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Optimizing Pharmaceutical Quality Audits: Enhancing Compliance and Performance through Best Practices

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ABSTRACT

This insightful review explores the pursuit of excellence in pharmaceutical quality audits through regulatory compliance and continuous improvement. It highlights key factors and best practices that contribute to successful audits in the pharmaceutical industry. The review emphasizes adherence to regulatory guidelines and standards and examines the importance of implementing risk-based approaches and effective practices. The review delves into essential elements such as comprehensive document review, assessment of data integrity, and evaluation of suppliers to ensure thorough quality oversight. It underscores the significance of post-audit analysis, corrective actions, and effective communication of findings to drive organizational change. By adopting these best practices, pharmaceutical companies can elevate the quality of their audits, meet regulatory requirements, and continuously improve their performance in delivering safe and effective products to patients. The review underscores the value of optimizing pharmaceutical quality audits to enhance compliance and performance within the industry. This review provides valuable insights for pharmaceutical organizations seeking to optimize their quality audits, enhance regulatory compliance, and improve overall performance. By following these recommendations, companies can strengthen their quality management systems and ensure the highest level of product quality and patient safety.

Keywords: Pharmaceutical quality audits, Regulatory compliance, Continuous improvement, Best practices.

1. INTRODUCTION

Quality audit is indeed an essential component of pharmaceutical organizations, playing a crucial role in ensuring compliance with regulatory standards and maintaining the integrity of processes and products. The main objective of an audit is to assess how effectively an organization controls and manages its processes and products, while also validating and ensuring the reliability of information. The FDA's current Good Manufacturing Practice (cGMP) guidelines provide the fundamental requirements and guidelines for conducting audits in pharmaceutical organizations involved in product development and manufacturing. These audits are conducted to determine the effectiveness of the organization's quality systems [1].

A quality audit is an independent evaluation that takes place periodically. It involves the verification of activities, processes, records, and other elements of the quality system. The observations made during the audit are systematically documented to assess their conformity with quality standards such as those set by the USFDA and GMP [2].

The International Organization for Standardization (ISO) defines an audit as a systematic, independent, and documented process for obtaining audit evidence and objectively evaluating it to determine the extent to which the verification criteria are met. This definition highlights the structured and unbiased nature of the audit process [3].

Joseph M. Juran, a renowned quality management expert, defined a quality audit as an independent review conducted to compare certain aspects of quality performance with established standards for that performance. This definition emphasizes the comparative nature of audits, where the performance of processes and products is assessed against predetermined benchmarks [4].

Pharmaceutical organizations should view audits as a quality control mechanism rather than consider them troublesome. Audits, including self-inspections, play a critical role in the decision-making process for batch release. They ensure that the necessary quality standards and regulatory requirements are met, ultimately safeguarding patient safety and maintaining product quality [5].

The Goals and Objectives of Pharmaceutical Quality Audits:

1. Evaluation of Activities and Documents: Quality audits aim to evaluate an organization's activities and existing documents to determine if they meet predetermined regulatory standards. The focus is on assessing compliance and identifying any non-conformities that need to be addressed.
2. Corrective Actions and Prevention of Non-Conformities: In cases where non-conformities are identified during an audit, the goal is to plan and implement corrective actions to eliminate the root causes and prevent their recurrence. This helps in maintaining and improving the quality of processes and products [1].
3. Assessment of Strengths and Weaknesses: Audits provide an opportunity to assess the strengths and weaknesses of the quality control and quality assurance processes within an organization. This assessment helps in identifying areas of improvement and enhancing the overall credibility and trustworthiness of the organization in the eyes of customers [6].
4. Independent Advice and Assurance: Quality audits provide independent advice and assurance to management that the policies, operations, systems, and procedures they are responsible for comply with relevant regulations, legislation, and standards. This helps in ensuring regulatory compliance and maintaining the integrity of the organization's quality systems.
5. Identification of Non-Conformances and Recommendations for Improvement: Audits assist in identifying non-conformances and deviations from quality standards. This enables the tracking of recommendations for improvement, leading to a continuous cycle of enhancing the organization's quality performance.
6. Brand Reputation and Compliance: Effective auditing and compliance with standards contribute to building a strong brand reputation. By avoiding the negative consequences of non-compliance, such as fines, negative public relations, and legal proceedings, organizations can maintain customer trust and confidence in their products [7].

Benefits of Quality Audits:

- Facilitates continuous improvement by identifying areas for enhancement within processes and systems.
- Encourages self-evaluation, allowing organizations to identify strengths and weaknesses for proactive measures.
- Ensures compliance with regulatory requirements, building customer trust in quality standards.
- Prevents quality failures by detecting and addressing issues before they impact product safety and efficacy.
- Identifies and eliminates potential threats to quality, mitigating risks.
- Highlights areas for improvement, enabling focused corrective actions and enhanced quality performance [8,9].

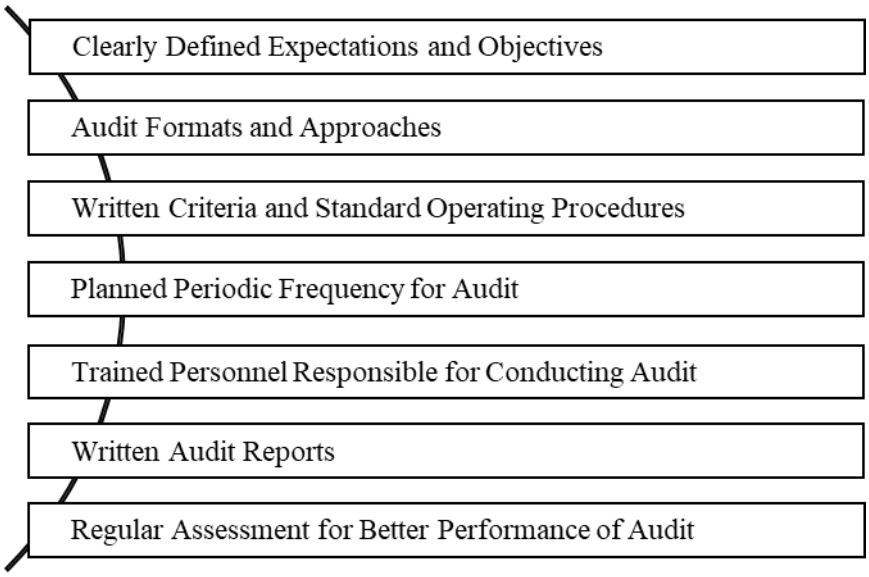

Fig. 1: Elements of Quality Audit

Types of Audits:
The quality audit system is mainly classified into three different categories:
1. Internal Audit
2. External Audits
3. Regulatory Audits

Internal Audit: Internal audits, also known as first-party audits or self-audits, are conducted by an organization internally. Both the auditors and the auditees belong to the same organization [10]. The purpose of internal audits is to evaluate organizational problems and systematically establish solutions. The internal audit typically reports to the owner or management of the company [11].
The Institute of Internal Auditors defines internal auditing as an independent and objective assurance and consulting activity that adds value and improves an organization's operations. It helps organizations achieve their objectives by applying a systematic and disciplined approach to evaluate and enhance the effectiveness of risk management, control, and governance processes [12].
The Purpose of Internal Audits:
- Identifying compliance insufficiencies and deviations.
- Benchmarking compliance efforts.
- Informing management about compliance status and risks.
- Encouraging continuous improvement.
- Identifying non-conformities and enabling corrective action [13].

Depending on the complexity of the internal auditing processes, it can be categorized into 3 categories[14]:

Types of Internal Audit:

	Tier One	**Tier Two**	**Tier Three**
Carried out by:	The staff of a section or department of the company	Local quality assurance group	Corporate compliance group and external consultant

Purpose:	Require short time and focus on housekeeping and documentation	Require longer period and more focus on the system than housekeeping	More focusonassessing the readiness of regulatory audit
Frequency:	More	Less	Less than tier two
Qualification:	Receive some basic training	More exclusive training	Highly trained and experienced specialist with expert knowledge of GMP

External Audit: External audits, also known as second-party audits, are conducted by a company on its vendors or subcontractors. These audits are not legally required but are carried out to evaluate the compliance of suppliers with quality system standards and ensure that the products or services purchased are of consistent quality [15].
The Purpose of External Audits:

- Promoting knowledge and trust in partnership agreements.
- Decreasing the risk of failure by ensuring compliance with quality standards.
- Confirming requirements understanding and compliance.
- Reducing certain activities through reliable vendor/subcontractor compliance.
- Utilizing knowledge for quality, operations, and risk management improvements [16].

Regulatory Audit: A regulatory audit also referred to as a third-party audit, is conducted by a regulatory agency or an independent body to assess regulatory compliance. These audits are not conducted by customers or suppliers but are carried out by authorized regulatory bodies. Examples of regulatory bodies include the United States Food and Drug Administration (USFDA), Medicines Control Council (MCC) in South Africa, Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK, Therapeutic Goods Administration (TGA) in Australia, and others.
The primary purpose of a regulatory audit is to determine whether an organization complies with the regulatory requirements and standards set by the respective regulatory body. Regulatory audits are typically conducted regularly by the national regulatory body and cover all areas of a facility over a specific period [17].
Audits by the regulatory body of another country may be general in nature or may be linked to a specific regulatory event. For example, the pre-approval inspections conducted by the FDA are linked to the submission of a new drug application. These audits assess compliance with the country's regulatory requirements where the product is being submitted for approval [18].
Regulatory audits are crucial for ensuring that organizations adhere to regulatory standards and guidelines. They help regulatory bodies assess product quality, safety, efficacy, manufacturing processes, and quality systems. Non-compliance with regulatory requirements identified during these audits can result in regulatory actions such as warnings, fines, or even product recalls [19].

Standard Operating Procedure (SOP) for Audit:

1. **Policy Statement:** Clearly state the organization's policy regarding auditing, emphasizing its importance and commitment to regulatory compliance and industry standards.
2. **Formation of Competent Auditing Team:** Define the qualifications, experience, and training requirements for auditors, and specify their roles and responsibilities in planning, conducting, and reporting on audits.
3. **Purpose and Scope of Audits:** Clearly state the audit's purpose and specify the areas or processes to be audited, ensuring a comprehensive assessment.
4. **Frequency of Auditing:** Establish the frequency of audits based on regulatory requirements, industry

standards, risk assessments, or internal guidelines.

5. **Audit Reports and Distribution:** Outline the requirements for written audit reports, including format, content, timeline, and distribution to relevant personnel, management, and departments.
6. **Corrective Actions:** Define the process for identifying, documenting, and addressing noncompliance issues, including responsibilities, timelines, and monitoring of corrective actions.

The SOP should be periodically reviewed and updated to ensure its effectiveness and alignment with current best practices and regulatory standards [8,20].

Principles of Auditing:

The principles of auditing provide a framework for conducting reliable and effective audits. Compliance with these principles is essential to ensure consistency and integrity in audit processes. Here are the key principles of auditing:

I. **Integrity:** Auditors and audit staff should demonstrate professionalism, honesty, and responsibility in carrying out their work. They should remain fair, unbiased, and competent, avoiding any influences that may compromise their judgment during the audit.
II. **Fair Presentation:** Auditors must report the audit findings, conclusions, and reports truthfully and accurately. Any problems encountered during the audit and differing opinions between the audit team and auditees should be transparently disclosed.
III. **Due Professional Care:** Auditors should apply diligence and judgment in conducting audits. They should recognize the importance of their role and the trust placed in them by the audit client. Logical and systematic judgment should be exercised in all audit situations.
IV. **Confidentiality:** Auditors must ensure the security of information obtained during the audit. They should use and protect audit information appropriately and refrain from exploiting it for personal gain. This principle includes the proper management of sensitive or confidential information.
V. **Independence:** Auditors should maintain independence from the activity being audited to ensure unbiasedness and objectivity in audit conclusions. They should act free from prejudice and conflicts of interest. Systematic criteria should be maintained throughout the audit process to base findings and conclusions solely on audit evidence.
VI. **Evidence-Based Approach:** Auditors should adopt a methodical and evidence-based approach to achieve reproducible and dependable audit conclusions. Audit evidence should be verifiable and can be based on samples of available information. The use of sampling should be appropriate to support the audit conclusions.
VII. **Risk-Based Approach:** Audits should be conducted with a risk-based approach, incorporating risk assessment and opportunities. This approach influences the planning, execution, and reporting of audits, ensuring that audits focus on significant matters for the client and achieve audit program objectives [21,22].

By adhering to these principles, auditors can enhance their audits' reliability, objectivity, and effectiveness, providing valuable and trustworthy information to stakeholders.

Fig. 3: Methods of Data Gathering During an Audit[23]

Auditing Procedure [2,25]:

Steps	Description
Notification	▪ Inform the party about the scheduled date and time for the audit. ▪ Also notify the list of documents that the auditor needs to check, to understand the policies of the organization.
Planning	▪ Done by Auditors to identify risk areas and areas of interest.
Initial Meeting	▪ The gathering involved auditing personnel, senior management, and administrative staff. ▪ An auditor will explain the process they will undertake and management will explain the area of risk and interest to them.
Field Work	▪ Employees are notified about the audit, and schedules are planned regarding the activities of the audit after learning business procedures, interviewing staff, and testing current business practices by sampling.
Communication	▪ The audit team established contact with the corporate auditor to streamline processes and obtain document access.
Draft Audit	▪ It contains detail about what was done and what has been found, a distribution list of parties to receive preliminary results, and a list of concerns.
Response Management	▪ By making necessary changes and corrections reports are given to management for management response. ▪ Management is expected to answer the report by stating whether they agree with the problems mentioned and the expected date by which all issues have been corrected.
Final Meeting	▪ Planned to discuss the management response and address the scope of the audit.
Report Distribution	▪ The completed audit report is distributed to relevant officials both within and outside the audit area.
Feedback	▪ The audited company implements the recommended changes and the auditor review and test the adopted change's quality, adherence, and effects.

Audit Report: Audit reports should be precise, practical, clear, concise, and timely. They serve as the principal

means of communicating audit findings to management. Each finding should be classified as a major control weakness, minor control weakness, exception, observation, or violation of law/regulation. The report should sufficiently identify these issues, providing supporting facts as necessary. Recommendations for corrective action should be included for each finding [26].

1. Audit Name and Date: Identifies the specific audit being reported and the date of the report issuance.
2. Audit Report Addressee(s): Specifies the individuals or departments to whom the audit report is directed.
3. Report Distribution List: Lists all parties who will receive copies of the audit report.
4. Scope and Objective: Describes the scope of the audit, including the activities, processes, and functions reviewed, as well as the period covered by the audit.
5. Auditor's Conclusions: Provides the auditor's opinion on the adequacy and effectiveness of the audited system.
6. Classification of Findings: Classifies each audit finding as a major control weakness, minor control weakness, exception, observation, or violation of law, rule, or regulation.
7. Detailed Explanation of Findings: Provides a comprehensive description and explanation of each identified finding, including supporting facts to the extent necessary.
8. Auditor's Recommendations: Offers specific recommendations for corrective actions to address each identified finding.
9. Management Response: Allows management to provide a written response to the audit finding, including any corrective actions taken or planned.
10. Target Completion Date: Specifies the date by which management expects to complete the corrective actions.
11. Comment Owner: Identifies the manager responsible for implementing corrective actions for each audit finding.

By including these elements, an audit report becomes a crucial communication tool that effectively conveys the audit findings, recommendations, and management's response, facilitating informed decision-making and driving improvement within the organization [27].

Nonconformities/Deviations: A nonconformity is a deviation or failure, either partial or complete, from the requirements of the quality management system or the applicable standards and regulations. It signifies that certain processes, procedures, or practices do not meet the established criteria or expectations. Nonconformities are recorded during audits to document and address areas of concern that require corrective actions to bring the system back into compliance and prevent its recurrence in the future [28].

Reasons for non-conformities:

- **Inadequate understanding of regulatory requirements:** Lack of knowledge or misunderstanding of applicable regulations and guidelines.
- **Failure to establish and maintain proper documentation:** Insufficient or incomplete documentation of processes, procedures, and records required by regulatory authorities.
- **Non-compliance with good manufacturing practices (GMP):** Failure to adhere to the quality standards and guidelines set forth by regulatory bodies.
- **Lack of regulatory oversight and control:** Insufficient monitoring and supervision of regulatory compliance activities.
- **Ineffective quality management system:** Inadequate processes and procedures for ensuring compliance with regulatory requirements.
- **Failure to perform timely and accurate reporting:** Delays or inaccuracies in submitting required reports and documentation to regulatory authorities.
- **Inadequate validation and qualification processes:** Insufficient validation and qualification of equipment, processes, and systems as per regulatory expectations [29].

Classification of Nonconformities/Deviations:

1. Major Nonconformities: These are significant deviations from the requirements of the quality management

system or regulatory standards that contribute significant risk to product quality, safety, or compliance. Major nonconformities typically require immediate corrective action and can result in the suspension or revocation of certifications or regulatory approvals.

2. Minor Nonconformities: These are minor deviations from the requirements of the quality management system or regulatory standards that do not pose a significant risk to product quality, safety, or compliance. While minor nonconformities may not require immediate action, they should still be addressed through appropriate corrective measures to prevent their recurrence.

3. Critical Nonconformities: These are nonconformities that have the potential to cause serious harm to patient safety, public health, or the environment. Critical nonconformities often involve severe breaches of regulatory requirements or critical failures in essential processes or controls. They require immediate corrective action to mitigate the risks involved [30,31].

2. CONCLUSION

Pharmaceutical quality audits are crucial processes that ensure compliance with regulatory requirements and industry standards in the pharmaceutical organization. These audits can be internal or external, to evaluate the effectiveness of quality control measures and identify areas for improvement. Compliance with regulatory requirements is essential, and pharmaceutical organizations must stay up to date with the regulations and guidelines specific to their markets to maintain product quality and safety.

Furthermore, audits promote transparency, accountability, and continuous improvement within pharmaceutical organizations, leading to enhanced product quality and reduced risks of adverse events. Ultimately, a robust quality audit process provides customers with confidence, satisfaction, and trust when it comes to the pharmaceutical products they rely on for their health and well-being.

3. CONFLICTS OF INTEREST: Nil.

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