SPAQA ANNUAL MEETING 2025

QUESTIONS TO GLP MONITORING AUTHORITIES

APPARATUS, MATERIAL, AND REAGENTS

Balance

- External Calibrations by Mettler are common but checking the reports shows that the calibrations often don't include the full weight range:
  - A precision balance to be used from 5 mg to up to 205 g is e.g., calibrated by testing 50 g and 100 g and the accuracy and precision of the balance are then calculated with the result of a minimum weight that should still be within the allowed tolerance and is given in the calibration report (in this case 5 mg).
  - Functional controls or internal checks with a check weight are done with 100 mg and 10 g.
  - The full range weight range of the balance is used although it is never tested.
- What is the range the balance can be used for?

Answer:

According to the OECD GLP-Principles: *Apparatus used for the generation, storage and retrieval of data, and for controlling environmental factors relevant to the study should be suitably located and of appropriate design and adequate capacity. Further, an apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. Records of these activities should be maintained. Calibration should, where appropriate, be traceable to national or international standards of measurement.*

The weight range of a balance is specified by the manufacturer and the test facility should ensure that the calibration covers the working range, the balance is used for.

APPARATUS, MATERIAL, AND REAGENTS

Balance

- In a GLP Facility the balances for animal weighing are regularly internally calibrated with check weights.
- These check weights are regularly placed on different balances (calibrated internally with the same process), to verify that they are still having the correct weight.
- Is this approach acceptable or would an external verification/ calibration of the check weights or the balance in a regular frequency be expected?

Answer:
Similar to the previous question (principles) but in the case of calibration specified in more detail in OECD Doc No. 5:
"It is the responsibility of test facility management to ensure that instruments are adequate and functioning according to their intended use. Test facility management should also ensure that instruments are inspected and calibrated at prescribed intervals. Calibration should be traceable to national or international standards of measurement as appropriate. If reference standards are kept by the user they should be calibrated by a competent body at prescribed intervals."

The frequency of checking the reference weights depends on the use pattern of the weights and the required accuracy and should be defined by the test facility management in its SOPs.

PERFORMANCE OF THE STUDY

Homogeneity

- In a toxicity study (one control and three dose groups), the homogeneity of the formulations is also determined.
  - Must homogeneity determination be carried out in all 3 dose groups or is the coverage of the concentration range by the lower and upper dose sufficient?
  - If the homogeneity must be determined in all 3 dose groups but only an analysis in the lower and upper dose has taken place, what documentation is expected by the authority regarding raw data and report (deviation, GLP exception)?

Answer:

According to OECD FAQ on GLP, Section "Test items, reference items and samples/specimens (including Biotechnology, GMOs, etc.), Section I":

"(a) General situation: If a test item is prepared in a vehicle for a GLP study and data on homogeneity, concentration and stability are not determined, this constitutes a deviation to GLP and the study director should report it in the GLP compliance statement of the final report and assess the impact of this deviation on the validity of the study (see OECD Document No. 1, section 6.2.5 and OECD Document No. 19, section 8.2) (as cited in FAQ …)"

=> All concentrations dosed should be analysed, if not all formulations were analyzed, this should be reported in the GLP compliance statement of the final report and the impact on the study should be assessed.

REPORTING OF STUDY RESULTS (APPARATUS, MATERIAL, AND REAGENTS)

Freezers/Refrigerators/Animal Housing

What is the authority's expectation for the scenarios regarding the content of the report and when a deviation is expected?

- **Scenario A :** Storage is planned in the Study Plan as follows: *"... in a deep freezer with the setpoint - 80°C..."*
  - The deep freezer has a different setpoint (e.g. -70°C)

    Answer: The measured temperature is relevant; however, a measured temperature that deviates from the setpoint may indicate malfunctioning of the cooling device and may lead to inconsistencies in the documentation.

  - The temperature deviate from -80°C but the default setpoint of the deep freezer is -80°C

    Answer: The measured temperature is relevant. The TF should define what temperature fluctuations (temperature limits, duration of exceedance) are relevant and should be treated as deviations. If the storage instructions in the study plan reflect these criteria, inconsistencies are avoided.

REPORTING OF STUDY RESULTS (APPARATUS, MATERIAL, AND REAGENTS)

Freezers/Refrigerators/Animal Housing

What is the authority's expectation for the scenarios regarding the content of the report and when a deviation is expected?

- **Scenario B:** Storage is planned in the Study Plan as follows: *"... target storage temperature -80°C +/- 10°C…"*
  - The measured temperature is above or below the limit

    Answer: If the temperature deviates from the limits that are set in the study plan, this is a deviation and should be assessed and reported.

  - The measured temperature is above or below the limit but within a larger limit that is defined in an SOP (-40°C to -90°C is allowed without issuing a deviation or taking an action up to 24h)

    Answer: It is still a deviation from the study plan, if the acceptable limits/duration in the SOP are not reflected/referenced in the study plan. The temperature limits should not be selected too wide just to avoid deviations, the limits should be justified.

Note: Often only the target conditions or planned conditions are reported. Some CROs start to use very large temperature ranges until they issue a deviation (-80°C defined as -40°C to - 90°C; -20°C defined as <0°C to -40°C) even so the study plan defines smaller ranges (-80°C +/- 10°C; -20°C +/- 5°C or only a fixed temperature)

REPORTING OF STUDY RESULTS (APPARATUS, MATERIAL, AND REAGENTS)

Freezers/Refrigerators/Animal Housing

What is the authority's expectation for the scenarios regarding the content of the report and when a deviation is expected?

- **Scenario C:** Storage is planned in the Study Plan as follows: *"... in a deep freezer at -80°C..."*
  - The temperature deviate from -80°C

  Answer: The TF should define what temperature fluctuations are relevant and should be treated as deviations. If the temperature deviates from the limits that are set, it is a deviation that should be assessed and reported. If the storage instructions in the study plan reflect these criteria, inconsistencies are avoided.

REPORTING OF STUDY RESULTS (APPARATUS, MATERIAL, AND REAGENTS)

Freezers/Refrigerators/Animal Housing

What is the authority's expectation for the scenarios regarding the content of the report and when a deviation is expected?

- **Scenario D:** The planned target conditions in the animal house is 20°C +/- 5°C; Humidity 40% - 60%
  - The temperature and or the humidity deviate from the target

  Answer: If the temperature / humidity deviates from the limits that are set in the study plan it is a deviation that should be assessed and reported in the study report.

REPORTING OF STUDY RESULTS

- A GLP study was initiated, but due to issues with the test item stability the initial results were not interpretable in a meaningful way (phase 1).
- When the study director became aware of the issue the study was paused, the issues with the stability resolved and the work was repeated under the same study number with results that could be interpreted (phase 2).

- Would it be acceptable to report the results and interpretation from phase 2 only and keep the data from phase 1in the raw data or in an appendix to the study report with a statement that they are excluded from the evaluation and from QA audit?

REPORTING OF STUDY RESULTS

Answer:

The following answer does not discuss the «pausing» of the study or repetition of experiments under the same study number as no specifics are provided.

Overall, the proposal reporting the results and interpretation from phase 2 only and keeping the data from phase 1 in the raw data is acceptable, if the following conditions are met:

According to OECD Doc No. 22, section 6.8, *data may only be invalidated or excluded where it can be demonstrated through sound scientific or technical justification or logical sense that the data are not representative of the recorded event. [..] In all cases, the justification of the invalidation or exclusion should be documented and considered during data review and reporting. For common cases (e.g., incoherent analytical results for a single sample, or failure to meet acceptance criteria), the rules to exclude or invalidate data should be defined in advance in the study plan or in SOPs. All data (even if invalidated) should be retained with the data set and be available for review in a format that allows the validity of the decision to invalidate or exclude the data to be confirmed.*

It is expected that the final study report lists the observed deviations and subsequent changes of the study (i.e., exclusion of phase 1).

REPORTING OF STUDY RESULTS

SoC details regarding impact of Non-GLP activities on GLP study results

- In case of activities excluded from the GLP statement of compliance in the final report, to which extent the impact on the final result of the study has to be described in the statement of compliance (i.e. the impact on the scientific conclusions reported driven by data coming from non-GLP part of the study)?
- Especially when the data coming from the non GLP part of the study represents important evidence for the safety evaluation.

REPORTING OF STUDY RESULTS

Answer:

In general, all parts of a study relevant for the safety assessment of receiving authorities should be compliant to GLP as GLP ensures *i.a.*, the quality standard of a study.

According to OGLP (Annex 2, section 9.1): "*The final report should be signed and dated by the Study Director to indicate acceptance of responsibility for the validity of the data. The extent of compliance with the Principles of GLP should be indicated.*"

OECD Document No. 21 states in section 6.2 the following with regard to the selection of a non-GLP test site: [..] "*The study director should clearly indicate in the GLP compliance statement in the final study report the non-compliance of the test site and assess the impact of such a deviation to GLP and on the validity of the study.*"

This should also be considered for the study director's statement with regard to other non-GLP parts of the study.

However, if relevant information is derived from a non-GLP part, it should still be adequately considered in the scientific discussion of the study report despite of the apparent lack of GLP compliance.

ARCHIVING

According to Interpretation 9.1:

- GLP documentation for GLP draft reports waiting for the sponsor's comments should be transferred to the archive after 6 months irrespective of the status.
- Is it sufficient to describe this in an SOP or does it also have to be included in the test plan in the "Archiving" section?

Answer:

It is not necessary to include this in the study plan. It is acceptable to define the timelines for transfer of the study documentation to the archive in an SOP.

However, to avoid long delays for sponsor comments to draft reports, timelines for sponsor replies and consequences in case no reply is provided (i.e., finalization of the report without sponsors comments) should be defined in the study plan or in the service agreements or contracts (see also OECD Document No. 21, section 6.1).