1

INTRODUCTION TO THE STUDY DIRECTOR

Mary Ellen Cosenza, PhD, MS, DABT, RAC
Amgen, Inc., Thousand Oaks, CA

1.1 DEFINITION OF STUDY DIRECTOR

What is a *Study Director* and how does one become a Study Director? These questions are not new and date back to the first draft of the good laboratory practice (GLP) regulations (41 Federal Register [FR] 1976) in 1976. Yet, these questions are still being asked over 30 years later. As with many regulatory definitions, these simple words are open to interpretation which has adapted as the practice has evolved over the years.

The current Regulations (21 CFR 1999; Part 58 Section 58.33) state:

> 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 control.
>
> The study director shall assure that:
>
> (a) The protocol, including any change, is approved as provided in 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.

The GLP regulations were first published in 1978 in Title 21: "Food and Drugs" of the Code of Federal Regulations (CFR) as Part 58: "Good Laboratory Practice for Nonclinical Laboratory Studies" (43 FR 1978), and they applied to all nonclinical safety studies intended to support research permits or marketing authorizations of products regulated by the Food and Drug Administration (FDA). Since then, similar regulations (40 FR 1989) have been published by the Environmental Protection Agency (EPA, 1983) for studies supporting chemicals and pesticides. Internationally, these regulations and guidance have been adapted by other agencies including the Organisation for Economic Co-operation and Development (OECD) and the Japanese (PMDA, 2014) regulatory agencies (for drugs and for chemicals). In all of these versions, the scope and responsibilities of the Study Director role are consistent with the FDA regulations. In 1999, the OECD Environmental Directorate issued a consensus document (OECD, 1999) on "The Role and Responsibilities of the Study Director in GLP Studies." Although not specifically applicable to pharmaceutical toxicology studies, this document gives helpful

The Role of the Study Director in Nonclinical Studies: *Pharmaceuticals, Chemicals, Medical Devices, and Pesticides,* First Edition. Edited by William J. Brock, Barbara Mounho, and Lijie Fu.

suggestions on the scope, training, and responsibilities of a Study Director in all types of GLP studies.

When the GLPs were first released in 1978 (43 FR 1978) and implemented in 1979, they defined the Study Director as the person having "overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of the results, and represents the *single point of study control*." It also stated that Study Directors needed to have "appropriate *education, training, and experience*, or combination thereof." These two phrases are the most challenging and provocative parts of the Study Director sections. In addition, the Study Director has strict compliance responsibilities. A review of the history of these sections can help us understand the thinking behind these regulations. For simplicity, the current FDA regulations (21 CFR 1999) and the OECD Consensus Document (OECD, 1999) will be used as the main references in this chapter.

1.2 REGULATORY HISTORY ON THE SCOPE OF THE ROLE

To better define the role of the Study Director, we can look at several documents:

- the Good Laboratory Regulations, both the original 1978 final rule (43 FR 1978) and then the subsequent amendments of 1987 (52 FR 1987) and 1999 (21 CFR 1999)
- the preambles to the proposed and final regulations
- the GLP questions and answers documents, several of which were combined and issued as a guidance document in 2007 (FDA, 2007).

There are consistent themes in both the questions and comments from the public to the FDA on this topic and in the responses and comments back from the FDA as well.

When the first draft of the GLPs was released for comment in 1976, there were over 50 specific comments on the scope of responsibilities for the new Study Director role. Many of the comments suggested that the role was too broad and/or suggested that some of the responsibilities listed for the Study Director should be assigned to others (preamble to 1978 final rule). Although some parts were modified in the final rule, the single point of accountability section was not changed. When the GLPs were updated in the late 1980s, the definition and scope of responsibilities were again questioned in the public comments. Again, the FDA confirmed their original intent (52 FR, 1987).

1.2.1 FDA 1976 Proposed Rule (41 FR 1976)

At the time of the GLP proposal (1976), several alternatives to having these regulations were discussed and considered including the licensing of testing facilities, having the FDA conduct all safety testing, and placing full-time agency monitors on-site at testing facilities. Instead, the FDA adopted the GLP regulations largely as we know them today. One of the new "roles" set up as part of the regulations was that of the "Study Director."

Many of the problems found in the investigations and Congressional hearings that led to the development of the GLPs were attributed to unqualified, insufficient, or improperly supervised personnel. This led to the requirements for *education*, *training*, and *experience* and the documentation of these attributes. The single point of accountability of the Study Director comes from a desire for clear direction and implementation of the protocol (eliminating conflicting instructions).

1.2.2 FDA 1978 Final Rule (43 FR 1978)

The discussion in the preamble to the final rule gives us insight into the thinking behind the final regulations. There were many comments requesting more clarification from FDA on the training, education, and experience needed for study personnel. FDA declined to be more exact as it was felt that these requirements would vary from study to study. This was confirmed in question-and-answer documents when asked about the "minimal" acceptable educational requirements for a Study Director. Here it was also noted that a "wide range of nonclinical laboratory studies and numerous combinations of education, training and experience" would be acceptable (FDA, 1981). It is expected that management and Study Directors would carefully consider personnel qualifications as they relate to each particular study. One can then expect that management would have the final authority on determining if a Study Director had the necessary qualifications for their role. As stated in the preamble: the "Study Director should be viewed as the Chief Scientist in charge of a study." All of this is further confirmed by Section 58.185, which states, "The final report shall be signed and dated by the Study Director" and "corrections or additions to a final report shall be in the form of an amendment by the Study Director." This gives the Study Director the final approval of all aspects of the reporting of the study.

There were some additional tasks in the original draft that were changed to be management responsibilities when the final rule was issued in 1978. For those who still think the scope of the Study Director role is too broad, it may be of interest to note that it was even broader in the original 1976 proposed rules and some of

the original duties (scheduling personnel, resources, and facilities) were transferred to testing facility management (Section 58.31) in the 1978 final rule. This new section was added, defining the role of *testing facility management*. This section also gave the authority of assigning and replacing a Study Director during the conduct of a study to testing facility management. Management is also responsible for ensuring that there is a quality assurance unit (QAU), that personnel understand the functions they are to perform, and the testing of test and control articles. One other part that speaks to another aspect of the Study Director's role is Section 58.31(g), which states that management must "Assure that any deviation from these regulations reported by the quality assurance unit are communicated to the study director and corrective actions are taken and documented." This puts the Study Director squarely in the center of ensuring the compliance of the study and cements the communication pathway between the QAU, the Study Director, and testing facility management.

Several comments to the proposed rule concerned the question of more than one Study Director. It was confirmed in the final rule (43 FR 1978) and in subsequent question-and-answer documents (FDA HFC-30, 1979; FDA, 2007) that there would be no study direction "by Committee" and that there can only be one Study Director for each study. The requirement that the Study Director verify the study data (ensure accurate recording and verification), although confirmed in the 1978 final rule, was later deleted in the Amendment of 1987 (52 FR 1987).

1.2.3 OECD Consensus Document 1999 (OECD, 1999)

This document again confirms the scope and responsibilities of the Study Director as the single point of study control, stating that they have "ultimate responsibility for the overall scientific conduct of the study." It also mentions the concern the FDA had with the original GLPs for "conflicting instructions." Since many of the ecotox studies are multi-site, it notes that some of the "duties" can be delegated, but "control" cannot. "Principal investigators" at other sites act on "behalf of the Study Director." They also confirm that the Study Director is responsible for "drawing the final overall conclusions from the study."

The appointment of a Study Director is the responsibility of management and management should be "aware" of their "current or anticipated workloads." As with the FDA regulations, it is management's responsibility to replace a Study Director if necessary. These decisions need to be "documented in writing." This document also gives clarification of the need to temporarily delegate Study Director responsibilities during vacations, illness, or other short-term absences. Also, it further confirms that the Study Director has a "legal liability" to confirm compliance with GLP principles that stems from national legislation and not the principles of the GLPs.

1.3 GUIDANCE ON STUDY DIRECTOR QUALIFICATIONS AND TRAINING

What are the qualifications needed to be a Study Director? With no specific guidance, this is usually left up to the determination of management. Generally, an advanced degree in toxicology, pharmacology, pathology, or related disciplines has been preferred, although there are plenty of excellent Study Directors without advanced degrees. Board certification is another criteria often cited. This certification helps document a person's general knowledge of toxicology as a science, but being a Diplomate, American Board of Toxicology (DABT) does not directly qualify a scientist to be a Study Director. It does help ensure that a Study Director continues to keep abreast of advances in the science of toxicology as certification and recertification requires continuing participation and education in the field. A good background in these disciplines with strong knowledge of anatomy and physiology seems intuitive. Direct experience is probably the most vital of these requirements. The art and practice of being a Study Director is not something easily taught in a classroom, although "Study Director training" has advanced as well (discussed further). There are many other skills needed to be a Study Director, beyond the direct scientific background expected. This includes strong communication and team leadership skills (Rose and Mayer, 2005). The more complicated the study, the more important these skills become. A large 1-year study or carcinogenicity study needs a whole team supporting the study, and working well with other scientists, project managers, medical writers, and so on, is key to success.

The regulations are also clear that the Study Director role is not just a coordination role. As stated in the preamble to the Amended Rule of 1987: "Although 'coordination' of the pieces of a study logically is part of the study director's responsibilities," this is only part of the Study Director's responsibilities. The preamble then states that the Study Director is charged with the "technical conduct of a study, including interpretation analysis, documentation and reporting of results." Since the Study Director is the "single point of control" of a GLP toxicology study, there were uncertainties about how much the Study Director had to know about all of the

supporting functions (e.g., clinical pathology, cardiology, and pharmacokinetics). This has not been taken to mean that the Study Director has to be an expert in every subspecialty of the study but should have sufficient understanding to work with the specialists to coordinate, integrate, and interpret these integrated results. They should be able to determine if the other professionals working on the study are properly trained and qualified.

What is exactly meant by training was left to the interpretation of management, although the preamble gives some clues to what the FDA expectations were at the time. It was clear that training documentation is needed, and at first, everyone scrambled to update their curriculum vitae (CV). As this role was new to industry (in a formal sense), there were no well-established training courses and experience was indirect. Most Study Directors of the early 1980s were trained "on the job." Many company training sessions focused on training staff on the GLP regulations as they were new and the final version differed from the original draft.

1.3.1 OECD on Qualifications of the Study Director

As with the FDA regulations, specific qualifications are not defined but are dependent on the "requirements of each individual study." Furthermore, management has the responsibility for selection, monitoring, and support of the Study Director to ensure that studies are carried out in compliance with the GLP principles. This consensus document speaks to the various skills needed to be a Study Director with this statement: "In addition to a strong technical background, the coordination role of the study director requires an individual with strengths in communications and problem solving and managerial skills."

1.3.2 OECD on Training of Study Directors

Similar to the FDA regulations, the OECD Consensus Document states that it is management's responsibility to "ensure that there is documentation of training in all aspects of the Study Director's work. A training program should ensure that Study Directors have a thorough understanding of GLP Principles and an appropriate knowledge of testing facility procedures." (OECD, 1999)

They also provide the following enlightening suggestions on how training and experienced can be gained: "training may include work experience under the supervision of competent staff. Observation periods or work experience within each discipline involved in a study can provide a useful basic understanding of relevant practical aspects and scientific principles, and assist in the formation of communication links."

Of course, all training needs to be documented, retained, and available for inspections. "Documented records of such a program should reflect the progression of training and provide a clear indication of the type of study that an individual is considered competent to direct." Training should be continuous and updated as science, regulations, and procedures advance.

1.4 STUDY DIRECTOR TRAINING COURSES

Courses often focus on the regulatory and scientific aspects, as well as study management itself. How do you plan and control all of the different aspects of a robust GLP toxicology study? Is the training for a 2-week study different from that needed to run a 2-year carcinogenicity study? Does on the job experience start with the simpler studies (acute and 2 weeks) and then evolve over time to direct longer and more complex studies? The experiential training needed to be a fully rounded Study Director, one who can direct several types of studies, can take years to accomplish. The need for formal training has evolved as well.

Several years ago, the American College of Toxicology (ACT) Executive Committee and Council agreed with a proposal to include a Study Director training course as part of their continuing education course offering. Some thought this topic was not "scientific" enough. Yet, the ACT mission is to educate and to serve its members, and this was clearly a needed service, as evident by the large number of participants over the first 10 years the course was offered (ACT, 2012). Since then, several other organizations have started to conduct Study Director training courses, some taking place over several days, confirming that there is a general need for more formal training of Study Directors (or for those who participate in the GLP studies, even if not as a Study Director). These courses focus on several aspects including regulatory/compliance, scientific expertise (e.g., clinical pathology and pharmacokinetics), and the softer skills (communication and leadership). During the last 2 years, ACT has partnered with the Drug Information Association (DIA) to expand their Study Director training course to international regions, including India and China.

1.5 SUMMARY

This book is testament to the complexities and challenges of being a Study Director in today's modern world of GLP regulated toxicology studies. It covers a wide range of topics, from the detailed scientific aspects to the broad-ranging management responsibilities and coordinating parts of the role. Hopefully, it will add to

the toolbox needed to prepare new and to renew current Study Directors.

REFERENCES

ACT Study Director Training Course Records on file ACT Office Bethesda MD, 2012.

Code of Federal Regulations Title 21, Volume 1, Parts 1 to 99, revised as of April 1, 1999. 21 CFR 58 Title 21-Good and Drugs. Part 58- Good Laboratory Practices for Nonclinical Laboratory Studies.

Environmental Protection Agency. (1983). Good laboratory practice standards, 40 *Federal Register* Part 160, pp. 125–137.

Food and Drug Administration. (November 10, 1976). Nonclinical laboratories studies, proposed regulations for good laboratory practice, 41 *Federal Register* 51206–51230.

Food and Drug Administration. (December 22, 1978). Nonclinical laboratory studies good laboratory practice regulations, 43 *Federal Register* 59986–60025.

Food and Drug Administration. (August 1979). Bioresearch Monitoring Staff (HFC-30) *GLP Regulations (Management Briefings) Post Conference Report*, Rockville, MD, 5–12.

Food and Drug Administration. (July 2007; June 1981). Bioresearch Monitoring Staff (HFC-30) Guidance for Industry. *Good Laboratory Practices. Questions and Answers*. Rockville, MD. (Minor editorial and formatting changes made December 1999 & July 2007) 2–10.

Food and Drug Administration. (September 4, 1987). Nonclinical laboratories studies, proposed regulations for good laboratory practice, 52 *Federal Register*, 33768–33782.

OECD Consensus Document 1999 ENV/JM/MONO(99)24. (1999). OECD Series on Principle of GLP and Compliance Monitoring Number 8 (revised). Consensus Document, The Role and Responsibilities of the Study Director in GLP Studies, Paris, 1999.

PMDA. (2014). Pharmaceutical and Medical Device Agency. Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Drugs (English translation from Japanese). http://www.pmda.go.jp/english/service/pdf/ministerial/2012089-1.pdf.

Rose, C.A. and Mayer, D.E. (2005). The regulatory and business roles of a study director. *Quality Assurance Journal* 9: 273–282.