*International Journal of Research and Development in Pharmacy and Life Sciences*
**Available online at http//www.ijrdpl.com**
**June - July, 2013, Vol. 2, No.4, pp 493-498**
**ISSN: 2278-0238**

**Review Article**

# THE ROLE OF REGULATORY GMP AUDIT IN PHARMACEUTICAL COMPANIES

**Sumit Kumar, Deepika Tanwar, Nageen Arora***

Department of Quality Assurance, ISF College of Pharmacy, Moga, Punjab – 142001

***Corresponding Author: Email** nageenpharma@gmail.com

**(Received:** April 16, 2013; **Accepted:** May 17, 2013**)**

**ABSTRACT**

The goal of an audit is to express an opinion on the person, organization, system etc. in question, under evaluation based on work done on a test basis. Audits are performed to ascertain the validity and reliability of information; also to provide an assessment of a system's internal control. A company that makes medications today must be able to prove that it does so with absolute reliability, under optimal secure conditions, and with extreme uniformity to allow for exact reproduction. Pharmaceutical auditing expertise includes writing and review of validation policies, guidelines and SOP from design qualification to performance qualification steps.

**Keywords:** Auditing, Regulatory aspect, FDA, Audit program, GMP components, Importance, Purpose and procedure of an audit.

## INTRODUCTION

Auditing is a critical function within a pharmaceutical company. It provides management with information about how effectively the company controls the quality of their processes and products. The audit process is one means of reviewing pharmacy programs; it ensures that procedures and reimbursement mechanisms are consistent with contractual and regulatory requirements.**[1]**The general definition of an audit is an evaluation of a person, organization, system, process, enterprise, project or product. Internal Audit Standard Board (ICAB) defines auditing is the independent examination of financial information of any entity, whether profit oriented or not, and irrespective of its size or legal form, when such an examination is conducted with a view to expressing an opinion thereon." Internal auditing is fundamental to any quality improvement initiative. In particular, the FDA cGMP's for pharmaceutical products require that an organization conduct internal quality audit to determine the effectiveness of its quality system.

Auditors are typical part of the Quality Assurance (QA) or Regulatory Compliance function forexamine the data trail to determine whether company policies and procedures are followed.**[2]** This article presents an overview of the audit process and the programmatic issues related to this process.

**Analytical method Quality Auditing**

Though the analytical procedures may vary but a general proforma remains same for majority of techniques.

| Topic | Description |
|---|---|
| Procedures | Define the generation , approval, distribution, revision and review of SOPs and analytical testing procedures |

| | |
|---|---|
| Procedural deviation | Defines how to document deviations from written procedures |
| Investigation of out of specification results | Clearly defines responsibilities and investigation requirement |
| Employee training | includes the traning requirements, frequency document |
| Facilities /security | Includes general housekeeping, dress requirements and security related issues |
| Data handling | Defines the necessary steps for the generation, storage, archival and retrival of raw data |
| Review and release of analytical report | Define the necessary steps to ensure accuracy of calculated data and reported results |
| Use and storage of laboratory notebook | Defines the items that must be included in laboratory notebook |
| Instrument logbooks | Define the calibration and maintenance items that must be included in the instrument notebooks |
| Change control | Define documentation requirements for changes to methods, equipment, and computer systems and software. |

**Components of audit:**

Audit contains the following five components:

**1. Risk Assessment** identifies relevant risk factors that challenge an organizational area andfurther considers their relative significance.

**2. Scope Statement** identifies the activities that will be covered during the course of the audit.This includes the project justification, the project description, the deliverables, and the success criteria.

**3. Audit Program** is the document that contains the listing of audit procedures as well as the objectives of the audit. **[3]**

**4. Audit Procedures** are the specific tasks that the auditor follows to gather, analyze, and document during the audit.

**5. Workpapers** are the detailed documentation from interviews and testing that conducted to complete the audit program.

**Objectives of Auditing**

**1.** To determine the conformity or non-conformity of the quality system in meeting the specified requirements.

**2.** To determine the effectiveness of the implemented quality in meeting the specified Quality objectives.

**3.** To provide the Audit team with an opportunity to improve the Quality system.

**4.** To meet the regulatory requirement

**5.** To permit listing of the audited organizations Quality systems in a register.

**Audits are generally initiated for one or more of the following reasons:**

**1.** To initially evaluate the supplier where there is a desire to establish a contractual relationship.

**2.** To verify that an organization own quality system continues to meet specified requirements and is being implemented.

**3.** Within a framework a contractual relationship to verify that the suppliers quality system continues to meet specified requirements and is being implemented.

**4.** To evaluate an organization's own quality system against quality system standard.

**Importance of Audit in Pharmaceutical Industry:**

Auditing has become one of the important key for the success of a pharmaceutical company. Regulatory agencies play a very important role in the pharmaceutical companies by assuring the goodquality so that safe and effective product should be delivered to the public.**[4]**Worldwide, the expectation of a quality product is the same for regulatory agencies. Quality is determined by whether the firm complies with GMP requirements and makes scientifically justified decisions. Pharmaceutical companies are now taking a proactive stance with the new GMP Systems approach, more effective internal auditing and increased regulatory awareness throughout the company. Quality can only be

achieved when everyone works together to meet the challenge. **[5]**

**1.** Medicinal products have to be of high quality as people lives depend on it, although end product testing of samples from each batch is important, it is not enough to ensure quality which must be built in to the manufacturing processes.

**2.** To ensure the quality, all pharmaceutical manufacturers are required to establish and implement as effective pharmaceutical QA system.

**3.** To assess the effectiveness of these QA systems and to ensure it follow GMP, self inspection and other regulatory audits must be performed. **[6]**

**4.** Pharmaceutical manufacturers commonly use audits as effective mechanism to verify compliance with GMPs.

**5.** Audits are intended to verify that manufacturing control systems are operating under the state of control.

**6.** Audit can detect potential problems to permit timely correction

**7.** Audits can be used to establish with a high range of confidence to remain adequate level of control by management.**[7]**

**Purpose of FDA Audits**

The purpose of the Audits conducted by the Regulatory Authorities such as FDA is:

**1.** To determine that the rights, safety and welfare of subjects have been protected

**2.** To assess adherence to FDA regulations and statutory requirements

**3.** To determine the quality and integrity of data submitted in support of healthcare products registration pending FDA approval. **[8]**

**4.** To ensure that the facility is in compliance with FDA rules and regulations.

**5.** To know that product development was done appropriately and the cGMP are up to FDA standards.

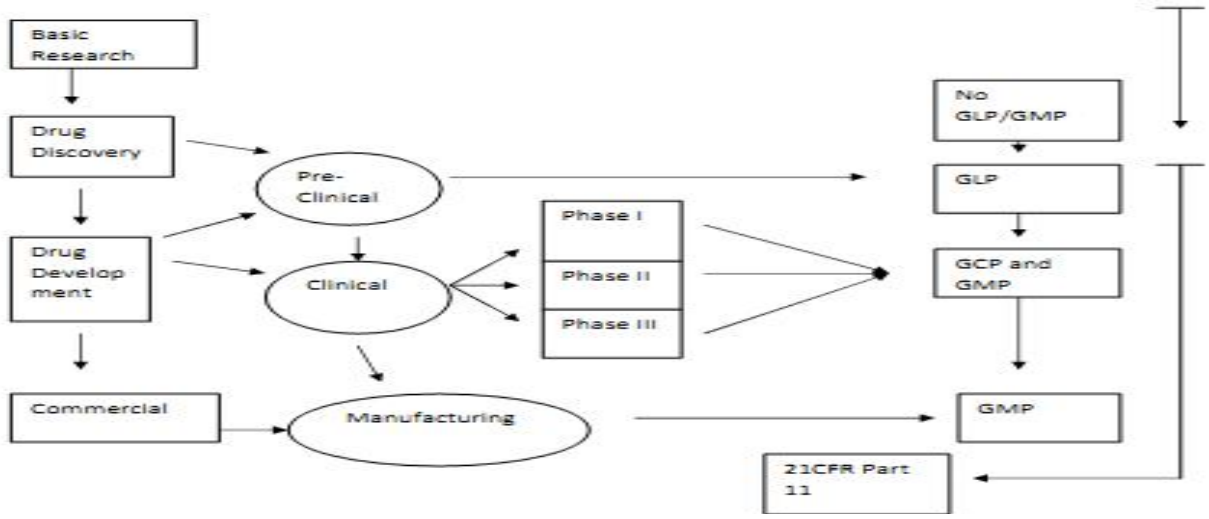
Under the cGMP regulations found in 21 CFR Parts 210-211 (Section 211.180), pharmaceutical companies are required to review the quality standards of each drug product on an annual basis.**[9]**

During the entire life cycle of a product the audits by the regulatory agencies and Compliance aspects plays a major role. Compliance aspects–GLPs (Good Laboratory Practices) – preclinical, GMPs (Good Manufacturing Practices) - clinical and market and GCP (Good Clinical Practices) – clinical.

Audit by a Regulatory Authority involve-Official review of following:

Documents, Facilities, Records, and other resources.**[10]**

**Figure 1: Phases of Drug Development and Compliance for Regulations**



**Standard Operating Procedures for Auditing**

A pharmaceutical company has to prepare a standard operating procedure for auditing which includes the following points:

**1.** Information regarding the company policy pertaining to auditing.

**2.** Composition of the auditing team with clarity on their authority and responsibility

**3.** Statement of purpose scope of audits

**4.** Chosen areas subjected to auditing

**5.** Frequency of auditing

**6.** Written reports on audits including their distribution

**7.** Corrective action to be taken as a result of deficiencies uncovered during the auditing including time-tables and provision for reaudits when appropriate.

**Compliance classifications:**

**1.NAI – (No Action Indication)**: No objectionable conditions or practices (e.g., violations of 21 CFR Parts 50, 54, 56, 312, 511, and 812) were found during the inspection, or the significance of the documented objectionable conditions found does not justify further FDA action. No objectionable conditions or practices were found by the FDA.**[11]**

**2. VAI – (Voluntary Actions Indicated**) :Objectionable conditions were found and documented, but the Center is not prepared to take or recommend any further regulatory (advisory, administrative, or judicial) action because the objectionable conditions do not meet the threshold for regulatory action (i.e., regulatory violations uncovered during the inspection are few and do not seriously impact subject safety or data integrity). A VAI classification should be made only if a FDA-483 has been issued.**[12]**

**3. OAI – (Official FDA Action Indicated):**If objectionable conditions were found, one of the actions listed below should be recommended. Specifically, regulatory violation(s) uncovered during the inspection is repeated or deliberate and involve submission of false information to FDA or to the sponsor in any required report. The regulatory violation uncovered serious support a finding that:

**a)** Subjects under the care of the investigator would be or have been exposed to an unreasonable and significant risk of illness or injury. **[13]**

**b)** Subjects' rights would be or have been seriously compromised.

**c)** Data integrity or reliability is or has been compromised.

**Types of auditor:**

Auditors can be of 3 types:

**1. First-Party Audit:** This type of audit also known as internal audit or self-audit those auditing and those being audited all belong to the same organization. Internal auditors perform various audit procedures, primarily related to procedures over the effectiveness of the company's internal controls over financial reporting. Though internal auditors are not considered independent of the company they perform audit procedures for, internal auditors of publicly-traded companies are required to report directly to the board of directors, or a sub-committee of the board of directors, and not to management, so to reduce the risk that internal auditors will be pressured to produce favorable assessments.**[14]**

**2. Second-Party Audit:** A second-party audit refers to a customer conducting an audit on a supplier or contractor. For example, a medical device company that contracted a laboratory to do sterility testing may conduct a second-party audit to make sure that the lab meets QSR (Quality System Regulation) requirements and to be able to demonstrate to FDA investigators that the contractor is compliant. The same company may audit a parts supplier to make sure that it conforms to ISO 9001 or ISO 13485 standards. It may also evaluate a potential raw materials supplier through an audit, although some auditors might argue that such a process is more of a supplier survey than an audit. **[15]**

**3. Third-Party Audit:** Neither customer nor supplier conducts this type of audit. A regulatory agency or an independent body performs a third-party audit for the purpose of compliance or certification or registration. For example, FDA investigator conducting a cGMP inspection at a pharmaceutical company. Another example is a College of American Pathologists (CAP) team inspecting a blood bank for the purpose of accreditation. ISO conformity assessments are not carried out by ISO itself, but by private-sector third parties or regulatory bodies in countries where ISO standards have been incorporated into law.Second and third party audit are known as external audits.**[16]**

**Auditing procedure:**

There are total 10 steps of the audit process:

**1. Notification:** Audit process begins with notification. The notification process alerts the party to be audited of the date and time of the process. The notification also will list the documents that the order wishes to review in order to understand the organization of the company.

**2. Planning:** Planning is the steps the auditor takes, before the audit, to identify key areas of risk and areas of concern.

**3. Opening meeting:** Meeting between the auditing staff and senior management of the auditing target as well as administrative staff. The auditors will describe the process they will undertake. Management will describe areas of concern to them and the schedule of the employees that must be consulted. [**17**]

**4. Field work:** Fieldwork begins after the results of the meeting are used to adjust the final audit plans. Employees are notified of the audit, schedules are drawn up regarding the activities of the audit staff, and initial investigation begun after learning of business procedures, interviewing key staff, testing current business practices by sampling, reviewing the law and testing internal rules and practices for reasonableness.[**18**]

**5. Communication:** The audit team should consistently be in contact with the corporate auditor to clarify processes, gain access to documents and clarify procedures.[**19**]

**6. Draft audit:** At the completion of the audit, the next step, the draft audit, is prepared. The draft audit detail what was done and what was found, a distribution list of parties to receive preliminary results, and a list of concerns. [**20**]

**7. Management response:** The draft is given to management to review, edit and suggest changes, probe areas of concern and correct errors. Upon making final corrections, the report is given to management for the seventh step, the management response. Management is requested to answer the report by stating whether they agree with the problems cited, the plan to correct noted problem and the expected date by which all issues will have been addressed.[**21**]


**Figure 2:** Auditing Procedure

**8. Final meeting:** The final meeting is designed to close loose ends, discuss the management response and address the scope of the audit.

**9. Report distribution:** The ninth step is the report distribution, where the final audit report is sent to appropriate officials inside and outside the audit area. [**22**]

**10. Feedback:** The last step is the audit feedback whereby the audited company implements the recommended changes and the auditors review and test the quality, adherence and effects of the adopted changes. This continues until all issues are adopted and the next audit cycle begins.

**CONCLUSION**

While a letter notifying a manager of a pending audit may not be the most welcomed news, an audit should be viewed as a valuable management tool. It is an essential business process that results in recommendations for improvement. And from a "bottom line" perspective, organizational improvement reflects well on staff, the program, and the profession.[**23**]

**REFERENCES**

**1.** Cutting, Thomas (January 12, 2008). "How to Survive an Audit". PM Hut. http://www.pmhut.com/how-to-survive-an-audit. Retrieved December 13, 2009.

**2.** http://en.wikipedia.org/wiki/Audit"

**3.**http://ezinearticles.com/?10-Steps-to-Maximize-Your-Energy-Audit&id=3633861

**4.**"http://en.wikipedia.org/wiki/Management_representation"

**5.** Nyholm, J, 2009 "Persistency, bioaccumulation and toxicity assessment of selected brominated flame retardants"

**6.** Anderson, K. "Intelligence-Based Threat Assessments for Information Networks and Infrastructures: A White Paper", 2005.

**7.** Barry Commoner. "Comparing apples to oranges: Risk of cost/benefit analysis" from Contemporary moral controversies in technology, A. P. Iannone, ed., pp. 64-65.

**8.** Flyvbjerg, Bent, "From Nobel Prize to Project Management: Getting Risks Right." Project Management Journal, vol. 37, no. 3, August 2006, pp. 5-15.

**9.** Harremoës, Poul, ed. Late lessons from early warnings: the precautionary principle 1896–2000.

**10.** Mary O'Brien. Making better environmental decisions: an alternative to risk assessment.

**11.** Deborah G. Mayo. "Sociological versus metascientific views of technological risk assessment" in Shrader-Frechette and Westra.

**12.** Shrader-Frechette, Kristin and Laura Westra. Technology and values.

**13.** Hallenbeck, William H. Quantitative risk assessment for environmental and occupational health. Chelsea, Mich.: Lewis Publishers, 1986

**14.** Lerche, I. (Ian) Environmental risk assessment : quantitative measures, anthropogenic influences, human impact. Berlin: Springer, 2006.

**15.** A Review of risk assessment methodologies by the Congressional Research Service, Library of Congress for the Subcommittee on Science, Research, and Technology. Washington: U.S. GPO, 1983.

**16.** John M. Lachin. Biostatistical methods: the assessment of relative risks.

**17.** Science and judgment in risk assessment. Committee on Risk Assessment of Hazardous Air Pollutants, Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council. Washington, D.C.: National Academy Press, 1994.

**18.** Danny Lieberman, "Using a Practical Threat Modeling Quantitative Approach for data security", 2009

**19.** Merrill, Richard A. "Food Safety Regulation: Reforming the Delaney Clause" in Annual Review of Public Health, 1997, 18:313-40. This source includes a useful historical survey of prior food safety regulation.

**20.** Official (ISC) Guide to CISSP CBK. Risk Management: Auerbach Publications. 2007. pp. 1065.

**21.** Commoner, Barry. O'Brien, Mary. Shrader-Frechette and Westra 1997.

**22.** THE FOURTH QUADRANT: A MAP OF THE LIMITS OF STATISTICS Nassim Nicholas Taleb An Edge Original Essay http://www.fda.gov/RegulatoryInformation/Guidances/ucm125067.htm#toc

**23.** US FDA Compliance Program Guidance Manualhttp://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM,http://www.fda.gov/ICECI/ComplianceManuals/RevisionstoComplianceManuals/ucm198975.htm