The Art of Auditing Bioanalytical Laboratories

Sponsor Audits of Bioanalytical Laboratories

One of the critical tasks for a Good Laboratory Practices (GLP) nonclinical laboratory study or Clinical Trial team is choosing a bioanalytical laboratory vendor that will meet their study needs. Bioanalytical laboratories are on the critical path for generating bioanalytical data for both nonclinical and clinical studies. A well managed bioanalytical study with proper Sponsor oversight will go a long way to ensure the generation of accurate data and quality data. Many sponsors rely on Contract Research Organizations (CRO) to perform part of the services they require or they outsource their needs to larger CROs that will package all their requirements into a bundle of services.

In many sponsor companies this is when the quality unit is called upon to conduct a due-diligence audit and qualify their outsourcing vendors. This should initiate a series of events that cascades throughout the life of a study or series of studies at the specific bioanalytical vendor. Many companies have a Research & Development Quality Unit that includes people with auditing skills in Good Clinical Practices (GCPs) and Good Laboratory Practices (GLPs). Many R&D auditors have a background in what is required to audit a bioanalytical laboratory for either Clinical trials, GLP, GLP-Like or best laboratory practices. The key point to keep in mind is that bioanalytical laboratories should not be an afterthought; they will directly impact the data for the Sponsor's studies.

Bioanalytical laboratories generate the critical path data that is the pillar for all nonclinical and clinical studies and ultimately this data is submitted to the appropriate regulatory authorities in support of a regulatory filing. This article provides a sense of the audit process and things to consider when auditing a bioanalytical vendor.

Bioanalytical Laboratory Vendor Qualification Audits

The qualification audit is perhaps the most critical step in assessing a vendor. This is the step when the Sponsor QA unit must determine if the bioanalytical laboratory has the quality attributes and capacity to support a successful bioanalytical study.

Pre-Audit Preparation Tasks

To prepare for the audit, the Sponsor QA unit should:

- Understand what standards they are to hold the bioanalytical laboratory to (e.g. CAP/CLIA, GLP, GLP Like, GCP, ISO etc.)

- Read and understand the study protocols (Clinical or Nonclinical) and impact to overall protocol
- Know type of study: e.g., toxicology, carcinogenicity, biomarker, immunogenicity, adsorption metabolism and excretion (ADME)
- Determine whether project specific methods are being developed or validated for sample analysis or whether they are using established methods
- Review the capabilities and platforms of the bioanalytical vendor (ELISA, LC-MS, FACs, etc.)
- Have an estimate of expected duration for the study or studies
- Have an estimate of the projected number of subjects and samples
- Review past history with the vendor, if applicable
- Review previous audit reports of the vendor, if applicable
- Know who the Quality Assurance contact at the vendor site is
- For GLP nonclinical studies, know the name of the study director
- Investigate any regulatory actions against the vendor

Conducting the Qualification Audit

Set an agenda prior to the audit with the bioanalytical vendor describing the activities planned and documents to be reviewed while onsite.

Look for and assess the following during the vendor qualification audit:

- Type of regulations the facility follows
- Area(s) of expertise
- Inspection History
- Robust Organization Chart and a process to manage it
- A Quality Assurance Unit independent from operations
- The turnover rate at the company
- The training program with training plans and records
- A floor plan for laboratory
- An environmental monitoring for facility; monitoring of equipment such as refrigerators and freezers
- A secured and monitored data center, facility entry points, record room, and or archive
- Sufficient Disaster Recovery and Business Continuity Plans
- A master schedule for GLP studies

- Number of concurrent projects a project manager or principal investigator oversees
- A walk through of sample receipt, analysis , data analysis, to archiving (follow a sample through their process)
- A master list of SOPs
- Evidence that systems are 21 CFR Part 11 compliant and validated
  - Evidence that E-signature letter was sent to FDA if using Electronic Signature
  - Statement and signature linking Handwritten Signature to E-signature
  - List of qualified equipment and validated computer systems
  - Validation documentation for these systems
- The following are some processes and procedures that the Sponsor QA unit should also look for during the Qualification audit:
  - Internal, Study, and Regulatory Audits
  - Sample Handling, Sample Chain of Custody
  - Method Validation
  - Sample Analysis
  - Data Quality Control Process/Technical Review
  - Document and Data Archiving
  - Deviation/Corrective Action and Preventive Action (CAPA)
  - Study responsibility assignment
  - Project Management
  - Data and Document Management
  - Equipment Management
  - Computer System Management
  - Equipment Qualification and Computer System Validation
  - Change Control for Software/Equipment
  - Test Article, Reference Standard, Supplies & Request Management
  - Master Schedule for GLP studies
  - Good Documentation Practices

Interview the following personnel who may have major impact on the quality of data and control of the study:

- Project Management
- Principal Investigator/Principal Scientist
- Facility Management
- QAU Auditor
- Information Technology
- Data Manager if applicable
- Study Director if applicable

Assess consistency between what is documented and what personnel state during the interviews regarding processes and procedures.

Closing Qualification Audits

After the conduct of a qualification audit:

- Send a formal audit report to the potential vendor (typically within 30 days).
- Ask for an audit response to any observations requiring corrective actions or further clarification.
- Give the potential vendor a time period in which to respond with a corrective action plan (typically 30 days)
- Upon receipt of a satisfactory audit response, place the vendor on the approved vendor list.
- Scheduled a requalification audit every two years

NOTE: If the response is not agreeable, contact the vendor to discuss a corrective action plan.

Study Audits

During the conduct of the study the Sponsor QA Auditors return to the bioanalytical vendor site to ensure the study is being carried out with all applicable regulations and site procedures.

In-Process Study Audits

An in-process audit of the bioanalytical vendor is usually triggered when a critical phase of a study is being performed. Request an onsite visit and a supply the bioanalytical vendor with a tentative schedule detailing the specific studies that will be audited.

Request and review the following prior to and during the onsite in-process audit:

- Master Schedule for GLP studies / Current Project Timeline
- Training records of study personnel on methods, equipment, and processes pertaining to the study
- Sample inventory list
- Follow a sample from receipt to disposition
- Records of circumstance which may have impacted the quality or integrity of the study
- Study audit reports (critical phase, data, report)
- Data files
- Any concerns related to study or working relationships
- For GLP studies, ensure study personnel has access to the study protocol
- Communication between all applicable parties

For Cause Audits

During a for cause audit, the Sponsor QA auditor should focus on issues that impact the study or are of concern to the project team or senior management. The goal is to determine the root cause of repeat offenses or critical errors during a critical path of a study. There is no exact process or set of questions for conducting for-cause audits. However, commonly used methodologies include:

- Recreate timelines for when documents, data, or reports were reviewed and approved
- Review audit trails for data
- Review training of individuals involved in the studies
- Review all study samples' chain of custody
- Interview study personnel for any study related questions

Closing Audits and Audit Report

At the end of the audit, present any observations to the vendor at the close out meeting. Provide the vendor with a formal audit report within 30 days of the audit close out. The audit response should be received within 30 days of issuing the audit report. The Sponsor QA Unit must review and determine whether the response and any proposed corrective action is satisfactory. During the next re-qualification audit, the Sponsor QA should review the corrective actions with the vendor and determine if they are adequately closed.

Summation

Audits of bioanalytical laboratories should not be viewed as check box type of activities for an organization. When used properly, the Sponsor of a bioanalytical laboratory can help prevent critical path issues, remediate underlying issues, and refocus the team on the root cause of an issue rather than the symptom. Qualifications, in-process audits, and for-cause audits should be seen as tools that will add value to the drug development process. Audits of bioanalytical vendors can reduce risk for nonclinical studies and clinical trial, and help the project team stay on course by finding critical issue early, under budget and ensure the highest level of quality and compliance for subject and or patient safety, data quality, and integrity. Ultimately having a robust bioanalytical vendor auditing process will help minimize the risk of having issues with the regulatory agencies (FDA, EMEA etc.), when submitting for approval.

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