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Article: Implementing an Effective GLP Program at the Contract Laboratory

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Abstract

This discussion provides an overview of a GLP program at a contract laboratory. The objective of the GLP program is generation of analytical data in support of a GLP study. Understanding what is required to complete a single study leads to understanding what quality systems must be in place in order to complete multiple and simultaneous studies. Desired qualities of a GLP study include transparency, traceability, completeness, accuracy, precision, clarity, integrity, and retrieveability. Each will render the study easier to audit and minimize non-compliance. Administrative tools recommended for a GLP program include pre-printed workbooks and logbooks, standardized formats for result reporting, study-specifics, and peripheral records; study numbers, study files, and client codes; checklists, and other tools. A typical study workflow is presented. This basic workflow may be scaled for application to multiple simultaneous studies. Other useful information provided includes an experimental workbook template, instrument logbook template, information captured on controlled forms, GLP study requirements, some essential SOPs, and key quality subsystems to GLP. Elements of a quality systems approach to auditing GLP studies are discussed. Having and following good SOPs is the key to implementing the program described. Training personnel on SOPs and revisions, and dealing with deviations and change is also vital. The concepts discussed herein are critical to developing a compliant GLP program that will improve, become self-correcting, be stable and efficient.

Introduction

Implementing a GLP program in a contract lab such as ours at NSF Health Sciences is a large undertaking. It does not really help if the scale of the operation is relatively small: Small labs and large labs are held to the same regulatory standards. Good quality systems, once in place, should be scale-able. While it is true that “smaller” typically means fewer instruments and scientists to be qualified, it is also true that small and large CROs and big pharmaceutical companies all continually face risk vs. resources challenges. One must determine the right way to do something and how to pay for it. For the purpose of the present discussion, the “something” is generating analytical data to support a GLP study, while the “right way” is that way or ways that are in compliance with the GLPs and have a high probability of remaining in compliance during growth and change (1).The goal of this discussion is to provide useful, hands-on tools that have been tested in our laboratory over the past 15 years for implementing an effective GLP program.

Background

Many scientists approaching Good Laboratory Practice (GLP) for the first time are surprised to find that the subject matter lives up to its name. It is all about having and following good practices in the laboratory. For example, the importance of keeping a scientific record that is good enough to permit the reconstruction of the experiment at a later date and the importance of scientific honesty are at the heart of good scientific research and GLP. Keeping good lab records on the calibration, cleaning, maintenance, and performance of lab instruments is part of this, as is keeping a lab notebook or workbook that includes results from all attempts made in an experiment or study – both successful and unsuccessful. That this record has the qualities of being original, attributable to the author, contemporaneous, accurate, and legible is emphasized as part of a subset of good documentation practices. These and similar ideas have been taught in the undergraduate university curriculum for a long time. The 1952 text by Harvard Professor E.B. Wilson, Jr. entitled "Introduction to Scientific Research" remains an excellent resource (2).Still, the largest part of the burden of educating scientists in this area falls on the companies that use their talents. This discussion focuses more on the "how" than on the "why" of GLP. Readers will find an introduction to some of the early motivation in referenced literature (3).

Completing a Single Study

Understanding what is required to complete a single study leads to understanding what quality systems must be in place in order to complete multiple and simultaneous studies. Before we step through the flow of work, we point out some of the important qualities that a GLP study must possess. This will help the reader understand why certain steps are placed in the workflow. These include: transparency, traceability, completeness, accuracy, precision, clarity, integrity, and others such as being readily retrievable. Each will render the study easier to audit. One test of a good study is that it must be easy to audit and the audit not identify any GLP non-compliances. Such attributes can be built-in by thinking about how the GLP program will be administered. We believe good administration is a key to effective management.

Some simple examples of administrative tools follow.

Workbooks and Logbooks

We use pre-printed laboratory workbooks. Workbooks are designed to permit the capture of information deemed essential for later reconstruction of the experiment. The flow of information follows chronologically the steps taken in the lab to obtain the data. The design is pre-approved by lab management and Quality Assurance and changes to design are controlled. Workbooks are easy to use and to audit. Information appears time and again in the same location in the workbook, regardless of the particular analyst, analysis, or study. Workbooks are controlled documents and are printed by the Document Control Unit (DCU) only. **Table I** provides a list of typical information recorded in the workbook. The same logic applies to the various laboratory logbooks (**Table II**).

Table I: Experimental workbook template

Analyst name	Study number and date	Document number
Objective	Test method number or protocol number	Test specifications/ranges
Test article information (ID #, lot #, description, etc.)	Instrument set-up and parameters	Standards preparation
Instrument list (ID #, date of last calibration, next calibration due date)	Reference standard information (name, lot, expiration date, purity, manufacturer)	Reagents/solutions (name, lot, expiration date, purity, manufacturer)
Sample preparation (weights, volumes, dilution factors and final concentrations)	Solution preparation, diluents and mobile phases (lot #, manufacturer and expiration date of each reagent used)	Calculations (with units and proper significant figures)
Reporting results (with units)		

Table II: Instrument logbook template

Instrument ID number	Manufacturer	Model and serial number
Instrument custodian	Instrument location/ lab number	Qualification/Calibration status
Instrument type/description	Table of Contents: running list in chronological order of all instrument events (e.g. repairs, cleaning, preventative maintenance, calibration, etc.)	Date of IQ Details of IQ Reference the SOP (with version number) used in performing IQ
Date of last calibration Date when next calibration is due Details of PQ Reference the SOP (with version number) used in performing PQ	Details of OQ Reference the SOP (with version number) used in performing OQ	Date of PM Details of the PM Reference the SOP (with version number) used in performing PM
Log of Instrument failures	Details of instrument repairs and remedial actions	KEY: IQ/OQ/PQ, PM stand for Installation/ Operational/Performance Qualification and Preventative Maintenance

Reporting Results

Each data table in the GLP study final report includes reference to the lab workbook containing the original recording of the data. Each lab workbook also contains a summary table of the results. We call this section of the workbook "Reported Results" and it includes all results derived from that part of the experimental study that is represented by the particular workbook. When the results are numerical (as is typical) they are given with final units and rounded to the proper number of significant figures. The auditor then can easily work backwards and forwards between the GLP report and the raw data. In addition, since we use a different lab workbook for each attempt at completing the analysis, coupling the lab workbooks to the GLP study final report in this way adds integrity and helps to ensure transparency, traceability, and completeness in our reporting practices.

Study-Specific and Peripheral Records

A typical study generates a large number of records. An old joke is that GLP stands for "generate lots of paper." Some of the records are identified in **Tables I-IV**. Study recreation depends upon records that are study-specific and those that are not. For example, the analyst enters the instrument number into the workbook (a study-specific document) and this links it to the instrument logbook (a document used for multiple studies). Likewise, the analytical test method document number is entered into the workbook and this links to the approved written procedure. The integrity of the study depends in part on the strength of the links between the study-specific record and the record of events occurring simultaneously in the lab that impact upon the quality of the study. In **Table III**, we identify some of these peripheral records.

Table III: Some records peripheral to the study

Lab Operations	Training	Metrology
Test article (sample) log	Master signature list	Master equipment list
Reference standards log	Organizational chart	Instrument logs
Instrument use logs	Employee training binder (including training on SOPs, methods, protocols, quality agreements and other)	System suitability and instrument failure logs.
Workbook log	Employee job description	Environmental chamber logs
Change control log	Employee curriculum vitae	

Table IV: Useful information captured on controlled forms

Study Transmittal Form	Test Article/Sample Transmittal Form	Kick-off Meeting Checklist
Date of transmittal	Client code	Meeting date
Name of client-coordinator	Test article/sample description	Study director
Study director contact info	Number of units	Study number and client code
Study sponsor contact info	Lot number	Study personnel in attendance
Test article identification	Container-closure system	Check qualifications of all study personnel
Listing of tests to be done	Test article (sample) ID number	Review study protocol and quality agreement (if any)
Client code	Tests to be performed	Review test methods
Study number	Handling and storage conditions	Review test article handling and storage and MSDS data
Study title and objective	Test specifications or ranges	Review reference materials used
Is there a quality agreement in place (Y/N)?	Client, client-coordinator and QA signatures and dates	Review results reporting requirements
Date the study was forwarded to the DCU		Check qualification of equipment and instruments

Study Number, Study File and Client Code

GLP documentation has four simultaneous goals:

- Capture in the study record all the information required to reconstruct the study at a later date
- Contain an audit of the study to that study
- Facilitate rapid recovery of the complete study record and
- Protect client confidentiality.

The first goal is reached primarily by designing a workbook that is self-contained while also linking to all the supporting study records. The second is reached primarily by segregating lab work by study i.e. by study number. The third is reached primarily by creating for each study a study file. The study file is maintained by the DCU following an SOP that states what must be filed and when. The fourth is reached primarily by identifying clients by an assigned code that is unintelligible to outsiders.

Checklists

Checklists greatly simplify study conduct. For example, in order to start experimental work, the study director makes “readiness checks” using the Kick-off Meeting checklist (**Table IV**). This document ensures participating scientists understand the study protocol requirements and are qualified to perform the tasks they are being asked to perform. Checklists should reflect good planning and be placed in the workflow where they can aid in process execution.

Peripheral Records and the “Snap-Shot-in-Time” Idea

At any time the company should be able to demonstrate from the written record that at the time of the particular analysis or test, the following were true:

- All analysts were qualified to perform the analysis and followed a validated or verified test method using a qualified/calibrated instrument

- Test and control articles and reference standards were properly handled and stored at all times
- Workbook was used to record experimental data
- Instrument performed properly throughout the analysis
- Analyst did not deviate from approved procedures and
- If significant changes were made having the potential to impact the quality or integrity of the study (e.g., the study director was replaced), then these were logged in the Change Control Log and were evaluated and approved by the appropriate unit.

The reader following the work-flow (**Figure 1**) through a single GLP study should keep in mind that since it is a single study, all documents can be "one-time-use." Likewise, procedures such as test procedures, calibrations, and unit lab operations can be written into the study protocol and approved since they are not needed again. The company can set aside a limited number of instruments, equipment, and personnel to be qualified – those required to support the study. All of the experimental preparations and results can be recorded contemporaneously in a single lab notebook. For a one-time single study, gaining control over the study documents is a fairly trivial matter.

Even for a single study, however, the lab must meet a large number of GLP regulatory requirements. Those that are most relevant to the present article are paraphrased and listed in **Table V** with reference to the corresponding requirement found in Title 21 of the Code of Federal Regulations, Part 58 (21CFR, Part 58, for short).They were put into place by Congress in the late 1970s to ensure the Food and Drug Administration that results from nonclinical laboratory studies reported to the agency through new drug applications were valid and accurately reflect study conduct.

Table V: Some GLP study requirements (with reference to 21CFR, Part 58)

1	The study must at the start be identified as a "GLP study", meaning that the work is to be conducted in compliance with the GLPs.	
2	A study director must be assigned by Management.	58.31
3	The study director must write a study protocol.	58.120
4	The protocol must clearly indicate the objectives and all methods for the conduct of the study.	58.120
5	The study must be placed onto a Master Schedule.	58.35
6	Management must ensure that an independent Quality Assurance Unit (QAU) is in place to monitor the study, to report findings back regularly to the study director and study director Management, to review the study final report to ensure that it accurately describes the findings and conduct of the study and to write the Quality Assurance Statement.	58.31 58.35
7	The study director must ensure that the lab is prepared to start the study.	
8	The lab must have an area clearly designated for GLP test article (sample) receipt and ensure that the test article cannot be confused with other substances e.g. reagents.	58.47
9	Test articles, control articles and reference standards must be properly stored. It is typical to dedicate a space that is under environmental control and has limited access.	58.107
10	Participating scientists must be qualified to play their role, which must be clearly defined.	58.29
11	Written and approved procedures (e.g. SOPs) must be in place and followed.	58.81
12	Any and all deviations from written approved procedures (e.g. SOP deviations) must be approved by the study director and documented in the raw data (e.g. workbook).	58.31 58.33 58.35
13	All raw data collected in the conduct of the study must be recorded following good documentation practices and be readily retrievable.	58.130
14	Equipment and instrumentation must be shown to be fit for its intended use (e.g. calibrated or standardized or qualified) and there must be a written record of this activity.	58.63

15	A “responsible person” e.g. metrologist must be assigned to the inspection, cleaning, maintenance, qualification of each instrument or piece of equipment.	58.63
16	Instrument failures must be investigated and repairs documented.	58.63
17	All reagents and solutions must be properly labelled.	58.83
18	QAU must perform at least one audit of the experimental work in progress.	58.35
19	A final report must be prepared, signed and dated by the study director.	58.185
20	The study must be archived in accordance with the GLPs.	58.190

Completing Simultaneous, Multiple Studies

Resource sharing is key to scaling-up to perform multiple simultaneous studies. Scale-up is facilitated by copying procedures that are common to many studies from study-specific documents such as the study protocol and pasting them into templates under document control for use in other studies. This involves creating the following:

- Workbooks and logbooks
- Standard Operating Procedures (SOPs) that describe how to perform daily lab unit operations
- Analytical test procedures to be used by multiple studies
- SOPs that contain the procedures to be followed by the Quality Assurance Unit (QAU), Metrologist, DCU, and Archivist
- Templates for study final reports, protocols, workbooks and logbooks and
- Standardized forms to capture information in support of the study other than raw data.

Table VI contains a list of some of the essential SOPs that must be in place and **Table IV** is a list of useful information that is captured on standardized forms. The importance of having an SOP on “Definition and Preservation of Raw Data” cannot be underestimated. It will establish what must be recorded as raw data and how. Any and all documents used in recording raw data (e.g. workbooks and logbooks) must be under control by the DCU.

Table VI: Some essential SOPs

General lab operation	Metrology	Quality Assurance
Standard Operating Procedure: Administration, Distribution, Maintenance and Training on SOPs	Master Plan for Instrument and Equipment Qualification	Quality Assurance Unit Activities and Responsibilities
Management Commitment to Quality	The Master Instrument (Equipment) List	Qualification of QAU auditors
Training and Qualification of Personnel	Use of Instrument Numbers, Labels, and Responsible Persons	Master Schedule
Responsibilities of the Study Director	Creation and Use of Instrument Logbooks	GLP Study Protocol Review
Writing GLP Study Protocols	Installation Qualification (IQ)	Monitoring In-house GLP studies
Writing GLP Study Final Reports	Calibration Schedule	Audit of GLP Study Records
Receiving, Logging, Storing, Testing, Archiving and Disposing of GLP samples or test articles	Operational and Performance Qualification (OQ and PQ)	Audit of the GLP Study Final Report
Definition and Preservation of Raw Data	OQ, PQ and Preventative Maintenance on Temperature-controlled Storage Areas	Reporting QAU audit results to Study Directors

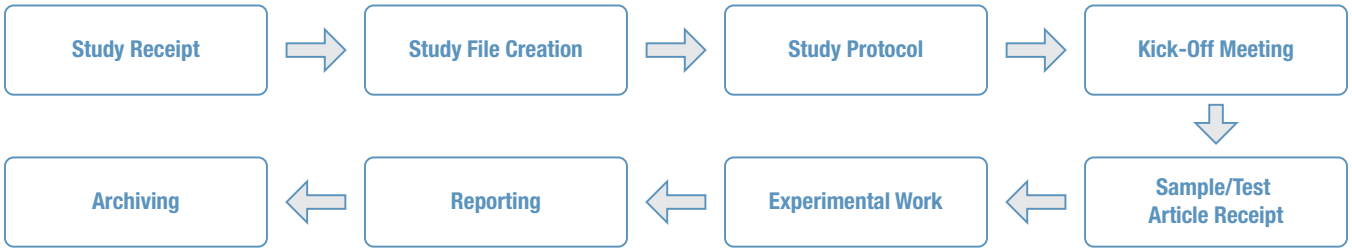
General lab operation	Metrology	Quality Assurance
Use of Lab Workbooks, Logbooks, and Instrument Use Logs	Analytical Balance	Writing the Quality Assurance Statement
Document Control	Lab Automatic Dishwasher	Quality Systems Audit Schedule
Archiving	Temp and Humidity Sensor	Hosting Regulatory Visitors
Change Control	Instrument Change Control	Handling Complaints
Investigations (suspect data and OOR data)	Metrology Investigations	QAU File Maintenance and Archiving
Deviations	Qualification by a Vendor	Vendor Qualification
Corrective and Preventative Actions (CAPA)	Lab Fume Hoods	Quality Agreements

Templates, standardized forms, and the company organizational (org) chart should be controlled by the DCU. Regarding the later, a format that identifies each employee by job title and function is helpful. For example, an employee might be identified on the org chart as Scientist II and reference standards coordinator. An auditor can review the org chart, single-out this employee, and find in the employee's training binder the following: a job description that includes the roles of reference standards coordinator and Scientist II, a curriculum vitae that shows the employee is qualified to serve as reference standards coordinator and Scientist II, and documentation of all the other relevant GLP training (e.g. training on SOPs) that the employee has received to date.

An outside auditor will review the org chart as part of their effort to determine that the company has adequate resources (e.g. space, qualified lab personnel, instrumentation, qualified QAU personnel, study director) to conduct all of the GLP studies that are on the Master Schedule. Keeping a master signature list that includes each employee's printed name, signature, and the initials they will use on GLP documents is an excellent idea. Similarly, keeping an updated master equipment list is expected of the lab.

Figure 1 provides the workflow through a study in brief. What follows is a fairly detailed look at the study workflow (starting with receipt of the study and ending with study archival) with references along the way to procedures and forms that are helpful.

Figure 1: Flow of work through a study



The Study Transmittal Form (**Table IV**) is used to identify the GLP study, test article, sponsor, and study director and provide information that is required for placing the study onto the Master Schedule and for creation of the study file by the DCU. By writing the study protocol, the study director establishes control over the study. The protocol and its template are controlled through the DCU. Once the protocol is signed by the study director, the QAU places the study onto the Master Schedule.

The Kick-off Meeting checklist (**Table IV**) is used by the study director to ensure that the lab is ready to start the study. Test articles are received in the designated area by the sample-coordinator following an SOP (listed in **Table VI** under the title "Receiving, Logging, Storing, Testing, Archiving and Disposing of GLP Samples or Test Articles)

and using the Test Article/Sample Transmittal form (**Table IV**). The later form prompts both sender and receiver to record vital information about the test article. Test articles (and control articles) are logged into storage under those conditions specified on the Test Article/Sample Transmittal form. Their condition upon receipt is noted and any chain-of-custody paperwork is filed in the study file. The DCU prints the workbooks for the study and logs them into the workbook logbook. Participating scientists log out the workbook they need and proceed to perform experimental work as per the appropriate study protocol, SOPs and written test methods, while recording raw data contemporaneously in the workbook (**Table I**).

The QAU will perform at least one audit of the experimental work while it is in progress. QAU uses an audit checklist and a standardized report form to report audit findings back to the study director and the study director's management. Workbooks are subject to peer-review then submitted to the QAU for review. The QAU will release the workbook after all corrections have been made, i.e., all related Corrective and Preventative Actions (CAPA)) are closed-out. The study director writes the study final report, which includes all of the data (i.e., good, bad and ugly). The study director references in the report the study protocol, all workbooks used in the study and all investigation reports (e.g. suspect data investigation) generated by the study. The study director attaches the compliance statement to the report that testifies to the fact that the study was conducted under GLP and lists out any and all significant non-compliances.

The QAU reviews the study final report to ensure that the report accurately reflects the conduct of the study. The QAU writes the Quality Assurance Statement, listing out each phase of the study that was audited, the date of each audit and the date that audit findings were reported to the study director and the study director's Management. The study final report, compliance statement, QAU audit checklist and QA Statement are all template-based, with the template and all its revisions controlled through one or more SOPs. The study director signs and dates the study final report and submits it and all other study materials to the archives. An exact copy of the study final report is issued to the sponsor.

The Quality Systems Approach

The QAU will acquire data on the performance of personnel, instrumentation, equipment, and facility from multiple studies over a period of time. Examples include the number of CAPAs identified with an individual and the number of instrument failures associated with an instrument. On a higher level, the QAU collects data on how well the various functions are performing. An example is the use of workbooks: Are the workbook templates being appropriately revised over time? Are workbooks being used properly? Logged properly? Controlled properly?

On still a higher level, the QAU collects data on the various systems in place to control the functions, e.g., the DCU, Training, Metrology, Vendor Qualification, Change Control, and Archiving systems. Are investigations conducted in accordance with the investigations SOP? Are personnel being trained on SOP revisions? Is Metrology on top of the calibration/qualification schedule? Are changes to the facility air-handling system receiving the proper review and approval before being made? We refer to these systems as "quality systems", although in the larger scheme, Good Laboratory Practice is the quality system (4). All of these data are developed by the QAU and reported to management with the aim of identifying and correcting negative or disruptive trends.

Some key quality systems used in a GLP program are listed in **Table VII**. They operate in cafeteria-like fashion, ensuring that the resources are available in order to meet the various requirements (on personnel, procedures, instrumentation, equipment, available lab space, proper storage conditions, data recording and retrieval, and others) for conducting the study under GLP. The performance of each quality system is continually monitored by the QAU, who reports back to management, who in turn, assures that corrective and preventative actions are taken when needed. The QAU will follow-up on the CAPA to ensure that it was effective.

Table VII: Key quality systems (sub-systems) to GLP

Written procedures (SOPs)	Test article (sample) receipt	Laboratory Information Management System (LIMS)
Metrology	Reference standards	Training
Quality Assurance Unit (QAU)	Deviations and planned changes	Complaints
Vendor qualification	Change Control	Investigations
Document Control (DCU) and Archiving	Corrective and Preventative Actions (CAPA)	Continuous improvement

Implementation

Having and following good SOPs is the key. Closely related is the job of training personnel on SOPs and revisions and of dealing with deviations and change. The former is handled through the training program, while the latter are handled through the CAPA and Change Control programs, respectively. It is important to understand that "implementing" is an iterative, learning process for the lab. Discrepancies (gaps), redundancies and inconsistencies in the program, along with other short-comings reveal themselves upon implementation. It is a goal for the process, through continual improvement, to converge on what we can call "absolute compliance." The adequately designed program will improve, become "self-correcting" and at some point "highly-stable" and efficient. The poorly designed program will not get there. It will grow into a beast, becoming a constant drain on resources, resulting in lower quality and a decreased potential for the lab to ever perform quality work. The company's leadership will reflect the will, drive, and commitment to implement the GLP program.

Summary

This discussion has provided detail in describing a real GLP program so that the reader relatively new to GLP can get a firm grip on the subject. Having the correct, clearly stated, and understood goal, one maps out a laboratory program, complete with the supporting functions of document control, records retention and quality assurance and backed by a committed management. When installed and implemented, it will become self-correcting and compliant with the GLPs. In this way, a quality culture will become a reality in the organization.

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