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Good Laboratory Practice. Part 1. An introduction

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ABSTRACT: The Good Laboratory Practice (GLP) regulations were put into place in 1978. They establish a standard of practice to ensure that results from the nonclinical laboratory study reported to the U.S. Food and Drug Administration (FDA) are valid and that the study report accurately reflects the conduct of the study. While the GLP regulations promulgate standards of laboratory conduct, for example, use of qualified personnel, instrumentation, and analytical methods, they also create a need to properly and thoroughly document such conduct. When this is done, it is easy to reconstruct and audit the study at a later date. Ultimately, the laboratory conduct in any particular study is compared to the FDA's expectations, which evolve over time within the framework of these regulations, thereby moving the entire pharmaceutical industry forward. Yet, few people learn about these GLP standards before entering the industry. It is simply a matter of time before American colleges and universities respond to a pharmaceutical industry need and introduce GLP to undergraduates.

KEYWORDS: *Upper-Division Undergraduate, Graduate Education /Research, Analytical Chemistry, Problem Solving/Decision Making, Laboratory Management, Drugs/Pharmaceuticals*

This article is the first in a series of three (DOI: 10.1021/ed3002557 and 10.1021/ed300256a) intended to educate the chemist so that he or she can intelligently meet many of the challenges unique to a laboratory operating under the Good Laboratory Practice (GLP) regulations such as those laboratories that are ubiquitously present in the pharmaceutical industry. Ultimately, professional chemists in GLP laboratories learn certain GLP regulations "by heart", as those regulations apply to the chemist's specific lab. For students, however, it is more important to learn overarching GLP principles instead of specific regulations and how those principles combine to form a coherent approach to conducting GLP-compliant experiments. Many laboratory practices learned in undergraduate lab classes are actually regulatory requirements in GLP practice, but are not labeled as such. For example, most students are required to keep lab notebooks that are sufficiently detailed and accurate to allow recreation of the experiments. In GLP regulations, it is stated that within a lab, "the study director shall assure that all experimental data, including observations of unanticipated responses of the test system, are accurately recorded and verified".[1] This regulation contains the same sentiment as the lab notebook rule. Yet, despite GLPs ever-present nature, few books are written about GLP practices and often go through the regulations one at a time, are lengthy, and are aimed at professionals (a short selection is cited)[2−4] making them relatively inaccessible to university audiences.

The present articles provide a good overview of overarching themes in GLP regulations, making them accessible to a wider audience. Most of the topics discussed are, in fact, addressed in various undergraduate laboratory courses including the importance of keeping a lab notebook, recording observations clearly and contemporaneously, calibrating instruments, and planning experiments.[5] These practices take on additional significance to students when they understand that (i) GLP guidelines must be followed for employment in GLP laboratories and (ii) the Food and Drug Administration (FDA) and Environmental Protection Agency (EPA) require that GLP guidelines are followed in all nonclinical lab study experiments. Yet, there are few degree programs in the United States that include direct study of GLP. One such program is the M.S. degree in Quality Assurance and Regulatory Affairs from the School of Pharmacy of Temple University. In addition, there are very few academic GLP laboratories in the United States despite the fact that it is feasible to operate such a laboratory. Those researchers interested in incorporating GLP practices into their academic laboratories should consult the literature.[6,7] It is simply a matter of time before American colleges and universities respond to a pharmaceutical industry need and introduce GLP to undergraduates.

BACKGROUND

The "Good Laboratory Practices" constitute the U.S. government regulations found in Title 21, Part 58 of the Code of Federal Regulations. These were put into place by Congress in the late 1970s, foremost to ensure the FDA that results from nonclinical laboratory studies reported to the agency through new drug applications were valid and accurately reflected the study conduct. Today, all data supporting applications to the FDA for research or marketing permits of FDA regulated products and product registrations submitted to the EPA meet

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the GLP regulatory requirements. Products regulated by the FDA include, but are not limited to, human drugs, medical devices, combination medical devices, and biological products; whereas the EPA regulations include pesticides, biocides, and toxic chemicals. To place this into perspective, the FDA currently has jurisdiction over approximately 20−25% of the U.S. gross national product.[8]

Under the Federal Food, Drug and Cosmetics Act, the sponsor of the regulated product (e.g., the drug manufacturer) is responsible for establishing the identity, purity, strength, safety, and efficacy of that product through appropriate laboratory testing. Amassing these data requires a multifaceted study that can involve many labs and investigators around the world. This varied and complex analytical chemistry support is conducted under GLP regulations to provide data used to decide whether approval for clinical (human) trials is received.

■ ORIGINS OF GLP

Although the original Food and Drug Act was passed by Congress in 1906, the next serious piece of drug regulation was passed in 1938 after the 1937 Elixir of Sulfanilamide tragedy. The S.E. Massengill Company sold a drug called "Elixir of Sulfanilimide" that contained sulfanilamide dissolved in diethylene glycol for treatment of *Streptococcus* infections. Although diethylene glycol itself is nontoxic, it is metabolized in the liver and kidneys into toxic metabolites.[9] If diethylene glycol is consumed in a high enough dose, similar to that found in Elixir of Sulfanilimide, the results are kidney failure and cardiac arrest.[9] Ultimately, the drug claimed the lives of approximately 100 people before it was recalled through a tremendous effort by the FDA.[8,10] However, as there was a lack of drug regulation before 1938, the court had to limit the ruling to "misbranding" the drug as an elixir, which implied an alcoholic solvent, not diethylene glycol. The next year, in 1938, congress passed a regulation requiring drugs to be shown as safe prior to marketing.[8] Further, it was not until 1962, after an additional drug tragedy involving Thalidomide, that the FDA law was amended (by the Kefauver−Harris Drug Amendment) and required drug manufacturers to prove the efficacy of a new drug in addition to its safety.[8]

Soon thereafter in the early 1970s, a scandal arose involving a company named Industrial Bio-Test, which held contracts on approximately 40% of all safety testing on products regulated by the FDA or EPA including drug, pesticide, and food additive products.[11,12] In April of 1976 the FDA, specifically Dr. Adrian Gross, an FDA pathologist, uncovered a massive fraud that included data falsification on an unprecedented scale and resulted, after a five-year investigation, in jail and probation time for three of the leaders of the company.[13] In response to this scandal, the government put together the U.S. Toxicology Monitoring Task Force to ensure the validity of the nonclinical laboratory studies. This task force was the origin of the GLPs. Now, a new drug for human use cannot be marketed without FDA approval of a new drug application, which is submitted by the drug manufacturer and must include safety and efficacy data developed in nonclinical and clinical GLP studies.[14−17] Furthermore, to transport such a drug across state lines, either a new drug application or an investigational new drug application must have been accepted by the FDA.[8] As such, drug manufacturing is more highly regulated by the government than previously.

■ WHEN DOES GLP APPLY?

The development of a new drug is completed in four distinct recognized stages, beginning with the discovery of a potential drug.[15] Animal studies, including toxicological and safety pharmacological studies together with pharmacokinetic and bioavailability studies, constitute the next stage and are referred to as "nonclinical laboratory studies" and this work is conducted under GLP. Clinical (i.e., human) studies make up a third stage and are designed to develop an understanding of the safety and efficacy of the drug in various human populations and such work is conducted under Good Clinical Practice.[18] The postapproval stage is the last and a drug at this stage is registered with the FDA and available on the market. Such drugs are monitored through pharmacovigilance procedures that may prompt further clinical studies.

■ THE ESSENTIALS TO LAB COMPLIANCE

Essentially, laboratory work in support of a GLP study is conducted by a qualified analyst, using a qualified instrument, and following a validated or verified analytical method or standard operating procedure (SOP). The procedure to "qualify the analyst" involves documenting in their training file proof of their qualification based upon a combination of their education, prior job experience, and specific on-the-job training. The goal of qualifying the instrument is to show the instrument is "fit for its intended use" and can be as simple as calibrating the instrument against a reference standard traceable to the National Institute of Standards and Technology (NIST). Quoting the regulations, "Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized".[19] Similarly, the procedure to validate or verify the analytical method may only require verifying that expected results are obtained when following the method as applied, for example, to a reference standard, or it may be more involved such as demonstrating that the method passes predefined acceptance criteria (such as those set on linearity, range, limit of detection, accuracy, and precision) when following a validation protocol in conformance with the appropriate International Conference on Harmonization (ICH) Guidance to industry.[20] All such qualifications of either instruments or analysts must be thoroughly documented and the documents properly archived so that, even years later, it will be possible to demonstrate to the FDA the "qualification status" at the time of the study. Doing these essential steps puts the laboratory on its way to becoming GLP-compliant.

■ ROLES AND RESPONSIBILITIES

All aspects of a GLP study are regulated, from the experimental design, through sampling and performing chemical analyses, to recording, reporting, and archiving experimental results and conclusions. Conduct of the study necessarily involves many people each playing a variety of roles and it is important to single out from the start who is responsible for what. Those persons who have the power and responsibility to direct resources (e.g., facilities, personnel, money, equipment, etc.) and to ensure that the study conduct is in compliance with GLP regulations are collectively called management. Management establishes a document control unit that ensures that any and all records used or generated in the conduct of the study and deemed necessary for its evaluation and (later) reconstruction are controlled, meaning that such documents are not lost, damaged, destroyed, altered, or revised without proper approval

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and documentation. Management also establishes a quality assurance unit to monitor the study at appropriate intervals and report back on a timely basis any and all noncompliances to management and the study director, which management assigns to each study.[21] The study director serves as the single point of study control and is responsible for the study design, technical conduct of the study, interpretation, analysis, documentation, reporting of the study results, and archiving of study materials. Each person or group involved in the study has a specific job that helps regulate and document the study in a controlled way.

WRITTEN PROCEDURES

The importance of having approved written procedures in place cannot be overemphasized. It goes back to the familiar accountability rule-of-thumb, "say what you are going to do and then do what you say". They provide instruction to the user and are reviewed and approved by management and quality assurance. A periodic schedule of review and revision is established for all procedures. The document control unit sees to it that only the recent version of the approved document is available for use. Quoting the regulations, "A testing facility shall have standard operating procedures in writing setting forth nonclinical laboratory study methods that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study".[22] Furthermore, written procedures facilitate a quality audit that takes place after the study is complete. Auditors ascertain from the selection and the organization of these procedures if the laboratory clearly understands the GLP regulations that apply to the work that they do. Typically, auditors want to see the index of the laboratory's standard operating procedures (SOPs) and scrutinize key procedures. Key SOPs include (i) document control, (ii) training and qualification of analysts, (iii) procedures for recording raw data, (iv) corrective and preventative actions, (v) change control, and (vi) quality assurance monitoring of GLP studies. Auditors check for documented evidence that SOPs are being followed and any deviation from an SOP is reported to the study director and study management.

Written procedures are also found in the study protocols. The study director obtains control over the study by writing the study protocol and then using it to communicate with the laboratory how the study will be conducted. The protocol is finalized and approved before the start of the study. Study-specific material that is generally not included in the SOPs is found in this document, including but not limited to the details of the experimental design, clear statements of the study objectives, details of the methods to be used in the conduct of the study (including methods for the control of bias) and the records to be maintained. Quoting the regulations, "Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study".[23]

Additionally, highly specific lab instructions are written into analytical test methods. Unlike SOPs, these laboratory procedures are specific to a certain analysis. Like SOPs and protocols, they are controlled documents, reviewed and approved by lab management and quality assurance. An analytical test method (simply called "method") will often be used in a number of very different studies that require the same specific analysis be performed. The study protocol need only refer to the method by document number (and usually, the method is then relegated to an appendix of the protocol). Quoting the regulations, "Each laboratory shall have immediately available laboratory manuals and standard operating procedures relative to the laboratory procedures being performed. Published literature may be used as a supplement to standard operating procedures".[24] However, methods change over time and such changes must be documented. Changes are annotated on the "change control" page of the method along with the justification for each change. Because it is required to document "in the raw data" the activities (e.g., steps taken in the analysis) taken by the lab to support the study, methods offer some relief to the analyst from continually writing these steps in their lab notebook or workbook. Rather, they simply reference the method document control number in their lab notebook or workbook. A contract research organization that has been operating for some time will typically have developed and validated (or verified) hundreds of analytical methods, but, not all methods are developed in-house. They can be transferred from another lab. Analytical test methods are also available through a number of organizations including, but not limited to, NSF International, USP (United States Pharmacopeia), ASTM (American Society for Testing and Materials), OECD (Organization for Economic Co-Operation and Development), and EPA (Environmental Protection Agency).

THE STUDY FINAL REPORT

It is a regulatory requirement that the study director prepare and submit a study final report providing the reviewing agency, for example, the FDA, with the *what*, *where*, *how* and *when* of the study.[25] The study final report includes among other things: (a) a statement of the objectives of the study, (b) a description of all methods employed, (c) all of the experimental data and results generated in the conduct of the study, (d) descriptions of all calculations, and (e) all conclusions drawn. Attached to the study final report is the "compliance statement", written by the study director, that provides a description of any and all circumstances that may have affected the quality and integrity of the study and attests to any and all noncompliances that occurred in the study.

RECONSTRUCTING THE STUDY

So much success in the GLP arena depends upon being able to reconstruct the study. "Reconstructing the study" means putting together a complete picture from the documented (largely, written) records of how the study was conducted: who worked on it, what were their qualifications, what instruments were used and were they properly qualified throughout the study, what reference standards were used, were they within their expiration dates, were they properly stored, and how were the samples prepared. These records must be written by persons who understand that the records will be used by others at a later date (perhaps, a much later date) and must support any claims made in the final study report. It helps to have good written procedures (protocol, SOPs, and methods) in place throughout the study and to be able to call them up at any time. The account of how the analysis was performed must be permanent and readily retrievable. The data to be captured are defined in the protocol. One strives to present a complete set of data. Having good lab notebooks and workbooks and instrument logbooks in place helps. Should some or all of the data be suspected as being in error or flawed in some way they may be invalidated (but still kept and not obscured in any way) following a predefined and management-approved procedure called an "investigation". Investigations are treated in the third

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article of the present series. Failing to reproduce an analysis can come about even though the original analyst was scrupulous. Even a study that generated data that were not very reproducible, can be reconstructed provided that the problems with reproducibility in the analytical results were properly investigated and documented. As one might expect, good science aids in good compliance, but does not guarantee it. First and foremost, the scientist must be honest and not bias the analysis. Scientific integrity rules the day, always.

Hand-in-hand with making the study easy to reconstruct, is making it easy to audit. A professional auditor possessing an appropriate level of experience in and knowledge of the type of work being performed in the lab must be able to quickly evaluate whether the study was conducted in compliance with GLP. Because the audit of the study may well be conducted by an EPA or FDA investigator months or even years after completion of the study, the "snap-shot in time" concept is important. This involves linking the study to a study file that is maintained by the document control unit and designated via a unique study identification number. Relevant information is simply added to the study file at the time it is generated. When this is all done correctly, it is easy to follow this "audit trail" from the study final report right back to experimental details such as the lot number of the solvent or reagent used to prepare the standard solution and to be able to say almost in the same breadth, what instruments (if any) had performance issues at the time of the study and what version of such-and-such an SOP was in place at the time. A good test of study integrity is the coherence and completeness of its records and the amount of time it takes to retrieve the study to the satisfaction of an FDA field investigator, say, 5 years after the study was completed.

■ CONCLUSION

One would anticipate that in a competent pharmaceutical analysis laboratory, reliable analytical results would be generated by trained, capable scientists, using instrumentation and equipment that are fit for their intended use and following accepted analytical methodology. Meeting the GLP regulations adds yet another dimension to this: to quote Taylor and Stein, "The proposed regulations placed a heavy emphasis on data recording and record and specimen retention to ensure that a study could be reconstructed at a later time if the need arose".[13] Study reconstructability remains a central pillar of the GLPs.

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Notes

The authors declare no competing financial interest.

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Good Laboratory Practice. Part 2. Recording and Retaining Raw Data

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ABSTRACT: A clear understanding of how "raw data" is defined, recorded, and retained in the laboratory record is essential to the chemist employed in the laboratory compliant with the Good Laboratory Practices regulations. This article is intended to provide an understanding by drawing upon examples taken from the modern pharmaceutical analysis laboratory.

KEYWORDS: *Upper-Division Undergraduate, Graduate/Research, Analytical Chemistry, Problem Solving/Decision Making, Laboratory Management, Drugs/Pharmaceuticals*

It is absolutely critical to operating a laboratory under the Good Laboratory Practice (GLP) regulatory requirements for proper identification, recording, and retention of raw data to ensure it is readily available and at the same time protected from corruption or loss. Nonclinical laboratory studies can be "invalidated" and marketed products that are regulated by the Food and Drug Administration (FDA) and consumed by humans can be deemed "adulterated" and recalled based solely on the deficiency of the laboratory to adequately and honestly document the conduct of their experimental studies done to support these products. The GLP regulations that apply to the testing laboratory apply equally to all supporting laboratories, academic and nonacademic.

This article is intended to provide guidance on what should be recorded and retained in a GLP complaint lab. The old rule of thumb, that "if you did not write it down, you cannot claim to have measured it" applies, but how should you write it down, where should you write it, and what must you claim to have measured? The GLP regulations described in Title 21 of the Code of Federal Regulations, Part 58 provide answers.[2] They are, however, left intentionally vague. The subject is "raw data" and has a clear place in the laboratory. Many of the concepts involved and strategies devised for dealing with this issue are already familiar to experienced researchers and some are taught in the undergraduate chemical laboratory. All students learn early on the importance of keeping a good lab notebook, without knowing this is a GLP regulatory requirement. Similarly, students in instrumental analysis class learn how to build a calibration curve but are probably not aware that retaining all the weights and volumes of the reference standards prepared and used to generate the curve is a GLP regulatory requirement. How raw data are recorded and retained is fundamental. Students near graduation and looking for employment in the pharmaceutical industry will find having read and understood the present article will provide them a "leg-up" on the job interview. Good documentation practices as discussed here are encountered by the chemist on his or her first day in the professional lab and in the specific case of the pharmaceutical analysis lab, the expectation is furthermore that the chemist will follow these practices before generating any data to support a GLP study. The instructor responsible for preparing the undergraduate for graduate research or a career in the pharmaceutical lab can draw upon the concrete examples provided here to educate, provide additional motivation, and show that the subject, "As with Wagner, it's not so bad as it sounds."[1]

RAW DATA

All raw data must be recorded and retained as part of the study. The GLP regulations define "raw data" as "any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a non-clinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study".[2] Raw data may include "photographs, microfilm or microfitch copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments".[2] It is obvious that the regulation was written to anticipate the role that technology does and will play in the future of recording and retrieving raw data.

It is important to distinguish between raw data and the media used to record it. For example, the laboratory may use an analytical balance that has both an LED display and a paper printout of the result of a measurement so that the analyst may choose to read the LED display and hand write the displayed

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value into their laboratory notebook or get an ink-on-paper printout from the balance printer. The raw data is the same, a recorded weight, though the media used to record it are different and will be treated differently. If the LED display is defined as the raw data, then the measurements must be directly recorded into workbooks or notebooks. However, if the lab defines the ink-on-paper printout to be the raw data from the balance, the analyst should immediately paste it into his or her workbook or notebook. However, this piece of paper could be altered or removed and replaced. As such, it is typical to write the date and the name or initials of the analyst across the seam of the print out and the page, thereby further integrating the printout and workbook or notebook. Furthermore, the analyst will write on the printout sample identification information. In his book, Professor Wilson[3] illuminates the importance of such good documentation practices by contrasting them with the practices of astronomer Le Monnier, who missed out on the discovery of Uranus as a result of writing his observations down on a paper bag.

Data must be entered in its unaltered raw form. For example, the concentration of a standard solution may be calculated from the ratio of the observed weight of reference material dissolved in the observed volume of solution (or solvent). The concentration is a calculated value and not raw data. It is expected that both the raw data, which is the weight of the standard and the volume of solution or solvent, and the calculated value both be recorded and that an example of the calculation (including appropriate units and considering the significant figures convention) be shown in the workbook or notebook. Similarly, it must be recognized that results from smoothing "data" and other data transformations, although perhaps necessary and useful, cannot take the place of contemporaneously recorded raw data.

DATA STORAGE AND RETREIVAL

Before modern computing technology became an integral a part of scientific research, following proper GLP guidelines for data recording and retention was simpler: write down everything exactly as it happened, do not change what was recorded, and keep all documentation. However, with the increased presence of technology in scientific research, the requirements of the GLPs are more complicated. A simple example illustrates nuances involved in data storage and retrieval under the GLP requirements. If the analytical balance is not capable of electronically storing the result, then the procedure to verify that the balance printout and the LED display are the same is easy to perform and document (typically in the instrument logbook). If, instead, the balance is capable of retaining in electronic memory (for printing at a later date) the old weight while generating a new weight, then the question arises: "What protects against confusing old with new data, altering or deleting data, or losing data when power to the balance fails"? In this case, the procedure for verifying that the lab has control over the raw data may become involved. And it may include some sort of "disaster recovery" to protect against the power failure or to mitigate its impact on studies. Furthermore, lab personnel other than those working on the study will typically have access to the balance and the data stored in its memory so that some sort of "logon with password" control may be required.

The same principles of data storage and retrieval under GLP apply, whether the media used for storage is ink-on-paper or not. Systems that store data in electronic form, for example, computer systems and laboratory information management systems in general, must meet the same requirements as ink-on-paper systems. To demonstrate to the FDA that the electronic record is "trustworthy, reliable and generally equivalent to paper records",[4] the laboratory must comply with the regulations set forth in Title 21, Code of Federal Regulations, Part 11, which, among other things, dictate the level of control that the lab must have over the electronic record and the extent that the computer system generating this record must be "validated". This subject is left for a later time in a future publication.

Furthermore, information, in addition to results, from measurements will typically be required to reconstruct the study. Examples include instrument conditions and parameters, records of instrument performance issues, and investigations into suspect data. Although some of these records are also stored in other places, for example, quality assurance keeps all audit reports, it is important to tie all records to their specific study so that they are an integral part and to make them readily retrievable. The ability to retrieve all study data in a timely fashion is important and helps to show compliance with GLP regulations, which is especially important when the lab is being audited by the FDA.

GOOD DOCUMENTATION PRACTICES

An old industry joke is that "GLP" stands for "generate lots of paper". It originates from the importance placed on documenting a study from beginning to end. A 1990 estimate of the amount of documentation provided in a typical new drug application is given as "2 to 15 volumes of summary material" generated during the safety and efficacy investigations as well as proposed manufacturing and analytical testing along with "10 to 100 volumes of raw data" to support the summary.[5] This magnitude should serve the reader as a benchmark. All of this information must be properly documented for a drug to be approved by the FDA.

Therefore, the Good Documentation Practices have been developed. A short selection is given in Box 1. Many of these practices have grown out of the research lab and are familiar to chemists and even students, with some practices specifically prompted by the need to support (in court) patent claims on products and processes.[6] Because it is required that raw data be readily retrievable and that the study itself be easy to reconstruct from the record, it is clear that a device such as a workbook or lab notebook along with the requirement that the analyst make entries directly to the workbook or notebook at the time of observation is helpful. It is expected that raw data be attributable, legible, contemporaneous, original, and accurate. By "attributable" is meant that the data are linked to their source, including the person making the observation and the record and the study, test article, instrument, and analytical run. It is a GLP requirement that the person making the data entry shall sign (or initial) the entry on the date it was recorded. Similarly, in automated data collection systems, the person responsible for direct data input shall be identified at the time of data input. By "contemporaneous" is meant that data are recorded at the time the observation is made. By "original" is meant the first recording of the data, which is assumed to be the most accurate and reliable recording of the data. Following good documentation practices helps to instill these quality attributes. Changes can be made to data entries but they must not obscure the original entry and they must, at the time the change is made, be signed (or initialed) and dated by the person making the change, who must also record the reason for

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Box 1. Examples of Good Documentation Practices

1. Record all data and observations legibly in indelible ink (except those generated by automatic data collection systems).[7]
2. Enter all data directly into laboratory workbooks, logbooks, or notebooks at the time of observation. Do not record any data on scraps of paper that can be lost.[7]
3. Date and sign or initial all entries in workbooks, logbooks, or notebooks.[7]
4. Changes in data entries should not obscure the original entry. Instead, strike out the original entry with a single line. Initial and date changes and document the reasons for change, perhaps with an error code.[7]
5. Shared workbooks or notebooks must clearly identify which analyst (student) performed what portion of the work.
6. Exact copies of originals can be included such as exact copies dilution schemes or instrumental conditions. Exact copies should be marked as such and signed and dated. Exact copy printouts from automatic data collection systems must contain all the information that is in the electronic record such that the experiment can be reconstructed. This includes a record of all changes made to the electronic file.

the change. To facilitate this, many laboratories create "error codes" (that are defined in a standard operating procedure) and simply write the error code alongside the change rather than use a full sentence to give the justification. For example, "MD" might be used for "Misdated".

WORKBOOKS AND NOTEBOOKS

To facilitate the orderly recording of raw data, most laboratories use a workbook or notebook. The notebook is a research notebook, issued to the analyst and tracked by a notebook number assigned by the document control unit. The document control unit tracks all official documents, including reports and lab workbooks or notebooks, using unique document numbers. The notebook consists of many bound, prenumbered, blank pages and a space for the analyst and witness to sign and date each page. The notebook is usually not specific to the analysis or the study and the analyst is expected to keep it until it is filled. How data are organized in the notebook is left up to the analyst and will differ from analyst to analyst. This format, though it works well for some laboratories, has many shortcomings when compared with workbooks, particularly in a contract research organization, where the analyst may be expected to work on a variety of studies supporting a number of different sponsors all of whom want their studies to be confidential. The workbook is also a preprinted with a document control number that is issued and controlled by the document control unit. The workbook template is created by the lab with a specific analysis in mind. Revision to the workbook template goes through a change control program that tracks all changes to laboratory operating procedures. Therefore, workbook template revisions must be justified from both a scientific and a compliance viewpoint (i.e., the revision simplifies the analysis and increase GLP compliance).

Regardless of whether an analyst uses a workbook or a notebook format to record data, certain information is important to include in both media. A list of examples of such requisite information is supplied in Box 2. Including such information in laboratory workbooks and notebooks facilitate both the peer-review and the quality assurance inspection of the work. Although building "prompts" into the workbooks for the analyst greatly increases analyst efficiency, such prompts are not meant to take the place of thinking. Workbooks and notebooks will typically contain a lot of data that is not common across all analyses, but is important and needs to be included nonetheless

Box 2. Examples of Information Required in Workbooks and Notebooks To Document the Study and Analysis

- Analyst Name
- Date
- Document Control Number
- Method or Protocol Number
- Study Number
- Test specifications or ranges
- Objective or Purpose
- Sample Information (sample ID #, lot #, description of the sample and sample container or closure system)
- Reference Standard Information (name, manufacturer, lot #, grade or purity, expiration date)
- Reagents List (manufacturer, lot #, grade or purity, expiration date)
- Instrument List (instrument ID #, date of last calibration, next calibration due date)
- Preparation of diluent ad mobile phases (lot #, manufacturer, expiration date of each reagent used)
- Reporting Results (include units and round to the proper number of significant figures)
- Instrument Setup and Parameters
- Preparation of Stock and Working Standards
- Preparation of Samples (including weights, volumes, dilution factors, and final concentrations)
- Calculations (with units)

LOGBOOKS

Not only is tracking data for a study important for GLP compliance, but tracking how the laboratory runs is also important. Much of this information is easily captured in a logbook and is helpful in reconstructing a study. Common examples include the instrument logbook and the sample logbook. Logbooks contain information supporting multiple GLP studies, making the ability to easily associate certain data or information with a certain study important in reconstructing study conduct.

Not only do logbooks make tracking certain information easy, such as instrument use, but using instrument logbooks in particular also fulfills a GLP requirement. It is required that "written records shall be maintained of all inspection, maintenance, testing, calibrating and/or standardization operations" performed on equipment and instrumentation used in the "generation, measurement, or assessment of data and equipment used for facility environmental control".[8] The instrument logbook serves this purpose. Data are recorded into logbooks following good documentation practices and the logbooks themselves are under document control. A list of typical information included in instrument logbooks is included in Box 3. The instrument logbook is commonly the single source of information on the history of the instrument including its

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Box 3. Examples of Information Included in Instrument Logbooks

- Instrument Identification Number
- Date of Installation Qualification
- Details of the Performance Qualification
- Instrument Type or Description
- Qualification (calibration) Status
- Identification of the SOP Followed for the Performance Qualification
- Manufacturer
- Date of the Last Calibration
- Details of the Preventative Maintenance
- Model
- Date when Next Calibration Is Due
- Identification of the SOP Followed for the Preventative Maintenance
- Serial Number
- Details of the Installation Qualification
- Log of Instrument Failure
- Instrument Custodian
- Identification of the SOP Followed for the Installation Qualification
- Details of Instrument Repairs and Remedial Actions
- Table of Contents: Running List in Chronological Order of All Instrument Events
- Identification of the SOP Followed for the Operational Qualification
- Instrument Location
- Details of the Operational Qualification

qualification and calibration. These activities ensure that the instrument is fit for its intended use. Instrument logbooks should not be confused with instrument use logs. The latter create a record (including when the instrument was used, by whom, for what study and test article) that can be very valuable in the event of an investigation into the validity of data generated on the instrument.

THE ARCHIVES

It is a regulatory requirement that all study materials required for the reconstruction of the study be archived. In deciding what to archive, one must consider the obvious, for example, all the study raw data, study protocol and report, and so forth and also the not so obvious, for example, those things required to prove that the study was conducted in compliance with GLP. For example, calibration and maintenance records for instruments generated by metrology, records showing how the test and control articles as well as reference standards were stored during the course of the study, and so forth. Samples of the test and control articles, reference standards, and wet specimens shall, if required, be archived for a time period dictated by their chemical stability, that is, "as long as the quality of the preparation affords evaluation".[9] The physical archives must protect documents and materials in general against theft, fire, water damage, pests, mold, and all other forms of deterioration. A system for archiving study materials that does all of this and at the same time ensures that materials can be rapidly retrieved at any time, that materials cannot be lost, cannot be replaced without proper prior approval, and that sponsor-confidential materials cannot be viewed by unauthorized persons must be in place. Study materials are typically archived for not fewer than 10 years. Although this may seem tedious, especially for academic laboratories, it is a significant requirement of the GLP regulations as it affords the ability to more completely reconstruct how a study was conducted in the context of laboratory operations.

CONCLUSION

Critical to performing laboratory work in compliance with the GLP regulations are the implementation of good documentation practices and the proper identification of what must be documented in addition to the raw data and data analyses. When this is done, it is possible to reconstruct the experimental study at a later date from archived study records. The examples provided of the standardized laboratory workbook and the instrument logbook should offer a fairly clear picture of the practical side of the subject. It is hoped that the reader, whether they go on to work in the GLP-regulated analytical or pharmaceutical analysis laboratory or the nonregulated R&D lab, will find this introduction highly useful.

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Good Laboratory Practice. Part 3. Implementing Good Laboratory Practice in the Analytical Lab

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ABSTRACT: Laboratories submitting experimental results to the Food and Drug Administration (FDA) or the Environmental Protection Agency (EPA) in support of Good Laboratory Practice (GLP) nonclinical laboratory studies must conduct such work in compliance with the GLP regulations. To consistently meet these requirements, lab managers employ a "divide and conquer" strategy: they break up the laboratory operation into key unit functions. Next they consider the regulatory requirements that must be met by each key unit function. This is called the quality system approach for implementing GLP in the analytical laboratory and it is embraced by nearly every laboratory endeavoring to perform this kind of work.

KEYWORDS: *Upper-Division Undergraduate, Graduate/Research, Analytical Chemistry, Problem Solving/Decision Making, Laboratory Management, Drugs/Pharmaceuticals*

This article is intended to provide the chemistry student considering a career in a pharmaceutical analysis laboratory an understanding of the key elements that go into the organization and management of the Good Laboratory Practice (GLP) -compliant laboratory. The specific organizational units are the quality systems or programs, such as the metrology program, the training program, and others that the lab puts into place to ensure that all GLP studies are conducted in compliance with GLP regulations.

LABORATORY MANAGEMENT

The focus of the GLP approach to ensure valid data are reported is on the *process* by which the testing laboratory carries out and documents activities, more so than on the product being tested (i.e., test article) or the test results. Companies in this regulated industry adopted a laboratory management program to ensure that (a) facilities are adequate;[1] (b) equipment and instrumentation are qualified and well-maintained;[2] (c) written procedures are in place;[3] (d) personnel are adequately trained to do their jobs, which are well-defined; (e) data are properly recorded, retained, and readily retrievable;[4] (f) samples, reagents, and reference standards are properly labeled, handled, and stored;[5] and (g) GLP documents are "living" and "controlled", meaning that a record of its "birth" is kept, a record of any and all changes made to it is maintained, and a record of when it is retired and archived is made.[6] A controlled document cannot be lost or destroyed.

Management puts this laboratory management program into place using a "divide and conquer" strategy. Each of the above requirements (a–g) gives rise to a corresponding quality system in the program. For example, requirement (b) gives rise to the metrology system; requirement (e) gives rise to a laboratory information management system, for example, laboratory notebooks and workbooks, logbooks, electronic information management systems, and the archiving system; and requirement (g) gives rise to the document control unit (DCU). In short, quality systems help management control the laboratory environment and ensure the proper resources (type and amount) are made available for the design, conduct, and maintenance of all GLP studies in compliance with the regulations. Aiding in resource allocation decisions is the master schedule,[7] which is a listing of all GLP studies planned for the lab along with (among other things) a description of the nature of each.

FDA INSPECTIONS OF THE LABORATORY

Historically (and still true today), the design and intention of GLP was (is) to provide a platform on which to conduct the study that facilitates its inspection. Quality system designs have workings that are transparent and it is desired that they have built-in mechanisms for traceability and accountability (as desired for any good management system). The main tool used by the U.S. Food and Drug Administration (FDA) to enforce GLP is the inspection of laboratories by FDA field investigators. The number of FDA field investigators employed at any given time as well as the "size" of the agency has historically been highly dependent on the politics of regulation and deregulation.[8] It is generally believed that there are not enough investigators for the workload, hence the FDA's expectation is that the quality assurance unit (QAU) of the

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company will stand in (advocate) for the FDA and that companies are to be self-inspecting and self-correcting.

The FDA will typically perform a facility audit of a contract research laboratory that is providing analytical or bioanalytical support to GLP studies under contract with a sponsor, every two years. All such GLP laboratory inspections by the FDA will include at least (i) an inspection of the QAU and (ii) inspection of one other quality system. Included in this audit, the FDA will inspect specific studies in the lab as needed. The FDA investigators typically conduct their inspection of the laboratory during normal business hours and without giving notice prior to their arrival. Most detrimental to the lab's success in an FDA inspection is failure to demonstrate a clear understanding of the GLP regulations as evidenced in the design of the quality programs. This is followed closely by failure to actually implement the programs. It should be noted that the FDA does not "certify" laboratories. Rather, the FDA will make public the results of all findings (in the Establishment Inspection Report) including all noncompliances found. Those laboratories that are not in good-standing with the FDA will receive a "Warning Letter". Those that fail to remove the deficiencies cited in the warning letter will be disqualified. Hence, the FDA cannot qualify the lab, but can *disqualify* it. Similarly, the FDA may "disqualify" a study.

THE TRAINING PROGRAM

Persons working on a GLP study must be qualified to do so.[9] Qualification may come via a combination of education, prior job experience, in-house training, outside professional training, and other forms of training. Training may be general, such as training on the GLP regulations or highly specific, such as training on the HPLC technique or even a specific HPLC analytical method. Each individual engaged in the conduct of (or responsible for supervision of) a nonclinical laboratory study must be able to perform his or her assigned functions and there must exist documented evidence of this. Personnel assignments are provided on company job descriptions, which are kept in the employee's training file along with their curriculum vita. Employee qualifications are documented in the employee training file as they develop. Training is the most important means to achieving the goal of good science conducted under GLP.

TEST ARTICLES, REAGENTS, AND SOLUTIONS

It is required that an area in the laboratory be designated and clearly marked-off for the receipt of GLP samples (test articles and control articles).[10] Having this GLP-sample receiving area reduces the chance that such samples will be confused with other materials such as those past their expiration dates to be disposed. Samples are typically logged in, using an assigned laboratory sample identification number and inspected to ensure that the sample meets the sample description (provided on the chain-of-custody paperwork sent along with the sample) and that the sample container is not damaged or flawed. Entries are made into the sample log indicating the date of receipt and the proper storage conditions for the sample. Other information such as the laboratory study identification number (that connects this particular sample to a particular study), lot number, and quantity of material received should be logged at this time. Finally, the sample is placed into the proper storage condition and made available to the analyst for testing. For reagents and solutions, the regulations are clear: the label on each must indicate identity, titer or concentration, storage requirements (e.g., store at room temperature and keep away from light), and expiration date.

THE METROLOGY PROGRAM

In reconstructing the GLP study, one must know what instrumentation and equipment were used to generate study data or to serve as environmental chambers to store test and control articles and reference standards, the condition of all such instrumentation and equipment during the study, and their qualification status during the study. To facilitate this, each instrument or piece of equipment is tagged with a unique identification number and a record (called a master equipment list) is made of them. A template for an instrument and equipment tag is the following: the name of the instrument custodian, the room number of the lab where the instrument is located, the date of the last qualification, and the date when the next qualification is due. The term "qualification" and "standardization" are used interchangeably and include the more specific case of "calibration". Instrumentation and equipment in the lab that are not intended to be used to support any GLP study, or those are "not qualified for regulated use" or "out of order", must be identified as such with a marker in clear view for the user and inspector. Additionally, a logbook is created for each instrument and kept under document control, meaning that each page is numbered, the creation of the logbook is recorded against a document control number assigned it by the document control unit (DCU), and eventually, the logbook is archived. The instrument logbook holds the history on the instrument including when it was qualified, cleaned, inspected, and repaired. It is expected that all GLP instrumentation and equipment will be placed on a "calibration schedule" that includes dates for inspection and routine maintenance and that all qualifications shall be performed following an approved standard operating procedure (SOP) that details the steps to be taken, identifies the person who is responsible for carrying out the procedure (i.e., the instrument custodian), and has clearly defined acceptance criteria for deciding on a "pass" or "fail" assignment to conclude the qualification procedure.

Many laboratories will have in place an instrument "use log" that is controlled by the DCU and captures the name of the person using the instrument, date of use, study number for the study being worked on at the time of use and the workbook number associated with the use.[11] At times these greatly facilitate instrument trouble shooting, for example, by helping the lab to identify analysts or analytical methods that may be causing an instrument problem and they can provide valuable information in the event that the instrument becomes involved in an investigation (see below), particularly as they help the lab to identify all studies that may have been impacted by the instrument problem.

The lab will usually have one "metrology" SOP for each type of instrument (equipment) and this SOP must be in place prior to starting the qualification activities on the instrument (equipment). Likewise, a significant effort goes into the metrology program and it is customary to employ a dedicated metrologist to administer the program and develop an overall master plan for maintaining compliance. This person will likely perform all the instrument qualifications. With a good program in place, it is a relatively simple task to collect at any time, all qualification data generated on all instruments and equipment used for generating data or otherwise critically supporting the GLP study.

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The reader can obtain further understanding of the metrology function simply by reviewing the titles to some of the key SOPs that go into creating the program: these are given in Box 1.

Box 1. Key SOPs for a Lab Metrology Program

1. Master Plan for Instrument or Equipment Qualification
2. The Master Instrument or Equipment List
3. Use of Instrument or Equipment Numbers, Instrument Labels, and Instrument Owners (Responsible Persons)
4. Creation and Use of Instrument or Equipment Logbooks
5. Installation Qualification of Instruments or Equipment
6. Instrument of Equipment Calibration, Maintenance, Inspection, Cleaning, and Repair
7. Creation and Use of the Calibration Schedule
8. Calibration and Maintenance of Analytical Balances
9. Calibration and Maintenance of Temperature and Humidity Sensors
10. Operational and Performance Qualification and Preventative Maintenance of Temperature-controlled Storage Areas
11. Instrument Change Control
12. Metrology Investigations
13. Calibration and Preventative Maintenance of Instrument or Equipment by a Vendor
14. Calibration and Preventative Maintenance of Laboratory Automatic Dishwashers
15. Calibration and Preventative Maintenance of Laboratory Fume Hoods and Bio-Safety Cabinets

Equipment used for the generation, measurement, or assessment of data will be adequately qualified. An SOP should be written on each instrument and piece of equipment in the GLP program that provides the procedures for qualification, maintenance (nonroutine, routine, and preventative), cleaning, and inspection. Such an SOP may or may not include a procedure for the use of the instrument or piece of equipment. What professor Wilson said many years ago is still true today, "The whole purpose of all these recording systems is to preserve values. They should be carefully thought out to fit the conditions of each laboratory and should be adequate but not over elaborate. If too much is demanded of human nature, the system will break down".[12]

DEVIATIONS

Once written procedures are in place, it is inevitable that personnel will from time-to-time deviate from them. Such deviations may or may not impact upon the quality and integrity of the study. When they do, they are major and require an investigation into what happened, the impact on the quality and integrity of the study, and the consequences (if any) to other studies. Investigations must be documented in the raw data (i.e., the workbook or logbook at the locations in the book indicative of the when the deviation occurred) and reported to and approved by the study director. The QAU will typically review and approve deviation investigation reports. Requiring the QAU to review and approve these reports aids them in logging, tracking, and trending deviations so that the company's continuous improvement plans can target the specific areas drawing larger numbers or more severe deviations.

CHANGE CONTROL

Changes that may impact the quality and integrity of the GLP program must be "controlled" in order for the company to remain in compliance with the regulations. What this means is that a proposed "change" should go through a review and approval process, typically through lab management and the QAU. The process will ensure that the change is desirable and specifically, that it either raises or leaves unaltered the level of compliance.

Regarding the critical area of document change control, the document revision must capture the justification for the revision: for example, when an SOP is revised, the new version is assigned a new document control number and an entry is made on the "change control page" of the SOP that gives the justification for the change. In this way, a "history of changes" made to the document is recorded. The new version must receive the same level of review and approval as the original.

INVESTIGATIONS

It is the responsibility of the study director to ensure that "unforeseen circumstances that may affect the quality and integrity of the non-clinical laboratory study are noted when they occur, and corrective action is taken and documented"[13] and that "all good laboratory practice regulations are followed".[14] Study directors and study director management are informed of such circumstances through the QAU.[15] Study director management will typically have a formal procedure in place, described in an SOP that defines the following: when to investigate, how to investigate, how to document the investigation, getting proper approval of the steps taken, and what to do with the results of the investigation.

Investigations are documented in the study raw data and this is often done by making reference to the investigation report (via its document control number). The investigation report is a controlled-document, having a unique document number assigned it by the QAU and containing a detailed summary of how the investigation was conducted along with the results and conclusions of the investigation, including any impact upon other studies and it will reference the raw data (often simply by referencing the document numbers of the lab workbooks and lab notebooks involved). The following criteria are used to judge the "quality" of the investigation: (i) Was it a scientific investigation starting with a provable hypothesis and ending with conclusions supported by the data? (ii) Do the results from the investigation either justify "invalidating" previously generated raw data or else, keeping the raw data "as they stand"? (iii) Was the investigation documented well enough that an independent, objective scientist can review it (years later) and come to the same conclusions?

CORRECTIVE AND PREVENTATIVE ACTIONS

In the quality systems approach to lab management, it is important to have a platform on which to stand where the lab manager can view compliance issues and productivity issues, separate from the individual studies and personnel that generate them. From this viewpoint, trends come to light as do the root causes for many of the issues. Although it is true that each study director must deal with the issues of their own studies, the lab manager must identify problem spots and allocate resources to remediate these as well as issues that extend across multiple studies. To facilitate this, the corrective and preventative action (CAPA) quality system is created and

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used. The lab manager is responsible for logging and tracking all issues requiring corrective and preventative action, for assigning personnel the task of completing such actions, for allocating appropriate resources for the completion of each on an "as needed" basis, and for following each action to completion. It is common to assign a number to each issue and to use this number in the CAPA log. It is also common for the QAU to assign these CAPA identification numbers, because most of the CAPA issues are findings that the QAU have reported to management as part of their audit of either a GLP study or a quality system. The CAPA log can be created in such a way as to make it possible to sort or search the log using key search parameters such as the study number, the name of the analyst or study director, the nature of the issue, for example, protocol deviation or instrument failure, the date the issue was detected, and others. The QAU will perform "trending" analysis using the CAPA log and report back to management.

THE DOCUMENT CONTROL UNIT

Controlling documents is necessary to ensure that proper written instructions are transmitted to the laboratory as well as for positioning the company such that it can accurately and completely reconstruct any study for the sake of an audit. The responsibility for achieving this level of compliance and maintaining this quality system falls on the DCU.

THE QUALITY ASSURANCE UNIT

Management puts into place an independent quality assurance unit (QAU), having responsibility for monitoring each and every GLP study being conducted by the laboratory and for reporting back to upper management and the study director any and all findings of noncompliances.[16]

CONCLUSION

A GLP study is one conducted in compliance with the GLP regulations. It is an honest, complete, and well-documented representation of experimental work that was designed to meet a clear, specific purpose. The study is conducted by qualified persons using qualified equipment and instrumentation following verified or validated analytical methods and written procedures included as part of a well thought out study protocol. The study is conclusive, and if not conclusive or if the study is invalidated, the reasons why are properly documented and supported by the evidence. The GLP-compliant lab will have those management mechanisms in place (such as a document control system, a change control system, a metrology program, and a quality assurance unit) that ensure all studies *can be done* in compliance and that the lab does not, over time, fall out of compliance. Such mechanisms will be constantly monitored by an independent quality assurance unit to ensure that each is functioning as intended. The single largest challenge for the lab is in implementing those standard operating procedures developed by the lab: as one FDA investigator put it, "that is where the rubber meets the road".[17]

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