



A commenting view on how additional results should be reported and linked to the original study report

A Data Integrity Issue – Report Amendment or additional new Study?

For the conduct and reporting of GLP (Good Laboratory Practice) non-clinical toxicology studies data integrity is one of the key pillars (as for other GxPs – Good X Practice). If important questions arise during submission review by authorities, additional data may need to be obtained and added to the study. This raises the question of how the additional results should be reported and linked to the original study report in accordance with the principles of data integrity.

| Nina Häuselmann

Introduction

Non-clinical toxicology studies of pharmaceuticals are conducted to obtain data on the safety of these products with respect to human health. Unless specifically exempted by national legislation, the Principles of GLP apply to those non-clinical toxicology studies.

Based on the OECD (Organisation for Economic Co-operation and Development) advisory documents, on guidelines and on national authority requirements no study is (normally) reopened to include additional work. This was differently handled in some countries in the past. Whereas in the United Kingdom (UK) this process is valid for a

while, the German authorities allowed to open a study with a study plan amendment that explained the additional work and its reporting. In a second step the results were reported in a report amendment. In Switzerland the authorities expected the study to be reopened with a first report amendment and the results of the

OECD Good Laboratory Practice: Frequently asked questions (FAQ)

Management of study

Study Reporting

«3. Under what circumstances can a GLP study be reopened after the final report has been finalised?

The OECD Principles of Good Laboratory Practice (GLP) 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 add new data to a final report except under exceptional circumstances.

Exceptional circumstances will 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.

As detailed in Section 9, Part 9.1 5) of The OECD Principles of GLP, reformatting of the final report to comply with the submission requirements of a national registration or regulatory authority does not constitute a correction, addition or amendment to the final report (posted on 21 January 2016).»

Source: www.oecd.org/chemicalsafety/testing/glp-frequently-asked-questions.htm#Managementofthestudy (last accessed: 08.11.2022).

additional work to be reported in a second report amendment.

The experience is that especially large Contract Research Organizations (CROs) avoid contacting the national authorities and are generating new studies that are linked to the original study, but the original study stays unchanged without a link to the additional work and additional or changed result. In times where data integrity is one of our number one topics and we control printing of new raw data forms, we do not question the integrity of additional studies with material coming from another GLP study that could lead to a situation where not all results are submitted.

The following example will show what happens in reality, and I believe that this is a data integrity issue. I think this is not what the authority expectation is or that the authorities want this to even happen.

The Example

A carcinogenicity study in rats (for those of you not so experienced with GLP and Tox-Studies:

this is a study running for 104 weeks with at least 400 animals) is conducted by a CRO (hereinafter referred to as CRO A). At the end of the study all animals of the control group, all of the high dose groups as well as all with macroscopic findings from intermediate groups, and any animal died during the study were examined by a pathologist. All study data are reported, and the study (hereinafter referred to as study 1 = original study) is finalized. Either during an expert review or during a review of a receiving authority during the submission process the overall result of the study is questioned: Is this compound really not carcinogenic?

The sponsor goes back to the CRO and asks to examine target organs in the intermediate groups (in this example organs that showed tumors or organs that showed findings in the high dose groups more than in the control group). Following the requirement that a finalized study cannot be reopened, and amendments are only to be written to correct errors, the CRO opens a new independent study (study 2). The additional examination of the in-

termediate groups by a pathologist links to the original study to describe the treatment and shows the origin of the samples used in this new study. But the original study stays unchanged – isn't this an integrity issue as well?!

In this example the CRO missed to include in the new study 2 that an evaluation including statistics of the results of both studies (study 1 and 2) would be needed to make a statement on the carcinogenicity of the compound. The sponsor asked for this – the CRO insisted and said this is not possible.

Two thoughts of topics missed so far

1. The CRO should have contacted the national authority and ask for an exceptional reopening of the study or at least the CRO should have used the 2nd study (study 2) to include an overall statistic.
2. The sponsor should not have accepted this and should have contacted the authorities. But small sponsors or those with no GLP facility somehow trust the

CRO to do the “right” thing and do not know what other possibilities they would have.

There are even more risks with the approach to start a new study as the ones described here. Imagine that it is recognized that a wrong analysis was done or wrong evaluation used. A new analysis is done within a new study (study 2) and the result shows that the original conclusion is wrong, the compound has a negative effect. But the original study (study 1) does not contain any link to the new study. No control is in place that this new study becomes part of the submission.

Coming back to the example

What we have now are two reports with results – but we miss the overall result of the original tox study (study 1). With the existing two studies (study 1 and 2) no overall conclusion of the carcinogenicity is made. The CRO is not willing to change this or does maybe not know what to do or eschews the additional actions. The sponsor on the other hand needs the result and starts contacting their community, experts, and other CROs. Another CRO (CRO B) takes over. As the sponsor is the owner of the data, slides are sent out for additional peer reviews, expert panels and additional evaluations outside of the two first studies. Isn't this a data integrity issue too?

Two more new studies

A new study (study 3) on pathology peer review for studies 1 and 2 is issued (at CRO B) – as the CRO A did not include the peer review within their studies (studies 1 and 2). Normally a histopathology peer review is part of a tox study and not a standalone study. Nevertheless, the CRO A amended the study plan of the 2nd study (study 2) (as the report was drafted but not signed at that point) to include a histopathol-

ogy review by an expert. The CRO A also amended the review on all slides from studies 1 and 2 but with the addition that no findings from this investigation will be relayed to the CRO A. In my opinion this is a violation of GLP and data integrity.

What about the overall conclusion on the carcinogenicity of the compound? This is still not the end of this example. An additional fourth study (study 4) is issued by the CRO B conducting the peer review. This study 4 has the purpose to perform the statistical evaluation on all pathology findings and answer the question on the carcinogenicity that was the purpose of the very first study (study 1).

In the fourth study (study 4) the overall question on carcinogenicity of the compound is evaluated. To be able to do so ...

- a. the original animal data is set up in the LIMS (Laboratory Information Management System) of the second CRO (CRO B),
- b. all original histopathology findings are manually re-entered from the original report one and report two,
- c. some of the original findings were changed after the peer review and an expert panel discussion – these are marked with “Peer Review” in the LIMS to show traceability,
- d. statistical evaluation is done.

The outcome and therewith the overall question on carcinogenicity of the compound is summarized in the conclusion of only the fourth study (study 4).

Conclusion

We end up with four studies and four reports that will be kept at different CROs. Whereas the fourth report includes a link back to the other three studies none of the first three has a link to include the overall picture.

I would expect that at least the original first study (study 1) should be amended to include the answer

to its purpose on the carcinogenicity of the compound.

In my opinion this is not a GLP process of integrity at all and should be avoided. The GLP facilities should not only strictly follow a rule – in this case: a study is not to be reopened. But common sense should be used, the national authorities should be contacted and be involved to find a better process that is compliant and guarantees data integrity. |

AUTORIN



Nina Häuselmann

has been working in the field of pharmaceutical research for more than 20 years as well as in quality management both from a CRO/Spon-

sors as well as from a consultancy perspective. She has extensive experience in auditing in all quality assurance fields (GxP, ISO, QMS) and a strong background in information technology (IT) and computer system validation (CSV). Currently she is first vice president of the German Quality Management Association e.V. (GQMA).

Kontakt:

nhauselmann@hauselmann-consulting.com