

PHARMACEUTICAL AUDIT PROCESS, OUTCOMES, AND IMPLICATIONS–OVERVIEW

KRUTHIKA R. K.¹, SANGITA MISHRA¹, ARJUN M.¹, M. P. VENKATESH^{2*}

¹Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Sri Shivarathreshwara Nagar, Mysuru-570015, Karnataka, India. ²Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Sri Shivarathreshwara Nagar, Mysuru-570015, Karnataka, India, and Guest Assistant Professor, Faculty of Pharmaceutical Sciences, UCSI University, Malaysia

*Corresponding author: M. P. Venkatesh; *Email: venkateshmpv@jssuni.edu.in

Received: 31 Aug 2024, Revised and Accepted: 09 Mar 2024

ABSTRACT

The audit process is a crucial component of regulatory compliance and quality assurance in both the United States of America (USA) and the European Union (EU). This review paper compares and analyses the audit processes, results, and ramifications in these two important markets.

The study investigates how pharmaceutical audits affect patients' trust, market stability, and profitability of a company while highlighting the need for adherence to quality standards. Data integrity, supply chain complexity, and adherence to exacting quality standards are just a few of the notable difficulties faced by auditors in the USA and EU. There is a need to have a strong pharmacovigilance system as well to guarantee the security and effectiveness of pharmaceutical products for patients.

This study can be useful reference material for stakeholders, decision-makers, and companies looking to increase accountability, reduce risks, and uphold the integrity of a firm's operations in the global market. A thorough analysis of audit procedures in the USA and EU will facilitate in promotion of effective and efficient manufacturing, control, and distribution of pharmaceutical products while boosting confidence among patients and in the healthcare system as a whole.

Keywords: Pharmaceutical audit, Process, Outcomes, Implications, Audit regulations, GMP audit

© 2024 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<https://creativecommons.org/licenses/by/4.0/>) DOI: <https://dx.doi.org/10.22159/ijpps.2024v16i5.49277> Journal homepage: <https://innovareacademics.in/journals/index.php/ijpps>

INTRODUCTION

A dynamic aspect of every pharmaceutical company is auditing. The goal of a carefully conducted audit is to ensure that all quality assurance and quality control (QC) efforts are of the highest quality possible. One approach to assessing a pharmaceutical manufacturing program is to ensure that its policies adhere to Good Manufacturing Practice (GMP) and regulatory standards [1]. External specialists or a team chosen by the management of pharmaceutical corporations typically conduct quality audits. The results of an audit will assist in improving the process and establishing a better system for the benefit of the organization. An audit will evaluate the strengths and weaknesses of quality assurance methods [2]. Pharmaceutical audits cover procedures for performance qualification up to design qualification. Standard Operating Procedure (SOP), guidelines, and validation policies were also provided [3].

By automating audit-related operations, including document routing, data collecting, notifications, approvals, and activity escalation, the Simpler Quality Management System (QMS) audit management software system may considerably minimize the time and effort required to pass audits. The audit procedure involves careful preparation, careful document review, physical inspection of facilities, and interviews with staff at all levels [4]. The purpose is to evaluate the organization's compliance with Good Distribution Practices (GDP) and GMP, which protect the correct handling and distribution of medicines and ensure safe, dependable, and effective drug manufacture. Auditors meticulously document all findings and observations made throughout the audit, including any deviations, instances of non-compliance, or possible hazards. These observations form the basis for the implementation of Corrective and Preventive Actions (CAPA), which aim to address identified problems and reduce possible new ones [5].

The FDA and EMA are only two of the regulatory organizations that provide recommendations that need to be followed by pharmaceutical quality auditors. Companies may improve their entire QMS by identifying inefficiencies, streamlining procedures, and putting best practices into exercise via regular audits. In the end,

these audits play a crucial role in preserving high standards for product quality, boosting consumer trust, ensuring patient safety, and preserving the pharmaceutical company's image in the competitive market [6]. Pharmaceutical firms show their commitment to providing consumers with safe and dependable pharmaceutical goods by following strict quality audit methods [7].

To rigorously assess and confirm pharmaceutical companies' compliance with strict GMP, robust pharmacovigilance procedures, and stringent data integrity standards, the FDA conducts thorough and systematic pharmaceutical audits. By conducting these thorough audits, the FDA makes sure that pharmaceutical products adhere to the highest standards of quality, safety, and efficacy. This ensures the protection of public health and fosters unwavering confidence in the pharmaceutical industry's morality intention, and commitment to patients' health and welfare. In these audits, the FDA's stringent monitoring and dedication to regulatory excellence are crucial in maintaining the highest standard of patient safety and encouraging ongoing research and development in the pharmaceutical industry [8, 9].

In the EU, EMA uses pharmaceutical audits to carefully evaluate adherence to GMP, GDP, and pharmacovigilance procedures. These audits are essential for assuring pharmaceutical goods' quality, safety, and efficacy. These also protect the public's health and increase patients' and customers' confidence in the pharmaceutical business. EU pharmaceutical audits work to reduce risks, stop the sale of fake medications, and promote an atmosphere of quality and accountability in the industry by ensuring adherence to strict standards and conducting ongoing surveillance to identify areas of improvement [9].

Methods and search criteria

The research carefully considers the activities of important agencies like the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in examining the regulatory frameworks controlling pharmaceutical audits in the USA and EU. It also examines the underlying ideas of the standards, formats, and audit methods in

the USA and EU. This paper utilizes guidelines (FDA/EMA) and existing literature on the subject published after 2005 to create a comprehensive representation of pharmaceutical audits. Keywords used to search relevant literature and guidelines are "Pharmaceutical Audit", "GMP Guidelines", "cGMP guidelines", "EMA Audit Regulations", "FDA Audit Regulations", "Pharmaceutical Audit Planning", "Corrective Action Preventive Action", "Pharmaceutical Quality Control".

DISCUSSION

Audits in the United States

Pharmaceutical audits are an essential aspect of the regulatory supervision process in the US, requiring pharmaceutical firms to adhere to GMP and other pertinent global and local laws. These audits, which are largely carried out by the FDA, are intended to maintain the efficacy, quality, and safety of pharmaceuticals and other medical items sold on the American market [10].

- **GMP audits:** The FDA's GMP audits examine how closely pharmaceutical manufacturing facilities conform to stringent Chemistry, Manufacturing, and Control (CMC) requirements. Aspects of the manufacturing process that are covered by the inspections include facility design, equipment, staff, paperwork, and product testing. The aim is to make sure that pharmaceutical firms continuously manufacture the highest-quality medications that are free from contamination and flaws [11]
- **Pharmacovigilance audits:** Pharmacovigilance audits are conducted by the FDA to evaluate a pharmaceutical company's procedures for tracking and disclosing adverse drug reactions (ADR) and other safety-related data. These audits assist in ensuring that companies quickly identify and address any possible safety issues related to their products [12]
- **Inspection and compliance monitoring:** The FDA often performs surprise inspections of pharmaceutical facilities to ensure that GMP and other legal criteria are being followed. These inspections are a part of the FDA's continuing efforts to make sure pharmaceutical firms uphold the highest standards of quality and comply with relevant laws [13]
- **Quality Systems Inspection Technique (QSIT):** The Quality Systems Inspection Technique (QSIT) is used by the FDA to inspect companies that make medical devices. This approach focuses on evaluating a business's quality management system to confirm compliance with FDA guidelines [14]
- **Current Good Manufacturing Practices (cGMP) Regulations:** Pharmaceutical firms are required to adhere to the extensive cGMP rules set out by the FDA to guarantee the quality and safety of their products. To ensure that production processes are standardized, properly managed, and compliant with rules [15]
- **Data integrity audits:** A crucial component of pharmaceutical production is data integrity. The quality, comprehensiveness, and dependability of data collected throughout the medicine's research and manufacturing processes are also evaluated during FDA audits [16]
- **Pharmacy inspections:** The FDA conducts inspections of pharmacies in addition to manufacturing facilities to make sure that laws governing the formulation and distribution of pharmaceuticals are being followed [17]

Audits in the European Union

Pharmaceutical audits are crucial parts of the regulatory framework in the EU to guarantee the safety, effectiveness, and quality of pharmaceutical goods. These audits, which are usually carried out by regulatory agencies, are intended to evaluate whether GMP and GDP standards and guidelines are being followed [18].

Key aspects of a pharmaceutical audit in the EU are: -

- **GMP audits:** GMP audits are conducted to make sure that pharmaceutical manufacturing facilities produce, test, and regulate the quality of pharmaceutical goods as per industry standards. These audits are carried out by the EMA and the national competent

authorities of EU member states. They evaluate several factors related to manufacturing facilities, such as the tools, procedures, workers, records, and cleanliness. GMP inspections are intended to ensure that pharmaceutical businesses consistently produce goods of the right quality and reduce and eradicate contamination or defects [19, 20]

- **Good distribution practices (GDP) audits:** The distribution and supply chain components of pharmaceutical goods are the focus of GDP audits. They monitor the storage, shipping, and handling practices used by wholesalers, distributors, and other parties engaged in the distribution process are reviewed. The goal is to detect and remove fake goods, protect the integrity of the supply chain, and guarantee that patients receive proper and excellent medications [21]
- **Pharmacovigilance audits:** Pharmaceutical companies' systems for tracking and disclosing ADR and other safety-related data relating to pharmaceutical products are evaluated through pharmacovigilance audits. These audits make sure that businesses are quick to recognize and address any possible safety issues relating to their products after those have been approved for marketing [22]
- **Inspections and compliance monitoring:** Routine and surprise inspections are carried out by regulatory agencies in EU member states to confirm adherence to GDP, GMP, and other pertinent laws. These inspections are a component of the ongoing compliance monitoring procedure used to make sure pharmaceutical businesses uphold high standards across the board [23]
- **Mutual Recognition Agreement (MRA):** Since the EU has agreements with several nations on mutual recognition, GMP inspections carried out in one nation may be accepted by other nations. This arrangement makes it easier for medications to be supplied across nations and lessens the need for repeated audits [24]
- **Qualified Person (QP) certification:** Before being put on the market, medical items must first have a Qualified Person (QP) certification, as required by the EU. Each batch of medicine must adhere to the necessary quality standards and regulatory regulations, and QPs ensure this [25]

The audit process

The flow of the audit process is depicted in fig. 1.

Constituents of the efficient audit process

Communication throughout the audit is crucial for knowing and being informed about the organization being audited. To promote transparency, enable compliance assessment, and address any issues or concerns, a seamless flow of information between auditor and auditee is required. This exchange of information generates a positive, cooperative atmosphere that enhances understanding of business practices and encourages the general improvement of quality and compliance [26].

Auditors can successfully prepare for the audit by requesting a wide range of data from the audited organization. This data offers a thorough picture of the business's operations, procedures, and compliance practices, allowing auditors to concentrate on the right areas throughout the audit and assuring a more focused and effective evaluation.

- A synopsis of the scheduled audits, a list of the units to be audited, their frequency, and an explanation of the audit process are all included in the audit plan. The scope, goals, and deadlines are outlined, assisting auditors in performing methodical, organized evaluations to guarantee thorough and on-time reviews
- Fixed times during which the audit will occur for a certain period are determined (often a year). The audit plan and audit schedule can be integrated into one document if they are not too complicated [27, 28]
- It is necessary to allow the auditee to organize himself. The auditor(s) should request an invitation well in advance of the

planned or scheduled audit for this reason. This might come in the form of a note, a letter (primarily external or internal), or even an e-mail

- A schedule of subjects to be covered and/or audited units that have been agreed upon by the auditor(s) and auditee
- A confidentiality agreement should be signed for external audits (supplier or contractor). Most frequently, the auditors access sensitive areas where information transfer generated by the auditor might compromise intellectual property
- The audit begins with a meeting between the auditor(s) and the auditee. All the organization's/firm's top personnel are expected to be present [29]

Typically, the following topics are covered:

- ✓ Description of the company's management and location
- ✓ Description of the consulting services
- ✓ Discussion of the audit's goals, strategies, and timetable

- ✓ General site and facility design and layout overview [30]
- A tour of the facility's receiving, storing, sampling, dispensing, manufacturing, packing, warehousing, and shipping facilities is followed by a discussion of the movement of materials and people. A visit to the QC Laboratory and a microbiological lab is scheduled
- The degree of compliance with all quality systems, including hardware, software, and employees, will be assessed. The audit report will list any issues found during the audits along with gap analyses and suggested remediation measures. The following, among others, may be examined as part of a pharmaceutical auditing process: documentation and record control, data integrity verification, and related control procedures, training for manufacturing processes, and equipment validation and qualification [31]

The findings should be properly documented and identify opportunities for improvements, non-conformance to procedures, deviations, and recommendations. Based on this, the auditee needs to create CAPA, perform root cause analysis, track changes to ensure conformance, and update actions taken to implement the recommendations [32, 33]

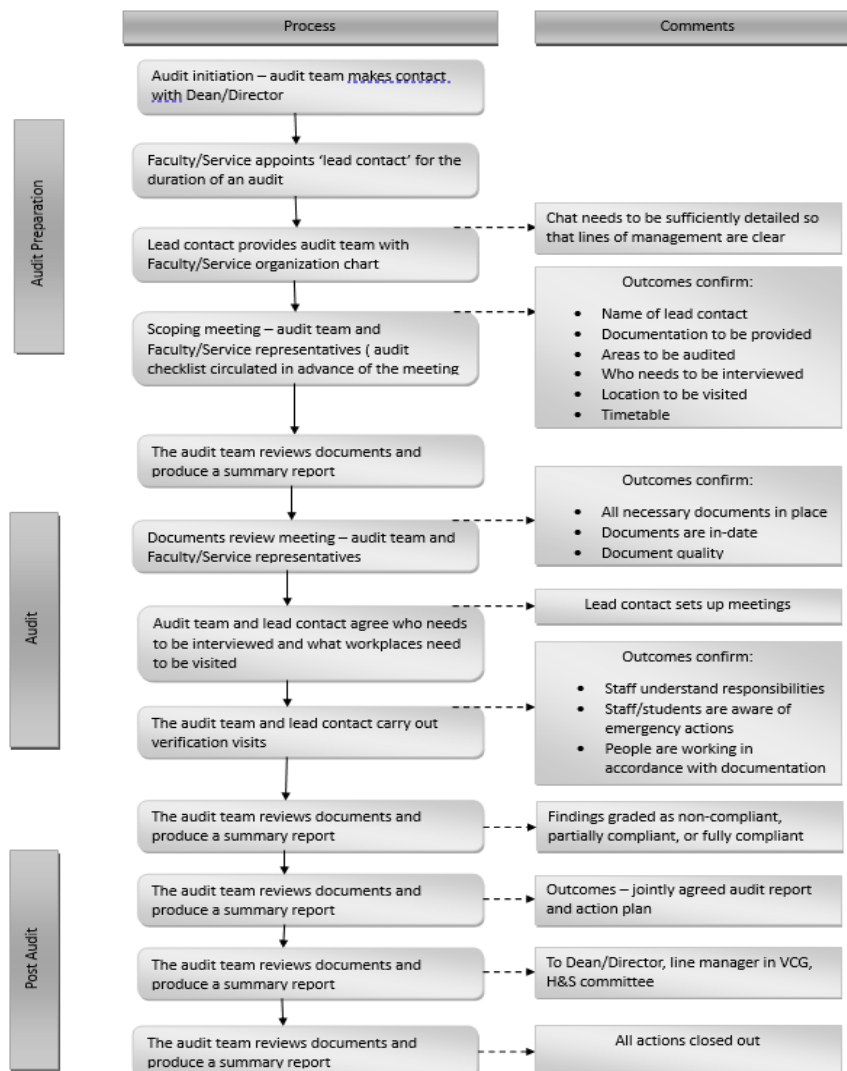


Fig. 1: High-level flow of the audit process [55]

Importance of auditing in US and EU markets

In the US and EU markets, CMC auditing is extremely important and serves several vital purposes, including the following;

- **Regulatory compliance:** Audits confirm that companies adhere to laws, rules, and industry standards through thorough inspections, fostering ethical behavior, lowering the danger of non-compliance fines, and maintaining the integrity of manufacturing and clinical practices.

This improves business reputation and reduces potential legal liability by encouraging trust among stakeholders and regulators. Additionally, auditing is essential for spotting areas that may be improved, which boosts productivity and effectiveness in operations [34]

- **Risk assessment and mitigation:** Internal controls and risk management procedures are evaluated by auditors, helping businesses to find and rectify weaknesses and possible hazards and ensuring continuity in delivering quality medicinal products
- **Quality assurance (QA):** In the pharmaceutical industry, auditing is essential for confirming adherence to strict quality standards, ensuring that goods are safe, effective, and of the highest caliber possible, for protecting customers' health and wellbeing. Maintaining these exacting standards through a robust QA program helps the pharmaceutical industry's image and credibility by inspiring trust in customers, medical professionals, and regulatory agencies [35]
- **Consumer protection:** The protection of customers' interests and safety is ensured by auditing, which confirms that pharmaceutical goods and services adhere to quality and safety requirements

- **Global competitiveness:** Businesses may create an atmosphere that is conducive to development, innovation, and investment by putting strong auditing practices in place. Companies that engage in these practices are more effective, credible, and compliant with rules, increasing their competitiveness and attractiveness in the international market. As a result, pharmaceutical companies acquire a distinct advantage over rivals, broaden their market, and prosper in a highly competitive and linked environment [36]

- **Operational efficiency:** Audits identify inefficiencies via meticulous review, allowing firms to optimize procedures, use resources more effectively, and increase production. Cost-effectiveness, higher profitability, and a stronger position in the market are the results of this optimization. Additionally, optimized and transformed drug manufacturing processes and distribution systems support long-term success and sustainability by improving client happiness and overall organizational performance [37]

Audit process flow-chart

The Process of audit is depicted in fig. 2.

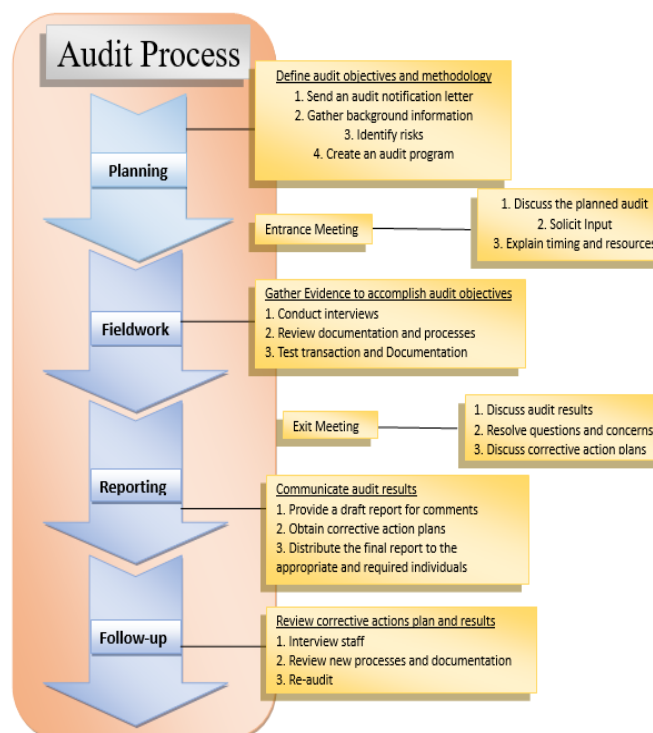


Fig. 2: Typical audit flow [56]

Understanding audit outcomes and their implications

Audits are essential in the pharmaceutical sector for assuring adherence to several regulatory obligations and industry standards. These audits may be undertaken by independent third-party auditors, regulatory bodies, or both internal and external auditors. Assessments of the quality, safety, and compliance of pharmaceutical goods and procedures are made in the audit results and reports for the pharmaceutical industry. The following are some significant characteristics of audit findings and reports in the pharmaceutical sector:

- **Compliance with GMP:** GMP audits are performed to determine if pharmaceutical producers follow the necessary standards in the creation, supervision, and distribution of medicines. The audit's findings can be categorized as follows:

- ✓ **No Significant Observations:** The audit reveals that the business complies with GMP requirements and that there are no significant problems or deviations.

- ✓ **Small Observations:** During the audit, a few small inconsistencies or deviations from GMP standards were found; however, they had no substantial effect on the quality of the products or the safety of the patients.

- ✓ **Important Findings:** The audit reveals significant departures from GMP requirements that may have an impact on the effectiveness or safety of the product. The problems require rapid correction [38, 39]

- **Good Clinical Practise (GCP) compliance:** GCP audits evaluate the ethics and integrity of clinical trials to make sure they are carried out following established protocols and legal standards. The audit's findings are categorized as No Major, Minor, or Critical observations, like GMP audits [40]

- **Pharmacovigilance audits** are centered on reporting and monitoring medication safety. If the pharmaceutical business has

effective mechanisms in place to identify, evaluate, and report adverse drug reactions, it may be determined from the results of these audits.

- **Audits of the QMS:** QMS audits assess the pharmaceutical company's overall quality management procedures, including its documentation, change control, training, and continuous improvement processes.

- **Regulatory compliance:** Inspections carried out by regulatory bodies, such as the EMA in the EU or the FDA in the USA, evaluate adherence to regulations and guidelines that apply to pharmaceutical products and processes

Audit reports in pharma

Pharmaceutical audit reports share similarities with general audit reports but are tailored to address industry-specific concerns. These reports typically include:

- **Objective and scope:** The report begins by outlining the goals of the audit and the topics examined throughout the evaluation

- **Findings:** The audit report gives a thorough explanation of the findings from the audit, which may contain both satisfying results and areas that require improvement

- **Compliance status:** The report makes clear if the pharmaceutical firm complies with all relevant laws, rules, and regulations

- **Corrective and preventive actions:** The report should describe the remedial and preventative steps the auditors advised to take if any non-compliance or shortcomings were found

- **Recommendations:** The report may include recommendations for process enhancements or best practices to improve the quality, safety, and compliance of pharmaceutical products

- **Conclusion:** The overall audit findings and the auditor's assessment of the pharmaceutical company's compliance status are summarised in the report's final section [41]

Pharmaceutical audit reports are important records because they offer insightful information about the organization's quality and compliance procedures, assisting in ensuring the safety and effectiveness of pharmaceutical goods on the market. If major non-compliances are found, regulatory authorities may utilize these reports to determine a company's capacity to maintain compliance and may take additional steps based on the audit results, such as issuing warning letters or enforcing their findings.

Audit implications

Implications of an audit include both positive and negative outcomes. They may consist of:

- **Improved internal controls-**Internal control problems are discovered during an audit. This forces the business to enhance these controls by taking remedial action. The business lowers the possibility of future mistakes or non-conformance by taking proactive measures to correct these problems. Consequently, stakeholders have more faith in the organization's products, assuring the legitimacy and quality of the medicines

- **Increased costs-**Costs associated with the audit process vary according to the complexity and size of the firm. The total cost of the audit is influenced by elements including organizational structure, geographic presence, industry rules, and the strength of internal controls. Although audits might be expensive, they have a significant positive impact on stakeholder confidence, compliance, and financial transparency

The audit consequences will change based on the audit's conditions. These are some of the most typical audit implications, nevertheless. Here are some additional examples of audit implications:

- Future deviations or non-conformance may be more likely to occur if the auditor discovers lax internal controls at the organization that may result in sub-standard medications being marketed

Overall, there may be both good and negative audit effects. The precise ramifications will change based on the audit's conditions. Before conducting an audit, it is crucial to be informed of any potential repercussions [42].

Common pharmaceutical audit challenges

- **Complex regulatory environment:** Sometimes, varying rules and regulations apply to the pharmaceutical sector, making it difficult for auditors to interpret and ensure that all standards are being met. To overcome this difficulty, auditors can maintain compliance by staying informed of changes to rules and standards and modifying audit procedures as necessary

- **Changing regulatory landscape:** The local and global rules and regulations that apply to auditing might change often, so auditors must keep informed and modify their procedures as necessary. To get beyond this obstacle, auditors might align their audit procedures as per modifications in legislation and recommendations

- **Data integrity and accuracy:** Especially when working with huge amounts of data, auditors must overcome the issue of assuring the integrity and correctness of data utilized for auditing purposes. For this challenge to be overcome, auditors can use technology to automate audit procedures, strengthen data quality, and increase productivity. Examples of such technology include audit management software and data analytics tools [31]

- **Risk assessment and management:** Effective risk management and assessment are essential components of the audit process. It may be difficult to identify and prioritize risks, particularly in a fast-paced and complicated sector like pharmaceuticals. To effectively prioritize audit areas and manage resources, auditors can overcome this difficulty by using a risk-based strategy [43]

- **Resource constraints:** Limited manpower and technological resources might make it difficult to perform complete audits on time. Auditors can offer continual instruction and training to improve their expertise in the pharmaceutical sector and regulatory standards. To solve problems and exchange best practices, auditors can also promote cooperation and communication among themselves, regulatory agencies, and pharmaceutical businesses or use AI/ml models to reduce manual efforts.

- **Global operations and supply chain:** Due to their frequent worldwide activities and intricate supply networks, pharmaceutical businesses pose significant challenges in monitoring and auditing every part of their operations. To prevail over these, auditors can use technology to expedite audit procedures and boost productivity, such as audit management software and data analytics tools

- **Pharmacovigilance compliance:** Early identification and prompt reporting of adverse drug reactions are made possible by a strong pharmacovigilance system, assuring patient safety, regulatory compliance, and ongoing advancements in pharmaceutical product safety. This proactive strategy strengthens confidence in the pharmaceutical industry's dedication to safety and efficacy and improves public health protection [44, 45]

Strategies to overcome the audit challenges in the pharmaceutical industry

Pharmaceutical audit issues must be overcome through careful preparation, close attention to detail, and a dedication to regulatory compliance. Here are some tactics to use when tackling typical problems:

- **Comprehensive compliance training:** Assure full training on cGMP, pertinent laws, and internal rules for all people engaged in the audit process, including auditors and auditees. Staff with more knowledge can address problems more successfully.

- **Clear communication:** Make sure there are open channels of communication between the audit team and the facility being reviewed. To prevent misconceptions and promote a smoother audit process, it is important to communicate audit objectives, expectations, and scope well in advance

- **Pre-audit preparation:** The pharmaceutical business should perform an internal audit before the actual audit to find any potential gaps or concerns of non-compliance. This initiative shows dedication to quality and rectifies any flaws proactively before external parties or auditors identify those.
- **Risk-based approach:** In pharmaceutical audits, a risk-based strategy entails methodically assessing possible hazards connected to various processes, systems, and activities. The audit team may efficiently allocate resources, perform extensive assessments, and implement targeted changes by identifying high-risk areas to assure regulatory compliance and maintain the highest standards of product quality and patient safety
- **Experienced audit:** Employ seasoned auditors who are knowledgeable about industry best practices and pharmaceutical legislation. Competent auditors are more likely to properly pinpoint areas of concern and provide insightful recommendations for advancement.
- **Data integrity:** The pharmaceutical sector places a high priority on data integrity. It is important to ascertain the accuracy, completeness, and dependability of all data created and used in the production, testing, and QC processes.
- **Corrective and preventive actions (CAPAs):** Create a strong CAPA system to resolve any non-compliance concerns as soon as they are discovered. The audit team should evaluate the efficacy of previously deployed CAPAs and ascertain if they were useful in fixing earlier findings and those that have been tracked and documented [46]

Guidelines for GMP audit in the pharmaceutical industry

The FDA has established cGMP guidelines, which are used as a standard for evaluating the quality of pharmaceutical goods to make sure they meet the required parameters. These rules attempt to guarantee that a drug's potency corresponds to its claims for the product's safety. The main goal of cGMPs is to equip makers of pharmaceutical goods with guidelines for comprehensive QC. The FDA inspects and evaluates the manufacturer's capacity to produce human and veterinary pharmaceuticals and the machinery being utilized to determine compliance. Manufacturers must adhere to current requirements. The practice must meet these standards' requirements for both "good" and "current" practice. The manufacturer's controls, tools, and procedures must be up to date. Current can be taken to mean what is typically accepted in the field. Therefore, the manufacturer is required to follow the new processes if new standards are created that are superior to the present ones [47].

GMP audit plan

GMP audit plan typically consists of the following components as shown in fig. 3.



Fig. 3: GMP audit plan [48]

- **Review documents:** It is necessary to compile a list of all the documents involved in the audit. Batch production records, master formula records, standard operating procedures, the technique of analysis, deviations, change controls, stability testing data, etc. are some examples of documents that may be included. Before the GMP audit, it is necessary to check the qualification records for the water system, production and QC tools, process validation, and analytical technique validation. These documents should be checked for overwriting, updating, and other errors. Where applicable, supporting data such as

analytical data from QC and data produced by the manufacturing and warehousing equipment should also be added.

- **Prepare GMP audit plan:** Before the audit, a strategy should be created outlining how the GMP audit would proceed. Every department should concentrate on its areas of strength, which should be displayed to the auditor. The department's best and weakest components should be identified, and effort should be made to strengthen the latter before the audit. The auditors should organize their visits from the plant's strongest to weakest departments. The GMP Audit plan is depicted in fig. 3
- **Key persons:** Every department should choose one or two individuals as its key personnel. These individuals should have a complete understanding of the department's documentation and systems. The auditors will receive an explanation from these responsible individuals.
- **Audit responsibilities:** Each department member should be given a specific area and task. Each person is accountable for the completion and accuracy of the assigned area. Before the audit, the department head should make sure that the assigned job is finished.
- **Internal audit:** Before the GMP audit, internal audits should be carried out to verify the audit preparations. Additionally, it will boost the trust of those who will be subject to the audit. The cornerstone of any effective audit is an internal audit.

These are some crucial elements for a GMP audit to succeed. This should prepare a company for a GMP audit in the pharmaceutical sector by providing proper guidance documents and highlighting key areas of focus [47].

Difference between US and EU audit regulation

Refer table 1.

Corrective actions and follow-up after the audit

The adoption of remedial steps once an audit is finished is crucial for dealing with any breaches or issues found during the inspection. Correcting systemic defects is a priority since it assures the avoidance of repeat occurrences and promotes a culture of improvement within the organization. By optimizing processes through these corrective measures, the company increases its chances of becoming certified, which would signify compliance with industry norms and enhance the company's credibility in the market.

Remedial action is a four-step procedure that includes cautious planning, painstaking implementation, watchful monitoring, and thorough review. The firm acquires a methodical way to recognize, address, and assess the success of the implemented corrective actions through these sequential processes. The company's continued adherence to rules is ensured by this cycle of continuous improvement, which also boosts overall operational effectiveness and fortifies the company's position within the sector [50].

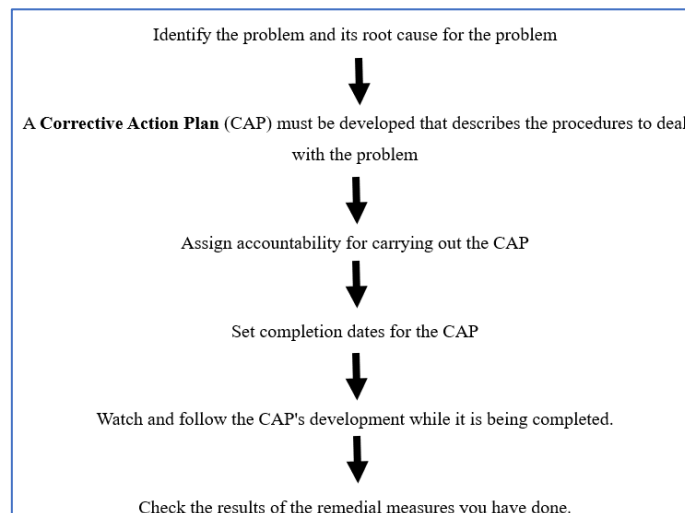
Corrective measures can assist a business in streamlining its procedures and winning certification. Here are some phases in the process of remedial action. Refer to 4.

A corrective action plan is a piece of writing used in quality management that describes a series of actions taken to rectify problems and gaps in organizational procedures.

To address any non-conformances found during the audit, the auditee is responsible for completing the corrective action plan (CAP). A CAP is a technique for recording non-compliance problems, pinpointing their underlying causes, and collecting quantifiable, doable fixes and reasonable dates. After a certain amount of time, it's critical to gauge and evaluate the corrective action's efficacy. A corrective action plan must be meticulously documented and closely monitored to remain on track. The CAP procedure is depicted in fig. 4.

Table 1: United States and European Union Audit Regulations

Aspect	US audit regulations	EU audit regulations	References
Structure	The FDA is a centralized organization that manages the process of promoting drug manufacturing and approval in the USA.	EMA is the centralized scientific evaluation body for therapeutics in the EU. It is governed by European Commission guidelines.	[48, 49]
Approval process	Preclinical research, Phase I, II, and III clinical trials, as well as a review procedure for New Drug Applications (NDAs), are all components of the FDA's multi-phase approval process for medications.	Similar procedures are used by the EMA for non-clinical testing, clinical trials (Phase I, II, and III), and the examination of marketing authorization applications (MAAs).	[48, 49]
Audit procedures	FDA refers to audits as internal audits. Additionally, the FDA examines its operations to make sure regulations are being followed.	EMA refers to audits as self-inspections. The Mutual Recognition Agreement (MRA) between the EU and the US enables reliance on one another's human medicine inspections inside their respective national borders.	[48, 49]
Audit trail discussion	FDA 21 CFR 11–Use of secure computer-generated time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records	EU GMP Annex 11–Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-Relevant changes and deletions (a system-generated audit trail)	[48, 49]
Jurisdiction and authority	The FDA employs people to keep an eye on drug assessment requests and the development of new drugs.	The ultimate regulatory decision is made by the European Commission (EC), and the EMA is not permitted to authorize or approve certain drugs.	[48, 49]
Drug approval process	The FDA is a centralized organization that manages the process of creating drugs in one nation. The FDA's personnel keeps an eye on drug review applications and the medication development process.	Many European countries have a reviewing authority called EMA that oversees the procedure. The national agencies of the member states evaluate the EMA.	[48, 49]

**Fig. 4: Corrective action plan procedure [51]**

Accepting the risk underlying the audit finding and its impact on eliminating or revising the offending control activity to the extent that compensating controls are in place to address the core risk(s) are the only two ways to resolve the audit finding if a company opts not to implement a CAP. However, the most efficient method to address an audit finding is to put a corrective action plan into place [51].

Follow-up after the audit

The audit process includes follow-up to make sure corrective measures have been taken and are working properly following an audit. To confirm that management action plans have been completed, follow-up audits are performed. The follow-up procedure entails keeping track of how management-communicated outcomes are handled. The steps in the follow-up procedure are listed below.

- The Audit Issue Tracker serves as a repository for management action plans and condensed audit issues
- A Recommendation Implementation Status Summary (RISS) document outlining the action plans' current status is created.

- The RISS document is shared with addresses listed in the audit report
- The most recent status of recommendations is added to the Audit Issue Tracker spreadsheet
- If activities that have been planned or implemented or the associated timetable has altered, it should be discussed with the manager or director [52, 53]

The implementation and ongoing monitoring of audit findings and their mitigation are greatly aided by the follow-up log used in internal auditing. It's crucial to share the follow-up log activities in fresh audit reports or by distributing an updated version of the relevant audit report that includes the new follow-up log activity. If areas suggested for improvement are not implemented by management, the internal audit's work fails to improve the internal control, risk, and governance frameworks and hence needs to be addressed. Audit committees and senior management need confirmation that controls are more effectively managing risk and that agreed-upon actions in internal audit reports have been executed appropriately and within the originally provided timeframes [54].

To verify that corrective measures have been implemented and are working, follow-up is crucial following an audit. The follow-up procedure entails tracking how outcomes conveyed to management are handled and confirming that track action plans have been completed. Internal auditing's follow-up log is crucial to the implementation, ongoing evaluation, and mitigation of audit findings. It is crucial to convey the follow-up log activities in fresh audit reports or by distributing an updated version of the relevant audit report that includes the new follow-up log activity.

CONCLUSION

Audits in the US and EU are crucial for maintaining integrity in manufacturing and research, ensuring regulatory compliance, and fostering public trust in healthcare. The contrast in regulatory frameworks underscores the need for stringent regulations to uphold independence and ethics in auditing. Businesses and auditors must adapt to changing criteria for optimal effectiveness, especially in dynamic regulatory environments affecting pharmaceutical operations. Auditors must identify the complexities of the pharmaceutical sector and stay updated on medical research, drug development, and regulations to ensure the relevance of their methodology. An effective audit process is essential for protecting public health, and financial integrity and fostering sustainable growth in healthcare. Emphasizing the importance of audits reinforces moral standards, ensures patient safety, and supports a robust healthcare system.

ACKNOWLEDGEMENT

The Authors express sincere gratitude to JSS Academy of Higher Education and Research and JSS College of Pharmacy, Mysuru for their support in carrying out their work.

FUNDING

No grant or funding was received or requested for this work

AUTHORS CONTRIBUTIONS

KR played a comprehensive role by conceptualizing and designing the study and was involved in literature search, data acquisition and analysis, statistical analysis, manuscript preparation, editing, and review. SM supported in study design and was actively involved in content preparation, data synthesis, manuscript preparation, editing, and review of the same. AM contributed to manuscript preparation, editing, and review. MP helped in the study conceptualization and review of the manuscript.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

REFERENCES

- Ghose A, Koliadis G. Auditing business process compliance. Lecture Notes in Computer Science (Including Subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics). 2007;4749LNCS:169-80.
- Agarwal P, Mishra A. Pharmaceutical quality audits: a review. *Int J Appl Pharm.* 2019 Jan 1;11(1):14-22. doi: 10.22159/ijap.2019v11i1.29709. Available from: https://www.researchgate.net/publication/330261216_Pharmaceutical_quality_audits_A_review.
- Karapetrovic S, Willborn W. Generic audit of management systems: fundamentals. *Manag Aud J.* 2000 Aug 1;15(6):279-94. doi: 10.1108/02686900010344287.
- Guide to quality audits in the pharmaceutical industry. Available from: <https://www.simplerqms.com/pharmaceutical-audits> [Last accessed on 04 Aug 2023]
- EMA. Guidance on good manufacturing practice and good distribution practice: questions and answers. European Medicines Agency. Available from: <https://www.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/guidance-good-manufacturing-practice-good-distribution-practice-questions-answers>. [Last accessed on 04 Aug 2023]
- Room 2201 Silver Spring. 2009;51:20852-1448. Available from: <http://www.fda.gov/cder/guidance/index.htm>, <http://www.fda.gov/cber/guidelines.htm>.
- Purdie FP. Data integrity and compliance with cGMP guidance for industry DRAFT guidance. Available from: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. [Last accessed on 04 Aug 2023]
- ema. Guidance on good manufacturing practice and good distribution practice: questions and answers. European Medicines Agency. Available from: <https://www.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/guidance-good-manufacturing-practice-good-distribution-practice-questions-answers>. [Last accessed on 04 Aug 2023]
- Current good manufacturing practice (CGMP) regulations. FDA. Available from: <https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations>. [Last accessed on 04 Aug 2023]
- Inokon UM. Approaches to GMP inspection CDER Small Business-Regulatory Education for Industry (REdI); 2014.
- The basics of pharmacovigilance audits; 2014. Available from: <https://www.pharmacovigilance-audits.thefdagroup.com/blog>. [Last accessed on 04 Aug 2023]
- Fisher AC, Liu W, Schick A, Ramanadham M, Chatterjee S, Brykman R. An audit of pharmaceutical continuous manufacturing regulatory submissions and outcomes in the US. *Int J Pharm.* 2022 Jun 25;622:121778. doi: 10.1016/j.ijpharm.2022.121778, PMID 35500688.
- FDA, QSIT. MasterControl. Available from: <https://www.mastercontrol.com/compliance/fda/qsit>. [Last accessed on 04 Aug 2023]
- Current good manufacturing practice (CGMP) regulations. FDA. Available from: <https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations>. [Last accessed on 04 Aug 2023]
- Charoo NA, Khan MA, Rahman Z. Data integrity issues in the pharmaceutical industry: common observations, challenges and mitigations strategies. *Int J Pharm.* 2023 Jan 25;631.
- Inspection basics. FDA. Available from: <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-basics>. [Last accessed on 04 Aug 2023]
- EMA. Guidance on good manufacturing practice and good distribution practice: questions and answers. European Medicines Agency. Available from: <https://www.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/guidance-good-manufacturing-practice-good-distribution-practice-questions-answers>. [Last accessed on 04 Aug 2023]
- EMA. Good manufacturing practice. European Medicines Agency. Available from: <https://www.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice>. [Last accessed on 04 Aug 2023]
- EMA. Good distribution practice. European Medicines Agency. Available from: <https://www.europa.eu/en/human-regulatory/post-authorisation/compliance/good-distribution-practice>. [Last accessed on 04 Aug 2023]
- Health W. The importance pharmacovigilance saf monit med prod; 2002.
- GMP; 2020-21. Available from: <https://www.gmp-journal.com/current-articles/details/gmp-update-2020-2021-new.html>. [Last accessed on 04 Aug 2023]
- EMA. Progress with EU-US mutual recognition agreement for inspections for veterinary medicines. European Medicines Agency. Available from: <https://www.europa.eu/en/news/progress-eu-us-mutual-recognition-agreement-inspections-veterinary-medicines>. [Last accessed on 04 Aug 2023]
- EMA. Template for the qualified person's (QP) declaration concerning good manufacturing practice compliance of active substance manufacture "The QP declaration template"-Scientific guideline. European Medicines Agency. Available from:

- <https://www.europa.eu/en/template-qualified-persons-qd-declaration-concerning-good-manufacturing-practice-compliance-active>. [Last accessed on 04 Aug 2023]
24. ECA. Communication in audit. Available from: <https://methodology.europa.eu/aware/GAP/Pages/Communication-in-audit.aspx>. [Last accessed on 04 Aug 2023]
 25. Audit plan-meaning, process, example, sample template. Available from: <https://www.wallstreetmojo.com/audit-plan>. [Last accessed on 04 Aug 2023]
 26. AS 2101: audit planning. PCAOB. Available from: <https://pcaobus.org/oversight/standards/auditing-standards/details/as-2101-audit-planning-2022>. [Last accessed on 04 Aug 2023]
 27. External accounting audit preparation checklist. Available from: <https://centricconsulting.com/news/audit-preparation-checklist/> [Last accessed on 04 Aug 2023]
 28. Audit plan and process | Audit services. Case Western Reserve University. Available from: <https://case.edu/auditservices/audit-plan-process> [Last accessed on 04 Aug 2023]
 29. A basic guide to good manufacturing practice (GMP) audits. Available from: <https://www.thefdagroup.com/blog/gmp-audits> [Last accessed on 04 Aug 2023]
 30. Internal audit in pharmaceutical industry. Compliancequest. Available from: <https://www.compliancequest.com/audit-management/internal-audit-in-pharmaceutical-industry>.
 31. A brief description of the entire audit process in pharmaceuticals: pharماغuideline; 2023/06. Available from: <https://www/brief-description-of-entire-audit-process.html?m=1>. [Last accessed on 04 Aug 2023]
 32. Annamalai University, Annamalai University. UNIT-1 pharmaceutical quality audit. Available from: https://annamalaiuniversity.ac.in/studport/download/engg/pharm/resources/MPHARM_QA_1Y_2S_203T_AuditandRegul.Compliance.pdf [Last accessed on 04 Aug 2023]
 33. Auditing best practices-office of internal audit-Wayne State University. Wayne. Available from: <https://internalaudit.edu/audit-practices> [Last accessed on 04 Aug 2023]
 34. Process optimization to increase productivity and profits in manufacturing. Available from: <https://blog.safetychainsafetychain.com/process-optimization> [Last accessed on 04 Aug 2023]
 35. GMP compliance audits. Available from: <https://www.pharmout.net/services/gmp-consulting/gmp-compliance-audits>. [Last accessed on 04 Aug 2023]
 36. A basic guide to good manufacturing practice (GMP) audits. Available from: <https://www.thefdagroup.com/blog/gmp-audits>. [Last accessed on 04 Aug 2023]
 37. Good Clinical Practice Inspectors Working Group, European Medicines Agency. Available from: <https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/good-clinical-practice-inspectors-working-group>. [Last accessed on 04 Aug 2023]
 38. Audit Report Contents-what a good report should contain. Available from: <https://www.inspiredpharma.com.2018/09/20/audit-report-contents>. [Last accessed on 04 Aug 2023]
 39. Hallman NJ, Schmidt JJ, Thompson AM. Audit implications of non-GAAP reporting. *J of Accounting Research*. 2022;60(5):1947-89. doi: 10.1111/1475-679X.12433.
 40. Hannon M. The challenges of remote auditing faced by the pharmaceutical industry. *Level*. 2020;3(2):10. doi: 10.21427/yj8x-cm05Availableat.tudublin.ie/level3/vol15/iss2/10.
 41. Internal audit in pharmaceutical industry. Compliancequest. Available from: <https://www.compliancequest.com/audit-management/internal-audit-in-pharmaceutical-industry>.
 42. How to do an external audit for a pharmaceutical company. Available from: <https://smallbusiness.chron.com/external-audit-pharmaceutical-company-81364.HTML> [Last accessed on 04 Aug 2023]
 43. Current good manufacturing practice (CGMP) regulations. FDA. Available from: <https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations>. [Last accessed on 04 Aug 2023]
 44. Preparation for GMP audit in pharmaceuticals: pharماغuideline; 2013. Available from: <https://www.pharماغuideline.com/2013/10/how-to-plan-for-gmp-audit.html> [Last accessed on 04 Aug 2023]
 45. Parkinson's Disease Foundation. Comparison of drug approval process in the United States and Europe. Available from: https://www.researchgate.net/publication/263657519_Comparison_of_Drug_Approval_Process_in_United_States_Europe. [Last accessed on 04 Aug 2023]
 46. Stage 4: Audit follow-up. Available from: <https://blog.bcm-institute.org/audit/stage-4-audit-follow-up> [Last accessed on 04 Aug 2023]
 47. Corrective Action. Plan [report], and Examples | SafetyCulture [Internet] [cited Aug 4 2023]. Available from: <https://safetyculture.com/topics/corrective-action>.
 48. Follow-up-office of internal audit office of internal audit. Available from: <https://www.oia.ufl.edu/home/services-provided/follow-up>. [Last accessed on 04 Aug 2023]
 49. Reporting and follow-up. Audit Services. Available from: <https://audits.umich.edu/the-audit-process/reporting-follow-up>. [Last accessed on 04 Aug 2023]
 50. A brief guide to follow up | ACCA global. Available from: <https://www.accaglobal.com/gb/en/member/sectors/internal-audit/learn/management-actions.html>. [Last accessed on 04 Aug 2023]
 51. Basic Audit Flow Chart Flow Chart Examples. Audit flowchart symbols | Audit flowcharts | Audit Flowchart. Available from: <https://www.conceptdraw.com/examples/audit-flowchart>. [Last accessed on 04 Aug 2023]
 52. Audit Process. Office of Internal Audits. Available from: <https://audit.utexas.edu/audit-process>. [Last accessed on 04 Aug 2023]