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Laboratory Auditing for Quality and Regulatory Compliance

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LABORATORY AUDITING FOR QUALITY AND REGULATORY COMPLIANCE

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PREFACE

There is an inherent similarity between planning and performing an audit of a laboratory and planning and operating a laboratory. Each area of operation that builds integrity and ensures accuracy and consistency in results is an area that is scrutinized by an effective audit. The laboratory is a facility requiring sufficient services (electrical, water, air) to keep it operating continuously and efficiently. The services that support the facility, its equipment, its operations, and its people should be monitored. An audit can determine if quality is built into the services. Laboratory space, the designation of areas for particular operations, flow of materials, and flow of people serve to design an appropriate plan to meet the needs of customers and employees for testing capability and laboratory safety. An audit can identify if the plans do indeed meet the needs of customers. Training and background of scientists who perform the sample handling, testing, and reporting of results must fit the expertise required to successfully carry out the laboratory operations. And an audit can identify strengths and weaknesses of staff expertise, hiring, and retention of scientists.

This book is focused on analytical (biology, biochemistry, chemistry, and microbiology) laboratories that support regulated industry. Our definition of regulated industry is consumer product industry where Good Manufacturing Practices (GMPs) and good laboratory practices are spoken in similar terms. Laboratory operations in pharmaceutical, food, cosmetic, diagnostics, and medical device industries follow some published standards and many best practices (Singer, 2001). This book is not intended to cover all laboratory operations, but to identify certain tools, techniques, approaches, and philosophies that can be used to evaluate the quality of most laboratory operations.

We challenge you to become a diligent student of successful auditing practices. We also challenge you to become an expert in the interpretation of published standards and best practices related to the laboratory operation

that you intend to audit. This is a dynamic practice, because it can and will change as your needs and your firm's needs change.

If you are a laboratory manager, it will also be beneficial to know how to scrutinize your own laboratory in preparation for an external auditor or just to help improve your laboratory operation.

We would like also to encourage you to network with the largest organization of quality professionals in the world, the American Society for Quality (ASQ). They can provide you with additional expertise in the areas of auditing, quality improvement, and quality management. They are the one-stop shopping source for quality. Don has been a member of ASQ and their Food Drug and Cosmetic Division for over twenty years, and the professional relationships and networking with colleagues have provided an ongoing resource of information-sharing and expertise about quality, laboratories, practices, and standards.

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INTRODUCTION

The first book about laboratory quality auditing (Singer and Upton, 1993) was written over ten years ago. Since that period of time, many changes have occurred that directly affect the survival of laboratories in GMP-regulated industries. Mergers of large corporations on the one hand decreased the number of internal quality control laboratories, but on the other hand influenced the increase in size, number and capabilities of contract laboratories. Much more testing is being outsourced than ever before and thus dependency on the quality of outsourced services is critically increasing. The development of global standards through international collaboratives of scientists (International Standards Organization, ISO; International Conference on Harmonization, ICH) have not only developed manufacturing quality criteria, but also have developed improved laboratory standards. As laboratory accreditation became a familiar term to global manufacturers and regulatory agency support laboratories, available guidance such as ISO Guide 25 (1990) had to evolve, and the result was ISO 17025 (1999). Additional industry-specific interpretation followed the original ISO 17025 with the AOAC version (2001) that was written for food and pharmaceutical quality testing laboratories. Regulatory agencies such as the Food and Drug Administration (U.S.) began to implement a plan to have their laboratories evaluated and meet the criteria of ISO 17025. The increasing influence of computers and information technologies on data generation, data analysis, and data storage has caused an increasing regulatory scrutiny on this type of data handling in our laboratories.

All of these significant changes are the reasons that we developed a more thorough, up-dated book to build around the basic knowledge of the quality audit relevant to laboratories.

We have also developed a more global perspective of this critical area to fit in with the dynamic environment laboratory management finds itself. My fellow authors, Dr. Stefan and Dr. van Staden, add a strong international

experience and flavor to quality auditing of laboratories. We are very excited to offer our readers this desk reference and resource of pertinent information that will help design an effective audit and will help improve quality of a laboratory operation.

Donald C. Singer

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I

QUALITY AND AUDITING

QUALITY CONTROL AND QUALITY ASSURANCE IN A LABORATORY

A quality assurance (QA) program must be planned and implemented to provide confidence in a laboratory's execution of its business. The most effective means of evaluating a QA program is auditing.

The quality audit has been defined as a "management tool used to evaluate, confirm, or verify activities related to quality." It is a constructive process (Mills, 1989).

Performing a quality audit has become a routine activity of any business that seeks quality improvement. The results of a quality audit are carefully evaluated and used for developing objectives, which will assist a business in improving the quality process that is already in place. Alternatively, the results can also be used to develop a quality improvement plan that will improve the strengths and reduce or remove the weaknesses that could create future problems.

Every product that is manufactured by pharmaceutical, food, cosmetic, medical device, or biotechnology firms has characteristics that need to be quantified or qualified by laboratory testing. Every sample of body tissue or fluid submitted by a physician, veterinarian, clinic, or hospital for diagnosis requires laboratory testing. Diagnostic test kits for use at home by the public or in laboratories are batch sampled and tested by the manufacturers' laboratories prior to their release for sale. Often, some diagnostic test kits are collaboratively tested (Association of Official Analytical Chemists) by a number of laboratories to confirm (or validate) the accuracy of their results. Just about anything that is used to improve, prevent deterioration of, maintain, or diagnose health in humans or animals is subjected to testing in a laboratory. Quality control and quality assurance are the necessary processes that play the role of a check and balance system in a laboratory.

Analytical testing for known characteristics should have corresponding known standards for comparison. Analytical testing for unknown characteristics must have both known standards and controls to ensure that whatever result is obtained is reliable. The reliability of analytical testing is the means for building trust in the customer and credibility of the testing laboratory. Customers demand trustworthy, consistent analytical practices, which result from tight quality control and quality assurance processes.

The laboratory environment consists of people, facility, instrumentation, chemicals, supplies, and samples submitted for analysis. There has to be a logical and scientific manner of organization and management that can drive the laboratory system. Each laboratory works in an individual manner, so it requires a customized approach and attitude. Every laboratory depends on consistency, and the development of a system which will ensure consistency is dependent on the following factors: well-managed and adequately trained people, well-maintained facilities, calibrated instrumentation, high quality chemicals, adequate supplies, and proper handling of samples. Safety must also be woven through the fabric of the laboratory. These factors will help to form a laboratory environment that can meet the requirements of any kind of laboratory quality audit.

The laboratory quality audit can be used as a tool to help to increase credibility and substantiate trust and confidence of the customers for the laboratory's capabilities. The laboratory quality audit will evaluate the strengths and weaknesses of the quality control/quality assurance processes. Then, the audit can be used to improve the processes and build a better system for the benefit of the laboratory owners, employees, and customers.

What is quality control of a laboratory? Quality control is defined as the operational techniques and activities that sustain quality of a product or service that will satisfy given needs (American Society for Quality Control, 1983).

Each instrument requires periodic calibration, by physical or chemical means, where appropriate. Chemicals used in analytical testing should be of the purity required by the procedures. Known standards, where available, are routinely used to check instrument and method variation. When testing unknown materials, known standards can be used for benchmarks. Consistency in the preparation of testing materials (samples, reagents, media, etc.), in the use of instrumentation, in following appropriate methodology, and in documenting results are results of a successful quality control process.

What is quality assurance in a laboratory? Quality assurance is defined as all those planned or systematic actions necessary to provide adequate confidence that a product or service will satisfy given needs (American Society for Quality Control, 1983).

Written procedures and adequate documentation of all quality control practices, training, and analytical results make up one part of a laboratory quality assurance process. The other part of the process is an experienced quality assurance staff who manages and performs internal audits of the quality control and quality assurance processes.

The quality control and quality assurance processes in a laboratory are usually defined by internal and external regulatory requirements. The

minimum criteria for quality control and quality assurance processes should not differ significantly from regulatory requirements and guidance, and thus can provide a more defined basis for an audit. Employees of the laboratory directly affect the quality control and quality assurance processes. Hiring and training criteria have become an important part of quality control and quality assurance, and should be a significant measurement in an audit.

Employees, quality control/quality assurance, and customer interactions are the three most important areas in an audit of a laboratory. If these three areas are well developed and documented, and if the laboratory can satisfactorily perform the testing of which it claims to have experience and capability, then having a larger facility and higher levels of instrumentation technology are advantages and not requirements.

THE REGULATED INDUSTRIES

Many consumer product or service industries are regulated. Where laboratory testing is utilized in these industries, predetermined guidelines are followed for evaluating the safety, efficacy, and overall quality of the products or services. These guidelines originate either internally or externally. There are many external organizations which develop guidelines that have become industry standards, such as government agencies, accreditation groups, or industry forums.

The United States Food and Drug Administration (FDA) enforces the 1938 Food, Drug, and Cosmetic Act, which was revised in 1976. The FDA inspectors follow guidelines set forth in an Investigations Operations Manual (2003). The FDA monitors how industry follows guidelines set forth in documents called current Good Manufacturing Practice (GMP) in Manufacturing, Processing, Packing, or Holding of Drugs (1978), and current GMP in Manufacturing, Processing, Packing, or Holding of Foods for Human Consumption (1979), and Good Laboratory Practices for Nonclinical Laboratory Studies (1978). Food and Drug Administration inspections occur either on a periodic basis or with higher frequency based on the following:

1. Customer complaints or reported adverse reactions.
2. Voluntary recalls by a firm.
3. Food and Drug Administration product sampling program finds a deviation from product quality or product claim.
4. Raw material or packaging component manufacturer problems.
5. Pre approval inspection for a new drug application (NDA).
6. Current GMP inspection for manufacturing of new clinical supplies, medical devices, or diagnostic products.
7. Approval of a sterile product manufacturing facility.
8. Good Laboratory Practice inspection for support of nonclinical testing.

The 1997 FDA Modernization Act was an initiative that was developed to help streamline FDA organization and procedures. The initiative was followed by a "21st century" approach to inspections. A document titled "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach" was written to explain

a new effort to bring together science-based risk management and quality control systems. One intent of the approach was to increase the responsibility of the manufacturer for quality systems and direct FDA resources for inspections to the higher risk (to patient safety) product manufacturing operations, while reducing inspections of low-risk product manufacturing operations. Complementing the GMP approach to FDA inspections, the FDA has published some guidelines for laboratory competence. Two useful documents are, Guide to Inspections of Pharmaceutical Quality Control Laboratories (FDA, 1993), and Guide to Inspections of Microbiological Quality Control Laboratories (FDA, 1993).

The United States Department of Agriculture (USDA) oversees the agricultural industry, which includes meat, poultry, egg, and dairy products. Testing for microbiological quality attributes, defect action levels, nutritional labeling, and pesticide residues are part of product evaluation programs. United States Department of Agriculture and Food Safety Inspection Service (FSIS) regulated laboratories follow standard methodology such as the Official Methods of Analysis (AOAC, 2003). In 2001, the USDA/FSIS laboratories established a program called Accredited Laboratory Program (ALP) and contracted AOAC to assist in performing onsite evaluations of private laboratories, which helped ensure compliance to the regulations under the Federal Meat Inspection Act and Poultry Products Inspection Act.

The United States Environmental Protection Agency (EPA) has the authority to monitor for air, soil, and water pollution and to enforce standards to protect natural habitats. Sampling techniques and methodology for testing samples have been approved by the EPA for public drinking water and wastewater (American Public Health Association, 1999). Maximum allowable levels of contaminants in public drinking water have been set (Environmental Protection Agency, 1988).

The United States Pharmacopeial Convention oversees a forum of professionals who represent the pharmaceutical industry. The forum consists of a committee of experts (COE) and each expert leads a specialty area committee of professionals (e.g. analytical microbiologists, analytical chemists, pharmacists, pharmaceutical scientists, and physicians). The "bible" of this forum is the US Pharmacopeia and National Formulary (USP-NF XXVII, 2004). The USP-NF is a reference for the biological, chemical, and physical attributes that are used to determine the purity of pharmaceutical raw ingredients or compounds. Published annually, the USP-NF also recommends test protocols for laboratories evaluating the attributes of each pharmaceutical material. A growing new addition to the USP is an informational guidance about nutritional and dietary supplements. Other countries have similar references of pharmacopeial standards, such as the European Pharmacopeia, the British Pharmacopeia, the German Pharmacopeia, and the Japanese Pharmacopeia.

The World Health Organization (WHO) is a forum of professionals who represent various nations' interests in health. Expert committees have written documents which include GMP for pharmaceutical products (WHO, 2003) and Good practices for national pharmaceutical control laboratories (WHO, 2002).

Since "there has been an increasing trend towards the development of broad spectrum accreditation programs that apply the same principles of good laboratory practices to laboratories working in any field of science or technology" (Bell, 1989), the International Organization of Standardization (ISO) published a set of documents which were developed by the International Laboratory Accreditation Conference. The ISO Guide 25, considered to be a generic accreditation document of criteria (Bell, 1989) for technical competence of a testing laboratory, was the first relevant document from ISO. The ISO 9000 series, published in 1987, partially revised in 1999 and again in 2001, is becoming the single source of standardized requirements for the design and implementation of a quality system. These requirements were initially interpreted and adapted in an industry-specific manner (Marquardt et al., 1991). To prevent movement away from standardization, the ISO Technical Committee TC176 met in 1990. They agreed on a strategy for developing worldwide acceptance of global standardization. One of their goals was to seek harmonization between ISO guides and European Community standards (EN 45000 series) dealing with, in part, operation assessment and accreditation of laboratories. International Organization of Standardization 17025, general requirements for the competence of testing and calibration laboratories, were written, and approved in 1999. The AOAC Analytical Laboratory Accreditation Criteria Committee (ALACC) improved ISO 17025:1999 by adding text relevant to chemical and microbiological laboratories in the pharmaceutical and food industries (AOAC, 2001).

An organization formed in 1990 to develop harmonized guidelines for the pharmaceutical industry as the need for global standards increased over time. Representatives from regulatory agencies and industry associations from Europe, United States, and Japan met and formed an International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. International Conference on Harmonization implemented the formation of technical committees to develop such guidelines as Validation of Analytical Methods (ICH, Q2), Stability Testing of New Drugs and Products (ICH, Q1), and Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (ICH, Q6B).

GOALS OF A LABORATORY QUALITY AUDIT

The simple objective of the complex process, if thorough, of auditing a laboratory's quality program is to evaluate the activities and existing documentation and determine if they meet predetermined standards. A total quality program in a laboratory is usually developed to assure that all activities are performed with the objective of meeting certain standards, both internal and external. Some standards are generated internally, e.g. corporate quality improvement process, routine quality assurance/quality control protocols (including Standard Operating Procedure), or annual accreditation. A corporate quality improvement program may, in part, require that certain laboratory operations become routine and that customers are given informa-

tion when they need it (for example, a customer service agreement is written and a customer service contact person is identified, facsimile capabilities exist and a computerized database is used that can track samples). Quality assurance programs often provide standards for receiving, handling, coding, and testing samples, and for recording and reporting test results. Quality control programs usually provide the standards for validating instrumentation, determining the suitability of reagents and test procedures, and provide requirements for training of analysts.

A laboratory quality program should have an established set of goals, which every effort is made to reach. Objectives are set to provide the means for achieving the established goals. These objectives must be measurable. It is these measurable objectives on which an audit is based.

Competency is the key objective of any laboratory quality program. Laboratory accreditation is a "formal recognition that a testing laboratory is competent to carry out specific tests or specific types of tests" (Schock, 1989). The accreditation of a laboratory can be either an internal or external standard, or both. The audit for accreditation is an on-site examination of the laboratory to determine if it meets the accreditation criteria (Schock, 1989). Some sources of standards or criteria that are generated externally are government agencies, customer requirements for contracted laboratory services, and procurement quality control requirements. The standards generating agencies in the U.S. government that are concerned with foods, drugs, cosmetics, and medical devices are at all levels of government, i.e. federal, state, and local. Some of the federal agencies are the FDA, EPA, USDA, and FSIS. Internationally, as mentioned in an earlier chapter, the standards generating group has developed a basis for laboratory competency, which is now known as ISO 17025. Laboratories in the food, drug, cosmetic, and medical device industries must meet specific criteria developed and enforced by the U.S. government's FDA. The EPA has set standards for air, water, and ground contamination levels, as well as standards for testing for contaminants in these natural resources.

When a contract laboratory provides testing support for a manufacturing facility, the manufacturer usually provides the laboratory with the test methodology, and criteria must be met to ensure consistency in testing and reporting. Routinely, some overlap exists in the criteria that a laboratory must meet originating from a food, drug, cosmetic, or medical device manufacturer and the criteria generated by government agencies related to the same products. If products must be registered or licensed prior to marketing approval by an agency such as the FDA, all documentation relevant to finished product testing could be evaluated first. The supporting infrastructure and quality programs of a laboratory can lend credence to the integrity of the testing results.

Procurement quality programs usually require sampling and testing of purchased materials, ingredients, and finished products. Testing and documentation criteria are commonly set by the clients, including requirements for calibration of instruments, use of reference standards, and other laboratory control measures.

AUDIT TOOLS: OBSERVATION, WORKING KNOWLEDGE, AND AUDIT DOCUMENTS

A properly conducted audit of a laboratory should be documented thoroughly in a format that will make information simple to find and evaluate. Documenting data and recording comments are the most effective permanent record of pertinent information. An auditor should rely on memory only for a short time (minutes or hours) and only if carrying a pen and notepaper or a microcassette recorder is not possible, for example, in a sterile testing area.

Prior to conducting an audit, the laboratory is contacted to set a date for the on-site visit. An agenda must be prepared, listing the areas to be evaluated and specific testing to be observed. Results of previous audits should be reviewed to determine if follow-up to previous concerns is necessary. Results of recent government agency inspections should be requested, although proprietary information may need to be hidden before the evaluations are shared. Any documentation that can be shared prior to the on-site audit should be requested and reviewed ahead of time. The laboratory is sent the agenda ahead of time. They are then asked to confirm that the time and personnel will be available when the actual on-site audit takes place.

There are three areas in a laboratory from which information should be derived during the on-site audit: personnel, documentation, and observation of testing procedures. Even under the best circumstances and relationships, there is usually a limit to an auditor's contact with the personnel who actually perform the testing. Almost every analyst, when correctly performing a test procedure, does it in a unique way. These unique differences provide a challenge for the auditor. An auditor must observe the performance of the procedure.

First, the auditor reads and interprets the procedure. Then the auditor observes the actual conditions and manipulations of the test procedure by the individual who is routinely assigned to perform that procedure.

The preparation of supplies, materials, test site, and instruments that will be used are all significant parts of a properly performed test procedure. As the analyst performs the test, reads the results, and records the results, the auditor should note any aspects of the test that could lead to error. There are a few test procedures, which are repeated on consecutive days or require more than 1 day to complete (e.g. microbiological testing). Since most laboratories carry out routine testing daily, enough overlap of tests occur that allow an auditor can observe the different steps of a single procedure in 1 or 2 days, even if they are performed on different samples.

If a reference standard calibration is a preparatory step in a procedure, the auditor observes where the standard was stored and how it was handled before and during the calibration. It is also important to observe the type of documentation kept to assure the stability and confidence of the standard, as well as consistency in the calibration.

The laboratory director or supervisor of the specialty area (toxicology, microbiology, chemistry, etc.) usually responds to questions from the auditor. It is not only logical, but imperative that audit questions be directed to the

most knowledgeable person in a laboratory area. Those key persons are the only sources of complete, up-to-date information about the test procedures that are being followed. Those individuals know the background of the changes that have been made to procedures in their fields of expertise. They are also familiar with the precision and sensitivity of each procedure performed in their areas. Nowhere else could an auditor expect to find a resource more familiar with the specialized synergy of the laboratory, procedures, and personnel in their area of scientific testing.

Observation permits the auditor to see the actions required to perform a test. The analyst should carry out the test as it is written. If an analyst deviates from the written procedure, the deviation(s) can be a source of error and invalidate the test. A deviation must be documented and reviewed before any further testing is performed. A procedure should be revised, reviewed, and revalidated before changes are implemented.

If an auditor is to observe and accurately evaluate an experienced analyst performing a test, the auditor should understand the technical intricacies of the test. In other words, the most accurate evaluation is made by a qualified auditor who has performed the test enough times to become intimately familiar with it.

The auditor who is experienced in the test methodology will be the best person to make a fair, accurate evaluation of the client laboratory's test conditions. Thus, it is strongly suggested that a chemist audit chemistry testing, a microbiologist audit microbiology testing, a toxicologist audit toxicology testing, and so on. Since there are many laboratory audits that involve a variety of testing areas, it is not uncommon to have more than one specialist perform an audit. In fact, a team approach to an audit is common and very productive when a variety of specialty areas are involved. A team composed of qualified individuals with different fields of expertise (e.g. chemistry, microbiology, metrology, and toxicology) can audit many areas in a laboratory at the same time. The team concept is effective, efficient, and professional. The preparation for a team audit is very important. A plan must be well thought out and agreed upon in order to accomplish daily objectives.