Welcome to “GLP Forum.”

This feature addresses practical “hands-on” matters useful to practitioners in good laboratory practice. These include discussions on problem areas, FDA warning letters, interpretations of guidelines, strategy and approaches to compliance issues, audit experiences, and similar areas. The first installment, addressing the difference between good laboratory practices and good manufacturing practices, exemplifies the future content of this column. We intend this column to be a useful resource for daily work applications. The key objective for the column: Useful information.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Manuscripts submitted by readers are most welcome. We need your help to make “GLP Forum” a useful resource. Please send your comments and suggestions to column coordinator Steven Kuwahara at stevekuwahara@yahoo.com or to journal coordinating editor Susan Haigney at shaigney@advanstar.com. Your comments and suggestions are invited and most welcome.

KEY POINTS

The following key points are discussed:

- There is confusion regarding the appropriate applications of good laboratory practice (GLP) regulations and good manufacturing practice (GMP) regulations, especially with regard to when they should be applied
- There may be a preference for working under GLP based on the belief that GLP regulations are less onerous and less costly than GMP
- The GMP definition of “manufacturing” includes testing and quality control of drug products
- GLPs are intended for non-clinical laboratory studies
- GMPs apply to products manufactured for administration to humans
- FDA has recently issued CGMP for Phase 1 Investigational Drugs that removes rules not appropriate for early stage development
- Current good manufacturing practice regulations clearly apply to phase 2 and phase 3 clinical materials
- GLP has specific requirements not common to GMP laboratories that potentially add cost and time to project completion
- All things considered, there is nothing onerous or particularly difficult about the GMPs.
INTRODUCTION
Contract testing laboratories (CTLs) that deal with clients in the drug and biologics industry frequently find that they are asked to perform testing under good laboratory practice (GLP) rather than good manufacturing practice (GMP) regulations. This often occurs because some clients believe that all testing before licensed product manufacturing may be done under GLP rules and that this is somehow less costly than work done under GMP rules. The CTL is usually willing to comply because this helps the CTL to capture more business and the prevailing attitude is that “the customer is always right.”

THE PROBLEM
The real underlying cause of this situation is usually an ignorance of the regulations on the part of the client and the CTL. The CTL may be staffed with people who have only a limited exposure to pharmaceutical industry practices and who fear the GMP rules because of the many stories that they have heard about difficulties in complying with GMPs. The client is often under the impression that compliance with GLP rules is easier and that this will lead to lower costs for the testing. This creates a situation where clients, even those from large pharmaceutical companies, will try to have as much work done under GLP as possible, even if the situation has passed beyond the scope of the GLP regulations. For example, it is quite common for clients to ask laboratories to follow GLP regulations for the release testing of product lots that are produced for use during clinical trials even as late as those in phase 3.

REGULATIONS
An examination of the GLP and GMP regulations, however, shows that when they are properly applied, there is little difference in the time and effort needed for the application of GLP versus GMP regulations. It actually appears that the advantage of GLP practices over GMP procedures is more imagined than real. In some ways, because of specific requirements, GLP regulations may actually appear to be more costly to the CTL and its clients.

The Meaning Of “Laboratory”
In some instances there is a belief that because GLP includes the word “laboratory,” as opposed to “manufacturing” in the GMPs, the regulation must apply to all laboratory work. This impression can be corrected by an examination of the GMP definition of “manufacture” given in 21 CFR 210.3(b)(12) (1) where the term “manufacture” is found to include the testing and quality control of drug products. Also, the statement of scope found in the GLP at 21 CFR 58.1(a) (2) states that GLPs are intended for non-clinical laboratory studies that support applications for research or marketing permits. The key term here is “non-clinical laboratory study.” This term is defined in 21 CFR 58.3(d) (3) as follows:

“(d) Nonclinical laboratory study means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.”

This definition specifically excludes studies utilizing human subjects or clinical trials, and states that the GLP study is done for the purpose of determining the safety of the product. Thus the “laboratory” work under the GLPs is limited to specific situations. The object of the GLP regulations is to address the testing practices during preclinical safety testing that is done in vitro or in animals. Safety studies (i.e., pharmacological studies) in humans that are normally done during phase 1 clinical trials are regulated under 21 CFR 320 that are not GLP regulations.

The requirement for following GMP regulations during clinical trials is brought out in a regulation presented in 73 FR 40453 (4). The US Food and Drug Administration published a final rule, effective September 15, 2008, stating that products for phase 1 clinical trials are exempt from GMPs given in 21 CFR 210 and 21 CFR 211. This document made it clear that clinical trial material is covered by the GMPs and contained the interesting proviso that under certain circumstances the manufacture and testing of phase 1 clinical trial material is exempt from GMP in the regulations, but they are still subject to GMP as stated in the Food Drug and Cosmetic Act of 1938 (FDCA). These requirements for GMP compliance are found in subparagraph 501(a)(2)(B) of the act and again in 21 USC 351(a)(2)(B) (4) which define the conditions that cause a substance to be regarded as adulterated.
The subparagraph in the United States Code (USC) reads:

“(B) if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess;”

As this is the original law and not a regulation, it creates the question of “what is good manufacturing practice?” According to FDA, the specific GMP in the CFR do not apply, but the worker is left with the question of what to comply with, if not the GMP given in the CFR. Because the GMPs in the CFR were created in response to the requirements of the FDCA, one would think that these are the GMPs that the FDCA is addressing.

**CGMP For Phase 1**

FDA did provide some guidance in the original form of the proposed final rule (71 FR 2458) (5). This document mentions that FDA can still regulate phase 1 clinical material under the IND regulations (21 CFR 312) (6) and its general GMP authority as given in the FDCA. Thus they believe that product safety will not be compromised even if specific GMP requirements that are considered to be difficult to meet for early stage products are ignored. In addition to the existing regulatory controls, FDA did publish a guidance document describing the GMPs that do apply to phase 1 products (7). This guidance document contains many of the GMP requirements that are present in 21 CFR 211, but does remove some of the rules that would create difficulties for producers of small, early stage lots of products. Test and testing requirements are still present, except that they are now a part of a guidance rather than a regulation.

Section 105 of 21 CFR 58.105 (8) provides the regulations for the preparation and characterization of the test material to be used in nonclinical laboratory studies. While these regulations are not as detailed as those in the GMPs, the net effect of compliance with them should be similar to those of the GMPs. Given that the GLP regulations are being strongly enforced, this suspension of GMPs, described in 21 CFR 210.2(c) (9), would suggest that at phase 1, it is possible that experimental studies in humans may use material that is manufactured with less stringency than that manufactured for nonclinical testing in animals. This new regulatory paragraph in the “applicability” section of the GMP is useful in that it exempts phase 1 material, but it does make it clear that GMP regulations apply to material used for phase 2 and 3 clinical studies. One of the problems here is that FDA has not issued a guidance document that covers the manufacturing of products intended for use in nonclinical safety studies, and people working under the GLP regulations have little guidance in this respect.

It has previously been noted (10) that there are many similarities between the GLP and GMP regulations. The requirements for personnel, equipment (e.g., test instruments), manufacturing documentation, stability studies, and even assay validations are so much alike that it really does not make good sense to separate compliance with the GLP from the GMP. The primary difference is that the GLP apply to work done on drugs and biologics to be used during nonclinical laboratory testing and the test samples derived from those studies, while the GMP apply to products manufactured for administration to humans. This distinction has actually been clear since the issuance of a guidance document in 1981 (11).

**COSTS OF GLP**

With respect to laboratory operations, the GLPs have several specific requirements (12) with regard to personnel and organization that create situations different from those found in the average GMP-regulated laboratory. There are requirements for study directors and a quality assurance unit (QAU) that are designed to avoid conflicts of interest, but also create specific restrictions on work assignments. Even if these work assignments are made within the context of existing personnel, the separation of duties and activities can result in additional costs.

In addition to these personnel requirements, the GLPs in 21 CFR 58.35(b)(1) (2) require the QAU to maintain a current roster of the testing projects that are being performed within the test facility. Other requirements for the QAU in 21 CFR 58.35(b) (2) and for the study director in 21 CFR 58.33 (2) create a need for activities that add to the cost of testing. For instance, there is a need for a study protocol as defined in 21 CFR 58.120.
Unlike routine quality control (QC) testing where samples can be submitted with a simple test request, GLP testing should be a part of a study that is defined by this prospective protocol. While the testing is proceeding under this study protocol, the QAU must periodically audit the work as required under 21 CFR 58.35(b)(3) (2). The results of these audits must then be transmitted to the management of the test facility and the study director in the form of written reports. At the end of the testing a final study report must be prepared as prescribed by 21 CFR 58.185(a) (2). Both the final study report and the initial study protocol have specific elements required by the GLP regulations. The final study report must be reviewed and approved by the QAU, and this often results in the need for a final audit of the study before the QAU can approve the final audit report.

All of these additional requirements for administrative activities and document preparation and review usually create additional costs, such as additional fees charged by the test facility when informed that GLP testing is being requested. These notifications that work is to be done under GLP regulations are required by 21 CFR 58.10 (2). It is not possible to allow a contractor to ignore the GLP requirements that apply to them.

In addition to the direct costs, there are time constraints that develop because of the additional time needed for the audits, the protocol and report preparation, and overall planning that must go into these testing programs. These time factors can become important since most GLP and GMP work is done during early stages when the company is trying to initiate or complete its clinical trials and early development of product.

**IMPLICATIONS FOR COMPLIANCE**

Workers in affected areas should clearly understand the regulations including definitions governing their responsibilities. Workers should know the scope of testing to be performed, and if materials are being used in animals only or in both humans and animals. Just because testing is done in a laboratory does not mean that GLP requirements should be applied. The scope, objectives, requirements, and costs of GLP and GMP are clear. Consideration of all requirements indicates that costs under each requirement are really not that different.

**CONCLUSIONS**

Given the additional activities and management required for compliance with GLPs, it is necessary to ask why companies and their workers persist in requiring GLP studies when GMP work would do as well. In many cases it appears that these ideas have been passed down to workers from supervisors who feared the GMPs. This fear of the GMPs is somewhat amusing to managers with experience in the industry. Experienced managers know that the GMPs are basically a system for maintaining consistency of work and have accepted them as a part of the quality requirements of the pharmaceutical business. When managers mature, they usually find that there is nothing onerous or particularly difficult about the GMPs.

**REFERENCES**

7. CDER, CBER, and ORA, FDA, DHHS, Guidance for Industry: CGMP for Phase I Investigational Drugs, 2008.
8. FDA, CFR, Title 21, Volume 1, 21CFR58.105, Revised as of April 1, 2008.

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