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QUESTIONS AND ANSWERS
CONCERNING THE IMPLEMENTATION OF DIRECTIVES 2004/9/EC AND 2004/10/EC ON GOOD LABORATORY PRACTICE (GLP)

INTRODUCTION

This document gathers some questions and answers concerning the interpretation of the two GLP Directives.

The questions were discussed between the Commission services and the representatives from the Member State GLP monitoring authorities and the answers were approved by the EU GLP Working Group.

The document attempts to provide guidance to monitoring authorities, regulatory authorities and test facilities. The answers represent the opinion of the EU GLP Working Group.

This guidance document does not constitute any formal commitment on behalf of the Commission. Only the European Court of Justice can give an authoritative interpretation of European Union legislation.

The guidance document will be regularly updated and published on the website of the European Commission.

Contents

1) TEST FACILITY ORGANISATION AND PERSONNEL

Q&A 001: Deputy of a study director

Q: Under what conditions if any is a deputy of a study director allowed to sign a study plan or a final report?

A: The GLP Principles do not refer to a "deputy study director". It was agreed that there can only be one study director responsible for a study, and that his core tasks cannot be delegated to a deputy.

Additional information on the replacement of study directors can be found in OECD consensus document 8, page 11: "replacement of the study director".

Q&A 005: Test Facility Management Organisation

Q: Test Facility Management – should it be an individual or a team?

A: The GLP principles allow having either an individual or a team. In the latter case, the management responsibilities (as defined in the OECD GLP Principles) allocated to each individual have to be clearly defined. Each individual may hold all or only some of these responsibilities depending on their role within the facility as long as it is clearly documented what their role and responsibility is, communication lines are clearly defined, conflict of interest is avoided and the requirements of the Principles are met.

2) QUALITY ASSURANCE PROGRAMME

Q&A 014: Head of test facility management as QA

Q: Can the head of test facility management be responsible for quality assurance?

A: There would be a conflict of interest, and therefore the facility would not be in compliance. An external QA could be used (in particular in the case of very small test facilities).

3) FACILITIES

No current Q&A entries.

4) APPARATUS, MATERIAL AND REAGENTS

Q&A 024: Verification and calibration of anemometers in field studies

Q: What are the verification and calibration requirements for anemometers in field studies?

According to the principles, a test facility should have established clear SOPs for the periodic inspection, maintenance, cleaning and calibration of the equipment. Anemometers are expected to be calibrated to show that they are fit for purpose. High wind speed might result in reduced amounts of test item applied to the crop and, as a result, in an underestimation of residue levels in crop samples. For that reason study plan and/or SOPs on spraying should define the conditions during spraying including the maximum allowed wind velocity during application.

5) TEST SYSTEMS

Q&A 027: Verification requirements for plants and seeds in field trials

Q: In light of the provision in OECD Document No 5 (paragraph "Test systems"), how should plants, seeds, soils and other materials used as test systems be documented as to their source, date of acquisition, variety, strain, cultivar or other identifying characteristics?

Even if it is required by the study plan to report the variety/strain of the crops used, all handlings by the farmer until application of the test item can be seen as not falling under the GLP requirement.

However, the acceptability of a simple declaration by the farmer that he/she supposes to use a specific variety of the seed depends on the type of treatment. If the application concerns the seed treatment, the seed collection should be documented, while if the treatment concerns the application after growing of the plant, no information on the seed is required.

As it cannot be confirmed that this information is verified by the Study Director (SD) or Principal Investigator, this can fall under the non-GLP claim in the statement from the SD, as it is not in the remit of the SD.

6) TEST AND REFERENCE ITEMS

No current Q&A entries.

7) STANDARD OPERATING PROCEDURES

Q&A 006: Test Facility Management and SOPs

Q: Should Test Facility Management be involved in the approval of SOPs?

A: SOP approval should always be performed by someone who is designated as Test Facility Management (no exceptions).

Q&A 009: SOPs in two languages

Q: Original SOPs in one language have been translated into another language. Do the translations have to be approved in the same way as original SOPs?

A: The OECD's multi-site study document states that in any translated SOP reference should be made to the original. Both versions need to be authorised by management if the SOP is available as an original in two different languages.

Q&A 012: Circumstances under which the study plan provisions may take precedence over SOPs

Q: Is QA allowed not to highlight differences between study plans and facility SOPs as deviations claiming that SOPs are superseded by study specific methods and procedures detailed in the study plan?

A: Such a practice can only be accepted under certain conditions. Deviations from the study plan should also be documented in the study records and, additionally, be presented

as such in the study report. There should be a very detailed study plan signed by the study director and approved by QA and there should be no ambiguity between the study plan and the SOP. In cases where the study director overrules the SOP (which has been approved by his test facility management) it is expected that management also signs the study plan.

8) PERFORMANCE OF THE STUDY

Q&A 017: GLP and study design

Q: Are GLP inspectors authorised to comment on study related scientific issues?

A: Whether or not a GLP inspector should comment on scientific issues must be assessed on a case by case basis. If the test facility does not follow the methodology outlined in the study plan or if the issue has an impact on the validity of the data then it is a GLP problem. If it is a question of study design, the decision is up to the judgement of an assessor in a receiving authority. If the receiving authority is known, it should be informed.

Q&A 025: Amendments to a study phase plan or report

Q: Study phases may be designed in a phase plan and reported in a phase report. How can these be amended?

The only official GLP documents are the study plan and study report. Procedures for study phases can only be modified by an amendment to the study plan, which should be approved by the study director. Principal investigators, responsible for a delegated phase of the study, can propose modifications to the study director.

The study director is also responsible for the final report. An amendment to the phase report can be proposed by the principal investigator prior to the finalisation of the final study report. When receiving an amendment to the phase report after the completion of the study report, the study director should consider whether an amendment to the study report is needed.

Q&A 019: Study plans and confidentiality

Q: The study plan can contain confidential items which the study director may not wish to disclose to all test sites to which experimental phases are delegated.

Is it acceptable that in the copy of the study plan that is sent to some test sites certain parts are blackened? Would it be acceptable that test sites just receive the information they need to perform the delegated phase in a study plan amendment (with no copy of the blackened study plan)?

A: All personnel involved in a study need to have full access to the complete unedited study plan and its amendments. If the identification of test items or reference items systems is a concern, the GLP principles allow the use of codes to conceal the identity of the test items or reference items.

Q&A 013: Actual concentration of the test item varies significantly from the nominal value

Q: Should an amendment be drawn up in the situation where the actual concentration of the test item varies significantly from the nominal value of the test item stated in the study plan?

A: The actual values should be given in the study report and it should be made clear that the concentration of the test item varies significantly from that stated in the study plan.

GLP requires a full description of all findings and a discussion on the potential impacts on the study results.

9) REPORTING OF THE STUDY RESULTS

Q&A 002: How many "original" (signed) reports?

Q: How many original versions of final reports are acceptable?

A: There must be one signed original report, which should be archived by the study director. However, some regulatory authorities require more than one signed report. In such a case, all signed reports have to be identical, identifiable (e.g. original 1 of 2) and originally signed.

Q&A 023: Multiple study reports for one study plan

Q: *If two different formulations are tested in a study, can there be two different independent study reports, reporting the results for each formulation?*

No, according to the principles, the final report should contain *"all information and data required by the study plan"*. This means that there cannot be two different final reports, each reporting only half of the data required by the study plan. A GLP study strictly has one study plan and one study report (the so-called 'rule of ones'). This also applies to multi-site studies, as outlined in OECD consensus document 13 on 'The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies'.

Q&A 015: Preparation of the final report by the Study director

Q: Is it a significant GLP deficiency when a study director prepares his (her) final report based in part on unsigned draft reports of contributing scientists?

A: The study director may prepare the final report based on unsigned draft reports, but before the final report is signed, all reports of the contributing scientists have to be signed by them in order to make sure that the content has not been changed.

The QA statement should also be available. According to OECD Consensus Document 4, the QA audit of all final reports for which GLP compliance is claimed should be conducted at the final draft stage, when all raw data have been gathered and no more major changes are intended. Please note that contributing scientists may also directly transfer raw data to the study director.

Q&A 021: Electronic signature of the final report of a GLP study

Q: Does an e-signature for GLP reports mean (1) a signature by the study director with his personal login + password in a secure IT environment or (2) the study director should fulfil the requirements of a qualified signature – qualified certificate by a qualified body?

A: The GLP Principles require that study plan, final report (SD statement) and QA statement are signed by dated signature. According to Directive 1999/93/EC on a Community framework for electronic signatures, only advanced electronic signatures which are based on a qualified certificate and which are created by a secure-signature-creation device satisfy the legal requirements of a signature in relation to data in electronic form in the same manner as a handwritten signature and are admissible as evidence in legal proceedings.

Q&A 016: Involvement of sponsors

Q: Is it a significant GLP deficiency when a study director invites the study sponsor to comment on his/her draft report before editing the final version?

A: It is standard practice for the sponsor to comment on the draft report. However, the study director signs the study report and carries the responsibility for compliance with GLP. The sponsor must not have any influence on the interpretation of the study data. To ensure this, correspondence between the study director and the sponsor should be retained and archived.

10) STORAGE AND RETENTION OF RECORDS AND MATERIALS

Q&A 020: Test item stored by sponsor

Q: If the test item is sent back to the sponsor after the study, is it acceptable that it is stored in the freezer of the sponsor and not in a GLP compliant test facility?

A: No, a test item sample should be archived in accordance with the GLP principles (par. 10.1) for the period specified by the appropriate authorities or, if not specified, at least for the time that its quality permits evaluation.

Q&A 007: Archiving of original QA notes

Q: Are the notes of QA during a GLP-inspection considered as raw data - and if yes, are these notes to be archived (or is the QA-inspection report considered as being sufficient)?

A: QA notes are not considered to be raw data. However, there should be sufficient information available to demonstrate that QA is working effectively. The QA report must always be archived.

Q&A 011: Electronic archives in third countries

Q: Is it acceptable to use IT companies based in third countries [non-EU or covered by a Mutual Recognition Agreement] to perform electronic archiving and data back up? What measures should test facility management take to ensure that the facilities are fit for purpose?

A: Such an arrangement could be acceptable, but adherence to the requirements of the GLP Principles has to be assured by test facility management.

Q&A 022: Archives of a test facility leaving programme

Q: In Member State A, a test facility closes down and transfers all GLP-documentation to a GLP archive in Member State B. The test facility is now operating only as a sponsor. Does this sponsor have to be in the GLP monitoring programme of Member State A?

A: The sponsor does not have to be in the monitoring programme of Member State A, but the archives may be monitored by Member State B.

According to Document 15 of the OECD Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring, after the transfer to a new archive facility has taken place, the GLP monitoring authority will normally inspect the new archive. In case records or materials are transferred to facilities located in another country, the GLP monitoring authority in that country should also be informed and take this into account during inspections. In any case, the sponsor should be able to obtain copies of his studies at all times.

Q&A 018: Contract archives

Q: Do EU Member States grant GLP certificates to archives without any other GLP activities?

A: Most Member States will not give a separate compliance statement to the contract archives facility, but inspect it as part of a test facility inspection. In principle, the test facility management is responsible for archiving, including contract archives.

11) SCOPE OF GLP

Q&A 026: Wording of GLP claims

Q: What constitutes a claim of GLP compliance for a non-clinical safety study by a test facility?

A claim to GLP constitutes any claim of having conducted a non-clinical study in accordance with or in compliance with the principles of GLP (or using any other expression with the same meaning), as outlined in Annex I to Directive 2004/10/EC, as transposed into national legislation under the relevant national GLP Compliance Monitoring Programme.

Q&A 010: GLP and efficacy studies for medicines

Q: In some situations human efficacy studies cannot be conducted because it would be unethical and efficacy of new products needs to be derived from an animal model. Is the conduct of these efficacy studies covered by the OECD principles?

A: Normally GLP is not required for efficacy studies. However, studies for medicines linked to developing or confirming safety information (e.g. such as efficacy studies for vaccines) should be done under GLP.

12) MULTI-SITE STUDIES

Q&A 004: Individual reports of delegated phases

Q: The OECD consensus document 8, page 7, 4th paragraph specifies that "As the lead scientist, the Study Director must coordinate with other study scientists, and/or Principal Investigator(s) keeping informed of their findings during the study and receiving and evaluating their respective individual reports for inclusion in the final study report." Does this phrase mean that the principal investigator is obliged to prepare an individual report of his delegated phase?

A: The principal investigator should either produce a signed and dated report or transfer the raw data to the study director.

The OECD consensus document 13 specifies that "The PI should provide the SD with contributions which enable the preparation of the final report. These contributions should include written assurance from the PI confirming the GLP compliance of the work for which he/she is responsible"[1] … "Alternatively, raw data may be transferred from the Principal Investigator to the Study Director, who should ensure that the data are presented in the final report"[2]. Taking this information into account, a single final report should be issued for each multi-site study.

Q&A 003: Raw data not sent to Study Director

Q: During GLP inspections it is often observed that the raw data of the delegated phase are not sent to the Study Director. In some cases certified copies of raw data are sent to the Study Director and in other cases only reports of the Principal Investigator. The OECD consensus document 13 defines that "alternatively, raw data may be transferred from the Principal Investigator to the Study Director, who should ensure that the data are presented in the final report"[3]. Is this an obligation or not?

A: There is no obligation to transfer raw data to the study director under OECD rules if the principal investigator has provided the study director with a phase report. Raw data can be archived by the study director or the principal investigator.

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[1] The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies, ENV/JM/MONO(2002)9, p. 7

[2] The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies, ENV/JM/MONO(2002)9, p. 16

[3] [3] The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies, ENV/JM/MONO(2002)9, p. 16

Q&A 008: Field trials in other EU Member States

Q: If a phase of a field trial is conducted in another Member State under the supervision of a principal investigator and a GLP compliance claim is made, should the principal investigator's test site be a member of the national compliance monitoring programme of that Member State?

A: The study director (or the principal investigator at the local test site) should inform the compliance monitoring authority in the country where the site is located before the start of the study phase. The compliance monitoring authority of the country where the site is located will then take a decision on a case by case basis.