

## CURRENT ROLE OF GMP AUDIT FOR MARKETING AUTHORIZATIONS OF API

<sup>1</sup>KOMANDLA ANUGNA, <sup>2</sup>K.KIRAN KUMAR

<sup>1</sup>Assistant Professor , Department Of Drug & Regulatory Affairs, Vijaya College Of Pharmacy Munganoor (V), Via - Sanghinagar Post, Hayathnagar (M), Hyderabad.

<sup>2</sup>Student, Department Of Drug & Regulatory Affairs, Vijaya College Of Pharmacy Munganoor (V), Via - Sanghinagar Post, Hayathnagar (M), Hyderabad.

### ABSTRACT

Any alteration to a pharmaceutical item's characteristics after support ends is considered a post support change. The Cert of Sensibility of the European Pharmacopoeia (CEP) and the Calm Pro Record (DMF) are two ways to choose an energetic pharmaceutical product, or API. There is a separate set of official specifications for every part. The idea revolved around the requisites for post-approval API source changes in the EU and the US, as well as the means by which to implement these changes. Since CEP guarantees conformity to standards and conformance to excellent manufacturing sharpens, the leading pharmaceutical companies prioritize using APIs from CEP certified sources instead of DMF. While the change from CEP to DMF is seen as a significant adjustment in both countries because of the necessity to affirm standard compliance, the transfer from DMF to CEP is seen as a minor alteration because of the extended affirmation of quality and standard. This line of thinking observed the resulting differences.

**Keywords:** *Active Pharmaceutical Ingredient (API), Good Manufacturing Practices (GMP), Certificate of Suitability (CEP), Drug Master File (DMF), Post-Approval Changes, Regulatory Framework, Pharmaceutical Compliance, EU Guidelines, FDA, Quality Assurance.*

### I.INTRODUCTION

#### 1. API Registration and Its Global Importance

Active Pharmaceutical Ingredients (APIs) serve as the fundamental building

blocks of all pharmaceutical products, defining their therapeutic activity and effectiveness. API registration is a critical regulatory requirement ensuring that only high-quality, safe, and

efficacious substances are used in drug manufacturing. This process involves a comprehensive review of the API's production process, characterization, impurity profile, analytical methods, and stability data. Regulatory agencies worldwide, such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Central Drugs Standard Control Organization (CDSCO) in India, require detailed documentation known as the Drug Master File (DMF) or Certificate of Suitability (CEP). These documents provide transparency and traceability throughout the drug manufacturing chain. API registration ensures consistency in product quality across global markets and facilitates international trade by harmonizing safety and efficacy standards. Furthermore, it supports pharmacovigilance by maintaining accurate records of the origin and production methods of all active ingredients. With globalization of the pharmaceutical supply chain, ensuring compliance with international API registration guidelines has become more essential than ever. It enables manufacturers to gain market access, strengthens quality assurance systems, and protects public health from substandard or counterfeit substances.

## **2. Historical Evolution of Good Manufacturing Practices (GMP)**

The concept of Good Manufacturing Practices (GMP) evolved in response to increasing awareness of product safety, quality, and the ethical responsibility of pharmaceutical manufacturers. Its roots trace back to the early 20th century, when several drug-related tragedies highlighted the need for systematic regulation. One of the most significant milestones was the introduction of the 1906 Pure Food and Drug Act in the United States, followed by the 1938 Federal Food, Drug, and Cosmetic Act, which mandated safety verification before marketing. Over the decades, as pharmaceutical science advanced, GMP regulations became more comprehensive, focusing not only on the end product but also on manufacturing environments, personnel training, equipment calibration, and documentation control. The World Health Organization (WHO) published its first version of GMP guidelines in 1968, which laid the foundation for international harmonization. These regulations ensure that every stage of pharmaceutical production meets stringent quality standards to protect patient safety. Today, GMP compliance has evolved into a global benchmark,

influencing regional frameworks such as the EU GMP guidelines and the FDA's Current Good Manufacturing Practice (CGMP) standards. The historical evolution of GMP underscores the shift from reactive to preventive approaches in pharmaceutical regulation, aiming to build quality directly into the manufacturing process.

### **3. International Framework for GMP Implementation**

The international framework for Good Manufacturing Practices (GMP) establishes standardized requirements to ensure the quality, safety, and efficacy of pharmaceutical products across global markets. Various international organizations, including the World Health Organization (WHO), International Council for Harmonisation (ICH), and Pharmaceutical Inspection Co-operation Scheme (PIC/S), play a pivotal role in harmonizing GMP guidelines. WHO's GMP framework serves as the foundation for many national systems, particularly in developing countries. The ICH guidelines, such as Q7 for API manufacturing, emphasize risk-based approaches and continuous quality improvement. In the European Union, GMP compliance is verified through the

issuance of Certificates of GMP Compliance, while in the United States, the FDA enforces CGMP regulations through regular inspections. Countries like Japan, Canada, and Australia align their GMP systems with these international standards, promoting mutual recognition and reducing duplication of inspections. Additionally, the Pharmaceutical Inspection Co-operation Scheme (PIC/S) fosters cooperation among regulatory authorities to ensure consistent implementation and inspection practices worldwide. This global collaboration enhances regulatory efficiency and facilitates the free movement of pharmaceuticals without compromising quality. The international GMP framework ensures that every batch of medicine, regardless of where it is produced, adheres to uniform standards of safety, purity, and performance, thereby reinforcing global public health protection and building trust in the pharmaceutical industry.

### **4. Role of GMP in API Registration and Pharmaceutical Quality Assurance**

Good Manufacturing Practices (GMP) play a fundamental role in ensuring the integrity and reliability of Active Pharmaceutical Ingredient (API)

registration. GMP compliance confirms that APIs are consistently produced and controlled according to quality standards appropriate for their intended use. During API registration, manufacturers must demonstrate adherence to GMP through audits, quality control testing, and detailed documentation of manufacturing processes. This ensures that APIs are free from contamination, meet specified purity levels, and maintain consistent potency. The GMP framework requires meticulous oversight of critical parameters such as raw material sourcing, equipment maintenance, personnel hygiene, environmental control, and validation of manufacturing procedures. Adherence to GMP also supports regulatory transparency, as every batch produced must be traceable through batch records and analytical test results. When APIs comply with GMP, they provide a strong foundation for the safety and efficacy of the final pharmaceutical product. Global regulatory authorities, including the US FDA, EMA, and WHO, evaluate GMP compliance as a prerequisite for granting API registration approvals or DMF (Drug Master File) acceptance. Non-compliance can lead to serious consequences such as suspension of licenses, import bans, or withdrawal of approvals. Thus, GMP acts as a quality

backbone, safeguarding patient health and reinforcing trust in pharmaceutical production. Its integration into API registration ensures that only high-quality substances enter the global drug supply chain, promoting both regulatory efficiency and public confidence in medicinal products.

## **5. Comparative Overview of Regulatory Frameworks: EU vs. US**

The regulatory frameworks governing pharmaceutical manufacturing in the European Union (EU) and the United States (US) share a common objective — ensuring the production of safe, effective, and high-quality medicines — but differ in their approaches and implementation. In the European Union, GMP compliance is guided by EudraLex Volume 4, which provides detailed guidelines for both medicinal products and APIs. The European Medicines Agency (EMA) oversees coordination, while national competent authorities conduct inspections and issue GMP certificates. Manufacturers outside the EU must also comply with equivalent GMP standards to export products into the European market. In contrast, the United States follows the Current Good Manufacturing Practice (CGMP) regulations enforced by the Food and Drug Administration

(FDA) under Title 21 of the Code of Federal Regulations (CFR) Parts 210 and 211. The US approach is more performance-based, allowing manufacturers flexibility in demonstrating compliance, while the EU framework is more prescriptive and documentation-focused. Despite these differences, both systems emphasize risk management, data integrity, and continuous quality improvement. The two frameworks are increasingly converging through international harmonization efforts, such as ICH and PIC/S, which promote mutual recognition of inspections and regulatory decisions. Understanding these distinctions is crucial for multinational pharmaceutical companies to streamline global regulatory submissions, minimize compliance risks, and ensure efficient product registration in both jurisdictions.

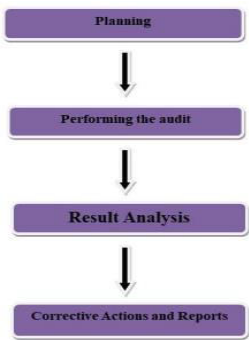


Fig1: Flow Chart For Audit

II.LITERATURE SURVEY

**Md Rehan Alam et al.,(2023)**  
Good Manufacturing Practices (GMP) is a collection of standards, norms and recommendations for the production of drug substances and drug products, as well as medical devices. It aims to maintain the standards laid by the regulatory agencies throughout the world such as U. S. Food & Drug Administration, Therapeutic Goods Administration, European Medicines Agency, Medicines and Health products Regulatory Agency, International Council for Harmonisation to provide quality products to the general population of the world at continuous and reproducible pace. Drug product manufacturing is a complex process involving raw materials (Active Pharmaceutical Ingredient, excipient, solvents), packaging materials, manufacturing equipment, laboratory glassware, manpower and transportation that are prone to potential risks. The quality risk could be attributed to any of the steps of product manufacturing and could impose serious threat to quality of the drug product. To overcome these risks, audits are conducted (internal and external). Audits are time consuming and are thought to be troublesome by the smallscale industry due to lack of experience, manpower and economical constraints which results in regulatory

non-compliance. This review discusses the practices to make audit easy, convenient and reliable to industrialists. The decision tree approach could be easily understood and followed to maintain the state of readiness for a quality audit.<sup>22</sup>

**Sharma, Akash et al.,(2023)** In the healthcare industry, maintaining high-quality standards is crucial to ensure the safety and efficacy of medical products. Good Manufacturing Practices (GMP) provide a set of guidelines and regulations that help ensure the consistent production, control, and quality assurance of pharmaceuticals, medical devices, and other healthcare products. This paper explores the significance of GMP in the healthcare industry, highlighting its background, objectives, role in safeguarding patient health and maintaining public trust. It examines the key principles of GMP, its regulatory framework, and its impact on various aspects of the healthcare sector, including drug manufacturing, quality control, product safety, and regulatory compliance. Furthermore, the paper discusses the challenges and future perspectives of GMP implementation, emphasizing the need for ongoing advancements to meet the evolving demands of the industry. To summarize, adherence to GMP standards is crucial

for the healthcare industry to produce high-quality, safe, and effective healthcare products. GMP compliance promotes patient safety, regulatory compliance, and innovation in the pharmaceutical industry.<sup>23</sup>

**Jayant Kumar et al.,(2023)**

Medications that are no longer covered by a patent and that are made by companies other than the original inventor are known as generics. In recent years, the use of generic medications has grown, principally as a cost-cutting tool in the delivery of healthcare. The typical price difference between generic and brand-name medications is 20 to 90%. The principal objective of laws governing pharmaceuticals in the US, Europe, and Japan is to protect public health. Good Manufacturing Practice (GMP) requirements in the United States, European Union, and Japan are designed to ensure that products are consistently produced and controlled according to quality standards. In the US, GMP regulations are enforced by the Food and Drug Administration (FDA). The EU has GMP guidelines that are enforced by national authorities, and Japan has its own GMP regulations that are enforced by the Ministry of Health, Labor, and Welfare. These regulations cover a wide range of areas including facilities, equipment, production processes and

record keeping, which are put in place to ensure product quality and safety. Adhering to GMP requirements is essential for ensuring that products are manufactured to the highest standards and meet the expectations of consumers and regulatory authorities. Overall, the GMP requirements in these regions play a vital role in maintaining the safety and quality of products and are crucial for the pharmaceutical and food industries.<sup>24</sup>

**Muthukumar Subramanian et al.,(2022)** These days, finding new marketing authorizations, guaranteeing regulatory compliance, and keeping labour costs competitive are extremely tough. Many pharmaceutical companies also struggle to deal with local regulatory issues and stay up with changes in key pharmaceutical markets. Regulations are thoroughly reviewed before being given to the RA department. This team compiles the most critical prescription information for global approval and marketing. This category accepts both new and revised product submissions. This is mostly handled by the RA department. RA's job is to provide feedback on proposed or disputed legislation. This is a proactive measure. The ICH framework allows for more early intervention. Regulators have a wide range of responsibilities. In the US, the FDA must register and clear the

goods with the export company's regulatory professional.<sup>25</sup>

**Sia Chong Hock et al.,(2020)**

Biopharmaceuticals belong to a class of medicinal products whose active pharmaceutical ingredient (API) is manufactured using living systems such as microbial and mammalian cells. With the patent expiry of the originator biopharmaceuticals, a surge in the production of biopharmaceuticals in the form of biosimilars is to be expected. However, biopharmaceuticals are inherently more complex than conventional chemical-based pharmaceuticals, hence requiring a more complicated manufacturing process. This paper provides a brief overview of the biopharmaceutical manufacturing processes and reveals that most biopharmaceuticals share similar processes and considerations. The complex nature of biopharmaceuticals presents various manufacturing challenges such as the inherent variation in quality and demand for extensive process and product understanding. Furthermore, downstream processing bottleneck also presents another manufacturing challenge. A brief comparison of the good manufacturing practice (GMP) standards of various regulatory authorities (RAs) and



international organizations (IOs) reveals that the standards are largely similar and appropriate in addressing the manufacturing challenges. This review is one of the few covering the biopharmaceutical industry and the regulatory framework of the Association of South East Asian Nations (ASEAN). However, GMP alone does not address regulatory challenges such as evaluation of biosimilarity, differing outlook on interchangeability and a growing occurrence of data integrity lapses. Solutions such as the implementation of Industry 4.0, improved harmonization of regulatory efforts and creating a culture of quality within the organization may help to address the forgoing challenges. Keywords: ASEAN, biopharmaceuticals, biopharmaceutical manufacturing, good manufacturing practice, harmonization, regulatory guidelines.

### III.METHODOLOGY

The methodology adopted for this project on API registration and GMP audit framework analysis follows a systematic, multi-phase approach combining regulatory document review, comparative analysis, and qualitative evaluation. The study begins with a comprehensive review of global regulatory guidelines from key

authorities such as the World Health Organization (WHO), European Medicines Agency (EMA), United States Food and Drug Administration (USFDA), and the Pharmaceutical Inspection Co-operation Scheme (PIC/S). These documents were examined to understand the principles governing Good Manufacturing Practices (GMP) and their integration within Active Pharmaceutical Ingredient (API) registration procedures. In the next phase, a comparative analytical framework was developed to evaluate the regulatory processes between major regions—specifically the European Union (EU) and the United States (US). The comparison focused on the structure, documentation requirements, inspection procedures, and compliance criteria related to DMF (Drug Master File) and CEP (Certificate of Suitability) submissions. To ensure consistency, data was gathered from official regulatory portals, pharmacopeial monographs, and published scientific literature. Further, the methodology incorporates case-based analysis by reviewing real-world examples of GMP audit findings, post-approval variations, and corrective actions recommended by regulatory agencies. This helped in understanding the practical implications of GMP compliance and identifying patterns of



non-compliance that lead to regulatory actions such as warning letters or suspension of manufacturing licenses. The collected data was synthesized through qualitative analysis, emphasizing harmonization challenges, risk-based inspection models, and international collaboration among regulatory bodies. The outcome of this methodology provides a holistic understanding of how GMP principles ensure consistent quality and safety in API manufacturing and how robust regulatory frameworks facilitate market authorization across global jurisdictions.

The methodology of this project on *Good Manufacturing Practice (GMP) Audit and Compliance in Pharmaceutical Manufacturing* is designed to ensure a systematic understanding and evaluation of how GMP principles are implemented, monitored, and regulated in the pharmaceutical sector. It follows a structured approach that includes data collection, audit classification, analysis, and evaluation of compliance effectiveness.

**1. Research Design:** The study adopts a descriptive and analytical research design, focusing on analyzing GMP compliance and audit procedures as per the regulatory frameworks of global

health authorities such as the USFDA, WHO, MHRA (UK), and TGA (Australia). The design emphasizes identifying critical areas of compliance—quality assurance, personnel, premises, equipment, documentation, and manufacturing practices—through both primary and secondary data.

**2. Data Collection :** The methodology involves the collection of data from multiple sources including:

1. **Primary Data:** Observations from GMP audit processes, audit checklists, and interviews with quality managers and auditors in pharmaceutical companies.

2. **Secondary Data:** Reviewing regulatory guidelines, inspection reports, published WHO and FDA audit data, and GMP compliance case studies. The collected data provides insights into how various pharmaceutical manufacturers implement and maintain GMP standards and respond to inspection findings.

**3. Audit Framework :** The auditing process is categorized into internal, external, regulatory, product, and clinical audits. Each audit type serves a specific purpose:

1. Internal Audit evaluates the efficiency of internal control systems and adherence to SOPs.
2. External Audit (or second-party audit) involves evaluating suppliers and contract manufacturers for compliance.
3. Regulatory Audit is conducted by international bodies to verify adherence to global standards.
4. Product and Clinical Audits assess market performance and safety compliance.

Each audit follows a structured life cycle including planning, execution, reporting, corrective action, and verification.

**4. GMP Assessment Parameters:** The study identifies core GMP principles such as quality management, hygiene, equipment validation, documentation control, and personnel training. For each principle, compliance parameters are developed and compared against regulatory benchmarks. Data from real-world inspection cases (e.g., FDA warning letters) are analyzed to identify common non-compliance areas such as documentation errors, poor sanitation, or inadequate process validation.

**5. Data Analysis and Validation:** The audit findings are analyzed using a qualitative risk-based assessment approach. Non-conformities are

categorized by severity (critical, major, minor), and root cause analyses are performed using Fishbone Diagrams (Ishikawa Analysis). Validation is achieved through cross-verification of audit reports, CAPA (Corrective and Preventive Action) implementation, and trend analysis over repeated audit cycles.

## **6. Training and Compliance**

**Evaluation:** An essential component of the methodology is the assessment of personnel training effectiveness. Employees' awareness of SOPs, documentation accuracy, and adherence to cleanliness standards are evaluated through pre- and post-training performance analysis.

**7. Outcome Measurement :** The methodology concludes with an evaluation of GMP audit impact on product quality, regulatory compliance, and company reputation. Key performance indicators (KPIs) such as audit success rate, number of recalls, and reduction in deviations are used to measure improvements post-audit.

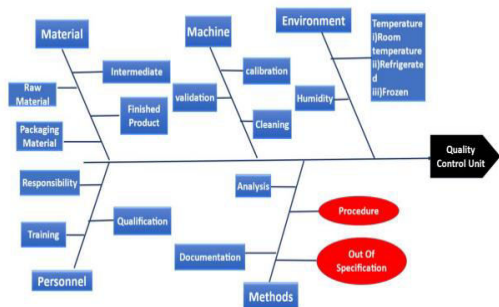


Fig2: Fish Bone Daigram

#### IV.CONCLUSION

In pharmaceutical industries the API is having a key role for preparation of drug substances. It helps to maintain quality by innovation of new drugs into the market which finally ensures the safety and efficacy to protect public health. The Manufacturing Authorization holder is responsible for taking appropriate action to ensure API sources are GMP compliant. Adverse findings from inspections may result in various action steps taken by EMEA. In general since the introduction of the new legislation dose form manufacturers are taking steps to assure GMP compliance of the API supply chain.

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