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OECD Position Paper Regarding Possible Influence of Sponsors on Conclusions of GLP Studies

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OECD Position Paper Regarding Possible Influence of Sponsors on Conclusions of GLP Studies

1. FOREWORD

The following paper was developed by a drafting group of the OECD Working Group on Good Laboratory Practice (GLP). The drafting group was under the leadership of Thomas Lucotte (France Medical Products) and Stephen Vinter (UK) and included representatives from Argentina, Belgium, Denmark (Medical Products), Denmark (Industrial Chemicals), Germany, Japan (Medical Products), South Africa, Switzerland, the US (FDA) and the US (EPA). The paper discusses the relationship between test facilities and sponsors, and how the GLP Principles provide a framework for ensuring the independence of study directors against possible undue influence (both intentional and unintentional) on the conclusions of GLP studies.

This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology which agreed to its declassification on 30 April 2020.

2. INTRODUCTION

There is a perception that sponsors may have influence on the conduct of GLP studies. This document is meant to further strengthen the independence of the study directors.

3. SCOPE

The purpose of this document is to clarify the requirements of the GLP Principles regarding the relationship between test facilities and sponsors and the documentation test facilities are expected to maintain about those relations.

This document presents possible scenarios in which the sponsor could possibly influence the outcome of a GLP study and the steps a test facility can take to maintain confidence in the independence of the study director.

OECD Advisory Document No 11[1] discusses the role and responsibilities of the sponsor in the application of the Principles of GLP and outlines both the explicit and implicit responsibilities of a sponsor necessary to fulfil his or her obligations. Although this new document is addressed to test facilities and test sites, it will also provide valuable guidance to sponsors of GLP studies.

4. RESPONSIBILITIES

The sponsor initiates and supports, by provision of financial or other resources, non-clinical health and environmental safety studies and/or submits such studies to regulatory

[1] *The Role and Responsibility of the Sponsor in the Application of the Principles of GLP* (ENV/MC/CHEM(98)16)

authorities in support of a product registration or other application for which GLP compliance is required.

The study director has the ultimate responsibility for the scientific validity of a study. To ensure proper independence, it is strongly recommended that the study director and the sponsor representative are not the same individual.

Test facility management has the formal responsibility for the organisation and functioning of the test facility in compliance with the Principles of Good Laboratory Practice, and, as such, should ensure that the conduct of studies are free from external influence that could impact the compliance and conclusions of the studies and/or the test facility.

5. A SPONSOR WHO MAY DIRECTLY BE INVOLVED IN THE STUDY

The sponsor organisation can be directly involved in the conduct of the study in the following scenarios.

The sponsor and the test facility belong to the same organisation. The sponsor representative and the test facility management could be the same person. This situation is often encountered with larger organisations that possess their own GLP test facilities. In this scenario, the sponsor organisation will have full responsibility for the conduct of studies.

The organisational design of the sponsor and the test facility should ensure that roles are clearly defined. Transparency regarding study and facility management decision-making is critical; therefore, systems should be in place to retain documentation and correspondence required to verify study conduct and demonstrate compliance with the GLP Principles.

In a multi-site context, the sponsor and one of the test sites involved in the study belong to the same organisation. For example, bioanalytical phases in non-clinical safety pharmaceutical studies are often performed by the sponsor as they have the experience and knowledge of the test item molecule.

In such a situation, communication between the study director and principal investigator should be suitably documented and retained to allow study reconstruction. The study director must take the overall responsibility for the conduct of the entire study. Therefore, direct communication between the sponsor and the principal investigator about a study that excludes the study director must be avoided.

In a multi-site context, the sponsor conducts the pathology peer-review. In this situation, it may be justifiable based on the fact the sponsor has experience with the test item gained during the development of the test item and has a greater understanding of its toxicological profile.

To allow for the full reconstruction of the histopathology outcomes, it is expected that the test facility will document and retain all relevant details on the organisation of the peer review including all correspondence regarding the histopathological evaluation of the slides used for peer review between the sponsor and representatives of the test facility and the peer review pathologist in the study file.

In a multi-site context, the test facility and the sponsor are in the same organisation and the role of the test facility is limited to the location of the study director. Under this scenario, all the experimental phases of the study are carried out by principal investigators in contracted test sites that could be located in other countries.

For such a situation, it is expected that the final phase reports or all the raw data generated in the study phases (or authenticated copies) should be available at the test facility.

The test facility where the study director is located should implement systems to comply with the GLP Principles and is subject to a GLP inspection by their local GLP compliance monitoring authority.

Staff from the sponsor can act as study personnel. This may occur when the routes for administration to animals require a specific surgical procedure or in viral clearance studies where the experience of sponsor staff is requested to mimic the process in a reduced scale.

In such a scenario, sponsor staff should be considered as study personnel and fall under the control of the test facility.

Therefore, documentation on competence, training of the sponsor staff in the GLP Principles and in relevant test facility SOPs should be retained at the test facility. The competence of the sponsor staff to carry out their tasks in the study should be approved by the test facility management. These requirements should be fully described within a contract or technical agreement.

The involvement of the sponsor staff should be described in the study plan and the fact that they were supplied by the sponsor organisation must be clearly stated.

Any work carried out by the sponsor staff should comply with the GLP principles and facility procedures and be fully documented. Any deviation from the study plan or from the SOPs in the sponsor staff work should be reported directly to the study director.

The final study report should describe the role of the staff from the sponsor in the study experiments. As the study director should state any deviations from the Principles and their impact in the study report, deviations generated by the sponsor staff should also be reported and their impact assessed.

The sponsor assumes the role of Quality Assurance (QA) for the study (or nominates a contractor to conduct the study specific audits).

Such a situation may create a conflict of interest and jeopardize the independence of QA. If this situation cannot be avoided, it should be fully justified in the study plan (for example specific critical phases that require specialist QA personnel to be inspected). The test facility management should officially appoint this external QA in order to approve their appropriate qualifications and independence.

Documentation on training for the necessary expertise and experience of the external QA should be available at the test facility.

Any audits should follow the test facility systems for reporting to test facility management and the study director.

6. A SPONSOR WHO MAY BE INDIRECTLY INVOLVED IN THE STUDY

Contract Research Organisations (CROs) that act as test facilities and test sites undertake GLP studies on behalf of a sponsor. The nature of this relationship could potentially lead to a sponsor exerting pressure on the test facility and/or test site with respect to the conduct and reporting of the study. It could also lead to a desire by the CRO to meet the customer's needs while neglecting the need to ensure that the compliance of the study and the integrity of the data are not compromised.

Therefore, correspondence between the sponsor and CRO should be retained to allow full verification of all study decisions and the input received from the sponsor.

6.1. Common scenarios

In a multi-site context, the test sites could be chosen by the sponsor and not by the test facility management.

If parts of the study are contracted to subcontractors by the sponsor, the sponsor should be aware that the responsibility for the whole study remains with the study director, including the validity of the raw data and the report.

Therefore, communication between the test facility and the test sites should be retained by the test facility to ensure that the study director is the single point of control. Direct communication related to the study phase between a test site and the sponsor without the involvement of the study director must be avoided.

The draft study report is reviewed by the sponsor before being finalised.

To demonstrate the extent that the sponsor commented on the final study report, it is recommended that relevant correspondence between the study director and the sponsor and/or draft versions of the study report be retained by the test facility.

It is strongly recommended that the study report be audited by QA at least after the comments of the sponsor have been integrated by the study director.

The sponsor may delay the review of the draft study report, the provision of test item documentation, or the completion of the study after the end of the experiments. Such a scenario could lead to delays in the prompt reporting of the study, failure to close the study, or a delay in study archiving (which increases the risk to the integrity of the study recorded).

To avoid this situation, it is strongly advised that test facilities define required timelines in the study plan or in any service agreements or contracts. For example, a test facility could include a maximum time for the sponsor to review the draft report after which the final report will be issued by the study director with or without comments or additional required information from the sponsor. This scenario should also be considered in multi-site studies.

Sponsors always play a primary role in test item management. The supply of test items by the sponsor without an appropriate level of characterisation information (especially when pre-prepared) can be problematic. The transportation of the test item to the test facility is also a critical phase for the integrity of the test item and is often managed by the sponsor.

Test facility management is responsible for the test item received by the test facility being fit for purpose.

OECD Advisory Document 19[2] provides guidance for test facilities on the expectations of national GLP compliance monitoring authorities on how, among other things, test items are transported and characterised. It will not be repeated in this document.

Communication between the sponsor and the test facility related to the test item should be retained by the test facility.

If characterisation data are not fully disclosed by the sponsor to the contracted test facility, and the test facility has not performed a characterisation themselves, this fact should also be explicitly mentioned in the final report. Incomplete information on the characterisation of the test item may result in a critical deviation from the GLP Principles depending on the extent and nature of the missing information.

6.2. Less common scenarios

In a multi-site context, some sponsors indicate that a phase of a study is too technically difficult to be performed at a GLP test facility and wish to conduct the phase in their own non-GLP laboratory, even if potentially suitable GLP test facilities exist.

The study director must maintain his or her responsibility for the conduct of the study, and must be aware that some GLP monitoring authorities require notification of the proposed activity and will need to give their approval of the use of any non-GLP facilities.

When commissioning a non-clinical health and environmental safety study, the sponsor should ensure that the test facility is able to conduct the study in compliance with GLP and that it is aware that the study is to be performed under GLP.

Nevertheless, if a sponsor chooses to conduct a study phase in a non-GLP site, communications related to this choice should be maintained in the study files by the test facility.

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.

A sponsor may decide to perform vendor audits during the conduct of a study to ensure that the study is conducted in compliance with the principles of GLP.

In this scenario, the audit, if conducted during or after the study, should remain independent of the test facility's systems and not influence the outcome of the study (see scenario above: "The sponsor assumes the role of Quality Assurance (QA)"). The test facility is responsible for documenting any deviations relevant to the study in their own systems.

A sponsor may decide to terminate the study in progress before it has concluded.

The early termination of a study may occur prior to, or after, the completion of the experimental phase of the study, but before the data has been assessed or incorporated in a final report. In both situations, a study plan amendment must be produced in order to

[2] *Advisory Document of the Working Group on Good Laboratory Practice on the Management, Characterisation and Use of Test Items* (ENV/JM/MONO(2018)6)

provide an explanation of why the study was terminated. Some compliance monitoring authorities may expect that the key findings up to the point of termination are summarised and that the summary report is subject to a QA audit.

To ensure the termination of the study is done in a controlled and transparent way, the test facility should retain communications from the sponsor that justify the decision to stop the study. The same process about documentation should apply when the sponsor asks for a GLP study to be changed to a non-GLP study.

Terminated studies and studies for which the requested status changed from GLP to non-GLP should be indicated as such in the master schedule.

Sponsors can request test facilities to generate interim reports or intermediate results of studies that are conducted in accordance with GLP. An interim report is a report of a non-completed study. Interim reports are requested by some receiving authorities in specific circumstances, for example, in case of public health alerts to expedite the availability of the test item for clinical purposes or to collect information on its toxicity.

It is important to note that the GLP Principles only recognise the final study reports to report the study results. Thus, there is a risk that an interim report will not be accepted when submitted to a receiving authority for decision making if such a report is not requested by the authority.

Nevertheless, there is no objection to issuing interim reports or intermediate results that do not contain any study director's claim of GLP compliance.

A sponsor can decide to conduct a complex study across several studies (not in a single or multisite study but split across several individual studies). For example, the in vivo phase of a chronic toxicity study may consist of one independent study, the bioanalytical phase on the plasma specimens may constitute another study, and the calculation of the toxicokinetic parameters a further study.

When several studies are presented to a regulatory authority in a single package, the responsibility for the integrity of the assembled package of unaltered final reports lies with the sponsor. However, it is essential that if this approach is adopted then all studies must be suitably transparent to reconstruct the performance of the work package. Each single study must comply with the principles of GLP with study plans and reports containing clear links to the other related studies.

Some receiving authorities may not accept a safety study that is conducted as a number of independently organised GLP studies.

In the context of each single study, study directors should define the test item and the test system in the study plan and provide a conclusion for their study in the final study report.

To define and characterise a test item of a stand-alone analytical or calculation phase could be challenging. Furthermore, references to the other studies that generated the specimens that will be examined in the study or the dosage results should be available in the study documentation (including the study plan and final report) to allow for a full reconstruction of the entire package of work. Transfer of study materials between test facilities involved must be fully documented and the documentation should be retained.

Sponsors may request CROs to reopen reports by amending them to add additional data.

The OECD Principles of Good Laboratory Practice provide provisions for errors in the final report to be corrected and admissions to be addressed by issuing a study report amendment. However, it would not be appropriate to use a study report amendment to facilitate the reanalysis of data or the addition of new data to a final report except under exceptional circumstances.

Exceptional circumstances would include requests from receiving authorities to reopen a GLP study. Such requests are usually made so that data can be reanalysed. For example, studies may be reopened to reassess statistical analyses or to review histology findings.

Monitoring authorities will usually not allow a study to be reopened if the test facility or study sponsor wants to reanalyse or add data. However, most monitoring authorities will assess each request to reopen a study on a case-by-case basis.

If a GLP study is reopened, any changes to the original text or the addition of new text must be presented in the form of a report amendment. All the original data must be retained in the final report and the reason for reopening the study should be documented in the amendment. If additional work is performed that was not required in the original study plan, it should be covered by a study plan amendment.

Sometimes a sponsor can supply specific reagents, equipment or other resources for the conduct of the study.

In this case, the test facility management should ensure the conformity of these resources and retain the documentation to demonstrate it. Attention should be given to the transportation step that could affect the conformity of the resources supplied (e.g. thermos-sensitive reagent or equipment that may require new calibration after the relocation).

Some sponsors may request, for exploratory research purposes, the test facility to collect specific samples of the preparations of the test item or of specimens.

Such tasks must be scheduled in the study plan to inform the study personnel of such specific handling requirements. In such cases, these activities should also be reported in the final report. Nevertheless, the study director should clearly state in the final report that such sampling and handling was out of the scope of the GLP study, including an assessment that the additional sampling did not interfere with the conduct of the study and did not jeopardize the GLP compliance of the study.

The GLP Principles require that all information and data required by the study plan should be included in the study report. Some GLP monitoring authorities may therefore require that all data, including results from exploratory research analyses, be reported.

7. CONCLUSION

The potential influence by sponsors on non-clinical study outcomes is an important issue and is not sufficiently covered and clarified by the GLP principles and guidance. The sponsor's actions and behaviours as described in the scenarios above could possibly compromise the GLP compliance status of the studies and/or the integrity of the data and the study outcomes. This position paper clarifies the expectations of national GLP compliance monitoring authorities and includes recommendations in this area.