Questions for GLP Monitoring Authorities 2014

Follow-Ups from Previous Roundtables

Modifications of Interpretations
In response to the questions raised during the last GLP Roundtable, the authorities had stated in their answers that interpretation 8.16 would be modified. When will the interpretations on the authorities' website be modified to reflect the answer given?

Various interpretations are currently under discussion. Any modifications will be highlighted in the GLP Newsletter 2014 which will be published before the end of the year.

GLP/ GCP

Joint inspections:
The revised Swiss GLP Compliance Monitoring Programme (version EL02.02, dated 25 February 2014) section 2.2 Monitoring of GLP compliance, refers to the conduct of joint inspections between Swissmedic and the GCP inspectorate unit at the Clinical Trials Division of a test facility performing bioanalytics of animal and human plasma samples. In relation to this statement, please clarify the following points:

- Is there a requirement for a test facility which undergoes routine GLP inspection by Swissmedic to notify the GCP inspectorate unit at the Clinical Trials Division that analysis or evaluation of human plasma samples is being performed/will be performed at their facility?
  There is no such requirement.

- Are joint inspections scheduled in addition to the routine GLP monitoring inspections performed by Swissmedic, or would they be conducted as part of the routine GLP inspection?
  GLP inspections are always performed as stand alone inspections and in accordance with the OGLP and GLP Compliance Monitoring Programme; an inspector from GCP can accompany the GLP inspectors and focus on GCP relevant aspects.

- If not conducted on a routine basis, how will joint audits be scheduled; for example, will they be dependent upon regulatory submission of a relevant clinical trial?
  After the pilot phase 2012 to 2014 it was agreed with the GCP inspectorate that joint inspections will not be performed on a routine basis. We exchange our inspection programme, in case of a joint inspection, the concerned test facility is informed prior to the inspection.

- Apart from the Swiss GLP Ordinance, the Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples, EMA/INS/GCP/532137/2010 and the revised Clinical Trials Directive 536/2014, will test facility compliance with any other regulations be considered during joint inspection of the bioanalytics of animal and human plasma samples?
  For GLP aspects the above mentioned regulations are sufficient, GCP aspects are out of scope.

Status of GLP/GCP joint inspections conducted by Swissmedic?
How many joint inspections have been performed to date?

Three inspections have been performed during the GLP/GCP pilot 2012-2014.

Harmonization/Information Exchange re GLP/GCP?
The GCP Inspectorate at Swissmedic has communicated to SPAQA in the past that they do not wish to participate in an Authority Round Table Discussion. Nonetheless, it would be beneficial for Bioanalytical Test Facilities to clarify questions concerning their daily business, but related to GCP with the relevant Authorities. Could the GLP Inspectors (from Swissmedic) show a way/give suggestions where and how such questions could be raised and the answers shared in order to achieve harmonized interpretations?

Questions regarding GCP may be sent to ct.medicinalproducts@swissmedic.ch.

Standard Operating Procedures

Frequency of SOP Review:
What is the expectation concerning the frequency of SOP reviews? Would it be possible to use a risk-based approach to determine the frequency of the of SOP review cycles (e.g .per SOP category/business criticality)?

An SOP is defined as documented procedure which describes how to perform tests or activities normally not specified in detail in study plans or test guidelines. These procedures should be checked on a regular basis if a revision is necessary. A risk based approach can be described and should include a rational for the review intervals and a maximum time period (e.g. 2-3 years).

Training

Refresher Training:
There is an expectation from the authorities to include refresher training in GLP. However, training should be relevant or it has limited/no value and those attending find it a waste of time. Training for specific issues is, of course, delivered to those who need it and is well received. However, it becomes ever more difficult to provide relevant, interesting general refresher training.

- Can the periodicity of refresher training be defined in the Test Facility ‘s SOPs?
  The periodicity of refresher training should be defined in an SOP.

- When study directors and staff are experienced and there are no changes to the regulations, is general refresher training mandatory?
  The TFM should ensure that the staff of the test facility is trained for the respective roles and functions. The regular training might be focused on specific aspects based on QA findings for example and intervals may vary according to the needs of the test facility.

Quality Assurance Activities

Review of Study Plan (SP) Amendments:

According to GLP, QA should verify that the Study Plan contains the information required for compliance with GLP and this verification should be documented. What are the expectations of Swissmedic regarding the Study Plan Amendments? Should QA review the SP amendments in a similar way as the SP?

Amendments to study plans also contain information required for compliance with GLP. According to principle 8.1, al. 2, let a, amendments should be: justified, signed by SD and maintained with the study plan (understand: amendments are part of the study plan). Amendments can also contain important information required for compliance with GLP according to principle 8.2., which were not available at the time the study plan was signed (eg. Identification of personnel and activities at a test site).

In consequence, QA should verify that amendments to study plans are compliant with these GLP requirement. They should be verified like the study plan.

Use of contract QA services:

If an external QA professional is used for a very specific purpose (for example a lab inspection for a single study), is it sufficient for GLP purposes to have a service level agreement defining the SOPs to be used for the inspection, a CV for the appointed auditor and a demonstration of training in the relevant inspection procedure?

A service level agreement (SLA) can be used to contract specific QA activities. For GLP compliance, the SLA should define the activities to be conducted and the SOPs of the test facility to be used (inspection and reporting). CV and specific training of the person conducting the contracted activities should be available at the test facility.

Study Conduct and Reporting

Labeling of sample aliquots:

- What is the minimum information expected on labels of sample aliquots used to validate storage stability?
- Would it be acceptable to use 'to be determined' instead of an expiry date on such a label, and update the label on the storage box adequately, in addition to the documentation related to the preparation of these samples?

"Sample aliquots" produced in a GLP study and submitted to storage stability test should be labelled with the study number and identification described in the study plan. An expiry date is not required in case the objective of the process is to determine the stability of the sample during a specified period.

Final Reports:
What kind of recommendation can be given concerning correction of a signature date on final documents, when it is uncovered at a later time point that one of the signing parties has mixed-up the date? Example: instead of 21-Jan-2014 it was written 21-January 2013. Could a handwritten correction be accepted, if justified appropriately, or is always an amendment necessary? What if the error is related to the sponsor signature on the document?

According to principle 9.1, al. 4, any correction to a final report (after signature by the study director) should be in form of amendment. As mentioned at the 2013 SPAQA roundtable, wrong dated signature from the study director should be corrected in form of an amendment. Signatures which can be collected after finalisation of the report, e.g. test facility management or sponsor, are not concerned by the GLP requirements and can be corrected on the document.

Records Archival

Document page numbering:
Before archiving final study documentation, our archivist numbers each page.

- Is this an expectation of the authorities?
- Would alternative procedures be acceptable?
  Examples:
  a) A list of documents with the total number of pages per document "Plate reader data xx pages"
  b) Separate but related documents (for example "experiment xxx on day yyy" which could consist of data, working procedures, solution preparation etc) and the total number of pages

Numbering each page of a study documentation represents the "state of the art". This procedure ensures an easy completeness check of the documentation, a correct sequence of the pages and makes difficult a (voluntary or not) replacement of specific pages.

Alternative procedure allowing a check of the completeness of archived documents is acceptable. The numbering per section is a possibility. The index should show the total number of pages per section and of the complete document.

Archiving of Manuals:
Equipment instruction manuals:
Routine use and maintenance are described in SOPs but manuals are kept with equipment for non-standard use and "troubleshooting".

- When the equipment is retired is it necessary to always archive these manuals?
- Some equipment is transferred to other laboratories/companies and they will also expect to receive the manuals. Must we make copies for the archive?
- Is the answer different for simple equipment (for example, pipettes or pH meters) where manuals are rarely used, than for complex equipment (for example: clinical chemistry analyzers, HPLC, spectrophotometers for which the manuals are extensive and used more often)?

According to principle 10, al. 1, let d records and reports of the maintenance and calibration of apparatus should be archived. Requirements concerning the maintenance and calibration (type, frequency, acceptance criteria) should also be archived, to allow checking their correct execution based on the records.

The requirements are normally written in SOPs, which are also archived. If these requirements are only available in a manual, then the manual – or a verified copy of the relevant part- should be archived.

Computerised Systems

Data migration:

When significant changes such as additional fields and functionality are made to a validated software program that is linked to a database of information (for example to store the equipment inventory, routine calibration data etc.), it is clear that the system must be partially or fully revalidated, and AGIT guidelines are used for this stage before the revalidated system is released. However, data migration is also required to ensure historical data remain accessible.

a) Should the data migration be run as a "study" in a similar way to that recommended in the AGIT guidelines for validation?

This is possible but not required. The migration and any tests (e.g. function tests) should be documented.

b) What documentation is expected to be available to assure that the data migration is accurate?

The result of the tests and the confirmation regarding the completeness of migrated data should be documented. The extent of the tests (e.g. number of files, spot check of data, exact number of bytes) and the tests themselves should be described.

Use of electronic pens:

Products are now available (e.g. the "lifetrons business note writer" https://www.lifetrons.ch) which allow hand-written notes on normal paper to be recorded into the pen and transferred either directly or later to PC, iphone, ipad, ipod etc. The potential to use these in both the laboratory and in QA activities is significant and could improve record keeping (and legibility). Handwriting recognition software is included for conversion to digital format for edit or distribution.

a) What is the raw data (especially when transfer is direct because both will be the "first human readable form")?

Handwritten notes are still the raw data. Transferred data are copies thereof. If the electronic file is the first version, it should be regarded as raw data. This refers to the captured image of the handwriting before optical character recognition (OCR).

b) What validation should be performed to check the handwriting recognition software (all users, a selection of users, text, numbers, graphics etc.....?)

The handwriting recognition software should be validated against the defined requirements. The scope can be defined by the test facility. This can include the limitation on trained users or on certain applications, pre-defined keywords or on numbers.

c) How are such devices viewed by the authorities?

We have no experience so far with such devices. In principle, they are treated as computerized systems; the practical challenges are similar as in the case of optical scanners.

Cloud computing, software as a service (SAAS) and data storage:
Many larger companies now start to move away from the traditional on-site data control and storage/server services. What is the GLP authorities' opinion on:

- internal (test facility) control of the computerized system but with storage of electronic records (i.e. GLP study data) in "the cloud" during study conduct and during the defined archive period?
  Same requirements apply as for "normal" servers (data security, backups, procedures in place for electronic archiving, definition of access authorization and administrator rights). SLA should ensure that all requirements of OECD Doc. Nr. 10 and 15 are fulfilled, see also Interpretations 10.10.

- use of external computerized software (SAAS) including provision of storage of electronic records (i.e. GLP study data) in the "cloud" owned by the service provider during study conduct and during the defined archive period?
  The SLA should ensure that all requirements of OECD Doc. Nr. 10 and 15 are fulfilled, see also Interpretations 10.10

This answer will be updated in about 2 years: new OECD guidance on IT systems and AGIT paper on SLA's in preparation.

Archiving of electronic raw data:
For many years it has been standard practice to archive GLP data/electronic records on a separate, dedicated server upon finalization of a study. As data collection software becomes more and more complex and advanced, nowadays options are usually available within the computerized system/software itself to lock, segregate and "archive" records pertaining to completed GLP studies. This approach also helps to ensure the raw data remains readable for prolonged periods within the generating system and avoids storage on alternative media that may need periodic migration or may become damaged or not readable. The OECD advisory document Nr. 15, sections 4.8 and 8.3, implies that such approach would be acceptable. What is the authorities' opinion on this topic, particularly with respect to the appointment of an Archivist, their responsibilities and read-only access permissions to the records?

This approach is acceptable if validated and described. If the archiving of electronic raw data leads to a situation where the data of a study are archived at different places (e.g. LIMS and archive), it should be documented in the archive index.

The archivist of an electronic archive should be trained for this task. The responsibilities of the archivist remain the same, but maybe he needs to involve other persons from IT or technical personnel. Read-only access can be granted to a broader community.

IT Infrastructure Records:

What is the expectation regarding the retention (including duration) for change & incident records pertaining to IT infrastructure and services. Are the same rules applicable to internal IT departments supporting a GLP environment, external IT service providers, as well as to cloud IT services?

Records include the documentation of the nature of the change or incident, the actions, tests and release of the change (see AGIT guideline on Change Management / Risk Assessment).
The same rules apply in all cases. The records should be archived by the test facility. The retention period is 10 years.

Electronic Submissions in Send Format:

Tabulated data is a submission requirement per 21 CFR 312.23(a)(8)(ii)(b) and SEND will standardize the submission of electronic nonclinical data. FDA will require the SEND format.

- Are Swiss Authorities planning to make this a requirement as the Japanese Authorities have done?

No.

If SEND is utilized for report table generation or analyses presented in the report, an output from SEND may become a report element requiring GLP audit.

- What is the Swiss Authorities opinion on this?

- What will happen with the "GLP status of the data/ report if a Test Facility would outsource (e.g. to a software provider) the formatting of electronic data to the SEND format?

- Should the Software provider become a Test Site and the responsible person for the data transfer a PI even if no raw data will be produced but changed to another format?

Please contact the competent GLP Compliance Monitoring Unit for discussion.

Destruction of Paper Raw Data:

In the Position Paper #1 on the Destruction of Raw Data issued by the AGIT on October 2nd, 2014, it is stated that "the scan process should be validated regarding readability, resolution, contrast and color balance, page size, counting of pages, error handling etc. The scan process should produce a read-only image file, in a non-editable form." It is also stated each individual scanned page should be compared with the original paper and checked for accuracy, completeness, and content. This 100% check should be documented by signing electronically the electronic file containing the scanned paper data".

- If a 100% check is still required after full validation of the scanning process, what is the purpose of the validation?
  Validation: to demonstrate that the technical requirements can be met with the equipment; leads to a process/SOP how to do it, under the responsibility of a validation director and typically with a release of the process by TFM or a designated system owner. 100% check: checks if all pages are correctly copied. This can be done by a trained individual.

- Why would it not be OK to just do the 100% verification check and sign the electronic file, i.e. to skip the validation altogether?
  It might be ok if during the 100%check also resolution and all other requirements are checked and the study director confirms that it is ok.

- How do the authorities expect the verification of each page to be documented – i.e. a dated time stamped signature on each page? If this is done on paper, this becomes a process with no end- if it is done electronically, the verification process itself would need to be validated.
  One single confirmation that each page has been scanned successfully is enough, e.g. by an electronic signature on the scanned file.

The position paper does not appear to discuss that some test facilities have defined the output of certain instruments as paper raw data (e.g. chromatographic/ HPLC data).

- Are there additional requirements in the case that the original data was not hand written but was stored electronically on durable medium prior to being defined as "paper raw data"?
  Electronically generated raw data should be handled electronically until archiving as described in the AGIT papers. The requirements are different.
  The position paper addresses only the question whether the data on paper can be discarded if verified copies exist.