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SPAQA Behörden Diskussionsrunde / SPAQA Regulatory Round Table 25. November 2009, Basel, CH

Fragen & Antworten / Questions & Answers

Organisation und Personal / Organization and Personnel

Q 1. How should the Master Schedule sheet be annotated in the case that a GLP study or phase is aborted after the study/phase has started (i.e. after study plan signature/after experimental start of the phase)?
(Example: A GLP study is terminated due to a decision to discontinue the development of a compound prior to the completion of all analyses or of reporting)?

A 1. In their GLP-Newsletter 2004/1, the monitoring authorities defined the minimal content of information of a GLP Master Schedule. The "status" (e.g. aborted) of the study was not included in this minimal requirement; however the monitoring authorities will recommend such an information.

Possibilities to give information on the study in the MS:
- add a footnote to the study completion date
- have a column "remarks"
- have a column "status"(e.g. planned, on-going, aborted, completed, ..).
This solution requires continuous up-to-dating of the MS.

Q 2. A training session is organised for a GLP-relevant topic.
The training session is conducted and attendance is documented using a paper form. Each attendee signs and dates the form to confirm their attendance.
Subsequently (within a defined time period), information regarding the individuals who attended the course is entered (transcribed) into a validated computerised system by the System Administrator. This electronic record is the employee's official personal training record.
The System Administrator initials and dates the paper form to confirm correct entry of information into the electronic training records. The form is then scanned and a PDF copy retained with the training material within the validated computer system.
From a GLP perspective, is it necessary to retain the paper form in the archive if SOPs accurately describe the responsibility for data transfer into the validated system? *(Actelion)*

A 2. Personnel records (job description, training) are not study data and some flexibility in the handling of the documents, e.g. up-dating training records is possible. A copy (paper or electronic) of original certificates (attendance, graduation) may be archived in the personnel documentation; however the original should not be destroyed. List of attendance, after up-dating of the personnel records and scanning of the form do not need to be archived on paper.

Organisation und Personal / Organization and Personnel

Qualitätssicherung / Quality Assurance

Q 1. Risk Based approach for QA inspections:

1. In order to reduce costs, process-based inspections have become very popular. In many CROs, the number of these inspections/year/process is often not dependent on the frequency of the process but is fixed at e.g. quarterly inspection intervals. Is this acceptable? Is there a minimum frequency?

2. Is it permitted to perform Study plan reviews as process-based inspections (e.g. for short term studies?)

A *1.* In 1996, the Swiss monitoring authorities published their interpretation regarding the frequency of process-based inspections:
1 - 10 studies/year/process: only study-based inspections
11 - 50 studies/year/process: at least 20% study-based inspections
> 51 studies/year/process: at least 10% study-based inspections.
The inspections should be distributed along the time / number of studies.

2. No. Every study plan has to be verified by the QAU, also in the case of the general study plan and study specific supplement (consensus doc. 7)

Q 2. QA receives a draft final report for review. They check this report and prepare a list of things the SD should modify/correct.
Is it acceptable to issue the QA Statement without verifying that all the changes requested were actually made by or commented by the SD? Is a final report check mandatory before signing the QA statement?

A 2. Consensus doc. 4 indicates "before signing the QA statement, QA should ensure that all issues raised in the QA audit have been appropriately addressed in the final report, that all agreed actions have been completed, and that no change to the report have been made which would require further audit".

Q 3. Are the verifications (reviews) performed on final study plans and amendments to be listed on the QA statement as inspections i.e. with dates performed and when SD and management were informed?
Can the GLP monitoring authorities provide a recommendation for the content of a QA statement?

A 3. According to consensus doc. 4, the QA statement should report "dates and phases of relevant QA monitoring activities". The GLP principles mention

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only "types of inspections and their dates including the phase inspected".

The verification of the study plan is considered as a relevant study related QA monitoring activity and should be mentioned in the QA statement. Amendments to study plan should be checked by the QA, however this activity is normally not reported separately in the QA statement.

The situation is different regarding the final report. In case of final report amendment the QA must audit it and provide an additional QA statement (cons. doc. 4) as part of the amendment.

Content of a QA statement:
- full study identification (number and title)
- list of activities, including:
  date, activity, date reporting to management and SD
- declaration confirming that the final report correctly reflects the raw data.

Geräte / Apparatus

Q 1. In den "Guidelines for the validation of computerised systems" der Working Group on Information Technology, Version 02 vom 14. Dezember 2007 kann man in Tabelle 2 ("Responsibilities/activities and documents for validation") lesen, dass sowohl Validation Plan als auch Validation Report von einer "Person responsible for IT" optional unterschrieben werden können. Im ganzen Rest dieses Dokuments ist der Begriff "Person Responsible for IT" nirgends erwähnt, auch kennt die GLPV diesen Begriff nicht.
Können Sie bitte erklären, was die GLP-Behörden unter dieser Rolle/Funktion verstehen? (DSM Nutrional products Ltd.)

A 1. The need and responsibility of such a person is to be defined by the Test Facility Management (... according to Ordinance GLP Appendix 2, 1.1 2 q..... to establish procedures to ensure that computerised systems are suitable for their intended purpose). The TFM can delegate this task, for example to an IT expert, within the Test Facility, if required.

Q 2. Validation of Computerized Systems and Amendments:
Although the concept of Amendment(s) to a Validation Plan is fully practicable, applied and make absolutely sense, how about amendment(s) to a Validation Report? The AGIT guidelines recommend this approach. Is this the solution if in a particular context, the Validation Report should be entirely rewritten due to missing parts and gaps observed in version 1 related to the reporting of the activities, the results and the documentation created? Wouldn't a new version of the Validation Report (with indication of the

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changes done in the document history) be more appropriate? *(Livec)*

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A 2. AGIT documents are considered recommendation documents. Hence, the test facility has flexibility in a particular context as long as it is compliant with GLP requirements.

In particular, all modifications have to be listed and the reason(s) for the revision(s) to be explained. Further, it is to be made clear that we deal with a revised final report, e.g. the document should be labelled on each page that this is an amendment 1 to the final report.

Prüfungsablauf / Study Conduct

Q 1. Bei 15 Kurzzeitprüfungen mit 15 verschiedenen Prüfgegenständen vom gleichen Sponsor, durchgeführt von ein und demselben Prüfleiter, ändert sich das Reagens MTT von 0.3% auf 1%.
Besteht die Möglichkeit diese geplante Änderung mittels eines „Sammelamendment“, unter Auflistung sämtlicher 15 Prüfungsnummern zu erstellen?

A 1. Yes, with 15 copies to be be added to the individual plans. Also to be considered should be that one of the study plans has already been subject of another amendment (numbering of amendments!).

Q 2. Es ist gefordert, dass Amendments zeitnah, möglichst vor der Umsetzung geschrieben und finalisiert werden, da es sich bei einem Amendment ja um eine geplante Änderung handelt.
Wenn sich nun herausstellt, dass Amendments nicht zeitnah bzw. vor Umsetzung geschrieben wurden, wie ist vorzugehen?Wird dann ein nachträgliches Amendment erstellt, oder wird eine Deviation geschrieben?
(Harlan)

A 2. If a change at a point of time of the conduct occurs on purpose (and was noticed) an amendment can be established. If there has been a non-scheduled change (was noticed after the conduct only), a deviation has to be established.

In exceptional situation a late amendment is justified and necessary to inform other collaborators involved in the study.

See also OGLP 8.1 (performance of the study; study plan)

Q 3. Zum Thema Multi-Site taucht folgendes Problem auf:

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Vermehrt stellen von uns subkontraktierte GLP Prüfeinrichtungen (aus Frankreich, Deutschland, Italien) sogenannte "Phase Plans" aus. Wir versuchen dem zu begegnen indem wir die PI-Beiträge rechtzeitig in den Prüfplan einbauen oder aber spätestens per Amendment to Study Plan berücksichtigen.
Nun aber wird uns im Verlauf der Prüfung oft ein " Phase Plan" zugestellt, meist von PI/QA und Management unterschrieben. Oft bemerken wir den Phase Plan zufällig, erst bei erhalt der Rohdaten oder des Phase Reports. Wir bemühen uns diesen "Phase Plan" dann sofort per Amendment to Study Plan aufzunehmen.
Im Gegenzug werden wir, nun in der Position als PI, oft gebeten einen Phase Plan auszustellen. Generell versuchen wir dem auszuweichen indem wir rechtzeitig, per Word-doc den PI-Beitrag dem Prüfleiter zustellen. Ist aber ein QA gecheckter, vom Management unterschriebener PI-Beitrag gefordert folgen wir dem mit der Bemerkung, dass wir in dem ausgestellten Dokument kein offizielles GLP Dokument sehen und es nur akzeptieren wenn es entsprechend an den Prüfplan gekoppelt wird. Dem wird mehr oder weniger entsprochen.
Leider beobachten wir eine Zuname dieser "Phase Plans", ebenso erhält es mittlerweile bei einigen Firmen den Status als "unabhängiges GLP Dokument". Wir möchten gerne Ihre Meinung zu dieser Entwicklung erhalten. *(Harlan)*

A 3. Wir können nur unterstreichen, dass „Phase Plans“ keine GLP-Dokumente darstellen. Die Angaben sollen in den Prüfplan integriert sein, oder per Amendment zu einem Prüfplan gehören.

Q 4. Für die Zählung von Kleinstlebewesen werden innerhalb einer Studie Fotos erstellt.
Diese Fotos werden per Computer/Beamer vergrössert, die Zählung anhand des vergrösserten Bildes vorgenommen. In den zugehörigen Rohdaten gibt es eine Tabelle mit der Zuordnung von Foto und Replikat/Datum etc.
Die Ergebnisse der Zählung werden auf einer Tabelle als Rohdaten GLP-gerecht erfasst.
Die Fotos werden nicht ausgedruckt, da auf dem Ausdruck die Kleinst-lebewesen nicht zu erkennen wären.
Fragen:
a) müssen die erstellten Fotos als „erste“ Rohdaten ausgedruckt werden, auch wenn nichts zu erkennen wäre?
b) Könnte man die Fotos auf einer CD speichern und diese CD mit den Rohdaten archivieren, unter der Voraussetzung, dass in einer SOP der Vorgang genau beschrieben wird (auch wenn in der Firma keine generelle Möglichkeit zur dauerhaften Archivierung elektronischer Unterlagen besteht)? *(Harlan)*

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A 4. a) Nein; die Protokollierung der Zählung kann (wie beschrieben) als Rohdaten dieser Prüfung definiert werden.

b) Ja, als Backup; siehe bereits publizierte Interpretation zum Thema CD ROM (BAG-GLP-Webseite).

Q 5. We are currently introducing General Study Plans (GSP) to simplify the documentation for acute inhalation studies within our company. We propose to include the intitial concentration in the study specific supplement to the GSP. The selection criteria and guidance for selection of subsequent concentrations would be included in the GSP with the actual concentration documented with the Study Director's prior approval in the study data. Would this adequately describe the testing to meet the GLP requirements? *(Harlan)*

A 5.

General comments:

i) The concept of "general & study specific supplement" study plan is defined in the GLP principles. It can be used, but only for short- term studies.

ii) The full study plan (general & study specific supplement) must be available to all personnel concerned with the study and archived with the study.

iii) The information concerning the material and method could also be described in an SOP, and the study plan could make reference to these SOPs. We consider such a solution easier to control than working with general and study specific supplements.

Specific:

Yes, the criteria for selection of subsequent concentrations should be clearly defined and correspond to the selected dosages. If other criteria are finally chosen, an amendment to the specific supplement has to be established.

Q 6. Peer Review Questions:

1. Is it necessary that Peer Review within a GLP study be conducted under GLP?
2. Under what circumstances should the Peer review pathologist be considered a PI?
3. May the peer reviewer be considered as an expert reporting only to the Study Pathologist (i.e. not a PI)?
4. To whom must the Peer review Pathologist address his peer review report

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(SD and/or Study Pathologist?)

5. In case this is defined to be a PI activity, is a Statement of Compliance and QA statement expected in addition to the peer review report?

The scope of the peer review is not normally detailed in the study plan. In many cases, the peer review process is defined in SOPs (e.g., minimum number of animals per group per sex to be examined, minimum examination of defined target/non-target organs).

6. What raw data do peer reviewers generate?
7. What additional documentation is necessary for QA to assure that the peer reviewer is following the SOPs of his test facility and the study plan?

A 6.

1. According to OECD-WG interpretations: Yes
2. If she/he is distinctly geographically separated from the pathologist/histopathology assessor; (as defined in the SOP)
3. Yes, if geographically similarly located and/or part of the histopathological evaluation process (as defined in the SOP)
4. As defined in the respective SOP (e.g. study director, if pathologist for peer review to be cited in the study plan).
5. In case of a PI situation: QA statement required.
6. and 7. Examples of raw data are documentation of slide tracking for incoming and outgoing samples. Further, macroscopic data may be considered as raw data, and for IT validation of documentation, logon procedure, backups, and contracts, etc. Eventually the QA should inspect the phase of peer review to verify its proper conduct in accordance with GLP.

The topic on peer review will be further discussed on an international level (e.g. European Technical GLP Meeting)

Q 7. <u>Destruction of raw data</u>

1. Is it acceptable to digitalize original paper raw data using a validated process, and consider them to be the raw data? If the digitalized documents would then be archived, can the original paper data be destroyed?
2. Is the answer the same if the raw data is microfiched using a validated process?

A 7.

1. They can be considered verified copies, if it is verified and documented that the electronic data are complete and correct copies, and if the electronic

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data storage system is validated and fulfils the applicable requirements (especially consensus document No. 10). However, the paper data remain the raw data itself and should kept archived over 10 years (see also AGIT paper "Guidelines for the Archiving of Electronic Raw Data in a GLP Environment").

2. Yes. Microfiche is a photographical technique, comparable to a photocopy. Preferably, the transfer by scanning is avoided. From a safety/ security point of view, it is much easier to work with a validated system and with electronic raw data from the beginning on, than to transfer hardcopies into electronic data. We recommend keeping paper data on paper and switching to electronic data with newly generated data, not transferring the old data.

Prüf- und Referenzgegenstände / Test and Reference/Control Items

Q 1. If you prepare a large batch of the test article formulation (e.g., for an entire week), and then dispense the batch into individual daily use containers:
Do you expect a uniformity assessment of the large batch only, or is it necessary to assess the uniformity of the individual daily dosing containers by doing a top, middle and bottom sampling, respectively?

A 1. Homogeneity and concentration of the test item should be determined as close as possible to the application. In your example it seems more adequate to make this assessment on the individual dosing.

SOPs

Q 1. In Prüfeinrichtungen, die sich mit Analytik beschäftigen (Area 8: Analytic and clinical chemistry testing), stehen selbstverständlich Analytische Methoden im Vordergrund. In unserer Prüfeinrichtung haben diese den Status von „SOPs", was natürlich Konsequenzen im Falle von z.B. Abweichungen hat. Können Sie bitte mitteilen, ob die Analytischen Methoden als SOPs gelten müssen, oder ob sie einer anderen Dokumentkategorie (wenn ja, welcher?) angehören können? *(DSM Nutrional Products Ltd.)*

A 1. Test methods can be identified differently then SOPs (e.g. test method) and do not need formal approval from the TF management. However "internal" test methods should be approved by a designated person, have a date of validity and a version number and be archived.

Deviation to test method during the study should be documented and

SOPs

treated as other deviation (assessment by study director)

Q 2. Genehmigung der QA-SOPs
Gemäss Kapitel 7 der GLP-Verordnung müssen SOPs zum „Qualitätssicherungsverfahren" von der Leitung der Prüfeinrichtung genehmigt werden.
Unser GLP-Qualitätssicherungsprogramm besteht aus einer allgemeinen SOP, die die Regularien, die inspizierten Prüfeinrichtungen und die QA-Verantwortlichkeiten grob beschreibt sowie aus einer Reihe von zusätzlichen SOPs, die die einzelnen Aktivitäten der Qualitätssicherung detailliert umschreiben.
Bis jetzt wurden alle QA-SOPs von den Prüfeinrichtungsleitern genehmigt. Da dies sehr zeitaufwändig ist und für die Qualität der Prüfungen wenig bringt, schlagen wir das folgende alternative Vorgehen vor: Alle Leiter der Prüfeinrichtungen genehmigen die allgemeine SOP zum Qualitätssicherungsprogramm. In dieser SOP steht ausserdem, dass die Leiter der Prüfeinrichtungen alle QA-SOPs überprüfen und dass dieser Check dokumentiert wird. Die einzelnen QA-SOPs werden jedoch nicht von den Prüfeinrichtungsleitern genehmigt.
Wie stehen die Schweizerischen GLP-Behörden zu diesem Vorschlag? *(Novartis)*

A 2. The full QA program should be approved by each test facility manager. If the program is described in several SOPs, each SOP should be approved.

Within a same company in Switzerland it is acceptable to delegate the written approval (=signature) of certain QA-SOPs to one test facility manager, if the procedure is clearly defined in an overall SOP, signed by all the test facility managers.

Abschlussbericht / Report

Q 1. One test item has several trade names. The sponsor requires several reports, one for each name.
a) is this possible?
b) if not, who could the sponsor's request be fulfilled? *(Harlan)*

A a) No

b) Use a neutral code for the substance in the whole study. Eventually document the assignment of trade names to the code in the correspondence between sponsor and test facility. For notification purpose, the sponsor has to indicate the official name of the test item (IUPAC, CAS,..) and the synonyms

Abschlussbericht / Report

Q 2. Each GLP study should contain a statement of the SD to what extent the study was conducted in compliance with the applicable GLP regulations. In the case that a part of the study is not conducted in compliance with the GLPs, **must** the reason for the non-compliance be included in the SD statement?

A 2. No, but it could be in the interest of the test facility to indicate the reason

Archivierung / Archiving

Q 1. A global company has 3 testing facilities, one in the US, one in the UK, and one in Switzerland. The company plans to establish one archive for all electronic data from the 3 testing facilities on a virtual server.
As a result, the testing facilities will not have their electronic raw data managed locally nor in a local archive on site. They only have online access to these remote data. Is this approach acceptable?

A 1. Yes, as long as the system is validated and fulfils the applicable requirements (especially consensus document No. 10). Hardware aspects: safety against disasters (fire, flood) and physical security aspects must be addressed by contracts (defining responsibilities) and QA inspections in the frame of a national GLP program (e.g. US or UK or Switzerland). Software aspects, e.g. logical security, backup procedures must be addressed by the validation of the virtual server. Provide SOPs for the relevant procedures.

Q 2. How long does a GLP test facility have to retain their archive access logs?

A 2. 10 years

Q 3. Sponsor Role:
In case a study is fully outsourced (no study-related activities at the Sponsor), does the Sponsor have to store/archive all correspondence in his/her GLP archive?
Must this study be listed in the Sponsor's MSS?

A 3. No (to both questions)

GLP Behörden / GLP Monitoring Authorities

Q 1. Während der letzten Behördenrunde wurde von Seiten der Behörden erwähnt, dass der Begriff "Auditor" den Behörden vorbehalten ist, und der

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Begriff "Inspektor" für die Prüfeinrichtungen verwendet werden soll. In der GLP Verordnung werden aber beide Begriffe (auditieren und inspizieren) verwendet. Uns bereitet die Behördenaussage Probleme, da durch das globale Job Titeling der Begriff "QA Auditor" vorgesehen ist. Ist es nun wirklich so, dass der Begriff "Auditor" in einer Prüfeinrichtung nicht verwendet werden darf? *(Harlan)*

A 1. No, it is not so. At the last meeting the question concerned the difference between inspection and audit. We answered that "audit" was mentioned in relation to "study audit" done by a monitoring authority.

We have no objection against "QA auditor". However the verification of the final report should be mentioned as "inspection of the final report" and not as "audit of the final report".

Q 2. Has international consensus been reached on the definition of a short term study?

A 2. Only as far as described in the GLP cons. doc. 7 in the note by the OECD Working Group on GLP, p. 5

Q 3. Schnittstelle GLP/GCP
Bereits im Jahr 2003 wurde in der Behördendiskussionsrunde das Thema Good Clinical Laboratory Practices besprochen (anlässlich der Herausgabe der BARQA Guideline zu diesem Thema).
In der Zwischenzeit sind die folgenden beiden Dokumente zum gleichen Thema herausgegeben worden:
World Health Organization (WHO) Good Clinical Laboratory Practice (GCLP), 2009
MHRA: Good Clinical Practice; Guidance on the maintenance of regulatory compliance in laboratories that perform the analysis or evaluation of clinical trial samples. Issue 01-Jul-2009
Richtlinien zu den Schnittstellen zwischen GLP und GCP sind für die pharmazeutische Industrie von grosser Wichtigkeit. Welche Bedeutung hat vor allem das WHO Dokument für Swissmedic? *(Novartis)*

A 3. Swissmedic participated on the EMEA „ad hoc GLP inspectors working group for requesting and reporting GLP inspections for centrally authorised products“, which was held in London on 28 April 2009, and which was discussing interfaces between GLP and GCP.

Generally, WHO documents are accepted by Swissmedic, and hence the indicated document is under discussion within between the GCP and GLP departments within Swissmedic. However, the present document will particularly require discussions on the OECD GLP-WG level so that a harmonized approach can be taken. For instance, the WHO GCLP

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definitions of the indicated document will have to be reviewed, and practical consequences with regard to inspections be considered:

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki (ICH GCP Guideline).

Good Laboratory Practice (GLP) is intended to promote the quality and validity of test data. It is a managerial concept covering the organisational process and the conditions, under which laboratory studies are planned, performed, monitored, recorded and reported (OECD GLP Guideline).

Good Clinical Laboratory Practice (GCLP) applies those principles established under GLP for data generation used in regulatory submissions relevant to the analysis of samples from a clinical trial. At the same time it ensures that the objectives of the GCP principles are carried out. This ensures the reliability and integrity of data generated by analytical laboratories.