

The Role of the Study Director in GLP

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Summary

With the complexity of today's studies, it has become increasingly critical that Study Directors understand all disciplines involved in studies under their responsibility. Every phase of a study directly impacts the outcome. If the Study Director does not have sufficient expertise to evaluate problems and issues in all areas as they occur, then study integrity is compromised. The physical location of the Study Director in a multi-site study is of less importance than the education, experience and expertise of that individual. The Study Director must be the single point of control and truly qualified to evaluate all the phases of the study, troubleshoot problems, draw appropriate conclusions, tie all aspects together and write the final report.

Keywords

Good Laboratory Practice, Study Director, FDA GLPs, EPA GLPs

1978: FDA GLPs

Who would have imagined in 1978 when the Food and Drug Administration (FDA) went forward with the first set of Good Laboratory Practices (GLPs) that almost 30 years later, Study Directors and their roles and responsibilities would still be a main issue? In 1978, FDA declared that the Study Director is the single point of control for the study and is responsible for the analysis, interpretation and reporting of results [1]. Several comments relating to the Study Director's responsibility are discussed in the preambles of the US GLP Regulations as indicated in Boxes 1 – 4 [1-4].

More recently, the OECD Consensus Document 'The Applications of OECD Good Laboratory Practices to the Organisation and Management of Multi-site Studies' [5] further discusses the importance of a single Study Director who is the single point of control. However, this document also provides excellent guidance regarding delegation of certain tasks and phases of the study to qualified individuals. Based on the consistent interpretation across all sets of GLPs that the Study Director be the central point of control in a study, it is alarming that FDA continues to issue FDA 483s and warning letters on this very topic.

Whether the practice was in compliance with GLPs or not, in the first 10 – 15 years of the 1978 FDA GLPs, protocols often contained statements such as ‘Bioanalytical analysis is the responsibility of the Sponsor and will be reported separately’. This statement was also often linked to characterization of the test articles as well as analysis of dosing solutions. Study Directors were often only designated responsibility for the toxicology portion of the studies, not the entire study.

1989: EPA GLPs

The 1989 revision of the US EPA GLPs [3] forced the issue of the Study Director being the single point of control, as there was again much discussion and challenges to the single Study Director per study mandate. The most often heard argument was that with most field and environmental studies, two distinct unrelated disciplines are involved (chemistry and agronomy/biology) and, therefore, two Study Directors should be allowed. In keeping with FDA’s opinion, EPA remained steadfast that there could only be one Study Director per study. In any given study, all parts of the study are in some way or another related to the other parts, thus the necessity for a single point of control and oversight.

The effort to identify a person who has the education, training, and experience to fulfill the Study Director role led most companies to the conclusion that the person who is most qualified to oversee all aspects of a study resides at the Sponsor. The primary factor in this determination was identifying the person who would ultimately be responsible for the evaluation and reporting of results and drawing conclusions on the study. Many of the Study Directors were chemists located at the Sponsor company, and were assisted by a wide variety of experts such as agronomists, soil scientists, hydrologists and other professionals depending on the nature of the study. Although not located at what was traditionally referred to as the ‘testing facility’, the Study Director controlled the logistics of the study, oversaw the technical conduct, and delegated responsibilities as required.

The end result was usually a very well run study, with the impact of any deviations determined by the Study Director in consultation with the appropriate principal investigators. The other advantage to this approach was that the Study Director at the Sponsor had direct control over the various test sites selected, so that he/she was not responsible for any aspect of the study they did not control.

Late 1990s

In the late 1990s, it became apparent to many contract laboratories in the United States that the studies they had been conducting under FDA GLPs may have been out of compliance with that rule. Questions began filtering into the authorities in the FDA Bioresearch Monitoring Program (BIMO) about the common practice of separating studies into two distinct components – the toxicology phase and the bioanalytical phase. It was not uncommon for the bioanalytical analysis to have its own Study Director

separate from the toxicology work and to be run as a separate study. The results of these bioanalytical ‘studies’ were often submitted to the Sponsor and never reached the toxicology Study Director. Once FDA made it clear that a study not only encompassed the in-life phase, but also all components linked to the in-life portion (such as dose solution analyses, bioanalytics, toxicokinetics, etc.), an entire new set of issues arose.

Sponsors had been used to soliciting the expertise of the professionals needed to adequately evaluate a compound in a given study, many times contracting the bioanalytical phase to a laboratory separate from the animal facility and at times conducting dose solution analyses and toxicokinetics in house. In tissue residue studies required for food production animals, the animal facility is often simply responsible for dosing the animals and collecting tissues whereas the Sponsor (or another designated laboratory) is responsible for analysis of the residues, interpreting the data and drawing the conclusions for the study. Although many argue that the Study Director must be located where the animal or in-life portion of a study is being conducted, it was (and still is) very difficult to conduct complex studies following that model.

FDA realized this in the early days of GLP as indicated in the Post Conference Management briefings of 1979 (see Box 5) [4].

Medical Device Studies

To further complicate the current FDA GLP arena, medical device companies are conducting studies on combination devices – those that are not only a medical device, but also have a drug delivery component such as drug-coated stents. Many GLP studies in the United States are often designed to evaluate a particular product and, therefore, have unique study designs and objectives. A typical delivery device study requires close cooperation of the engineers who designed the device, the interventionalist who is implanting the device, the bioanalytical laboratory, the histology laboratory and the consulting pathologist. Product safety is determined based not necessarily on traditional toxicology, but more often on the bioanalytical data and pathology measurements in relationship to the engineering of the device and the possible coatings and polymers.

With so many elements and facilities involved in a single study, it is imperative that the Study Director have the knowledge base and experience to oversee the entire study, determine whether issues identified at any of the sites impact other components of the study, and pull all phases of the study together. The Study Director must be able to evaluate and interpret the data from all components of the study in order to adequately draw conclusions regarding the safety of the device.

For Study Directors to truly fulfill their roles under GLPs they must be able to monitor and make changes at all test sites involved in their study. This is virtually impossible when the Sponsor is contracting one or more of the sites, when competing laboratories are used to conduct portions of the same study (a laboratory is often unwilling to allow a

competitor access to their SOPs and methods), or if the Study Director does not have a working knowledge of all disciplines involved in his/her study.

Where to locate the Study Director?

The model commonly used in EPA studies where the Study Director is located at the Sponsor solves most of the issues raised in complex and multi-site studies. This model is further defined and discussed in the above-mentioned OECD consensus document on multi-site studies [5].

Based on Warning Letters recently issued by FDA [6, 7], it is apparent that many companies are still insisting that the study director be located at the animal facility, even when that study director is not responsible for the overall conduct of the study and may not have the education, experience and training to adequately evaluate all aspects and issues that may arise during the study.

From the FDA Warning Letter issued to North American Science Associates, Inc. on 11 May 2006 [6]:

‘Your study director did not have overall responsibility for the technical conduct of the study, as well as for interpretation, analysis, documentation, and reporting of results, and she was not the single point of study control. [21 CFR 58.33].

The approved protocol dated July 9, 2001, stated that animals designated for 9 month termination would be re-implanted with test article rods at 6 months or when levels of [redacted] had dropped to 80 % of the initial steady state values, whichever came first. The protocol also stated that re-implantation would be on the left side of the chest/back and that the original implants on the right side of the chest/back would be removed at the time of re-implantation. The sponsor changed the procedure on March 21, 2002 so that re-implantation would be based solely on the blood levels of [redacted] and the original implants on the right side would remain in place. However, the study director never saw the pharmacokinetic data needed for her to determine whether blood levels met the criteria for re-implantation. She merely followed the sponsor’s instructions to implant the rods based on pharmacokinetic data in the possession of the sponsor. For the study director to fulfill her responsibility as the single point of study control, she should have reviewed the actual pharmacokinetic data to determine when to implant the additional rods. The study director also failed to document these changes to the protocol until August 15, 2002, five months after the re-implantations procedure was performed.

The signed and dated reports of each of the individual scientists or other professionals involved in the study were not included in the final report. [21 CFR 58.33, 58.185 (a)(12)].

The final study report must include the signed and dated reports of each of the individual scientists or other professionals involved in the study. The study report did not contain the pharmacokinetic data and analyses, did not address why they were missing, and did not identify the scientist or other professionals involved in that portion of the study.'

From the FDA Warning Letter issued to Gene Logic, Inc. on 28 January 2005 [7]:

'You prepared final study reports that failed to include a description of all circumstances that may have affected the quality or integrity of data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.. [21 CFR Parts 58.185(a)(9) and 58.185(a)(11)].

For study [redacted] the final report failed to discuss that the lack of information on stability of the test or control article under the conditions of administration and on uniformity of the mixtures of test article and vehicle are circumstances that may have affected the quality or integrity of the study data. The study director also failed to discuss that the bioanalytical method for concomitant toxicokinetic measurements was not sufficiently sensitive and specific to detect or measure [redacted] concentrations in the bloodstream. The sporadic findings of [redacted] in plasma samples could only have resulted from assay non-specificity, sample contamination, or accidental release from blood platelets. The study director did not discuss these implausible toxicokinetic results, except to say that they had no toxicologic significance.'

Discussion

With the increased complexity of today's research studies and increased expertise in a wide variety of disciplines that are needed for these studies, it is imperative that all parties involved re-evaluate who is designated as the Study Director. Although many arguments can be made regarding the advantages and disadvantages of the Study Directors' physical location, there is no 'gray' area regarding his/her responsibilities. These responsibilities are applicable to *all test sites* that are involved in the study, not just the animal facility. Each site should be critically evaluated to assure the Study Director can effect change at any and all test sites and that they have the appropriate education, experience and training to identify and correct potential issues at the sites before study integrity is compromised.

One common factor in many studies with significant scientific issues was that the Study Director did not know enough about the other disciplines in his/her study to realize how the data and errors impacted the overall study until it was too late. Study Directors who cannot understand and evaluate analytical/bioanalytical chemistry cannot adequately link the bioanalytical/analytical results to the actual dose applied or given to the animal. If the Study Director is not making this connection, then who is?

Of further concern in a multi-site study is the responsibility of testing facility management. In reality, the entity that appoints and replaces the Study Director is testing facility management. This management (according to OECD GLPs and logic) must approve all test sites and assure that these sites operate in compliance with GLP.

Further, they must receive all QA inspection reports from all the sites and assure that appropriate corrective actions are taken in response to QA findings. They must also evaluate the adequacy of QA arrangements and assure clear lines of communication exist between all applicable parties. It is again difficult for management at an animal facility to fulfill these roles when a Sponsor is selecting most of the test sites and may be one of the test sites themselves. It is equally as difficult for management at the animal facility to assure appropriate corrective actions are taken at sites that are not under their direct supervision or within their area of expertise.

In today's research studies involving numerous disciplines, it is widely agreed that the most critical element of study design is assuring the Study Director has the education, experience and expertise to adequately manage and oversee the study. The Study Director must be made aware of and react positively to the developments at each test site and be able to determine the impact of such on the overall study.

Testing facility management must be equally involved in assuring appropriate corrective actions are taken in response to QA issues at the various sites. If a person at the Sponsor is going to be responsible for placing the studies at the various sites, making decisions based on data and results from such sites, evaluating the entire study and drawing conclusions on the overall study, it would only make sense that this person be designated the Study Director. By default (and in keeping with EPA and OECD principles), testing facility management would then be the entity that appoints and replaces the Study Director, not necessarily the management at the animal facility.

By following this model, appropriate actions can be taken when necessary to assure that studies are well run and any unforeseen circumstances or unusual responses are adequately assessed and mitigated.

References

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Box 1

Excerpts from FDA GLPs [2] (Environmental Protection Agency (EPA) GLPs [3] read similarly):

§ 58.33 Study Director

‘For each nonclinical laboratory study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, shall be identified as the study director. The study director has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of results, and represents the single point of study control. The study director shall assure that:

- (a) The protocol, including any change, is approved as provided by § 58.120 and is followed.
- (b) All experimental data, including observations of unanticipated responses of the test system are accurately recorded and verified.
- (c) Unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study are noted when they occur, and corrective action is taken and documented.
- (d) Test systems are as specified in the protocol.
- (e) All applicable good laboratory practice regulations are followed.
- (f) All raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study.’

Box 2

Excerpts from the Preamble to the 1978 FDA GLPs [1]:

59. More than 50 comments addressed the scope of responsibilities proposed for the study director. Many comments stated that these responsibilities were much too broad for one person.

In the proposal, the Commissioner advanced the concept of a single fixed point of responsibility for overall conduct of each nonclinical laboratory study. Experience has demonstrated that if responsibility for proper study conduct is not assigned to one person, there is a potential for the issuance of conflicting instructions and improper protocol implementation. The study director is charged with the technical direction of a study, including interpretation, analysis, documentation, and reporting of results. As discussed in paragraph 58, several of the responsibilities proposed for the study director have been transferred to testing facility management. This transfer should allay concerns regarding the magnitude of the responsibilities assigned to the study director.

60. Nine comments object to the term ‘ultimate’ as applied to the study director's responsibility.

The Commissioner agrees that ‘ultimate’ responsibility for the study rests with facility management and/or the sponsor. Therefore, the word ‘ultimate’ has been replaced by ‘overall’ in § 58.33.

61. Several comments argued that more than one study director should be allowed for each study.

The Commissioner rejects these comments. As noted above, there must be a single point of responsibility for overall technical conduct of the study. The potential for conflicting instructions and confusion in study implementation is too great to diffuse the responsibility by, for example, study direction by a committee. The regulation does not, however, preclude the study director from directing more than one study.

69. Three comments suggested deletion of the phrase ‘and verified’ from the proposed requirement that the study director assure that all data are accurately recorded and verified. Four comments requested definition of the term ‘verified’.

The Commissioner disagrees with the requested deletion. Recording and verifying data are key operations in the successful completion of a study. The Commissioner intends that the study director assure that data are technically correct and accurately recorded. ‘Verified’ is used in its ordinary sense of ‘confirmed’ or ‘substantiated’. The process by which verification is achieved may be determined by the study director.

72. Two comments stated that the requirement that the study director assure that good laboratory practice regulations are followed either should be modified to make it more flexible or should be deleted. One comment suggested that the study director should be allowed to delegate the responsibility.

The Commissioner rejects these comments. The regulations constitute an effective means to aid study directors in achieving better control of complex studies. Responsibility for assuring compliance properly rests with the study director. While delegation of authority is always the prerogative of a manager, responsibility cannot be delegated.

Box 3

Excerpts from the FDA Post Conference Report [4]:

14. Study directors are frequently unfamiliar with certain aspects of their studies (e.g. chemical analyses, histopathology, etc.). Is it appropriate for the study director to authorize all deviations from standard operating procedures?

Yes. As the focal point for study direction and conduct, the study director must be made aware of and react positively to any deviation from a standard operating procedure. Where necessary, a study director should consult with other scientists to determine the impact of a deviation on the study.

Box 4

Excerpts from the Preamble to the 1987 FDA GLPs [2]:

9. Several comments objected to § 58.33 in its entirety on the grounds that (1) the regulation does not clearly define the responsibility of the study director and (2) the wording of the regulation implies that the study director must be technically competent in all areas of a study. One comment argued that the study director should be responsible only for ‘coordinating’ the technical conduct, interpretation, analysis, documentation, and reporting of results.

FDA discussed at length in the preamble to the GLP final rule the intent of § 58.33 and the requirements applicable to the individual who is designated the study director for any study (43 FR 59986, 59995; December 22, 1978). As discussed in that preamble, the study director represents the single, fixed point of responsibility for overall conduct of each study. Although ‘coordination’ of the pieces of a study logically is part of the study director’s responsibilities, to limit his or her responsibilities to mere ‘coordination’ would compromise public protection if another person were not such designated fixed point and would add an unnecessary burden if FDA were to require a laboratory to employ an additional person to provide such a point. The study director is charged with the technical conduct of a study, including interpretation, analysis, documentation, and reporting of results. FDA does not intend, however, that the individual is to be technically competent in all areas of a study. FDA’s inspectional experiences have demonstrated that if responsibility for proper study conduct is not assigned to one person, a potential exists for the issuance of conflicting instructions and improper protocol implementation.

FDA concludes that the comments did not provide any new data or information to negate the agency’s original determinations and that it should retain § 58.33 as it was established in the December 22, 1978, final rule.

Box 5

Excerpts from the FDA Post Conference Report [4]:

21. Company A is conducting a study. Company B performs animal work for Company A to the extent of implanting test material, recovering test materials and tissues, and returning these to Company A for analysis and conclusions. Which company is designated as the testing facility, which company designates the study director, and which company does the study director work for?

In the cited example, Company A would be the study sponsor while Company B would be a contract laboratory performing a portion of a nonclinical laboratory study. Both companies would be considered testing facilities, but, since the GLPs require a single study director for each study, Company A would designate the study director. Company B would, no doubt, designate a participating scientist in charge of the animal work and would have the responsibility of submitting a participating scientist's report to Company A for inclusion into the final report.