SPAQA Regulatory Round Table
06 November 2012, Basel, CH

Questions

Organization and Personnel

Question

Personnel must be trained to SOPs prior to their performance of the procedure. In order for this to happen, employees must know which SOPs they must read; they must be informed when there are changes to the processes they are to perform, and management should be able to define which SOPs must be read by which individuals.

What do the authorities expect to see in terms of management oversight? SD oversight? Employee documentation?

Answer

The authorities need to see:

A process in place (SOP) describing

- how personnel is informed about new or revised SOPs (e.g. during the process of distribution of SOPs)
- how management has the oversight that people are trained about new or revised SOPs.

Documentation of employees confirming the acknowledgement of new or revised SOPs. This can be documented in their personnel documentation or on a distribution list or similar document.

Quality Assurance

Question

It is clear that QA must be independent of the studies that they inspect.

In a small CRO, however, QA members may be asked to perform laboratory activities. In this role, they may generate facility and equipment records independent of a study.

Is it acceptable for this same QA member to inspect the maintenance and calibration records of the equipment for the studies that they inspect?

Answer

Yes, in the context of a facility based inspection.

They should not be involved in study or process based inspections if they perform laboratory activities for these studies.

Computerized Systems

A spreadsheet is used sequentially for direct data entry and printed for each additional set of information: for example:

Day 1: weights of test/reference item are entered. Spreadsheet is printed and wet ink signed.
Day 2: calibration/QC/working solutions preparation details are added. The spreadsheet is printed and wet ink signed.
Day 3: Analytical measurements are added (e.g. pH, after an incubation step). Spread sheet is printed and wet ink signed.

The use of individual spreadsheets is not practicable due to correction factors that are embedded in the spreadsheet and automatically applied to the data.

- **Question**
  Are all printouts regarded as raw data? Is the "print date" sufficient to track between iterations?

  Answer
  According the procedure described above, the data remain in the spreadsheet between from day 1 to 3. If there are no means of protecting electronic raw data during this period, the file should be printed and signed daily. The printouts of all three days should be handled as raw data. The “print date” function can be used if the date is correct and then confirmed by the signature. In addition, all prints need to carry the study number.

- **Question**
  Are printouts alone sufficient to assure data integrity?

  Answer
  If all relevant information is printed, then they are sufficient. It must be possible to verify the calculations using the sheet of day 3 only (i.e. all weights, volumes and correction factors visible; the formulas should be printed or the spreadsheet validated). The sheets of day 1 and 2 are just documenting the current state of the data on these days.

See also AGIT Guidelines for the validation of spreadsheets.

Computerized Systems

Question

What is the documentation you would expect from an HPLC or LCMS system to consider the system as validated when the rawdata are defined to be the printouts of the electronic Chromatograms and the printed result of the Integration?

Answer

See AGIT Guidelines for the validation of computerized systems. A LCMS e.g. is a complex computerized system even if there are no electronic raw data. We would expect a validation plan, raw data and a validation report, all with involvement of QA, and a documented system release by the test facility management. Then, for the lifetime of the system since the initial validation, applicable SOPs and log books with the documented test and maintenance activities.

Question

Cloud Computing
It is more and more common in the GxP area to outsource IT services/infrastructure to IT service providers or to utilize cloud computing.

- Is the AGIT working group already discussing these topics?
- Will there be a new AGIT guideline in the future, covering IT infrastructure in general but also specifically IT outsourcing and cloud computing?
- If so, what would be the expected issue date for such a guidance document?

Answer

AGIT has discussed the issue several times and we came to the conclusion that it is too early for us to write a guideline. It may come in future, but the content of such a document is not yet defined.

Question

What are the expectations of the authorities regarding Cloud Computing?

Answer

Applicable requirements are given in OECD consensus document 10 and partly in Advisory document 15. Further, AGIT guidelines on computerized systems and handling of electronic raw data are to be considered. We are aware that more interpretation is needed.

We recommend to rely on industrial standards (e.g. ISO-Standards) in order to define a technical level of security and data integrity. GLP specific instructions are needed for the application in order to ensure a compliant way of using the system.

Test and Reference/Control Items

Question

When the reference item (used as e.g. a positive control) is a proprietary brand, purchased locally, there is no formal Certificate of Analysis. In this situation, is the following sufficient identification: the product name, description, supplier/distributor, batch/lot no. and expiry date, as quoted on the packaging?

Answer

The provided information is not considered sufficient since information on purity is missing. (OGLP Appendix 2, 6.2: letter 1 and 2)

Question

When the test item is defined to be a pre-formulated liquid product - which form must be maintained in the retention sample archive (powder or pre-formulated liquid product)? (Please note: The pre-formulated liquid product may have a considerably shorter shelf life.)

Answer

A sample of the test item (here pre-formulated liquid product) should be retained in the archive. If available, it is recommended to archive a sample of the powder.

Question

Characterization of internal standard for chromatographic assays:

It is common practice to have an internal standard in combination with the analytical reference item within chromatographic assays.

- What is the authorities' expectation in regard to the characterization of the internal standard?
- Is there a general recommendation that could be made to identify the internal standard within a study, as it is related to the reference item but is not the same?

Answer

If the internal standard is pivotal for quantitative analyses as a reference parameter, information on characterization as requested for chemicals, reagents and solutions should be available. This information should be stated in the method validation reports or (supplements to) SOPs for example.

(OGLP App. 2, chapter 7, letter 2 and chapter 9.2 letter e)

Study Plan

Question

Is there an official term for a person working under the responsibility of a PI (e.g. a Peer Review Pathologist who does not issue a separate report, but reviews the Study Pathologist's interpretations).

Answer

There is no official terminology.

Study Conduct

Question

Reagents are prepared for a specific study. If subsequent studies can use the same reagents (before they are expired), what needs to be documented in the subsequent studies and is this a deviation to the GLPs?

Answer

A verified copy of the raw data concerning the preparation of the reagent should be archived with the new study. Using the reagent prepared for a previous study should not be described as a deviation to the study plan, unless the preparation of the reagent is specified in the study plan.

Question

Is the answer the same if these are QCs or calibration solutions? (In many cases these solutions are prepared to validate the method, i.e. long before the first GLP study is initiated)

Answer

QC and calibration solutions can be described in specific SOPs and the preparation documented with the equipment data. Alternatively, they might be prepared and documented within a validation study, if it was done according to GLP requirements.

Study Reporting

Question

If, as a CRO, we are asked to perform bioanalysis on samples for which there are no stability data known in the actual matrix and the Sponsor does not want us to generate the information, how should this deficiency be reported? Is it sufficient to ensure that the Study Report includes a statement to highlight this lack of data (for example in the "Sample description" section)?

Answer

The lack of stability data of the test item in the matrix (e.g. plasma) should be documented in the GLP compliance statement of the study director.

Archiving

Question

In the SPAQA Authority Roundtable 2005, it was stated that if a CRO returns materials to a Sponsor, that the CRO must maintain copies of all the raw data and be able to provide the Swiss Authorities with the originals within a reasonable timeframe (nützlicher Frist).

After recent discussion with authority representatives we have been told that retention of the copies of the raw data is no longer necessary.

- Is this the consensus of all Swiss GLP Monitoring authorities?
- What documents must we now retain?

Answer

If the original study documentation is available within a reasonable time frame, the retention of copies is not necessary. Otherwise, verified copies of study plan, amendments, raw data and study report should be available for inspections.

Question

We, a CRO, would like to implement a new archiving policy for new clients: 3 years archival at our CRO with the possibility to return materials to the sponsors after 3 years. If the sponsor does not want to pay us for the rest of the 7 years in CH and asks us to send the documents to the Sponsor, how must this be handled?

- What do we as a CRO need as documentation?
- What do the authorities require?
- What documents do we have to maintain (see also question/answer above)?

Answer

The location where the study documents are to be stored (during 10 years) should be indicated in the final report. If it is clear from the beginning of the study that the documents are transferred to the sponsor after three years, this can be described in the final report. In this case, no amendment is needed for this study.

If the sponsor's archive is not under supervision of a GLP monitoring program (as part of a test facility or as archive only), the archiving period in this archive should be excluded in the GLP statement of the study director.

If the location of the archive as mentioned in the final report is changed, an amendment to report is required. In case a great number of final reports is transferred a "Sammelamendment" can be generated. This should be discussed with the competent GLP Monitoring Authority beforehand.

If the transfer of the study documents to a non GLP archive is decided during the archiving period, a revision of the GLP statement is necessary by an amendment to the report. Since the change of location will require anyway an amendment or a "Sammelamendment", this information can be integrated.

Question

A multisite study is run in a country having an archive period less than 10 years. The Study Plan requires our Swiss Test Site raw data and original Phase report to be archived at the foreign Test Facility.

- How can we as a Test Site ensure that these records and materials are archived for at least 10 years?
- Is there something we should include in our Phase report?

Answer

The archiving period is regulated on a national level; the regulations of the competent foreign authority (*i.e.* country where the test facility is located) apply.

OECD

Question

News from the OECD Working groups?

- Peer Review?
- Timing of Pathology Peer Review: Must the Pathology peer review be conducted after the Study Pathologist has signed the report with their interpretations?
- Other topics?

Answer

At the OECD Working Group meeting in Paris in May 2012 a call for comments on the second draft of the "Guidance on the GLP Requirements for Peer Review of Histopathology" until August 2012 was made. Swissmedic and BAG sent comments on behalf of the Swiss GLP Monitoring Authorities. A third draft should be available to the authorities by the end of this year.

Question

News from FDA regarding modernization of 21CFR Part 58?

Answer

An Advance Notice of Proposed Rule Making (ANPRM) was published in the Federal Register in December 2010 to solicit comments and ideas from stakeholders. The comment period closed in February 2011 and the working group has reviewed all the comments. The working group is trying to incorporate the comments as well as harmonize with the OECD's Principles of GLP whenever possible. The working group is currently meeting weekly and the goal is to complete the preamble and NPRM and begin the clearance process soon. Assuming the clearance process will take about six months, the working group hopes to publish the NPRM in a Federal Register notice in 2013, hopefully early 2013.

The public will have an opportunity to comment on the NPRM when it is published in the Federal Register. The revision of the FDA GLP Regulations will not take effect until the comments have been reviewed, changes are made to the codified language where appropriate, and the final rule is published.

Other Related Questions

Question

Roundtable Followup
During the round table discussion last year, Swissmedic presented ideas for the future in regard to monitoring inspections for bioanalytical test facilities.

- What decisions have been made since then?
- What are the Swiss authorities doing in regard to the bioanalysis of samples from clinical trials?
- Are there any additional developments that the authorities can share with bioanalytical test facilities in regard to the analysis of samples from clinical studies?

Answer

Currently, there is the first pilot GCP-GLP joint inspection ongoing. Based on the results and experience we will then decide with the clinical trials unit on future procedures.

Question

Relationship between receiving authorities and GLP inspectors
In past years, on several occasions, it was mentioned that there is a close relationship between the receiving authorities and the GLP monitoring authorities. How close is this relationship, what are the interfaces between the two, and to which extent are the findings within one authority shared with the other? As this question arose during meetings with colleagues from other countries it would be very helpful to know more about this.

Answer

There is an established official communication channel. The Swiss annual report and current issues (e.g. non-compliant studies or test facilities) are systematically distributed to receiving authorities by the Notification authority.

At Swissmedic GLP inspectors also act as nonclinical assessors at the receiving authority. This is described in the corresponding job descriptions.

BAG and BAFU: personal contacts; occasionally on GLP related questions.

Question

Expectation on availability of QA documentation after the 10 year archival period
A few years ago, it was stated that Swiss GLP authorities expect QA documentation to be archived for at least ten years in Switzerland. During this year a sponsor, raised the question, to have this documentation ready until a product is on the market. Depending on the country and the time point, this might be much longer than 10 years.

- Is there any recommendation the Swiss GLP authorities can make to reply to such a request?
- Under what circumstances would regulatory bodies request to see QA documentation during the submission process?

Answer

We receive questions about the compliance status of test facilities in the early nineties. Therefore, it can be important to keep the study documentation (study plan, raw data, final report and other relevant documents) until the product is on the market. It is acceptable if the documents are transferred to the sponsor after 10 years if the delay is more than 10 years.

Regulatory bodies will not ask for QA documentation. They can refuse a study or ask for a study audit by a monitoring authority. It may be in the interest of the test facility to have the QA documentation if doubts about the QA involvement arise.