The Role of the Study Director in Nonclinical Studies

Pharmaceuticals, Chemicals, Medical Devices,and Pesticides

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FOREWORD

I was once asked the question "Why did the first person choose to eat a raw oyster?" The answer was simple—they were hungry! When I think about those early people eating and drinking a wide variety of plant, animal, mineral, and various other components that they came into contact with, I realize that those early people were truly the very first toxicologists. They served as their own control group and high-dose group at the same time, sometimes with satisfying results and sometimes with disastrous results. As mankind evolved and the basic knowledge of chemistry and biology became more understood, a better understanding of what was safe and what was unsafe began to develop. Although there was little understanding of the mechanistic attributes of such natural products, professions such as alchemists and food tasters (for the rich and powerful) developed, and Paracelsus's dictum "the dose makes the poison" probably stamped him as the first modern toxicologist. With the dawning of the twentieth century, the creation of the first pharmaceutical companies occurred, leading to a wide distribution of prepared products, although the use of local patented medicines with secret ingredients and misleading labels was still prevalent. Many of those products produced adverse effects with severe outcomes as there were no requirements to prove either safety or efficacy until the adoption of the Pure Food and Drug Act of 1906. This Federal Act mandated that drugs be accurately labeled with contents and dosage, but beyond that, the act had little effect on overall drug safety. In 1930, the Food and Drug Administration (FDA) was created, and in 1938, the Food, Drug, and Cosmetic Act was passed. This added both cosmetics and medical devices under the Act and mandated premarket approval of new drugs where the manufacturer would need to prove safety to the agency before they could be sold. A driving force for the passage of this act was the "Massengill murders" that occurred the previous year where over 100 died from receiving elixir sulfanilamide with diethylene glycol as the vehicle. Research activities during and after World War II exploded with the discovery of new antibiotics, antimalarials, and anticancer drugs; new pesticides such as DDT and the organophosphates; and the growing use of and interest in radionuclides. All of these new and exciting research discoveries put a greater focus on the need for a growing number of trained and experienced toxicologists, as was amply demonstrated in the early 1960s by the thalidomide tragedy in children and the publishing of Rachel Carson's seminal book, *Silent Spring*, regarding pesticides and pollution in the environment. Also in the 1960s, a growing number of private laboratories (contract research organizations [CROs]) sprang up (although a few were functioning earlier) that conducted third-party toxicology testing for the pharmaceutical, chemical, and pesticide industries. By the early 1970s, concerns were raised by the FDA regarding the quality and reproducibility of toxicity testing in both the major drug and chemical laboratories, and in the CROs, culminating with the exposure of significant fraud at one major CRO, International Bio-Test. Based on such findings, the FDA issued standards for conducting nonclinical studies in support of products regulated by FDA—the Good Laboratory Practice (GLP) Regulations in June 1979. For the first time, FDA published very specific rules for the successful conduct of such studies, including the creation of a new role, that of the Study Director (SD). The wording of those rules was very specific in terms of the SD, indicating that the

SD was to "serve as the single point of study control." The GLPs put the focus on an even greater need for trained and experienced toxicologists who could serve successfully in the role of SD.

For the 34 years that we have lived and functioned under GLPs, there have been many programs, courses, and symposia for SD training. In addition, the creation of certifications (DABT and ATS) within toxicology can now provide a degree of professional standardization in terms of scientific knowledge, experience, and expertise. However, what has been missing is a single source book dedicated totally to the roles and responsibilities of the SD in a regulatory environment. This need has now been filled by this new book, *The Role of the Study Director in Nonclinical Studies: Pharmaceuticals, Chemicals, Medical Devices, and Pesticides*. Edited by Drs. Brock, Mounho, and Fu, three scientists of great integrity and scientific understanding of the GLP-regulated world, they have gathered together an outstanding group of professionals representing many different areas who have coalesced together to create this book for current and future SDs. The 28 chapters of this book clearly and succinctly discuss the many challenges and functions expected of the successful SD, including a number of relevant and useful examples. While this book is focused on the SD, I believe that it will be useful to anyone who is involved in the drug, chemical, pesticide, or device fields, along with GLP regulatory professionals, leaders of testing facility management, and academicians who will be training the toxicologists of the future.

On a personal note, I would like to thank the editors for asking me to write the foreword for this book. Having been a practicing toxicologist in both the regulatory and CRO worlds for over 57 years, I have observed the tremendous growth and change of the world of toxicology over this time to where toxicology is now a fully recognized scientific discipline—this book will only further that recognition. I would also like to thank my friend and colleague at MPI Research, Dr. David Serota, for his assistance in helping me prepare this foreword.

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PREFACE

Several years ago, the lead editor (WJB) chaired two courses in the Asia-Pacific region on the role of the Study Director in the conduct of nonclinical studies. From those courses, this book was conceived.

The basic premise of this book—and this is reiterated in Chapter 28, "Lessons from the Front Lines"—is to present information that we, seasoned Study Directors, have learned over the years and that a new Study Director would want to know. In any nonclinical study, there are certain idiosyncrasies during the conduct of the study that require special attention. But managing those idiosyncrasies is learned only from "doing." Therefore, the editors and authors hope that these "lessons learned" will provide that guidance and understanding to the new Study Director.

The editors are particularly pleased that the Foreword was written by Dr. Edwin Goldenthal, MPI Research. Dr. Goldenthal's experience covers nearly 50 years in toxicology with a majority of his experience as a Study Director, mentoring those new to the field of toxicology and new Study Directors. Like the experiences of Dr. Goldenthal, a wealth of information is conveyed between the covers of this book that the editors believe is paramount toward becoming a good Study Director.

The book begins with basic concepts, including the regulatory definition of a Study Director and the role of the Study Director in understanding international testing guidelines and guidance and good laboratory practice (GLP) regulations, facility management, and regulatory inspections. It is critical, and yet sometimes taken for granted, how important facility management and animal and veterinary care are in the conduct of a nonclinical study. In addition, with the world becoming smaller and laboratories becoming specialized, multi-site conduct of different functions is becoming a standard. The Study Director needs to understand the ramifications of multi-site subcontracting of those phase studies. As pointed out throughout the book, the Study Director is expected to be a good scientific manager but also a good project manager, ensuring that the various phases of the study are on track for timely completion, that adherence to GLPs is as required, and, most important, that the study demonstrates science of a high quality.

The second part of the book is devoted to the conduct of a nonclinical study. Indeed, the second part of this book is core to a successful outcome of a nonclinical study. One of the more challenging tasks for a Study Director is developing a protocol. Although many laboratories and even Sponsors have a standard format for protocols, it is the planning and content of the protocols that is challenging. So many inputs from a diversity of experiences and expertise go into the protocol. And for the Study Director, managing the process often results in a "good" or "not so good" protocol. Included here is a chapter on dose formulation preparation and analysis, a most critical aspect of getting ready to conduct the nonclinical study. Without a good formulation and analytical method, the study would not happen. Many of us biologists dread statistics. However, as many of us learned over the years, statistical analysis is a key component of any nonclinical study. Once we get past all of the theorems and equations of statistics, we can appreciate what goes into preparing a good statistical analysis plan, a key event in many studies and particularly necessary in, for example, carcinogenicity studies.

With the advent of validated *in vitro* models, the scientific field has realized that reducing, replacing, and

refining (the "3Rs") is key to our science. A great deal of effort is expended in the development and validation of these models, and the chapter on *in vitro* models leads us in that direction and allows us to question the need for an *in vivo* study, something we should ask ourselves before animal orders are placed.

Once the nonclinical study is in progress, the Study Director's role is to manage that process toward termination of the study and managing, for example, the unplanned mortalities. How critical pathology has become in a nonclinical study! The Study Director does not need to become an expert in anatomic or clinical pathology, but must clearly understand the terminology and be able to interpret the outcome of pathological evaluations in the context of the entire study. Furthermore, with the evolution of personalized medicine, the Study Director needs to keep abreast of the ever-changing world of biomarker research and validation.

For pharmaceuticals, there is an expectation that the concentrations of the drug and metabolites be measured in nonclinical studies. However, over the last several years, this "requirement" is being seen with commodity chemicals and agrochemicals. These data are very helpful to the Sponsor and the Study Director in making risk determinations, but also these data are very useful in setting dose levels for the next study of a nonclinical program. Therefore, there is an expectation that the Study Director understand the basics of pharmacokinetics since the blood levels of the xenobiotic are a better measure of internal dose compared with administered dose.

The third section of the book provides the Study Director with those studies that are more specialized, that is, genotoxicity, carcinogenicity, and developmental and reproductive toxicity studies. Also, this section contains unique perspectives for the conduct of nonclinical studies for biotherapeutics, vaccines, and gene and cell therapy products as well as pesticides and commodity chemicals and medical devices. For each of these studies, there are some unique idiosyncrasies in the conduct of these studies.

The final chapter of the book brings together many of the "lessons learned" from previous chapters. This chapter is the result of a survey sent out to a large number of toxicologists in contract research laboratories and industrial laboratories. The results were compiled by the editor before being sent to the authors; that is, the laboratory submitting the data was blind to the chapter authors. However, it is clear from these results that no laboratory is immune to "issues" that arise in the nonclinical study. However, it is how the issue resolved that is critical to ensure good science and a positive outcome for the Sponsor. The new Study Director should study this chapter and recognize how the seasoned Study Director managed the problem. However, it should also be recognized that these are limited data and do not cover all potential issues that might arise during the conduct of a study. Therefore, the new Study Director should never assume and should seek out the more senior Study Director; there is always something to learn.

Finally, in spite of the experiences of the authors and the completeness of the chapters, there still remain a few "holes" in this book, for example, a chapter on animal models, although many of the chapters discuss the selection of animals models appropriate to the study. Regardless, this is the first book of its kind that is devoted specifically to a Study Director. The editors certainly hope that new Study Directors, as well as seasoned Study Directors, find the information helpful as they prepare for their next nonclinical study.

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INTRODUCTION TO THE STUDY DIRECTOR

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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

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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.

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2

GOOD LABORATORY PRACTICE REGULATIONS: ROLES OF THE STUDY DIRECTOR, MANAGEMENT, AND QUALITY ASSURANCE UNIT

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2.1 INTRODUCTION AND OBJECTIVES

U.S. Food and Drug Administration (FDA) good laboratory practice (GLP) is the regulation that applies to nonclinical research studies, those studies not using humans subjects or animal subjects in a clinical setting. Designed to build good scientific and documenting practices into nonclinical research, the regulation has provided a basis for industry practice for over three decades. Understanding where the GLP regulation fits into the overall product development process, how definitions of terms are used in the regulation, and applying the principles of the law are critical for successful product submissions to government agencies in the United States. The FDA GLP regulation has provided the basis for similar regulatory controls for the U.S. Environmental Protection Agency (EPA) as well as those implemented by other countries.

The objectives of this chapter are to introduce a brief history of the evolution of research law, the intent of the GLP regulation, when the GLP applies and why, roles of the major players (Study Director, management, and quality assurance unit [QAU]), GLP interpretation and guidance, current agency concerns, the possible future of the GLP, and comparisons of the FDA GLP to EPA and the Organisation for Economic Co-operation and Development (OECD) GLP. The importance of placing research into a controlled environment to produce high-quality data cannot be emphasized enough. The flexibility in the regulatory language often leads to varying methods or means to achieve an established goal. It is the author's intent to provide application examples; however, these examples may or may not be appropriate in a different situation from the one that is described.

On the highest overview level, GLP regulation applies to those studies that have progressed beyond discovery research but do not involve human subjects for testing. Test systems involve various animal models as well as *in vitro* (nonanimal model) testing that is performed on a promising product candidate prior to testing in human subjects. Early discovery work is not subject to regulatory controls, although good documentation employed during these experiments is essential to guide the regulated testing that follows. Good clinical practice (GCP) refers to a collection of regulations and guidelines that target human subject safety and controls in human testing (clinical study) research. Good manufacturing practice (GMP or current good manufacturing practice [cGMP]) encompasses regulations that apply in the product manufacturing setting. The three major regulations, GLP, GCP, and GMP, were designed for specific purposes and have differences in application that range from subtle to major. Use in the industry of the moniker "GXP" should alert professionals to

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similarities in methods to control variables within processes and systems, bearing in mind the differences in focus necessary for successful application of these very separate regulations.

Regulation of pharmaceutical research, in general, has developed gradually over a century and continues to evolve. To fully understand the intent behind GLP law, it is useful to trace this history and the major events that triggered growing government oversight. An understanding of the major events that led to increasing levels of control over research processes often causes one to acquire a greater appreciation for the time, effort, and attention to detail necessary to meet current regulatory requirements.

2.2 REGULATION ATTEMPTS PRIOR TO 1930

At the end of the nineteenth century, it was common for treatments and "cures" to contain a multitude of ingredients, some harmful and some harmless yet ineffective. Mercury, strychnine, and cocaine are examples of ingredients now universally recognized as harmful that were used in manufactured compounds for various treatments. The following is an example of a "formulary" pharmaceutical product taken from a pharmacy volume published in 1891. Note the use of ingredients now recognized as unsafe in addition to the imprecise amounts used in the formula. In addition, there is a wide range of doses prescribed per day.

> Compounding of Cardiene Tablets, used to slow the heart and increase its working and nutritive capacity:
>
> - Sulfate of Strychnine, 1-34 grain
> - Sulfate of Atropine, 1-300 grain
> - Sulfate of Morphine, 1-7 grain
>
> Divide into one hundred tablets, of which one to three can be taken three or four times daily. (Reed and Carnrick, 1891)

This example illustrates the lack of regulatory controls that are widely accepted today in this industry; up to this time, there were no laws written to require safety or efficacy testing of medicinal products. Unfortunately, many major laws controlling the testing and manufacturing processes in the pharmaceutical, biologic, device, and food safety industries have been triggered by tragic events.

The passage of the Biologics Control Act in 1902 marked the first effort to place requirements on product manufacturing. The law was passed in response to the deaths of 20 children who were given diphtheria or smallpox vaccines contaminated with tetanus. There was little comment, discussion, and even less publicity on the part of the lawmakers. This legislation mandated the adoption of rigorous standards by manufacturers producing viruses, serums, toxins, and antitoxins as well as requiring their licensure.

Around the turn of the century, food safety was also receiving a great deal of attention. The "Poison Squad" studies were initiated in 1902, led by Harvey Wiley, Chief of the FDA's predecessor, the Bureau of Chemistry. Recruited volunteers agreed to test preservatives used in foods to assess safety. Testing consisted of tasting substances such as borax, salicylic acid, formaldehyde, sulfuric acid, sodium benzoate, and copper salts. Results of these "tests," which were published in daily newspapers, became quite controversial; these studies were instrumental in bringing food and drug legislation to the attention of the general public. The publication in 1906 of *The Jungle* by Upton Sinclair exposed to the public the brutal conditions in meat packing plants in Chicago. Public outcry and subsequent government investigation set the stage for food and drug legislation at the federal level.

The U.S. Federal Food and Drugs Act of 1906 (the Wiley Act) established the federal Bureau of Chemistry as the agency responsible for administering the new law. Specific legislation centered on food safety and additives and did not address premarket approval of drugs. In general, the law prohibited misbranding and adulteration of drugs and directed that drugs must meet official standards of strength and purity. Subsequent amendments added over the next two decades attempted to address efficacy claims and labeling accuracy, but these laws were weak and enforcement was nonexistent.

From 1906 until 1930, many agency organizational changes and redirection of efforts occurred. During this time, the Bureau of Chemistry evolved into the Food, Drug, and Insecticide Administration and in 1930 acquired the current name of the FDA. However, administration of the 1906 law only emphasized omissions of the legislation and allowed shortcomings to be more evident. Misbranding was the source of considerable controversy. As a result of one challenge, the Supreme Court ruled that the law did not apply to false therapeutic claims. The law failed to mandate drug safety; dangerous products could not be seized by the agency. There was a need to expand regulatory scope to cover medical devices, cosmetics, advertising, the right of the agency to conduct inspections, and other issues. The inadequacy of the law at that time was demonstrated by the existence of a collection of dangerous products legally sold on the market throughout the United States. The stage was effectively set for a therapeutic disaster.

2.3 CRITICAL EVENTS LEADING TO REGULATIONS

The impending therapeutic disaster took place in 1937, following closely on the coattails of sulfa drug discovery. A raspberry-flavored elixir formulation of sulfa targeted for the pediatric patient population was developed using the solvent ethylene glycol, a highly toxic chemical analogue of antifreeze. The company distributed "elixir sulfanilamide" without any preliminary testing in animals or humans, since safety testing was not required by law. The product was first marketed on September 4, 1937, and the first death was reported on October 14, 1937. Documented fatalities numbered 107 and many of the victims were children. The disaster tragically illustrated the need to prove product safety prior to marketing. In the wake of public outrage, a new bill was hastily passed through Congress. The Federal Food, Drug, and Cosmetic (FD&C) Act was signed by President Roosevelt on June 25, 1938, 8 months after the first death was reported. The Act authorized FDA to promulgate regulations; this is the basic law under which industry legislation is still promulgated. For the first time, proof of product safety through investigational new drug (IND) and new drug application (NDA) submissions was required by law. The scope of the Act was broadened to specifically encompass cosmetics and devices. In addition, false therapeutic claims for drugs were prohibited and drugs were required to be labeled with instructions for use. The law gave the FDA enforcement power and authorized factory inspections by FDA investigators. Over the next 25 years, various laws were passed pertaining to prescription versus over-the-counter (OTC) drugs (Durham–Humphrey Amendment of 1951) and laws controlling drugs of abuse followed by the mid-1960s. With the advent of required submissions, applications for new drugs reached approximately 11,000 by 1962 (FDA Website, 2013).

Although the safety of medicinal, device, and cosmetic products had been addressed in the 1938 law, evidence of efficacy of drugs and devices was still not required by FDA. This improvement was triggered by the next major disaster in the early 1960s, the use of thalidomide to treat nausea during pregnancy. Treatment with this drug was discovered to be associated with a number of birth defects, with the most recognizable defect resulting in offspring with severely shortened arms. Thousands of women in Europe were affected where the drug was approved for distribution. It was prescribed less frequently in the United States under clinical study conditions; however, women who took the medication were not aware that it was an investigational drug. This event led to the passage of the Kefauver–Harris Amendment to the FD&C Act, which added a number of requirements to the underlying law. Premarket evaluation of both safety and efficacy data became obligatory, along with explicit FDA approval of the NDA. Other regulatory highlights required compliance of manufacturers with GMP (the birth of cGMP), compulsory subject informed consent (the basis for GCP regulation 21 CFR 50), and mandatory reporting of adverse events. In addition, the Amendment gave FDA greater power to access company records to verify implementation of good industry practices.

In summary, by the mid-1960s, the FD&C Act had a far-reaching industry impact. The basic purpose of the law is to protect the public welfare by saving the lives and money of all citizens. This is accomplished by the authority given to FDA by Congress to write the regulations it believes are necessary in the form of various food, drug, and cosmetic laws to carry out its task of enforcement for public safety. For the industry of medicinal products and devices, FDA rules shape the drug development process by regulating all aspects of the development, testing, manufacture, labeling, and approval for new drugs for public use. The basis of research is found in the law mandating substantial evidence of effectiveness (Section 505(d), FD&C Act of 1962):

> Evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved . . . that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

"Substantial evidence of effectiveness" is referenced in numerous parts of 21 CFR, including application for new drugs (21 CFR 314.126), application for new animal drugs (21 CFR 514.4), and is discussed extensively in a Guidance for Industry (FDA Website, 1998).

Regulations continued to evolve for different aspects of the drug development process. For example, more recent laws were passed for regulating human clinical trials to ensure the protection of rights and welfare of human subjects, which fall under the heading "Good Clinical Practices" (GCP). These include 21 CFR 50, which clarifies FDA requirements for the informed consent process, and 21 CFR 56, which establishes regulatory standards for the Investigational Review Board (IRB, an independent study monitoring group for human studies), both passed in 1981. As of 1998, obligatory disclosure of financial ties to product developers by the investigator involved in human research is spelled out in 21 CFR 54.

Meanwhile, with regard to submissions of nonclinical studies, up until the mid-1970s, the FDA more or less assumed that submitted data for nonclinical studies were accurate and reliable. Suspicion that this may not always be the case was raised during the review of studies submitted by G.D. Searle, a major pharmaceutical manufacturer, in support of two NDAs for therapeutic products and one for a food additive. Agency site inspections of toxicology facilities revealed multiple serious problems such as defects in study design, careless experimentation, poor recordkeeping, the masking of toxic effects by "resurrecting" (replacing) dead animals, removal of tumors and returning the animal to the study, tissues not examined prior to decomposition, lack of protocol adherence, failure of qualified experts to review data, unqualified personnel performing study tasks, improper lab procedures and animal care, lack of Sponsor monitoring, failure of Sponsors to validate data and reports, inaccurate analysis and reporting, and inadequate or absent retention of raw data and reports. Congressional task forces were formed to investigate the extent of the problems throughout the industry. There was talk of developing standards of quality for industry to follow on a voluntary basis.

However, investigation and inspections at Industrial Bio-Test (IBT) Lab revealed even worse research practices. IBT was a contract toxicology facility conducting approximately 40% of all U.S. toxicity testing, including safety testing of pesticides (under the auspices of the EPA), food additives, and drugs. Unacceptable study methods were identified, such as studies of questionable purpose and design, inconsistencies in data, inadequate environmental controls, dead animals unaccounted for, animals changing cages due to insecure doors, wild animals loose in the facility, data of questionable validity, and clear evidence of fraud. The IBT case required a 6-month trial and was resolved by rejection of all studies performed at IBT (thousands of studies); withdrawal of some marketed product approvals, thereby forcing Sponsor companies to repeat pivotal studies; three company officers were convicted for mail fraud and for making false statements to the government; one defendant was sentenced to a year in prison and 4 years' probation, the other two were sentenced to 6 months in jail and 2 years' probation; and the company went out of business.

After examining two large companies representing the majority of the industry, one can hardly blame the U.S. government for pursuing regulatory control. As one author put it, "I can't say that the standards (GLP) were an overreaction to finding out that nearly a quarter of the existing data was garbage" (Weisskopf, 1998). When faced with this evidence of extreme misconduct, both the FDA and EPA turned to enforceable regulation. The agencies concluded that the industry needed control standards to ensure quality and integrity of data generated during the conduct of nonclinical studies. FDA testimony in Congress (1975) resulted in a task force formed with agency and industry representatives who were responsible for developing ways and means of ensuring the validity and reliability of all nonclinical safety studies submitted to FDA. Standards were developed for measuring the performance of research laboratories and an enforcement policy was designed. The result of the task force's efforts was regulation located in Title 21, Part 58 of the CFR (21 CFR 58, Good Laboratory Practice for Nonclinical Laboratory Studies, referred to as the GLP in this chapter).

2.4 NONCLINICAL REGULATION

The GLP was proposed on November 19, 1976. Proposed rules were posted for industry and public comment for a fixed period of time. The agency then responded to submitted questions and comments. This question-and-answer series is referred to as the GLP preamble, and the agency's responses provide guidance to the intent and application of the GLP finalized law. Final GLP ruling was published by FDA in 1978 and became effective in 1979. The EPA followed with finalizing their GLP version in 1983. With some differences dictated by the nature of test substances, the GLPs for EPA Federal Insecticide, Fungicide and Rodenticide Act (FIFRA, 40 CFR 160) and Toxic Substance Control Act (TSCA, 40 CFR 792) are very similar to the FDA GLP.

The pilot inspection program, Bioresearch Monitoring (BIMO), was implemented with significant increases in FDA staff and budget. This program was designed to be a comprehensive, agency-wide group of investigators who conduct on-site inspections and data audits to monitor all aspects of the conduct and reporting of research regulated by the FDA. Investigators either reside at the FDA Center in Maryland or in various district offices located throughout the United States. The program objectives are basically twofold (Helfgott, 2012): (1) to protect the rights, safety, and welfare of human subjects by ensuring compliance with GCP principles of informed consent and independent ethics committee review; and (2) to assure the quality, reliability, and integrity of research data used to support FDA premarket submissions. BIMO field investigators conduct inspections of clinical investigators, Sponsors, contract research organizations (CROs), monitors, institutional review boards (IRBs), and facilities subject to the GLP. The procedures they follow are described in specific Compliance Program (CP) guidance documents; the one specific to GLP is CP 7348.808. As an aside,

today cGMP inspections are conducted by the Pharmaceutical Inspectorate staff of highly trained individuals who devote most of their time to conducting human drug quality inspections on prescription drug manufacturers and other complex or high-risk pharmaceutical operations.

It should be noted that GMP predates GLP and that GMP regulation was already in place at the time BIMO was implemented. However, in contrast to GMP, the target of the GLP was individual research studies as opposed to repetitive manufacturing processes. Since the regulations were designed for different target environments, GLP differs from GMP primarily in the following ways: The definition of a study is from initiation to completion; quality assurance (QA) oversight must be independent from study personnel to assure management that the study complies with the regulation; and the archive of records and samples for each study is required. An additional distinction of GLP from GMP regulation is the GLP specification that the Study Director appointed by management for each study is responsible for all aspects of that study.

The Study Director is defined in the GLP as the individual charged by management with the technical conduct of a study, including interpretation, analysis, documentation, and reporting of results. Industry initially objected to the Study Director being responsible for all aspects of the study, since it was universally accepted knowledge that the Study Director is unable to be technically expert in every area of all studies. Industry preferred the Study Director in a "coordinating" role only. However, FDA's response to this concern was that it recognizes that the Study Director will not be technically competent in all areas of the study. The agency felt very strongly about centralizing and focusing responsibility on one key contact person, and its intent has not changed. FDA's inspection experiences have demonstrated that if responsibility for proper study conduct is not assigned to one person, a potential exists for conflicting instructions to be issued by other individuals and the risk is higher for errors in protocol implementation. In addition, FDA emphasizes that it is the responsibility of the Study Director to assure that all experimental data are verified. By "verified," the Study Director assures the accurate recording of data; it is not necessary for the Study Director to witness all data recording. Reflecting the necessity for standardized procedures and an approved protocol, the Study Director must assure that the instructions detailed in the protocol are followed. One final Study Director responsibility, that for archival of all records at the close of the study, was challenged to be a facility management task. The agency responded that the study records allow reconstruction of all study events and constitute long-term proof of study validity. Since this is a critical control step in the study, the FDA felt accountability should be on the Study Director. Control over the study by the Study Director is further emphasized by the definition of study finalization as the date the final study report (FSR) is signed by the Study Director.

Prior to examining the FDA GLP regulations in depth, it is important to understand the distinction between federal regulations and agency guidelines. The Code of Federal Regulations (CFR) is a codified law of general and permanent rules published in the Federal Register. Guidelines are established principles and practices of general applicability that represent the formal position of the agency and obligate them to follow the guidelines until they are revoked or amended. It must be emphasized that guidelines are not legal requirements but acceptable practices to the FDA for the described subject matter. In other words, it is not required to follow the guideline instructions verbatim; however, if the choice is made to deviate from a procedure described in a published guideline, there should be a well-documented and reasonable explanation for the deviation. A comprehensive list of guidelines is available on the FDA website; lists can be found for both Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) using the site search function (FDA Website, n.d.a, n.d.b). The guidelines address fairly specific topics, such as validation of chromatographic methods, bioanalytical method validation, and guide for the care and use of laboratory animals.

A clear understanding of the distinction between regulations and guidelines can be acquired from a discussion of regulatory noncompliance consequences. If the GLP regulation is not followed, a series of events is set in motion. Noncompliance issues are usually identified during a directed or routine FDA inspection of a facility performing studies submitted to the FDA as part of a new product or device submission (see Chapter 5). At the conclusion of the inspection, a list of objectionable observations, called "483 items," may be given to the facility management. These items are nicknamed for the FDA form number used to report unsatisfactory inspection results, the FDA Form 483. Depending on the number or nature of 483 items, noncompliance issues may lead to product approval delay or rejection of certain studies. Although a response is not required, FDA states in the FDA Form 483 Frequently Asked Questions posted on the FDA website that "Companies are encouraged to respond to the FDA Form 483 in writing with their corrective action plan and then implement that corrective action plan expeditiously" (FDA Form 483 Frequently Asked Questions; FDA Website, 2012). Therefore, receiving 483 items requires

a response and remediation by test facility management and may trigger a follow-up reinspection by FDA to assess corrective action implementation. However, receiving 483 items does not usually lead to serious consequences, depending on the nature of the errors or omissions. The next level of consequence after 483 items is receipt of a warning letter. A warning letter is the result of serious compliance issues and/or failure to respond in a positive manner to 483 items from a previous inspection. Warning letters are published on the FDA website and usually result in serious loss of business for the receiving facility. A warning letter can also cause Sponsor submissions to be denied, approved drugs placed on hold, and refusal by the agency to review studies submitted for multiple submissions. Since warning letters and 483 items are addressed to facility management, it is in management's best interest to support regulatory compliance. Legal proceedings with associated penalties are known results in cases of suspected fraud. These results are indeed costly, frequently leading to dissolution of the company or acquisition by another firm.

2.5 THE PURPOSE OF GLP REGULATION

The primary purpose for the GLP is to ensure that the FDA has reliable and accurate data on which they can base regulatory decisions to protect public health and resources. An additional objective of the GLP was to provide industry with a basis for agency expectations for conducting nonclinical research. However, challenges to interpretation of regulatory compliance arise due to the lack of specificity in the GLP language with regard to approach for specific procedures. For example, words such as "adequate" and "appropriate" are necessary for needed application flexibility in a wide variety of nonclinical study settings. Whether or not a process control is adequate or appropriate is subject to interpretation and application. The means of communicating agency expectations and interpretations has evolved over the post-GLP implementation decades in the form of published agency guidelines, results of BIMO inspections, and industry outreach through liaising with professional societies and industry organizations. Industry, in turn, has found generally accepted methods to meet compliance requirements that are mandated in the regulations, but the "how-to" is not specifically described. These industry standards are recognized by most quality assurance professionals and agency reviewers as acceptable approaches. These methods may be altered if specific examples of compliance deviations are noted during agency inspections and methods are no longer found to be acceptable and/or if agency viewpoints change over time. Compliance methods should be traceable to the intent of the GLP law, which is to improve the overall quality of nonclinical research. The key element to improving research quality is providing complete documentation necessary to reconstruct all events that occurred during study conduct. When study details are completely and transparently recorded and explained, increasing one's confidence in the results of the study is a reasonable consequence.

QA review of the FSR is a process that has had heightened agency attention in recent years, and it is an example of a clarification of agency expectation leading many companies in the industry to revise a common practice. Although QA has always reviewed the "final report," documentation may not always clearly show that the final report version that is actually signed by the Study Director is the one that was reviewed by QA. The paradox that the Study Director's signature finalizes the study report and the QAU must review the "final report" is left up to individual facility managements to interpret. The process is necessarily described in detailed standard operating procedures (SOPs) and documented to reflect adherence to the SOPs and to meet agency expectations. Documentation of the process used by various facilities may vary from stating in the QA statement that final report verification is performed prior to report finalization, adding to the final report the QA statement signed on the same day that the report is signed by the Study Director, or SOP instructions of how review of the "final report" is documented as opposed to the review of the "draft final report."

During a presentation at the 2011 Society of Quality Assurance (SQA) Annual Meeting, an FDA presenter summarized that the agency expects to see organized and complete submissions (Luddy, 2011). It was pointed out that agency reviewers need to spend time on evaluation of science instead of confirming data integrity and identifying missing information. For this reason, it is essential to assure that data are accurately reported in the FSR and supporting tables, figures, and attachments. Similarly, it is important that protocol amendments, deviations and notes to file are well organized, easily interpreted, and readily located in the study records and final report, as appropriate. It was also emphasized that it is a GLP requirement (21 CFR 58.35(b)(6)) to submit the FSR to QA for confirmation that it accurately describes the raw data and meets required methods and SOPs.

2.6 INDUSTRY BENEFITS OF THE GLP

Although at times debated by industry, the GLP has led to implementation of quality management system

infrastructures that have been beneficial for companies in the nonclinical research business. A regulatory compliance support system firmly rooted in daily study procedures, staff training, and facility support functions allows the Study Director to demonstrate control over his/her studies. Quality checkpoints such as a second technical review, quality control (QC) review, and Study Director approval of collected data serve to ensure the reliability of the data. QA oversight provides tools in the form of SOP review, study phase audits, and periodic internal facility inspections to enable management to gauge process strengths and weaknesses. Controlled processes, standardized documentation methods, and trained staff lead to shorter review timelines and an expedited review of final reports by both QA and agency reviewers. The culmination of quality management infrastructure has increased client confidence in testing result validity and greater reliability of FSRs. Over time, the result is a positive reputation within the industry often leading to a competitive business advantage for CROs who implement successful GLP-compliant processes. In turn, reliable reports and successful BIMO visits to these CROs by the agencies can only facilitate rapid reviews of Sponsors' submissions.

2.7 REQUIREMENTS OF THE GLP

The difficulty of fully understanding the requirements of the GLP by simply reading the text is universally recognized and has given rise to much literature, various training programs, and numerous expert consultants. It should be recalled that in light of historical development, the basis of the requirements is implementation of good scientific practices to obtain reliable data.

A discussion of the requirements of the GLP in a general sense can begin with noting that use of the words "document," "record," and "verify" in the regulatory language is frequent. Although general in nature, these terms amplify the importance of the link between immediate documentation and reliability of original observations (referred to as raw data). In addition, documentation is critical to reconstruct study events and to generate reliable raw data. In their own words, FDA representatives have frequently offered the phrase, "If it isn't written down, it didn't happen."[1] It cannot be stressed enough that the ability to reconstruct the study from data and documentation is essential. To appreciate complete documentation, everyone in the nonclinical industry should be placed in a QA auditor's position to see what it is like to be required to reconstruct an entire study using *only* the generated data and associated study documents. This never fails to clarify the true meaning of "documentation"!

In addition to language that directs documentation, the GLP achieves flexibility by using general time interval terminology, allowing the law to be applicable to a variety of study models and test systems. Terms such as "adequate," "sufficient," "appropriate," and "periodically" necessarily lead to interpretation by management and scientific experts according to the applicable situation. In these cases, the regulatory agency expects facility or process SOPs to describe timing interval specifics. As types of studies and test systems have changed over the decades, it has sometimes been difficult to make the GLP "fit" into particular study models, so it is essential for nonclinical research professionals to understand the "intent" of the GLP. This is where understanding broad concepts and knowledge of the previously discussed industry standards play a role. As discussed in more detail later in this chapter, QAU regulatory guidance is often key in these situations.

If broad GLP concepts and the intent of the law are mastered, the rest of the regulation consists of details. Broad concepts of the GLP may be listed as appropriately qualified and trained study staff; study event reconstruction with thorough documentation practices; adherence to study protocol descriptions; method implementation according to management-approved written procedures; and retention of all study documents, data, and critical samples. These concepts are closely linked to the GLP-required responsibilities of management, the Study Director, study personnel, and the QAU. The following chapter sections discuss the specific roles and responsibilities of these parties stated in the GLP and integrate into the responsibilities some of the details of the broad concepts summarized earlier.

2.8 THE ROLE OF MANAGEMENT

The GLP provides the definition of the Testing Facility as a person (legal entity) or operational business unit who actually conducts a nonclinical laboratory study, that is, actually uses the test article in a test system. The GLP guideline established by the OECD, similar to the FDA GLP regulation and discussed later in this chapter, defines testing facility management (TFM) as the person who has the authority and formal responsibility for the organization and functioning of the test facility according to the Principles of Good Laboratory Practice. Although TFM is not defined in 21 CFR 58, responsibilities of the TFM are clearly spelled out in section 31 of the regulation. In short, TFM is the driving force behind the infrastructure necessary within the organization to meet GLP requirements. It is this individual or

[1]Author's experience, numerous FDA representatives' presentations.

individuals who have the responsibility and authority to acquire qualified personnel and direct critical processes that define all aspects of study control. This is reinforced by the fact that GLP noncompliance letters from FDA and EPA inspections are typically addressed to the highest-ranking member of TFM at the testing facility.

TFM responsibilities include designating a Study Director and assuring that there is a GLP-compliant QAU; appropriate testing (identity, strength, purity, stability, homogeneity) of test and control articles is performed; personnel, resources, facilities, equipment, materials and methods are available; study personnel understand the functions they are to perform; and any GLP deviations are reported by QA to the Study Director and appropriate corrective actions are taken. From this list of responsibilities, it is clear that responsibilities of TFM are administrative instead of scientific. In small organizations, the TFM may be the company CEO or operations manager. In larger organizations, TFM may extend to a level of upper management or vice presidents or various site operations managers. TFM may delegate appropriate administrative duties as long as these are clearly defined in written procedures or policies and are documented in internal memoranda or other means. Delegation must be to qualified personnel and these documents should describe the specific duties that are delegated. Some organizations use formal signed contracts to spell out specific delegated TFM duties to named individuals within the organization. It should be noted that GLP-compliant responsibility remains with TFM; however, the accountability is shared among TFM and the delegated individuals. In summary, if there is a question within an organization as to who is TFM, this question can be answered by identifying the management level that has the authority to designate, remove, or replace the Study Director; oversee the QAU; control the availability of resources; assure test articles are tested properly; assure personnel know what to do; and assure GLP deviations are reported to the Study Director and corrected.

Examining each of the responsibilities in turn illustrates the necessary cooperation, coordination, and communication required among departments and individuals within the organization to ensure compliance. Assigning or replacing the Study Director of a study should be performed according to a management-approved standard SOP and documented accordingly. Staff training is critical for smooth study conduct. Qualification and training documentation should include, at the minimum, the current curriculum vitae (CV), job or position description, and training documentation. CVs should include education, continuing education, professional organization involvement, publications/presentations, current position, and past work experience as appropriate to the position. The job or position description should list specific responsibilities and duties; minimum education, experience, and skills requirements; and the relevant organization reporting structure. Training documentation consists of SOP training, skills training, external educational seminars, internal educational meetings, regulatory training, and professional certificates/licenses. TFM should communicate regularly with the QAU, examine periodic QA status reports, and review individual audit/inspection reports. Review of responses to audit findings is particularly important to ensure that corrective actions are appropriate and that underlying procedure flaws are addressed. Types of audit findings often reveal quality process shortcomings and staff training weaknesses. In addition, feedback from client and regulatory inspections should have the highest priority for possible process improvement. Internal QAU facility inspections are also critical to indicate to TFM the general compliance status of the organization's processes. Project timeline oversight is important as an indicator that necessary resources are available as needed, including study personnel, animals, equipment, and supplies. The greatest challenge for TFM is assuring appropriate testing of the test article, since this is typically under full control of the Sponsor providing the test article. Some CROs have adopted a policy of refusing to begin a study if documentation of appropriate test article testing has not yet been received from the Sponsor. A situation to avoid is the lack of test article testing documentation leading to a delay in finalizing the FSR.

The importance of management's role in GLP compliance is emphasized by regulatory agency representatives invited to speak at professional society meetings. For example, one FDA Director pointed out that management is the most important element in GLP compliance (McCormick, 2004). In addition, FDA field investigator training for the BIMO program is focused on assessing management awareness and involvement. Investigators are trained to look for evidence that management understands their responsibilities under the GLP. They use inspection time to answer questions such as: How does management assure resources are available when needed? How does management assure that personnel understand and are qualified to perform their assigned duties? How does management delegate duties? Do the individuals to whom duties are delegated understand how to fulfill the duties? How does management assure that findings of the QAU are corrected? How does management communicate with the Study Director? How are conflicts between the Study Director and the QAU and other staff resolved? Nearly all GLP deviations are traceable to management deviations and regulatory agencies will hold management account-