Final report (i.e. who is usually the (Bio)Statistician).

- Why is it that a Statistician is named as a PI and the Statistician location is considered a test site when the statistician does not participate in the study conduct or experimental phase of the study, generate or collect study raw data but only analyzes the data after the conduct of the study or experimental phase of the study has been completed?
- In addition, if the statistician is considered as a PI and his location is a test site, then a test site QA is required and a GLP compliance statement from the statistician is required. There is no distinct description of the role of the statistician in OECD GLP. This seems to be an over-interpretation of the guideline. Please clarify.

A: The Statistician generates results and this generation should be done with a validated program as requested by GLP. Therefore he is somehow involved in the study performance. The statistician could be nominated as member of the test facility organisation. In this case he will be "study personnel".

If the statistician is not member of the test facility he should be member of a GLP test site. In this case he can be designated PI and has to sign a GLP compliance statement for his part of the study.

Finally, it the statistician is not working in a GLP structure, his contribution has to be excluded from the GLP compliance statement of the study director.

Study Conduct

Q: In order to calculate the concentration of test/reference item in study samples, chromatograms generated during analysis are subject to appropriate quantitation integration methods. Automated integration is used as the default method.

Please comment from a GLP perspective on the acceptability of re-integration of chromatograms. If re-integration is permitted, presumably this should only be under certain circumstances which are clearly defined by SOP and can be fully traced in the raw data.

A: Re-integration is permitted as long as the re-integrated chromatogram can be traced back to the "source chromatogram". The reason for the re-integration should be indicated. Re-integrated chromatograms must be clearly identify as such and the procedures needs to be described in a SOP. The original (source chromatogram) needs to be kept with the raw data.

See Swiss Ordinance on GLP and OECD Principles of Good Laboratory Practice (No. 1)

Report

On request of pathology and in agreement with the study director paraffin blocks of defined tissues from a finalized GLP toxicology study are retrieved from the archive and slides are prepared which are used for exploratory method development. These non-GLP investigations are not considered part of the GLP study and results of the outcome are not reported. After use the blocks are archived again. All activities are approved by the study director of the respective GLP study and test facility management.

Q: What is the opinion of the GLP authorities with respect to the documentation of such an investigation? Do you consider a final report amendment appropriate (which will become part of the submission package) or is a memo detailing all the necessary activities sufficient? (Novartis Pharma AG)

A: In our opinion, a memo will be sufficient. However, the archive database has to clearly document the samples which were dispatched, and to whom, with the respective in-and-out dates".

A label at the archive should indicate the absence of the samples, with the expected return date.

Q: Please describe the approach that should be taken in the event that:

a) the phase report has been finalized (signed/approved by the PI) but the sponsor requests some additional investigations. The study report has not yet been finalized by the SD.

A: An amendment to the study plan should be written. An amendment to the phase report could be used for the documentation or a new phase report could be written based on the extent of the additional investigations.

b) the phase report has been finalized (signed/approved by the PI) but the sponsor requests some additional investigations. The study report has already been finalized by the SD.

A: An amentment to the final report should be written by the study director with the contribution of the PI, describing the additional investigations. The results of the additional investigations should be reported in a further amendment to the final report.

A CRO drafts a phase report with data of performed analyses.
Tables show only single values but no averages or standard deviations.

After review the sponsor monitor would like to add tables with averages and standard deviations and results (e.g. bioanalytics) from other study phases in the summary. He delivers the tables to the PI for their integration into the report. The PI finalises the Phase Report with Tables he did not create.

Q: How should the PI respond if the study director or monitor wants to have data added to the phase report that the PI had nothing to do with?
What must the PI or the Study Director/Monitor consider and document?

A: Regarding other data, e.g. the results from other phases: It should be mentioned in the report that these data were provided by the sponsor. The PI statement of GLP compliance should reflect this fact.

Simple mathematical operations such as average and standard deviation can be calculated by the PI. He can calculate them from his data and include them in his phase report.

Archiving

The GLP ordinance states that the archiving period is at least 10 years after study completion.

Q: What is the authorities' expectation on the archiving period, when during this period an amendment to report is requested for any reason?

A: A prolongation of the archiving period due to an amendment to the final report depends on the impact to the study. Therefore an addition or correction of the final report without any impact to the study does not necessarily extend the archiving period of 10 years.

Q: Would it make any difference on the archiving period whether additional work was conducted for this amendment to report or only information was added or corrected?

A: If additional work was conducted or the study might otherwise be affected, the study should remain in the archive for 10 years starting with the finalisation of the amendment to the final report.

Q: Is there any QA documentation authorities expect to find for longer than ten years in the archive?

A: QA documentation should be kept in the archive as long as the corresponding study is kept in the archive. Therefore situations can arise in which QA documentation should be kept in the archive for longer than 10 years after the completion of the study.

GxP Questions

Q: When is it planned to implement GCLP principles in Switzerland or EU?

A: GCLP were created in 2006 by WHO/TDR for a special purpose:

TDR = Special Programme for Research and Training in Tropical Diseases for organizations engaged in clinical trials in disease endemic countries.

Aim: within this context, GCLP may be a valuable tool for improving quality laboratory practice, and that compliance with it can be considered to allow **clinical laboratories** to ensure that safety **and efficacy data** is repeatable.

OECD was not involved in this programme.

GCLP principles are not planned for implementation as a general principle by OECD – and also not by Switzerland.

Trend: cover the conduct of analysis or evaluation of samples collected as part of a human clinical trial within GCP.

New GCP Guidance:

26 August 2010
EMA/INS/GCP/532137/2010
GCP Inspectors Working Group

Reflection paper on guidance for laboratories that perform the analysis or evaluation of clinical trial samples
Draft

Adoption by GCP Inspectors Working Group for release for consultation	10 June 2010
End of consultation (deadline for comments)	28 February 2011
Adoption by GCP Inspectors Working Group	

Comments should be provided using this template. The completed comments form should be sent to GCP@ema.europa.eu

Keywords	***Clinical laboratory, Laboratory analysis, clinical trial***

Q: Why is there no VICH GCP inspection program for veterinary trials conducted in Switzerland and EU? Is there a plan for this in the future?

A: To be clarified with licence sector at Swissmedic.

GxP Questions

Q: For VICH GCP multi-site studies, the list of investigators is not definitive until final study report is written. Is it possible to waive the list of investigators in the protocol until the final study report, otherwise, several protocol amendments will be needed when investigators do not recruit or more investigators have to be included in the study?

A: To be clarified with licence sector at Swissmedic.

Q: In the early stages of new product development what quality standard is expected for production and release of product for the first clinical trials? Should all tests meet GLP or GMP requirements? (Assume that all the pre-clinical test requirements are met.)

A: According to Swissmedic licence sector:

First in man studies have to be conducted with products meeting GMP requirements.