“Selecting a Contract Laboratory for Regulatory Approval”

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Laboratory Focus

The importance of the laboratory cannot be understated in the regulatory approval process. The analytical and microbiological laboratory is the most essential element in consideration of a new drug approval for regulatory agencies. This includes inspections from PMDA, EMA and the US FDA. From the initial days of drug discovery, through product development and research, technology transfer and ultimately at the commercial product testing and release phase, the laboratory is the critical control point for product success and important business decisions. Data from the laboratory needs to be accurate, have integrity and be timely. Decisions made by scientists, developers, manufacturers and business development assume laboratory data to be accurate and reliable. These decisions ultimately affect the entire supply chain and patient safety. Access to reliable data in a timely manner is equally important.

Regulatory agencies have specific guidelines and regulations written for their investigators to evaluate good science and regulatory compliance practices during analytical laboratory investigations. Regulations span the discovery, development, technology transfer and commercial phases of products. Guidelines and regulations contain specific requirements and expectations of the laboratory and focus investigators on evaluation of the laboratory capability, data integrity, laboratory management and quality system. Drug development efforts require the investment of sums of money and years of research, development, clinical studies and manufacturing to bring new products to market. The capability of a laboratory supporting this effort is essential to the ultimate approval.

Capabilities

Investigators that inspect laboratories are expert at evaluating the capability, qualification and validation of laboratory facilities, instrumentation and equipment. They are seasoned by their personal lab work experience as well as having visited several other laboratories during their investigative experience. Investigators evaluate programs including the laboratory facility, work space, HVAC, sample handling and controls, sample inventory and storage, analytical instrumentation and equipment for adequacy, qualification, maintenance, fitness for use, compliance with compendia requirements and application to the test articles for which it is used. Personnel training and qualification are also targeted areas of great interest. Personnel must be trained on general lab systems and specific instrumentation for which they perform their work. Documentation of all of the above is required to prove compliance. Computer validation and analytical data management receive focused scrutiny.

Data Integrity

Data integrity is a primary concern for evaluating the reliability of reported laboratory results. Data integrity will be the focus of any regulatory inspection, but receives special attention during a pre approval inspection. Data generation, collection, documentation, transcription, reporting and archiving are the foundation for determining the capability, reliability and ethical practices of laboratory personnel. Too often, laboratory management does not place sufficient emphasis on designing adequate systems and controls to ensure data integrity. Having robust data integrity systems in place and supporting that with staff training programs and routine audits to verify data integrity practices are being followed is essential for success.

All data generation, collection, reporting and management needs to be clearly documented. An audit trail, from time of data generation through final reporting and archiving, must be in place, traceable and retrievable. Any gaps in data integrity places question on the reliability and authenticity of data reported by the laboratory. Many product approvals have been refused or delayed based on lack of supportive data integrity programs in the laboratory.

Management and Personnel

Successful laboratory management is dependent on good leadership. Throughout an inspection, investigators are constantly evaluating laboratory management through interviews with laboratory personnel, supervisors and managers. The investigator determines personnel qualification through documented training records, observation of personnel laboratory practices and interview. Personnel experience, performance of laboratory tasks and analysis correctly, compliance with current good manufacturing and laboratory practices and taking the correct action during the course of routine lab activities provide investigators an impression of personnel and management capability.

Programs should be established for handling Out of Trend, Out of Specification and Deviation management. These processes, and personnel execution of them, will receive regulatory focus. How laboratory management reacts to and manages deviations and unplanned analytical results provides regulators with insight into the mentality and philosophy in the laboratory. Providing good leadership and positive impressions to regulators will build confidence and trust.

The confidence and trust established between laboratory management and investigators is essential to convince regulators that the laboratory is under control and the data generated from the laboratory is capable, reliable and has integrity.
Additionally, the interaction and communication between a contract laboratory manager and the client is subject to scrutiny and evaluation by regulators. This includes the documentation of a Quality Agreement between the parties. How decisions are made and who makes what decisions is important. Management and follow up to deviations provides regulators insight to laboratory/client relationship. Follow up actions to laboratory decisions may occur at the client site and client site decisions may have impact at the laboratory. The relationship must be solid and clear. Decisions and responsibilities must be documented.

Quality System
The Quality System of a laboratory is at the heart a successful enterprise. Essential elements of the Quality System must be in place for the laboratory to be successful during and between regulatory inspections. Key areas of the Quality System include; lab design, controlled documentation system, description and execution of management responsibilities, personnel training programs, Quality Manual and procedures, Change Control, Deviation Management, OOS, OOT procedures, equipment and instrument qualification and validation and management review programs.

During the course of a regulatory inspection, the laboratory's entire Quality System is subject to review and evaluation. The regulators are interested in how the laboratory management addresses the entire laboratory operation, not just the product under review for approval. If there are examples where laboratory practices are different in depth and thoroughness from product to product or client to client, it may be interpreted to be a weakness in the laboratory Quality System. The same robust quality system elements are expected to be in place for all samples processed through the laboratory. Treating some product deviations with a thorough investigation, and others with a cursory review demonstrates inconsistency in the Quality System.

Inspection Management
Smart, flexible Lab Managers, who know the regulations and how to manage an inspection, will make a difference in the inspection outcome. There are no regulations that require a pleasant personality or firm defense for laboratory practices, but without bright, adaptive and creative management, a good laboratory may suffer setbacks during an inspection. Lab managers must know how to manage the inspection, and the individual quirks of an investigator, be able to determine when to agree with and when to push back on investigator comments and concerns. So many times this part of the inspection is not handled properly, and negative consequences occur. Being flexible, smart and having good team support during an inspection with answers to questions ready and explanations for actions is essential. Personal chemistry between lab personnel and investigator has impact and affects outcomes.

Continuous Improvement
After the inspection, follow up to areas identified during an inspection will ensure compliance to observations and continuous improvement of the lab. All observations, verbal and written, should be considered a learning experience. Relevant comments incorporated into lab programs ensure an enhanced and robust Quality System and compliance with current Good Manufacturing Practices. Proactive laboratories are always ready for an inspection. Reactive laboratories are always struggling to get ready. Building the knowledge of the inspection into the organization builds a "Culture of Quality", that benefits the lab and clients that rely on the importance of the lab for regulatory approval.
Selecting a contract laboratory is an important, long term decision. Product approval and business success depend on capability, reliability, data integrity and the client / contractor relationship. A wise choice will pay dividends for many years.

＜要訳＞承認のための委託先ラボの選び方

FDA などの当局による査察では，委託先ラボは重要な役割を果たします。ラボからのデータには，正確・完全性，信頼性が求められ，査察の焦点は，ラボの能力，データ完全性，管理体制，品質システム（QS）にあります。

ラボの能力自体は，その設備・機器の適格性確認やバリデーション等で評価され，試験分析者の資格・訓練状況の文書化も必要とされます。また，承認前査察で注目されるデータ完全性には，試験結果の信頼性のための堅牢なデータ完全性システムの確保，試験分析者の訓練，定期監査の実施やデータの文書化と調査記録が求められます。

ラボの管理能力は，試験分析者，管理者との質疑で評価され，特に OOT や OOS，逸脱時の判断や対応が印象を左右します。逸脱の取り扱いが明記された委託者との品質合意書を必要とし，さらにラボ全体の QS の整備とその一貫した実施が求められます。

ラボ管理者は，賢明かつ柔軟に，チームの協力を得て質問への機敏な対応をとり，査察終了時の指摘事項への対応措置を，継続的な GMP 遵守と QS の改善に取り入れ，積極的な「品質文化」を構築しなければなりません。

委託先ラボの選択は重要かつ長期間に渡る決定であり，製品の承認と成功は，ラボの能力・信頼性・データ完全性と両者関係に大いに左右されます。賢明な選択こそが長期間の恵みを生みだすでしょう。

略　歴

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1986- 2000 – Searle / Monsanto – Director, Quality Assurance International
2000-2002 – Pharmacia Corp. – Senior Director, Global Supply API Biopharmaceuticals
2002-2003 – Pfizer Corp. – Senior Director, Biopharmaceutical API
2003-2009 – Amgen – Director, Global Quality Systems
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