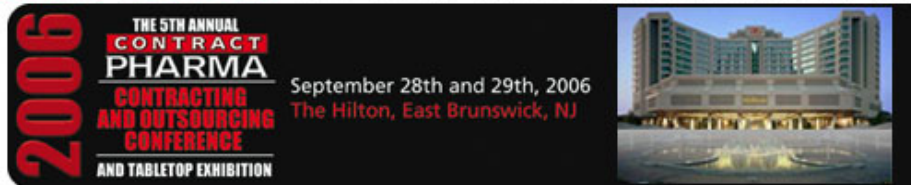




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Quality Assurance Inspections

Key elements of the laboratory auditing process

By Philippe Ourisson

As many contract labs know, audits are nothing new. After all, the FDA regulates the conduct of non-clinical laboratory studies within its "21 CFR Part 58 -- Good Laboratory Practice for Nonclinical Laboratory Studies." This federal regulation applies to non-clinical safety studies for food, drugs, and medical products and devices that are regulated by the FDA. These regulations are designed to address many operations, including a laboratory's personnel, facilities and operations, equipment, test and control articles, protocol, conduct of the study, quality assurance and archival of records and data.

While the FDA regulates all areas of non-clinical studies, no similar FDA requirements exist to cover the laboratory portions of clinical studies. While Good Laboratory Practices (GLP) in clinical studies may not be required, interest in these standards has been increasing the past several years because many pharma companies are now requiring that their contract labs adhere to GLP standards for both the clinical and the non-clinical portions of the research that they sponsor. In most cases, the technical work itself (e.g., bioanalyses) is exactly the same whether conducted for a GLP study (on animals) or for a GCP study (in humans). Of course, at least the same level of quality should be applied to clinical studies as it is to non-clinical studies. After all, regulatory decisions are made based on all of these studies.



Who Can Benefit from a Laboratory Audit?

While several entities can benefit from a laboratory audit, the ones that generally have the most to gain include the following:

Contract analytical laboratories that need to be pre-qualified by pharma companies or research sponsors before the laboratory portion of a clinical study begins. The majority of these labs tend to have self-imposed quality systems in place already; however, third party audits assure prospective sponsors that labs are GLP compliant before work begins. Contract labs can also undergo an audit as a way to fine-tune their methods of operation to ensure GLP compliance. Commercially funded labs that utilize less common techniques and procedures may not be GLP compliant, but may want to adopt GLP standards in order to be in a better position to obtain future work.

University laboratories that want to begin conducting contract or commercial work. Labs within major research universities that are interested in performing or entering the field of contract work have an incentive to voluntarily adopt GLP standards to ensure that they are competitive with contract laboratories. A University department may be world-renowned for its clinical expertise, but the quality of the documentation and the controls does not always approach the level required for regulatory studies.

Government laboratories: Historically, government-funded labs do not have rigorous quality systems in place. Some conduct clinical research in a specialized area (e.g., for tropical diseases) and have unique capabilities and mandates; their associated laboratories are accustomed to performing more routine health monitoring analyses than to regulatory work.

When it comes to contract and sponsor labs that perform clinical research and development work, many have minimal quality systems in place. Others, after weighing the costs and risks of not having a GLP quality system in



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place, implement more rigorous standards by choice.

Selecting an Auditor

To perform an audit, contract pharma labs must typically bring in an independent third-party auditing firm. In some cases, the selection of the firm is made by the drug company or research sponsor. A major advantage of a qualified outside auditor or auditing firm is that they are well-versed in the nuances of GLP and GCP requirements. Plus, they can often offer years of experience and innovative insight that can only be gained by working within a variety of laboratory environments.

When it comes to choosing an auditing firm, there are several key considerations and questions for the QA/QC decision makers to keep in mind. While it may be necessary to select an independent third party to perform the audit, it is up to the individual laboratory to evaluate its own needs and requirements and decide whether to work with an auditing consultant or an auditing firm that may assign a team to the project. It is also helpful to take a step back and examine the size of your own laboratory environment. Ask yourself if one individual could reasonably and successfully take on the task at hand, or would it be more beneficial and cost effective to contract with an auditing firm to get more depth of experience.

Before selecting a firm, you should conduct a qualification interview via phone with the individual(s) who will be performing the audit. Ask specific questions relating to their experience and education. In fact, it is perfectly reasonable to request a CV from each person who will be performing the audit. Why? Believe it or not, there are quite a few individuals who perform audits who have no practical, hands-on experience in working in a laboratory environment, or who are self-proclaimed QA specialists with superficial or irrelevant expertise. Others may lack a scientific background.

Another question to ask involves experience gained during visits, tenures or assignments abroad. Auditors who have worked with labs in a variety of countries, especially in the European Union, not only bring insight from nations that must typically follow GLP and other stringent standards, but they are also more likely to be involved or familiar with global quality assurance associations such as BARQA, the British Association of Research Quality Assurance (see side-bar for a comparison between the FDA GLP, and the BARQA recommendations for Good Clinical Laboratory Practices.) On a related note, auditors should be actively involved with professional associations, and it is extremely beneficial for them to have regular contact with regulators and the inspectors that perform the inspections.

Finally, ask for and check the provided references to help ensure that you select an auditing firm with a solid track record.

Goals and Scope of an Audit

Overall, the goal of the audit is two-fold. The first goal is to construct an accurate "snapshot" of various relevant aspects of current facilities, equipment, and procedures, while also examining the standards, such as chain-of-custody and controls, which are used. The second goal of the audit is to determine how the facility compares vis-à-vis established industry best practices – in this case, GLP. This "Gap Analysis" can then serve as a roadmap or guide that laboratories can use to improve their operations.

A thorough gap analysis should pinpoint the areas that are not addressed by a laboratory's current quality system, as well as areas that are included within the system but are not necessarily followed. For example, many labs have SOPs and documentation procedures, but not all have these at the level -- in terms of quality and consistency -- of GLP standards. Other labs may have a QA or QC group or staff and a solid QA program already in place, but it may not be GLP compliant. Still other labs may have implemented multiple quality systems, such as FDA GLP, FDA cGMP, ISO 9001:2000, ANS/ISO/IEC 17025:2005 and CLIA and need a way to unify these systems.

On the opposite end of the spectrum, some labs have few procedures in place and are capturing little of the required documentation. By identifying those areas that are in compliance and not in compliance, an audit can also serve as a starting point that labs can use for building a new program that is in keeping with the spirit of the GLP requirements. Without an audit, these labs are likely to have little or no indication of how they "measure up" to GLP requirements -- besides simply "doing great work".

The Audit Process

Most audits contain two parts, which include an inspection of paperwork and an onsite laboratory inspection. Both parts of the audit are designed to examine and evaluate specific aspects pertaining to laboratory operations. In brief, the paper audit involves the examination of documentation regarding current policies and procedures. The onsite facilities inspection focuses on personnel, laboratory and archival areas, and the equipment and supplies utilized for research.

Step One: Paper Audit

The motto in the QA world that emphasizes the importance of proper laboratory record keeping is: "If it isn't written down or e-recorded, it never happened." That said, a thorough audit often begins with an examination of paperwork and computer records relating to personnel, standard operating procedures (SOPs), and equipment.

For the audit, a laboratory must first provide the auditor or auditing firm with all SOPs related to its administrative, scientific and technical operations. This documentation is needed for the auditors to determine the laboratory's current organization, quality system, documentation procedures, and equipment maintenance program, among other areas.

For the purpose of the paper audit, the documents reviewed may be in an SOP manual, hand-written documentation in notebooks and logs, or on a network laboratory information management system (LIMS). Specifically, the auditor or auditing firm will typically require documentation within areas that include, but are not limited to, the following areas:

- Existing Quality Systems and Standard Operating Procedures (SOPs) applicable to GLP studies;
- Previous regulatory inspection records;
- Personnel organizational charts;
- Facility site plan;
- Equipment procedures;
- Solutions, samples, and chemical tracking procedures;
- Computer programs, LIMS and computer validation protocols;
- Methods of deviation reporting, and its associated corrective action – preventive action (CAPA) program;
- Methods of documentation control, security, storage and electronic storage; and
- Evaluation of the organization's QA unit.

Not surprisingly, paper audits reveal much about a laboratory. In many situations, it is actually possible for an auditor to get a fairly accurate view of a given laboratory prior to taking a single step into the facility!

Step Two: Onsite Laboratory Inspection

After the relevant paperwork has been examined, the auditing firm will arrange an onsite laboratory inspection, or laboratory site audit. To gain the most benefit from the audit, the "walk-through" or inspection should occur during the course of a regular business day, while the usual staff is working. The laboratory site audit can take as long as two full days, depending on the size of the lab and archiving facilities.

For this portion of the audit, auditors will observe and review personnel, practices and onsite facilities that include, but are not limited to, the following:

- Personnel qualification and training records;
- Laboratory areas;
- Specimen storage facilities;
- Equipment records;
- Records retrieval, storage and retention systems;
- Test, and control article (and reference standards) receipt, use and distribution procedures
- Samples and supplies receiving area;
- Reagents and solutions handling and labeling; and
- Analytical testing practices.

When at all possible, the auditors will use an ongoing or recently completed study to compare the practices required by the SOPs and the GLPs with the practices that are actually implemented and used. Of course, confidentiality issues often make this impossible for pre-placement inspections.

The onsite inspection may conclude with an exit conference, or de-briefing, that involves the auditors and key laboratory personnel, such as the general manager, the director of QA, and the scientific manager of the laboratory. The purpose of the exit conference is to provide a general summary of the initial findings of the audit. This session also gives the auditors the opportunity to ask questions regarding various practices and procedures that were observed.

In fact, in some — albeit rare — circumstances, the exit conference may lead to the discovery of new information that may have been initially overlooked. The new information can then be examined and incorporated into the audit. During the debriefing, laboratory personnel can also get a general understanding of the areas that are in need of improvement, so that steps can be taken immediately that will help the facility work towards GLP compliance.

The Report

The end product of the auditing process is a comprehensive report produced by the auditor(s) that systematically addresses how the contract pharma lab fared in various relevant aspects of each section of the FDA GLP regulations. Ideally, the auditor should prepare a report within a few weeks of the on-site inspection, while specific recollections from this visit are still fresh.

The report should provide an assessment of both the gaps that were found as well as the positive areas. For example, the audit report will point out what paperwork or documentation, such as SOPs, are not up-to-date, or which ones are lacking in accuracy, details or proper approvals. It will also describe which pieces of

documentation, such as personnel records, equipment calibration / maintenance, etc., are incomplete. On the laboratory side, the audit will determine if the test and control articles and reference standards are handled properly, if chemicals and reagents are properly labeled, if electronic archiving systems are secure, and if samples are stored under appropriate conditions with proper internal chain of custody.

Once the audit is complete, some auditing firms can also provide sample documents that can serve as models or templates, which can be modified for use by a lab. Such documentation can expedite the GLP compliance process by alleviating some of the burden of creating similar documentation "from scratch."

Looking Ahead

Once the report is submitted, the auditor or auditing firm may fade from the picture. In other cases, it is not unusual to continue the relationship in order to help in the compliance process. In this case, the auditor can also ensure that the lab does indeed improve on its existing systems and procedures.

No matter how thorough the audit, it takes work to improve any elements that are not found to be in compliance with GLP standards. This work can be done by the facility itself, contracted to the auditing firm, or contracted to another organization. It is imperative that the management team be fully supportive of any plans moving forward; otherwise, the laboratory will not receive the most benefit from the audit. However, labs that not only undergo a thorough audit, but also commit to long-term improvement, will be the ones that are most likely to achieve compliance to GLP regulations and will be able to demonstrate this accomplishment to future sponsors.

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