

Integrating FDA GLP Compliant Capabilities into a CAP/Clinical Trials Production Laboratory: An Alternate Approach

INTRODUCTION

What does “Good Laboratory Practices” mean? The answer to this question depends on the audience.

To a College of American Pathologists (CAP) compliant laboratory or CAP inspector, “good laboratory practices” refers to a common sense, scientific approach to processes in the laboratory and is a component of the more encompassing CAP regulations. CAP good laboratory practices (CAP-glp) is detailed in the document, “Good laboratory practices for waived testing sites: survey findings from testing sites holding a certificate of waiver under the Clinical Laboratory Improvement Amendments of 1988 and Recommendations for Promoting Quality Testing” (1). This document focuses on recommendations intended to enhance patient safety and improve the quality of testing performed in laboratories with a CLIA Certificate of Waiver. Many of the details discussed are common sense practices and documentation that a trained technician would naturally do when performing a test. Also included are descriptions of areas and processes that a laboratory should consider before adding waived testing to the panel of services. In particular, “good laboratory practices”

for pre-analytical, analytical, and post-analytical variables are discussed. Some examples are detailed in Figure 1 (2).

To a FDA GLP compliant laboratory or FDA inspector, “Good Laboratory Practices” refers to details in the document, “21 CFR (Code of Federal Regulations) Part 58” (3). This document provides a description of the components required for a company, not just the laboratory, before adding FDA GLP compliant study capabilities to the panel of services. While this document largely focuses on laboratory activities and documentation similar to that described in the CAP-glp, it also extensively covers activities and documentation involved in many other areas of a study, including project management, scientific oversight, data delivery, data and specimen archival, quality assurance, etc. The theme of 21 CFR Part 58 is control, oversight, and documentation of the processes used, results obtained, and any issues encountered for all facets of a study, not focused solely on those of the laboratory.

In summary, CAP-glp guidelines and FDA GLP regulations are similar in that they both strive to ensure that the data produced is reliable and traceable. While the FDA GLP regulations cover most areas of a company, CAP-glp guideline covers only laboratory processes. Other areas of the company are covered by other CAP regulations. The FDA GLP regulations focus much more on the documentation of the processes than execution. A more accurate description of these regulations might be “Good Documentation Practices.” Based on the similarities of CAP-glp and FDA GLP regulations, it would seem that executing studies for either set of regulations in the same space would be fairly simple, although in truth, technical, operational, and process-based issues become clearly evident when one attempts to do so.

PROBLEM STATEMENT

As indicated above, CAP regulations and FDA GLP regulations are similar in most areas. One key area of differentiation that can be problematic is that CAP-glp is a laboratory-based philosophy that is best executed through instrument, assay,

Table: Pre-Analytical, Analytical, and Post-Analytical Activities Associated with Good Laboratory Practices

PRE-ANALYTICAL ACTIVITIES	ANALYTICAL ACTIVITIES	POST-ANALYTICAL ACTIVITIES
Test ordering	Control testing/checks	Reporting results
Patient identification, preparation	Test performance	Documenting
Specimen collection, handling	Results interpretation	Confirmatory testing
Preparing materials, equipment, and testing area	Recording results	Patient follow-up
		Disease reporting
		Biohazard waste disposal

or department-based systems and processes. FDA GLP, however, is a study-based philosophy that is often, though not required to be, executed through study-specific systems and processes.

Often the client expectation for FDA GLP studies is that all study records for a particular study will be maintained together and separate from records of all other studies. This can be challenging for a laboratory that is CAP certified and designed to run clinical trials and service multiple studies simultaneously, who attempts to add FDA GLP capabilities to the same space and on the same instruments at a later date. CAP laboratory documentation is associated with study initiation to study completion and/or termination, including handling and testing of samples, specimen, reagent, calibrator, and quality control tracking, Laboratory Information Systems (LIS) printouts, instrument printouts, etc. is not divided by study or client, but rather by date. All this information in the CAP / clinical setting is recorded chronologically and by instrument or assay on specifically designed forms.

Pacific Biomarkers (PacBio) provides specialized biomarker laboratory services to support pharmaceutical, biotech, and diagnostic manufacturers conducting human clinical trial research. PacBio already incorporates many of the practices specified in the FDA GLP regulations as they are good scientific procedures, thus complying with FDA GLP regulations. There are several sections of the FDA GLP regulations that either do not apply (pertaining to animal facilities), are not requested by the client, or are resource intensive and do not add quality in a clinical study. For example, as an esoteric laboratory, many of the studies PacBio receives last only several months. PacBio could be active in 80-120 studies at any point in time. To maintain processes and corresponding laboratory records in a study-specific manner would be impractical. Therefore, PacBio is faced with the challenge of efficiently incorporating FDA GLP compliant study specimens into the flow of the CAP production laboratory while addressing our FDA GLP clients' desires to have study-specific laboratory records.

PREVIOUS MODELS

There are two common models used by a facility for incorporating FDA GLP capabilities into its CAP / clinical facility. The strategy chosen may depend on whether the rest of the facility is regulated by CAP, another regulatory body, or if it is used for research and development. Model one designates a separate "FDA GLP Lab" within the current laboratory where all specimens for FDA GLP studies are handled. The second model creates separate FDA GLP processes, Standard Operating Procedures (SOP), and documentation practices to

be used within the current laboratory setting when FDA GLP specimens are handled. These models have potential pitfalls and inefficiencies associated with them.

In the first model, FDA GLP study capabilities are brought into a laboratory and are set-up in a separate space in the facility, this often includes dedicated sample receipt area, instruments, and assay documentation. This is generally the preferred situation by clients and an acceptable solution for a company when the resources exist to do so. However, dedicated space, duplicate instruments, separate Standard Operating Procedures, and extra personnel may not be a wise business decision.

The second model is often used when dedicated space, instrumentation, and personnel are not practical. The execution includes having separate forms, processes, and filing systems for the FDA GLP studies. This may be an acceptable solution with only a few such studies. As the FDA GLP work increases this model will also become impractical and a drain on resources. More importantly, quality and clients expectations could be compromised. With hundreds to thousands of specimens moving through a laboratory per day, unclear labeling of FDA GLP compliant studies and corresponding specimens could result in specimens being run under the incorrect set of regulations, thus compromising client expectations.

PACIFIC BIOMARKERS SOLUTION AND IMPLEMENTATION

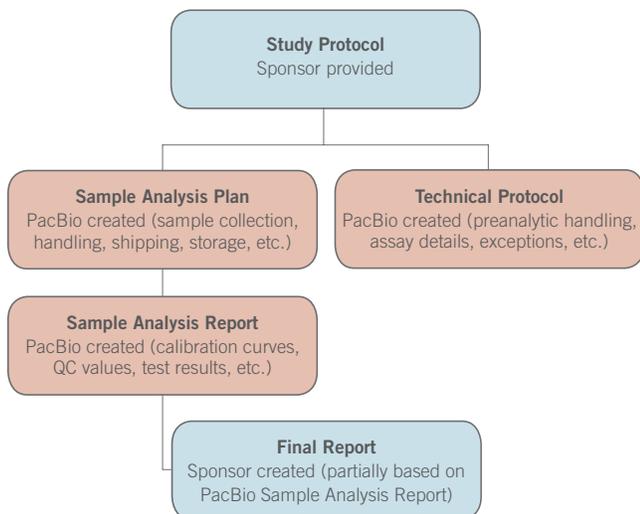
When PacBio decided to incorporate FDA GLP compliant studies into the CAP production laboratory, it was determined that neither of the above models was favorable. Based on the small initial number of FDA GLP studies expected, there was not a justified business case for incorporating model one. Likewise for model two, there was not an efficiency and quality case to be made for creating a separate set of FDA GLP compliant SOPs for all the production processes that would need to be conducted in a FDA GLP manner. Therefore, PacBio developed a third model that has allowed for significantly more efficient use of resources and more thorough documentation for all clients.

The two main goals in developing this model was to first maintain a laboratory environment where specimen preservation, high quality testing, quality systems, and efficiency continue to be the priority. Second, develop streamlined approaches in the non-laboratory departments for incorporating the additional project set-up, result reporting, and quality assurance oversight required for FDA GLP studies.

PacBio set up a two pronged approach to address both goals. First to address the slightly more stringent documentation requirements by FDA GLP, PacBio reviewed and modified procedures, forms, and documentation in the CAP production laboratory. This allowed all samples, whether CAP or FDA GLP to be analyzed using the same systems, personnel, and SOPs. The technicians were able to focus on executing the testing, instead of trying to determine which set of regulations were needed for a particular batch of specimens. All specimens were analyzed under a set of SOPs that addressed both CAP and FDA GLP requirements. This maintained the streamlined operations PacBio currently employed throughout the CAP production facility, satisfied FDA GLP requirements, and resulted in a higher quality of documentation for all of our clients.

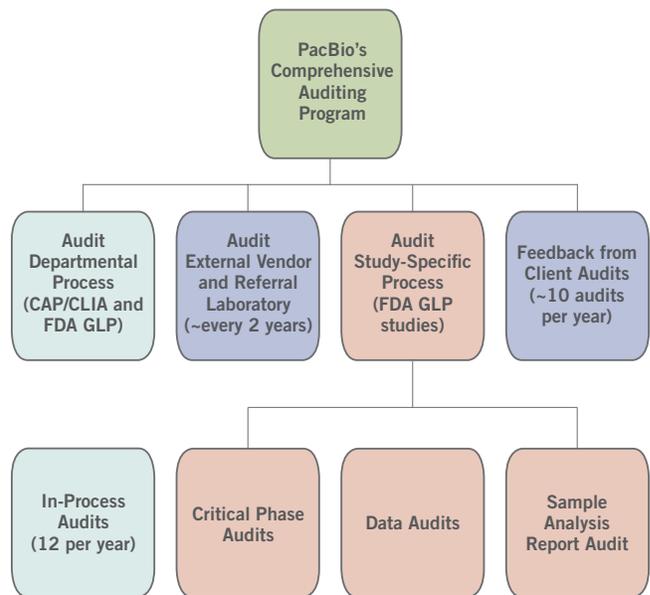
Secondly, members from the Project Management and Science and Technology departments developed a set of standardized templates that could be used to address the need for “Study Protocols” and “Final Reports”. With PacBio functioning as a contributing laboratory, PacBio was not writing the full “Study Protocol” or “Final Report” as defined in the FDA GLP regulations. Therefore, the templates were named “Sample Analysis Plan” and “Sample Analysis Report”. This served two purposes. First, to make a clear distinction to our FDA GLP clients that these documents covered the sample analysis that PacBio was responsible for, not the full study. Second, using terms that were not in the FDA GLP regulations allowed for PacBio to use these documents for CAP specimens without causing potential confusion that the specimens were run under FDA GLP conditions.

FIGURE 2: PacBio's flow from Sponsor's Study Protocol to Sponsor's Final Report



Streamlining Quality Assurance Unit (QAU) responsibilities is more difficult. FDA GLP regulations require data audits and critical phase inspections (QAU observing execution of various procedures during a study) whereas CAP regulations require an internal auditing program focused on systems. Due to the study specific nature of the FDA GLP critical phase inspections, these cannot be used to satisfy the CAP requirements without breaching client confidentiality. Therefore, a departmental, system-focused internal auditing program continues for company quality assurance for all studies and the data audits and critical phase inspections are layered onto this program to satisfy the study-specific nature of the FDA GLP studies.

FIGURE 3: PacBio's approach to the Quality Assurance Auditing Program



SUMMARY

There are challenges whether starting a FDA GLP compliant facility from scratch or bringing FDA GLP compliant capabilities into a facility that is established under a different set of regulations or practices. In 2009, Pacific Biomarkers chose to incorporate FDA GLP regulations into the well-established CAP production laboratory. The challenges were numerous and the solution required creativity and common sense problem solving. The result was a new model for companies to perform CAP and FDA GLP compliant testing in the same space.

REFERENCES

1. Centers for Disease Control and Prevention. Good laboratory practices for waived testing sites; survey findings from testing sites holding a certificate of waiver under the Clinical Laboratory Improvement Amendments of 1988 and Recommendations for Promoting Quality Testing. MMWR 2005; 54 (No. RR-13): 1.
2. Centers for Disease Control and Prevention. Good laboratory practices for waived testing sites; survey findings from testing sites holding a certificate of waiver under the Clinical Laboratory Improvement Amendments of 1988 and Recommendations for Promoting Quality Testing. MMWR 2005; 54 (No. RR-13): 8.
3. U.S. Food and Drug Administration. (2009, April 01). Title 21—Food and Drugs Chapter 1—Food and Drug Administration Department of Health and Human Services Subchapter A—General Part 58 Good Laboratory Practice for Nonclinical Laboratory Studies. Retrieved from <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58&showFR=1>