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Assessment and Trend Analysis of Good Manufacturing Practices Inspection Findings of the Ethiopian Food and Drug Authority

By

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A thesis submitted to the Department of Pharmaceutics and Industrial Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, in partial fulfillment of the requirements for the degree of masters of science in Regulatory affairs (medicine track).

January, 2026

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DECLARATION

I, Tibebu Abera, declare that this thesis, entitled "Assessment and Trend Analysis of Good Manufacturing Practices Inspection Findings of the Ethiopian Food and Drug Authority", is my original work and has not been presented for a degree in any other university or institution. All sources of materials used for this thesis have been duly acknowledged.

Acknowledgments

I extend my profound gratitude to my advisors, Professor Anteneh Belete and Mr. Getachew Genetie, for their invaluable guidance, insightful feedback, and support throughout the conceptualization, execution, and finalization of this research. Their expertise and mentorship were instrumental in shaping this study.

My sincere appreciation goes to Mr. Samuel Marie and Ms. Aynye for their assistance during the data collection process, particularly for facilitating access to the necessary documents (reports). I am also grateful to all other individuals who contributed to the collection of data for this research.

I wish to acknowledge the generous material and moral support provided by my family and friends, which significantly eased the demands of this academic endeavor.

Finally, I express my deep gratitude to the School of Pharmacy, Addis Ababa University, and the Ethiopian Food and Drug Authority for their financial sponsorship, which made this study possible.

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List of Acronyms and Abbreviations

API ---- Active Pharmaceutical Ingredient

CFR ---- US code of federal regulation

CGMP ---- Current Good Manufacturing Practice

CROs---- Contract Research Organizations

CPP ---- Certificate of Pharmaceutical Product

EDQM ---- European Directorate for Quality of Medicines

EFDA ---- Ethiopian Food and Medicine Authority

EFPIA --- European Federation of Pharmaceutical Industries and Associations

EMA ---- European Medicine Agency

EU ---- European Union

FPP ---- Finished Pharmaceutical Product

GDP ---- Gross Domestic Product

GMP ---- Good Manufacturing Practice

ICMRA ---- International Coalition of Medicines Regulatory Authorities

IFPMA ---- International Federation of Pharmaceutical Manufacturers and Associations

NMRAs ---- National Medicines Regulatory Authorities

PIC/S ---- Pharmaceutical Inspection Co-operation Scheme

QCLs ---- Quality Control Laboratories

SF ---- Substandard, Falsified

TRS ---- Technical Report Series

USFDA ---- United States Food and Drug Administration

WHO ---- World Health Organization

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Abstract

Introduction: The spread of poor-quality medicines, especially in developing countries, has been a global public health concern. Among the reported Substandard and Falsified medicines to the WHO Global alert system, 50% are from Sub-Saharan Africa, and 80% of these are for essential medicines. Adherence to GMP is a key requirement for ensuring that pharmaceutical products are manufactured and controlled to meet the quality standards set out by the regulatory authorities. This study assessed the GMP inspection reports of the Ethiopian Food and Drug Authority (EFDA) for both local and foreign medicine manufacturing facilities, conducted between 2015 and 2024, and the first 3 months of 2025, and compared the findings with reports from other regulatory authorities.

Objective: The aim of this thesis was to evaluate the GMP inspection findings of the EFDA over ten years period (2015 to 2024 and the first 3 months of 2025).

Method: A retrospective quantitative study design was used to evaluate the GMP inspection findings of the authority. GMP inspection reports from 2015 to 2024 and the first 3 months of 2025 were reviewed. Data was collected from December 2024 to January 2025 and March 2025 at the EFDA head office, Addis Ababa, Ethiopia. A total of 518 reports were reviewed.

Results: During 2016 – 2018, local inspections, 380 deficiencies were identified from the review of 7 GMP reports. The most common deficiencies were related to quality management, materials, production, quality control, materials management and water for pharmaceuticals. Only one facility was found acceptable. During 2019 to the first 3 months of 2025, local inspection, 33 reports were reviewed from the available 12 local facilities. Half (6) of the facilities were GMP compliant. A total of 288 deficiencies were recorded during this period, of which 17.7% were critical findings. The most common deficiencies were related to quality management, validation and qualification, premises, good practice in QC and HVAC. An additional 478 international inspections were conducted between 2015 & 2024 across 31 countries. The most common deficiencies were related to good practice in QC, material management, HVAC, production, and premises.

Conclusion: The finding of this study indicates that a significant number of both local and foreign pharmaceutical manufacturing facilities are not operating in adherence to GMP standards. Therefore, robust regulatory oversight and continuous improvement from facilities are required to ensure the safety and quality of medicines. Regular assessment, trending, and public disclosure of common deficiencies will contribute to the improvement of GMP compliance of facilities and ensuring the availability of safe and quality pharmaceutical products in the market.

Keywords: Quality, good manufacturing practice, Ethiopia, inspection, compliance, deficiencies**.**

1. Introduction

Background Information

Medicines are vital for protecting, maintaining, and restoring health. However, ensuring the quality, safety, and efficacy of medicines remains a significant public health challenge and a persistent concern of countries (Amor Rayco Cáceres-Pérez, 2025). National Medicines Regulatory Authorities (NMRAs) are indispensible elements of the health system that ensures quality, safety, and efficacy of medical products in the market and thereby protecting patients and the public at large (WHO, 2016). NMRAs worldwide use systems for the marketing authorization. These include assessment of submitted dossiers and variations files, and inspection of Finished Pharmaceutical Product (FPP) and Active Pharmaceutical Ingredient (API) manufacturers, Quality Control Laboratories (QCLs), and Contract Research Organizations (CROs) involved in the development, manufacture, and distribution of a medical product. Inspections are performed to verify dossier data and to provide evidence that the FPP and API manufacturers, QCLs, CROs, and clinical trial sites comply with the relevant good practice (GxP) guidelines and requirements (WHO, 2018).

According to the World Health Organization (WHO), Good Manufacturing Practice (GMP) is that part of quality management which ensures that medicines are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial authorization, or product specification (WHO, 2016). GMPs are important for managing and minimizing the risks inherent in the manufacturing of medicines to ensure quality, safety, and efficacy. GMP applies to the life-cycle of a medicine from the manufacture of investigational medicinal products, technology transfer, and commercial manufacturing, through to product discontinuation (EFDA, 2024).

GMP defines quality measures that extend across the entire pharmaceutical supply chain. While it provides core rules for production and quality control activities, GMP also defines general measures to ensure that all processes necessary for manufacturing and testing are clearly defined, validated, reviewed, and documented. Furthermore, GMP ensures that the personnel, premises, and materials are suitable for their intended roles. GMP also includes legal and quality components covering the entire product lifecycle, encompassing responsibilities for distribution, contract manufacturing and testing, warehousing, pharmacovigilance, and robust systems for addressing product defects, recalls, and customer complaints (Health Canada, 2020; WHO, 2019).

GMP standards and associated inspections are important components of strong regulatory systems. They are essential to ensure medicines are manufactured to high-quality standards. GMP inspections are conducted to evaluate commercial manufacturing capability, adequacy of manufacturing and control procedures, the suitability of equipment and facilities, and effectiveness of the quality management system in assuring the overall state of GMP compliance.

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) defines GMP inspections as an on-site evaluation of a manufacturing facility to determine whether such a manufacturing facility is operating in compliance with Good Manufacturing Practices and commitments made as part of the approval to market a product (IFPMA, 2017).

The integration of GMP inspection with other regulatory activities is of significant importance in safeguarding public health. Less stringent GMP standards can lead to the manufacture of substandard and falsified medicines, which may result in adverse outcomes for the patients. Recent global incidents indicate this issue. For example, the tragic deaths of several children in the Gambia in 2022, due to contaminated cough syrups with diethylene glycol (DEG) and ethylene glycol (EG), underscored the important role of vigilant regulatory oversight and the devastating impact of compromised manufacturing quality (WHO, 2022; Kaur, 2023). These incidents show inadequate GMP enforcement can directly translate into acute toxicity, organ failure, and fatalities, particularly in vulnerable populations.

Nitrosamines are organic compounds classified as impurities in the pharmaceutical industry. Many nitrosamines are potent mutagens and probable human carcinogens, capable of increasing the risk of cancer if exposure exceeds acceptable levels over an extended period (WHO, 2025). Contamination issues, often linked to the quality of raw materials, manufacturing processes, or storage conditions, require proactive and integrated regulatory efforts to prevent their formation and ensure patient safety (Vikram, 2024). These examples illustrate that GMP is not merely a procedural checklist but a foundational pillar of public health protection, demanding continuous study and adaptation within the regulatory framework to prevent future tragedies and maintain public health trust in medicinal products.

The purpose of GMP inspections is to ensure that pharmaceutical manufacturing operations are conducted according to approved standards, norms, and guidelines, and in compliance with the national medical products legislation and regulations. A key objective of a GMP inspection program is to provide the NMRAs with a proactive mechanism for identifying and preventing quality-related medicine efficacy and safety risks. Inspections reveal weaknesses and deficiencies, as well as actual or potential errors. Therefore, inspection activities are fundamental for guaranteeing the quality, safety, and efficacy of medical products used by the population (EMA, 2014).

The Ethiopian Food and Drug Authority (EFDA) is mandated to conduct GMP inspection as part of registration (pre-approval inspection) or for registered products (post-approval inspection) for medicinal products as laid down in Proclamation 1112/2019, article four, sub-article five. The authority has published a directive ' Medicine Good Manufacturing Practice Inspection Procedure – directive 1055/2025'which applies to all local and foreign Finished Pharmaceutical Manufacturing plants (EFDA, 2025). The authority also has a GMP guideline, which sets a minimum requirement for both local and foreign pharmaceutical companies for GMP

compliance. The guideline is also used as a reference and guidance tool to the Authority for GMP inspection (EFDA, 2024).

Evaluation of GMP inspection is crucial within the pharmaceutical regulatory landscape. It assists regulatory authorities in designing and implementing risk-based inspection programs, thereby optimizing resource allocation and focusing efforts where they are most needed to ensure patient safety and product quality (PMDA, 2023; EMA, 2024). Furthermore, the sharing of these findings facilitates transparency across the pharmaceutical sector, fostering public trust by demonstrating a commitment to robust oversight (ICMRA, 2023; PIC/S, 2023).

In addition, publicized inspection findings are an important resource to pharmaceutical quality compliance professionals and manufacturers. It indicates areas of non-compliance, enabling manufacturers to take a proactive approach to strengthen their quality management systems, streamline operational procedures, and develop strategic solutions for the major regulatory compliance issues (ISPE, 2024). This proactive approach minimizes the risk of product recalls, supply chain disruptions, and potential harm to public health (FDA, 2024).

Statement of the Problem

The absence of systematic analysis of GMP inspection findings by a regulatory authority presents significant challenges (EFPIA, 2022; Lebanova H, 2024). This lack of comprehensive and structured analysis of findings has negative consequences, endangering public health and affecting the growth of the pharmaceutical sector.

The absence of a sharing mechanism for GMP inspection findings deprives manufacturing facilities from getting crucial feedback and insights into common GMP non-compliance factors. (Altabrisa Group, 2024; ISPE, 2024). This results in a decrease in the overall GMP compliance level of the industry, or it may improve at a slower pace, potentially leading to more deviations and quality issues.

The absence of a public database for disclosure of inspection findings decreases public confidence and trust in the regulatory service (ICMRA, 2023; PIC/S, 2023). When regulatory findings are not transparently communicated or acted upon, public trust may decline, potentially weakening health system credibility and raising concerns about the integrity of medicine quality controls.

EFDA does not conduct a routine analysis of GMP inspection findings. As a result, EFDA is not running an effective risk-based inspection program, resulting in less effective use of limited regulatory personnel and budget (PIC/S, 2012; Qualityze EQMS, 2025). This is one of the challenges faced by most African countries, whose regulatory systems often operate under resource and technical constraints (Ndomondo-Sigonda, 2017; AUDA-NEPAD, 2022). Analysis of GMP inspection findings helps to design and implement risk-based inspection programs. Sharing the results of the analysis also helps to harmonize regulatory requirements for product registration and inspections (ICMRA, 2023; PIC/S, 2023).

Significance of the Study

GMP inspection finding evaluation and trending involve regular review of the data from inspection reports, warning letters, Form 483s, etc., for patterns, recurring findings, and overall trends in compliance from pharmaceutical facilities undergoing inspections. This will put NMRAs in a position to carry out effective oversight of the industry (Raphael Zozimus Sangeda, 2024). Such information being shared will eventually provide the pharmaceutical manufacturers with the necessary knowledge to ensure proper compliance with changing regulatory expectations (ISPE, 2024; Qualityze EQMS, 2025).

The EFDA started GMP inspections in 2004, inspecting numerous companies annually. However, the inspection findings have not been regularly reviewed for trends, and a centralized, publicly available database for inspected facilities is currently absent. Conducting such analysis is important considering regulation is becoming more complex and innovative as advanced

pharmaceutical products are entering the market (IFPMA, 2020; WHO, 2024). This study was designed to directly assist EFDA in designing and implementing such a risk-based inspection strategy and in establishing a crucial database for inspected facilities.

Recognition and reliance arrangement is a 21st-century best regulatory practice, necessitating increased cooperation among trusted regulators globally (IFPMA, 2020). Although EFDA's GMP inspection directive mandates document review for SRA-approved facilities and WHO prequalified products, formal mutual recognition or reliance arrangements with East African regulatory authorities are still lacking. This study provides the evidence base required to foster greater collaboration with both regional and international partners through structured information sharing (AUDA-NEPAD, 2022).

Regulatory transparency is critical for effective oversight of GMP. Disclosure of inspection outcomes and enforcement actions shows the public that decisions on product quality and safety are made, which builds public trust (Picorelli, 2020). Publicly available compliance data allows stakeholders (importers, distributors, etc.) to make informed decisions about which manufacturer to trust. Disclosure of common deficiencies (anonymously) provides a learning resource for the industry. Increasing transparency and sharing of inspection reports, via mutual agreements, facilitates regulatory harmonization (FDA, 2024).

This thesis has evaluated the GMP inspection findings of EFDA over ten year’s period (from 2015 to 2024 and the first 3 months of 2025) and compared these to those of other regulatory authorities. Conducting this kind of evaluation helps to identify patterns and trends, focus inspections at high-risk manufacturers, detect divergent issues with international regulations, seek regulatory convergence and international harmonization of GMP guidelines and inspection procedures. Besides, disclosure of deficiencies found contributes to regulatory transparency and improves GMP compliance of manufacturers. This improves the availability of quality medicines and contributes to a sustainable public health system.

2. Literature Review

2.1 Introduction to GMP

The right to health, ensuring access to essential medicines, has been one of the cornerstones of international human rights debates and public health policy for a long period of time. (WHO, 2022; OHCHR, 2020). A health system cannot function without access to medicines that are safe, effective, and quality-assured (WHO, 2022; OECD, 2023).

National medicine expenditures often represent a significant proportion of total health expenditure, a common trend in developing countries. In low-income countries, pharmaceutical budgets have consistently constituted a substantial portion of overall health spending, underscoring the critical financial commitment to this sector (WHO, 2023; World Bank, 2024). For Ethiopia, recent data indicate that current health expenditure as a percentage of GDP was 3.21% in 2021 (WHO, 2024; TheGlobalEconomy.com, 2021). While a precise, comprehensive breakdown of pharmaceutical spending as a proportion of total health expenditure for the most recent years can be complex to isolate in publicly available consolidated national health accounts, one report from 2023 indicates that pharmaceutical spending accounted for 39% of the total health expenditure (BMI, 2023). This highlights a notable allocation to pharmaceuticals, reflecting their perceived value in the national health system.

Individuals and governments willingly invest in medicines due to their profound capacity to save lives, restore health, prevent diseases, and mitigate epidemics. However, the transformative potential of medicines to bring about positive outcomes for patients and public health is critically contingent upon their being produced, distributed, and dispensed in a manner that unequivocally assures their quality, safety, and efficacy. This assurance is fundamentally achieved through robust and vigilant regulatory oversight throughout the entire pharmaceutical supply chain (WHO, 2023). Without proper regulation, medicines can be substandard, falsified or unapproved, which may lead to serious health problems such as treatment failure, adverse events, increased morbidity, and even death. These ineffective medicines result in wasted financial resource for patients and healthcare system (UNODC, 2020).

Pharmaceutical (medicine) regulation is the comprehensive system of laws, guidelines, standards, and administrative oversight established by governments to oversee the lifecycle of medicines. The purpose of regulation is to protect public health by ensuring all pharmaceutical products available in the market are consistently safe, effective, and of high quality (WHO, 2021). A robust medicines regulatory system is thus an indispensable component of any effective health system, serving to safeguard populations by ensuring that all medicines and other medical products meet stringent standards for safety, effectiveness, and quality throughout their lifecycle (USP, 2020). This assurance is primarily achieved through a comprehensive regulatory framework that subjects all pharmaceutical products to rigorous pre-marketing evaluation for

marketing authorization, continuous post-marketing surveillance, and diligent pharmacovigilance (EMA, 2024; FDA, 2024).

According to the WHO, GMP is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. GMP is aimed primarily at diminishing the risks inherent in any pharmaceutical production. These risks are cross-contamination (in particular of unexpected contaminants) and mix-ups (confusion) caused by, for example, putting false labels on containers (WHO, 2014).

GMP refers to an international set of regulations or guidelines devised for implementation in the pharmaceutical industries to assure the quality, effectiveness, and safety of pharmaceutical products. It is a matter of building in quality rather than testing quality. It is a system devised to ensure that products are consistently produced and controlled according to quality standards. It minimizes the risks involved in any pharmaceutical production that cannot be eliminated by testing the final product. GMP is a formal system of control in the pharmaceutical industry; adequately put into practice helps to prevent instances of contamination, mix-ups, deviations, failures, and errors. These assure that drug products meet their quality standards (PIC/S, 2023).

The subsequent paragraphs describe events and milestones in the development of GMP. The introduction of GMP and the subsequent development of robust regulatory systems worldwide were significantly driven by a series of catastrophic incidents. These collectively laid the foundation for the establishment of comprehensive regulatory laws and regulations, leading to the development and implementation of GMP requirements and guidelines worldwide.

The sulfanilamide elixir tragedy of 1937 in the United States, where over 100 people died after taking a diethylene glycol containing medicine, highlighted the dire need for drug safety regulations and pre-market approval (FDA, 1938). That event led to the passage of the 1938 Federal Food, Drug and Cosmetic Act in the United States.

In 1941, the Sulfathiazole contamination with Phenobarbital tragically affected about 300 people, because in 10 deaths and 250 illnesses due to the inadvertent mixing of sulfathiazole antibacterial tablets with Phenobarbital (Swann, 2005). This mix-up underlined the critical need for robust in-process controls, segregation of materials, and scrupulous quality checks against the potential for cross-contamination and the assurance of the correct API in every product. The incident pushed the FDA to re-evaluate and sharpen manufacturing and quality control requirements.

The Thalidomide tragedy during the late 1950s and early 1960s caused severe birth defects in thousands of children worldwide. The incident had a profound impact on drug regulation globally showcasing the need for rigorous drug efficacy and safety testing before market approval (Stephens, 2001; Kim, 2011). Another significant event was the Cutter Incident in

1955, where a polio vaccine produced by Cutter Laboratories inadvertently contained live poliovirus, leading to cases of paralysis and death. This incident emphasized the role of strict quality control and manufacturing standards for biological products and vaccines (Offit, 2005).

In 1962, the US Congress passed the Kefauver-Harris Drug Amendment. This amendment not only increased safety requirements, but it also required proof of a medication's effectiveness for the first time – retroactively for all prescribed products approved since 1938. These laid down the foundation for the statutory regulation of clinical studies along the lines of regulatory approval procedures and quality assurance measures involved in the development of drug products. Based on events and pressure from the FDA and the request from the 20th WHO assembly, the WHO formulated the first guidelines for the production of pharmaceutical products in 1967 (the first GMP guidelines) to ensure the traceability of the production process. The guideline was revised by the WHO expert committee on a specification for pharmaceutical preparations in 1968 (WHO, 2014; FDA, 2018).

In 1970, the Establishment of the Pharmaceutical Inspection Convention (PIC) in Europe subsequently issued guidelines for the appropriate testing of drug products. The WHO GMP text was further revised and reproduced in the Supplement to the International Pharmacopoeia in 1971. In the same year, the first British GMP was published in the United Kingdom, called the Orange Guide. In the US, writing GMP in the form of regulation in the US Code of Federal Regulations (CFR) under 21 CFR 210 and 21 CFR 211 came into effect in 1978.

The generic drug scandal of the late 1980s rocked the pharmaceutical industry. Several generic drug manufacturers were engaged in fraudulent practices, including submission of falsified data to the FDA to obtain approval for marketing (Congressional Record., 1989; Wall Street Journal, 1989). The investigation reports showed instances where companies fabricated bioequivalence (BE) study results, altered drug samples, and bribed FDA officials. The scandal significantly decreased public trust in generic medications and the regulatory approval process. The scandal led more stringent requirements for BE studies, enhanced FDA oversight and enforcement powers regarding data integrity, and a renewed emphasis on ethical conduct and transparency in all aspects of pharmaceutical development and manufacturing, particularly for generic manufacturing facilities.

In 1989, the main GMP document of the European Union (EU), the EU GMP guidelines, was published for the first time, as per Council Directive 89/341/EEC of May 3, 1989. This directive requires all EU Member States to comply uniformly with GMP standards during the industrial production of drug products, and thus serves as the basis for two separate sets of GMP guidelines issued by the Commission. In 1989/90, the generic drug scandal: several manufacturers of generic drugs fraudulently submitted products made by other companies (including some made by the original manufacturers) as their own products (Garth Boehm, 2013). In 1990, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (also known as the International Conference on Harmonization, ICH) was

established. In 1995, the Pharmaceutical Inspection Co-operation Scheme (PIC/S) was established.

In 2002, GMP for the 21st Century: A Risk-Based Approach was put forward for discussion and published in the US. However, published later as a binding requirement (FDA, 2004). In 2007/08, the heparin scandal: the anticoagulant produced in China was connected with 82 confirmed deaths in the US and several serious allergic reactions, including 27 serious reactions following administration via injection in Germany. Experts believed that the reason for the failure to identify the quality flaws was excessive demands placed on the authorities tasked with oversight because of the dramatic increase in the overseas production of starting materials and finished drug products (Mintz, 2103).

In 2017, a new Part IV (GMP requirements for Advanced Therapy Medicinal Products) of the EU GMP guidelines was published, which had to be implemented by May 22, 2018. Annex 13 (Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No. 536/2014) was published. In 2018, Annex 2 (Manufacture of Biologically active substances and Medicinal Products for Human Use) of the EU GMP guidelines was revised.

The recurrent incidents of DEG and EG contamination of oral liquid (syrup) preparations, in Panama (2006), in Nigeria (2008), and recently in several countries from 2022 to 2023, highlight the importance of strict GMP adherence for excipients and finished products. These incidents have driven the refinement and expansion of GMP requirements and regulatory oversight globally, demonstrating a continuous learning process in safeguarding public health (Abubakar, 2009; WHO, 2022).

The elements of GMP are a quality management system, personnel (qualified, trained, and supervised), personnel hygiene and sanitation, premises and equipment (location, design, construction, and maintenance), documentation (complete history of each batch and standard operating procedures for each activity), production (manufacturing operations), quality control (sampling, specifications, testing, release procedures), contract manufacture and analysis (agreed and controlled), complaints and product recall (complaints must be reviewed and documented), and self-inspection and quality audits (conducted to monitor implementation of and compliance with the principles of GMP) and validation (WHO, 2016).

2.2 GMP Inspection Approaches

Proclamation 1112/2019 provides that EFDA may approve a new or generic drug application to only be marketed if the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and testing of the drug were found adequate to ensure and preserve its identity, strength, quality, and purity (EFDA, 2019).

The two types of GMP inspections are pre-approval inspections and post-approval inspections. Pre-approval inspections are concerned with inspections of manufacturing facilities, quality control laboratories, and contract research organizations before granting a marketing authorization (product license or registration) for a pharmaceutical product. Post-approval inspections are conducted to control and enforce compliance with general GMP after approval of a pharmaceutical product (FDA, 2024).

Before any application is approved, it is necessary to determine whether all establishments participating in the manufacture of the finished dosage form comply with GMP and the application commitments. Pre-approval inspections have the following specific objectives: (1) evaluation of the establishment's compliance with GMP requirements, particularly regarding proper environment, quality management, personnel, facilities and equipment; (2) evaluation of the procedures and controls implemented in the manufacture of the product (pre-approval batches), to determine whether they conform with the application commitments; (3) audit of the completeness and accuracy of the manufacturing and testing information submitted with the application, and of the conformity of pre-approval batches with planned commercial batches (process validation protocol); and (4) the collection of samples for the validation or verification of the analytical methods included in the application (WHO, 2002).

The purpose of conducting of post-approval inspection is to provide continuing coverage of approved products regardless of whether or not these products were covered under the pre-approval inspection program. It is designed to audit for changes in the production and control practices that occur after approval and to confirm that the approved applications have been appropriately supplemented to reflect those changes. The main objectives of this continuing compliance program are: (1) to assure that any changes in manufacturing and process control comply with cGMP regulations; and (2) to assure that all changes are documented in supplemental applications or annual reports (FDA, 2024; PIC/S, 2023).

GMP inspections are also classified as general inspection, routine re-inspection, product-related inspection, and 'for cause' inspection. These types of inspections may be requested and carried out according to the activities of the manufacturers. The conduct of these inspections may vary according to the objectives and may focus, for example, on the general level of GMP (e.g., first inspection in a third country), or on the manufacture of a specific medicinal product or process (e.g., product-related inspection) (FDA, 2024). Types of inspections identified in the WHO text include: routine inspection, concise inspection, follow-up inspection, special inspection, and quality systems review (WHO, 1992).

According to Directive number 1055/2025: Medicine Good Manufacturing Practice Inspection Procedure of EFDA, there are four types of GMP inspections: routine inspection, concise inspection, follow-up inspection, and special inspection. The routine inspection involves reviewing all aspects and components of GMP within a facility. These inspections are conducted

when a newly established manufacturing facility or a manufacturer has expressed interest in expanding manufacturing activities, including the introduction of new products, modification of manufacturing methods or processes, or changes in key personnel, premises, or equipment, and when GMP certification has expired. Concise inspections are conducted when a limited number of requirements are selected to serve as indicators of the overall compliance with the manufacturer and are reserved for establishments that have been previously inspected for Good Manufacturing Practice. Follow-up inspections are conducted specifically to monitor the implementation and effectiveness of preventive and corrective actions of the manufacturer following a previous inspection. Follow-up inspections are limited to specified GMP non-compliances that have been observed. Special inspections are undertaken to conduct “spot checks,” which focus on one product, a group of related products, or a specific operation such as production, sterilization, labeling, and storage practice (EFDA, 2025).

The GMP inspection process can be announced or unannounced. It depends on the type of inspection and the policy of the regulatory authority. Most FDA inspections of domestic facilities have been unannounced. This prevents companies from "cleaning up" or altering practices specifically for an impending inspection. A significant majority (about 90%) US FDA’s foreign inspections of were pre-announced. This was largely due to logistical challenges such as visa requirements, travel arrangements, coordination with foreign regulatory authorities, and ensuring that relevant personnel and records would be available (RAPS, 2025). However, this practice led to concerns about a "double standard" compared to domestic facilities and the potential for companies to conceal deficiencies or falsify records before the FDA's arrival (Cooley, 2025). The FDA has recently announced its plan to expand the use of unannounced inspections at foreign manufacturing facilities that produce foods, essential medicines, and other medical products for the U.S. market (FDA, 2025). This is a significant shift aimed at ensuring foreign companies receive the same level of regulatory oversight as domestic ones. In the case of WHO, a routine inspection can be announced while other types are unannounced. In the case of Ethiopia, routine and follow-up inspections are announced while a sudden inspection is unannounced.

The frequency of inspection also varies from country to country. For routine inspection, the US FDA undergoes every two years for finished pharmaceutical products (FDA, 2014). The World Health Organization (WHO) recommends a routine inspection frequency of between three and five years. In the case of Ethiopia, a GMP inspection shall not exceed three years (EFDA, 2025).

A risk-based approach is recommended for GMP inspection. This approach ensures resources are used effectively and efficiently to address products or manufacturers with high public health risks (FDA, 2017). According to ICH Q9 guideline, risk, in the context of pharmaceutical quality, is defined as a combination of the probability of occurrence of harm and the severity of that harm (ICH, 2023). More specifically, the risk to pharmaceutical quality is intrinsically linked to the potential for harm associated with a medicinal product's failure to meet established

quality attributes (GMP Insiders, 2024). This means that the risk is determined by both the likelihood that a drug will fail to meet the needs and expectations of patients and their surrogates (such as healthcare professionals, regulators, and legislators) and the magnitude of the negative consequences should such a failure occur. The evaluation of risk to quality must therefore be rooted in scientific knowledge and ultimately focused on the protection of the patient (ICH, 2023).

With the increasing globalization of medicine manufacturing and supply chains, regulatory authorities across the world need to cooperate in the overall interest of public health. There are different initiatives implemented by national regulatory authorities on GMP inspections, allowing more sites to be monitored and reducing unnecessary duplication of inspection activities (EMA, 2014). National Regulatory Authority cooperation on GMP Inspection Programs include: (1) acceptance of GMP inspection/GMP Status certificates - recognition of GMP certificates/GMP inspection reports issued by another NRA or acceptance of GMP status based on a CPP issued WHO Certification Scheme; (2) cooperation approach between Authorities - relying on inspections previously conducted by other authorities, joint and observed inspections and accepting the Prequalification Program of the WHO or the Certificate of Suitability Program of the European Directorate for the Quality of Medicines (EDQM); (3) reliance approach - NMRAs can share GMP compliance information and assessment reports with other agencies to support decision-making related to GMP of a manufacturer; and (4) Mutual recognition - allows NMRAS to rely upon information from GMP inspections conducted within each other's borders (IFPMA, 2020).

The EFDA primarily uses the Reliance Approach to accept GMP compliance for foreign manufacturers. This practice is detailed in the Guideline on Reliance for cGMP Inspection (EFDA, 2024). This practice is described in the GMP Inspection Procedure Directive No. 1055/2025 and the Guidelines on Reliance for Medicine Marketing Authorization (EFDA, 2024; EFDA, 2025). The inspection directive explicitly recognizes and lists SRAs and WHO prequalification programs. For manufacturers located in countries with SRAS or those with WHO prequalified products, the GMP compliance is accepted through document review – a waiver for on-site inspection. However, whenever necessary, on-site inspection may be carried out. The directive also states that "special inspection can be conducted for mutual inspections organized by groups, Communities, IGAD and other organizations for harmonization of inspection activities." This indicates a mechanism for participating in cooperative or mutual inspections, even if a formal Mutual Recongnition Approach is not in place. Implementatioin of this appeach improves EFDA's regulatory efficiency and contributes to timely access to quality-assrued medicines within Ethiopia (EFDA, 2024; EFDA, 2025).

2.3 Importance of Evaluating GMP Inspection Findings

Evaluating GMP inspection findings is important for MNRAs, pharmaceutical manufacturers, and the public at large. For regulators, it ensures proper regulatory oversight via informed decision-making, enforcement actions, developing preventive policy (e.g., updating guidelines), and international harmonization. For manufacturing facilities, it facilitates continuous improvement via quality system improvement, effective CAPA implementation, and securing market access. Safeguarding public health by ensuring safety, quality and, supply of medicines and by creating transparency and accountability is the ultimate objective (FDA, 2024; EMA, 2023).

For example, looking at the EU GMP inspection outcomes for 2019 to 2023, the number of inspected facilities within and outside the EU that are GMP compliant is consistently very high. In 2019, 99.4% (2626 facilities) were found to be compliant; this healthy trend continued into 2023, when 99.7% of the facilities inspected reached a compliance level of 2388. Furthermore, for foreign sites in the USA, it has maintained 100% compliance with cGMP for these years, from 127 inspections in 2019 to 155 in 2023. For India, it is also highly compliant, with a large number of compliant facilities such as 105 in 2019; although for countries like India, several non-compliant companies have also been reported in 2019 (1), 2022 (2), and 2023 (4). Similar is the case for China; a large number of compliant facilities were reported, for instance, 51 in the year 2019, while 4 non-compliant companies were also reported in 2019. These figures mark strong evidence of global compliance with the EU GMP standards, with only isolated incidents of non-compliance that signal points where its regulatory focus should be centered (EMA, 2023).

Similarly, in analyzing the observations from US FDA Form 483 for routine inspection of finished drug and API manufacturing sites between 2014 and 2018, the most prominent observations were those related to laboratory controls with 2603 issues and records and reports with 2530 issues. Other GMP areas that presented high figures in terms of observations were those about production and process controls, organization and personnel, and equipment. Such findings provide pharmaceutical quality compliance professionals, managers, and operators with crucial insights to strengthen compliance and develop effective solutions for key regulatory challenges (Ajay Pazhayattil, 2024).

The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK regularly analyzes its GMP inspection deficiency data annually. In 2016, a review of FPP inspections showed quality systems (38), sterility assurance (34), and production (20) were the top three areas for critical deficiencies. Quality systems (449), production (191), and sterility (190) were also the top major deficiency classes (MHRA, 2016). Publishing such data allows manufacturers to conduct self-assessments and drive continuous improvement. Conducting such trend analysis enables regulatory authorities to enhance oversight by identifying common and emerging deficiencies, tracking changes over time, and prioritizing high-risk areas. This is important as it

enables proactive regulatory measures to safeguard public health by ensuring the ongoing safety, efficacy, and quality of medicines.

Analysis of the findings of GMP inspections by Brazilian Health Regulatory Agency (ANVISA) from 255 reports received in the period 2015 and 2016 shows that 62.75% of companies were "satisfactory," while 12.55% were "unsatisfactory." The most frequent deficiencies included documentation with 28.63% and premises with 26.27%**.** The study concluded that sharing this information can improve GMP compliance by promoting regulatory transparency, enabling manufacturers to identify common deficiencies, conduct self-assessments, and implement corrective measures to enhance their practices. Additionally, it enables reliance and mutual recognition among regulatory authorities by fostering international collaboration, harmonizing inspection standards and procedures, avoiding duplication of efforts, and allowing agencies to use each other's inspection outcomes for risk-based oversight, ultimately ensuring higher quality medicines (Geyer ARC, 2018).

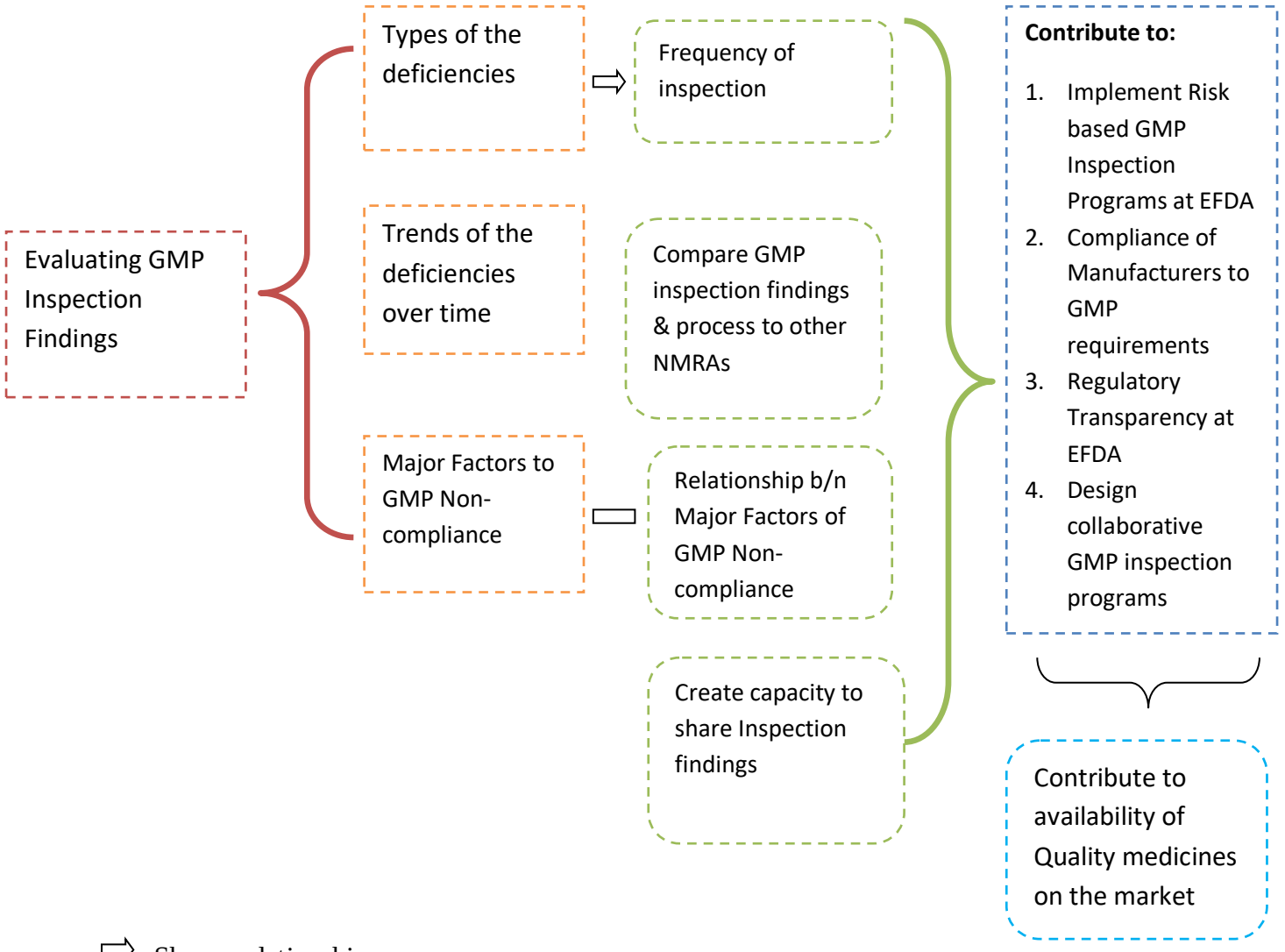
A comparative study of the GMP inspections done by the TMDA for the two fiscal years 2018/2019 and 2019/2020, was conducted in foreign pharmaceutical industries exporting medicines to Tanzania. A total of 196 inspections were conducted using the East African GMP Compendium as the benchmark. The critical non-conformances in the inspected facilities were observed to be dominantly related to laboratory quality control issues (48.5%) and premises (45.5%). Overall, the conformance to EAC GMP requirements developed a downward trend in 2019/2020 at 32.9 percent, compared to 50 percent in 2018/2019. It was observed that the majority of the inspected facilities were situated in India, representing 65.3 percent, followed by 6.6 percent in China and 4.6 percent in Kenya. The study concluded that continuous GMP inspection and corrective measures remain of great essence to enhance conformity to quality standards of the products in the market in Tanzania, and sharing such information increases compliance and enables reliance and mutual recognition (Raphael Zozimus Sangeda, 2024).

2.4 Research Question

This study was conducted to answer the following questions;

1. What are the major GMP elements for non-compliance with GMP requirements of Ethiopia?
2. What are the similarities and differences between the Ethiopian GMP inspection process and other regulatory authorities in terms of GMP requirements applied to the scope of the inspection and regulatory actions?
3. Does a relationship exist between major GMP elements of non-compliance?

2.5 Conceptual Framework



3. Objective

General Objective

The main objective of the study was to evaluate GMP inspection findings of the Ethiopian Food and Drug Authority over the years, from 2015 to 2024, and the first three months of 2025, in Addis Ababa, Ethiopia.

Specific Objective

- To identify the major GMP elements for non-compliance with Ethiopian GMP requirements;
- To assess trends of deficiencies found by year, country/region, criticality, production lines, conclusions, and chapters of the EFDA GMP guideline;
- To compare the GMP inspection process of EFDA with international best practices; and
- To identify any correlations between the major GMP elements of non-compliance with GMP requirements.

4. Methodology

Study Area and Period

The study was conducted at the Ethiopian Food and Drug Authority (EFDA) head office. EFDA is located in Kirkos Sub-City, Africa Avenue (Bole road), kebele 02/03, and house number 03, Addis Ababa, Ethiopia. The study period was from 2015 to 2024. However, due to the absence of inspection reports; 2015 (for local inspection) and 2020 (for foreign inspections) were not included in the study. To account for re-inspection of local manufacturers, the first three months of 2025 were included in the study period. The study was conducted from December 2024 – January and March 2025.

Study Design

A retrospective quantitative study design was used to evaluate GMP inspection findings of the EFDA. The information contained in GMP inspection reports of EFDA from 2015 to 2024 and the first three months of 2025 (ten years) was analyzed. An excel database which was developed, pilot tested and used for the data collection.

Population

Source Population

All GMP inspection reports of EFDA since the start of GMP inspection were used as source population.

Study Population

The study population was GMP inspection reports (40-local, 478-foreign) of EFDA from 2015 to 2025, which is a ten-year and 3-month report. This period is selected because (1) the GMP guideline was put into effect in 2014, and (2) the validity period for a GMP certificate is five years (currently changed to three years effective from April 2025) in Ethiopia, and to include the re-inspection progress of the companies (trend over time).

Sample Size Determination

All GMP inspection reports from 2015 to 2024 and the first three months in 2025 were included in the study by adopting the census technique.

Inclusion and Exclusion Criteria

Inclusion Criteria

Complete (as per the GMP report format of EFDA) GMP inspection reports from 2015 to 2024 and the first three months of 2025.

Exclusion Criteria

Any incomplete GMP inspection report was excluded from the study.

Variables

Independent variables

Criticality of deficiencies, GMP requirements (chapters of GMP guideline), type of inspection, production lines, country of origin

Dependent variables

Decision of inspection, number of inspections, frequency of inspections

Data Collection and Management

Data Collectors

Two pharmacists were recruited as data collectors. They were trained on the objective and the data collection tools. The data collectors had conducted a pre-test using 5% of the total data on data collection tools, as indicated in annex I. After the pre-test, the tool was modified to include a section for a specified list of common deficiencies.

Data Collection Tools

An Excel database was used to enter all the required information on the GMP inspection report. The data collection tool is indicated in annex I.

Data Quality Control

The principal investigator has coordinated the overall activities of the study. The principal investigator had regularly checked the validity of data entered into the database by the data

collectors. After data collection, the validity of the entered data (quality assurance) was also checked by peers (personnel from the GMP inspection department).

Data Analysis and Interpretations

After data collection, quantitative analysis on the deficiencies from the GMP inspection reports was conducted using a spreadsheet (MS Excel). First, the number of inspections conducted for local and foreign sites was presented in a table showing the overtime trend. Second, the inspection outcomes of the report were classified according to the reporting format as 'acceptable,' 'partially acceptable,' or 'unacceptable'. The results were grouped by production lines and whether the company was previously inspected or not. Third, classification findings were done as critical, major, and other. The mean, median, minimum, maximum (range), and standard deviation values were calculated per inspection conducted. Fourth, deficiencies were grouped based on the titles and chapters of GMP regulations in Ethiopia. Fifth, deficiencies found and the inspection process of EFDA were compared with published data of other regulatory authorities, in terms of the scope of the inspection and requirements applied, and regulatory actions. Sixth, deficiencies found more frequently were listed descriptively regarding the article (item) of the regulation and then quantified. Their frequencies were also quantified by the total number of deficiencies. Finally, a correlation for the major deficiencies (as per EFDA GMP guideline chapters) was calculated using the Pearson correlation coefficient.

Operational Definitions

Competent authority: refers to a medicine regulatory organization that has the legally delegated or invested authority, capacity, or power to perform a designated function.

Deficiency: is non-fulfillment of a requirement. In this sense, this term can be used interchangeably with "nonconformity".

Enforcement: means action taken by a competent authority to protect the public from products of suspect quality, safety and, efficacy or to assure that products are manufactured in compliance with appropriate laws, regulations, standards, and commitments made as part of the approval to market a product.

Falsified Medical Products: refers to medical products that deliberately/fraudulently misrepresent their identity, composition, or source.

Inspection: means an on-site evaluation of a manufacturing facility to determine whether such manufacturing facility is operating in compliance with GMP and/or commitments made as part of the approval to market a product.

Inspection outcomes: when all the production lines inspected fulfill the requirements of cGMP, the outcome will be "acceptable"; when some lines fulfill the requirements, the outcome will be "Partially acceptable"; and when all the inspected lines fail to meet the requirements, the outcome will be "Unacceptable.

Inspection Report: means the written observations and GMP compliance assessment completed by GMP inspectors of the competent authority.

Marketing Authorization: a legal document issued by the competent authority that establishes the detailed composition and formulation of the product and the pharmacopeial or other recognized specifications of its ingredients and of the final product itself and includes details of packaging, labeling and shelf life.

Mutual Recognition: refers to an agreement between two or more regulatory authorities to accept each other's GMP inspection reports and/or certificates.

Nonconformity: refers to a failure to comply with requirements. A requirement is a need, expectation, or obligation. It can be stated or implied by an organization, its customers, or other interested parties. There are many types of requirements. These include quality requirements, customer requirements, management requirements, product requirements, process requirements, and legal requirements. Whenever an organization fails to meet one of these requirements, nonconformity occurs.

Observation: also called “audit finding” or "inspection finding" in a GMP inspection, refers to a documented finding made by an inspector substantiated by objective evidence that indicates a deviation from GMP requirements, internal procedures, or industry best practices.

Risk-based approach: refers to the application of a systematic and defensible framework that formally prioritizes or selects activities for regulatory focus and then subsequently aligns regulatory resources accordingly.

Stringent Regulatory Authority (SRA): refers to a national drug regulation authority that the WHO considers to apply stringent standards for quality, safety, and efficacy in its process of regulatory review of drugs and vaccines for marketing authorization.

Substandard Medical Products: are authorized medical products that fail to meet either their quality standards or their specifications, or both.

Transparency: refers to putting more information in the hands of the public or increasing the availability of information to the public.

Unregistered/unlicensed Medical Products: are medical products that have not undergone evaluation and/or approval by the national or regional regulatory authority for the market in which they are marketed or distributed, or used.

Ethical Considerations

An ethical approval letter from Addis Ababa University, the School of Pharmacy Ethics Review Committee, was obtained to conduct the current research. An official letter from the School of Pharmacy, Department of Pharmaceutics and Industrial Pharmacy, was sent to EFDA and the

Head of Inspection Directorate, where the study was undertaken, to obtain consent to the research conducted. The source information, GMP inspection reports, was kept securely, and the information obtained was used for the current study only. The names of individual companies were kept confidential, and the analysis was done in aggregate.

5. Results

Local Inspections (2016 – 2018)

Between 2016 and 2018, the Ethiopian Food and Drug Authority (EFDA) carried out baseline gap assessments of the cGMP compliance level of six local pharmaceutical manufacturers in collaboration with the United Nations Industrial Development Organization (UNIDO). Of the six manufacturers assessed, follow-up inspection was conducted for just one manufacturing facility. The Manufacturers were categorized into three levels based on their compliance scores: Level 1 (Category C) for scores ≤50%, Level 2 (Category B) for scores between 50% and 80%, and Level 3 (Category A) for scores exceeding 80%. The distribution of the local manufacturers across the compliance categories is indicated in Figure 1 below.

A total of 380 GMP deficiencies were identified across these baseline assessments. The mean number of deficiencies per inspection was 54.3, with a standard deviation of 21.6. The median number of deficiencies was 63, and the range observed was 17 to 78 deficiencies. Out of these deficiencies, 53 were critical, 136 major, and 191 minor. Figure 2 below shows the frequency distribution of the identified deficiency types.

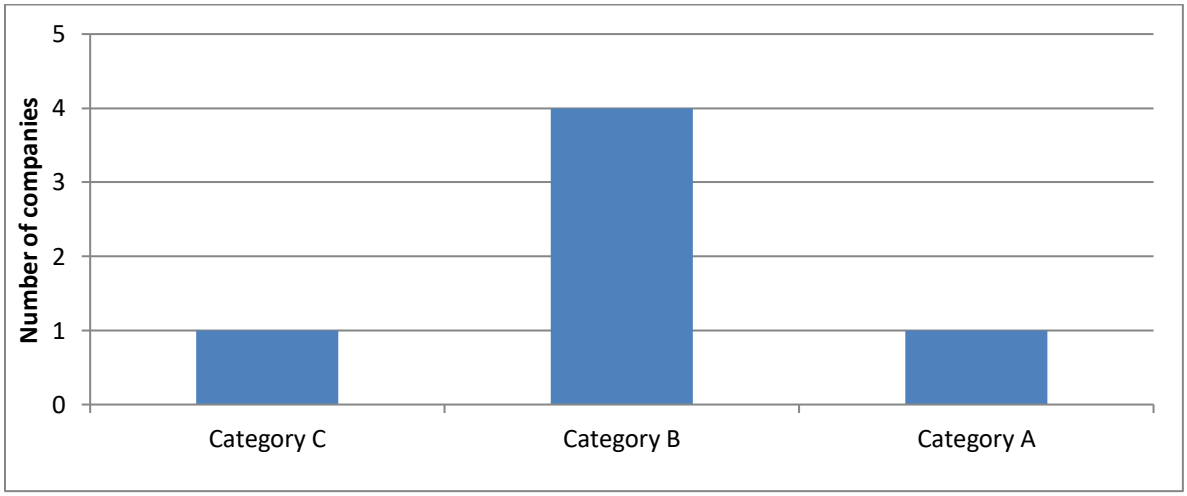


Figure 1: Distribution of Local Pharmaceutical Manufacturers Based on Compliance Scores, Local Inspection (2016–2018).

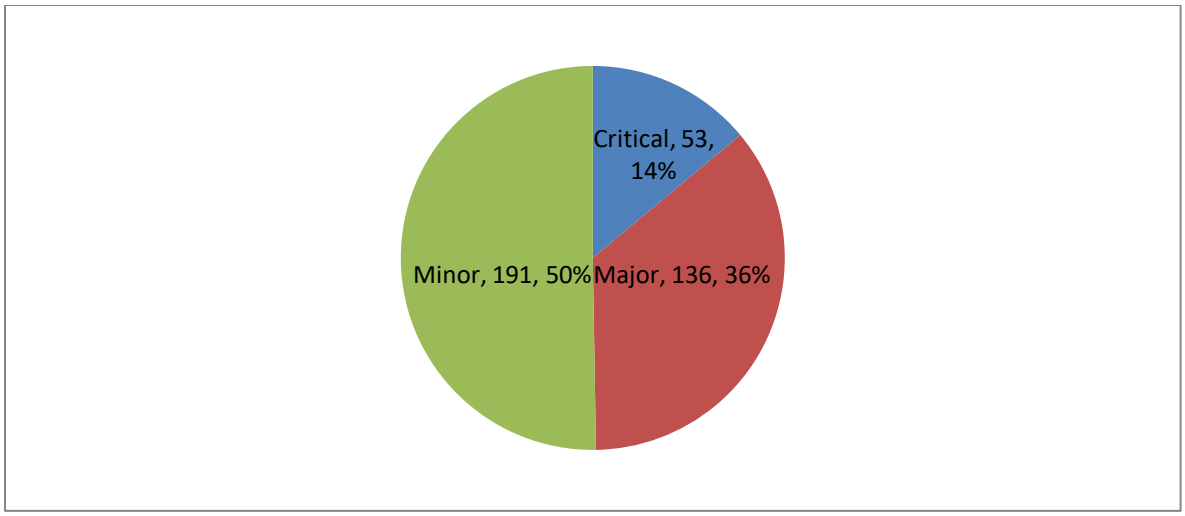


Figure 2: Frequency of type of deficiencies obtained from the Local Inspection (2016 – 2018).

Table 1 categorizes the deficiencies found during the local inspections between 2016 and 2018 by the EFDA GMP guideline chapters. As shown in the table, several chapters consistently had high deficiencies. Among the chapters, Quality Management, Materials Management, Production, Good Practice in Quality Control and Water for Pharmaceutical Use all have deficiencies in all (100%) of the inspections. Out of the total deficiencies, Materials Management accounted for 70 deficiencies (18.4%), followed by Good Practice in Quality Control with 65 deficiencies (17.1%), and Documentation with 60 deficiencies (15.8%) come third. In terms of GMP compliance, these chapters together represented a significant portion of all deficiencies found, indicating they are the major areas of concern.

Table 1: Distribution of deficiencies found per EFDA GMP Chapters, Local Inspection (2016 - 2018)

Chapter	**Inspections with deficiency (% of inspection)**	**Number of Deficiencies (% total of deficiencies)**
Chapter 1 - Quality Management	7 (100%)	39 (10.3%)
Chapter 2 - Sanitation and Hygiene	6 (85.7%)	22 (5.8%)
Chapter 3 - Premise	6 (85.7%)	43 (11.3%)
Chapter 4 - Equipment	5 (71.4%)	28 (7.4%)
Chapter 5 - Materials	7 (100%)	70 (18.4%)
Chapter 6 – Personnel	5 (71.4%)	26 (6.8%)
Chapter 7- Production	7 (100%)	32 (8.4%)
Chapter 8 - Quality Control	7 (100%)	65 (17.1%)

Chapter 9 - Contract Production and Analysis	2 (28.6%)	2 (0.5%)
Chapter 10 - Complaints and Product Recall	4 (57.1%)	8 (2.1%)
Chapter 11 - Self-inspection and Quality Audits	3 (42.8%)	8 (2.1%)
Chapter 12 - Validation and Qualification	5 (71.4%)	29 (7.6%)
Chapter 13 - Documentation	6 (85.7%)	60 (15.8%)
Chapter 14 - Water for Pharmaceutical Use	7 (100%)	13 (3.4%)
Chapter 15 - Heating, Ventilation and Air Conditioning Systems (HVAC)	6 (85.7%)	27 (7.1%)

As indicated in Figure 3 below, Quality Management, Materials Management, Production, Good Practice and Pharmaceutical Water have deficiencies in each of inspection, the highest proportion of deficiencies (100%), followed by Premise, Documentation, Sanitization and Hygiene and HVAC with 86.7% among the top ten EFDA GMP guideline chapters for local pharmaceutical manufacturers inspected from 2016 to 2018. These chapters represented the most significant areas of non-compliance.

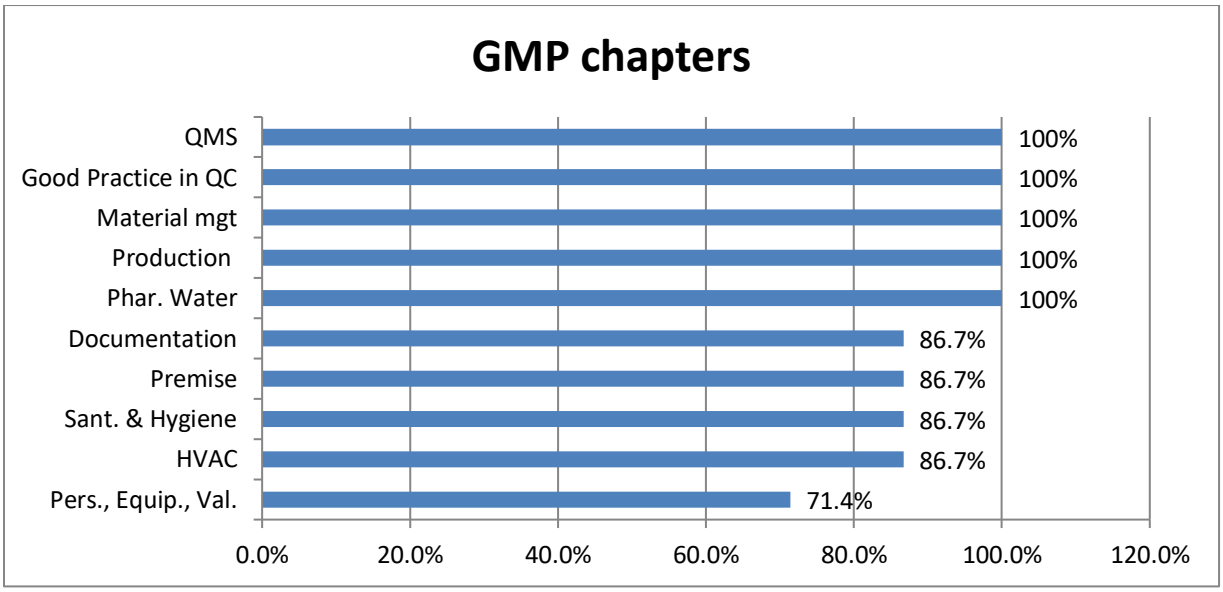


Figure 3: The top 10 EFDA GMP guideline chapters that exhibited the highest percentage of deficiencies, Local Inspections (2016 – 2018).

Local Inspections (2019 – 2025)

Between September 2019 and March 2025, the EFDA conducted a total of 33 local inspections across 11 manufacturing facilities. Of these inspections, 5 were new inspections and 28 were re-inspections (follow-up and renewal). Five of the companies did not comply with GMP

requirements. The analysis results of the local GMP inspection report of EFDA, during this period, are presented in tables and figures in the subsequent section of the document.

The distribution of inspections by product types showed that general oral solid dosage forms constituted the largest segment, with 27 inspections (42.9%). General oral liquids were second with 18 inspections (28.6%), general sterile products were third with 12 inspections (19.0%), and beta-lactam sterile products were inspected in 3 instances (4.8%). 39 (61.9%) of the production lines were acceptable, and the remaining 24 (38.1%) were unacceptable. A single inspection could encompass multiple production lines, and the GMP compliance conclusion (outcomes) could vary across these lines. A breakdown of the inspection outcomes by individual production line is presented in Table 2.

Table 2: Production Line Inspection Frequency and Outcomes, Local Inspection (2019 – 2025).

	Number of Inspected Lines	**Acceptable**	**Unacceptable**
General Oral Solids	27	18 (66.7%)	9 (33.3%)
General Oral Liquids	18	12 (66.7%)	6 (33.3%)
General Sterile	12	6 (50.0%)	6 (50.0%)
Topical Preparations	3	0	3 (100.0%)
Beta-lactam Sterile	3	3 (100.0%)	0
Total	63	39 (61.9%)	24 (38.1%)

The analysis of the GMP inspection reports during this period showed several deficiencies. A total of 288 deficiencies were found during the inspection. The distribution of deficiencies indicates an average of 8.73 per inspection with a standard deviation of 3.61, indicating considerable variability in the number of deficiencies from one manufacturing facility to another. The median number of deficiencies was 9, while the number of deficiencies observed in one inspection ranged from 4 to 16.

When deficiencies are categorized by severity, 15 out of 33 inspections had critical deficiencies (45.5%), 30 of the inspections had major deficiencies (90.9%), and all of the 33 inspections had minor nonconformities (100.0%). Major and minor deficiencies are very common across the inspected facilities. Among the reported deficiencies, 51 (17.7%) were classified as critical, 138 (47.9%) as major, and 99 (34.4%) as minor. Figure 4 shows the distribution of deficiency types.

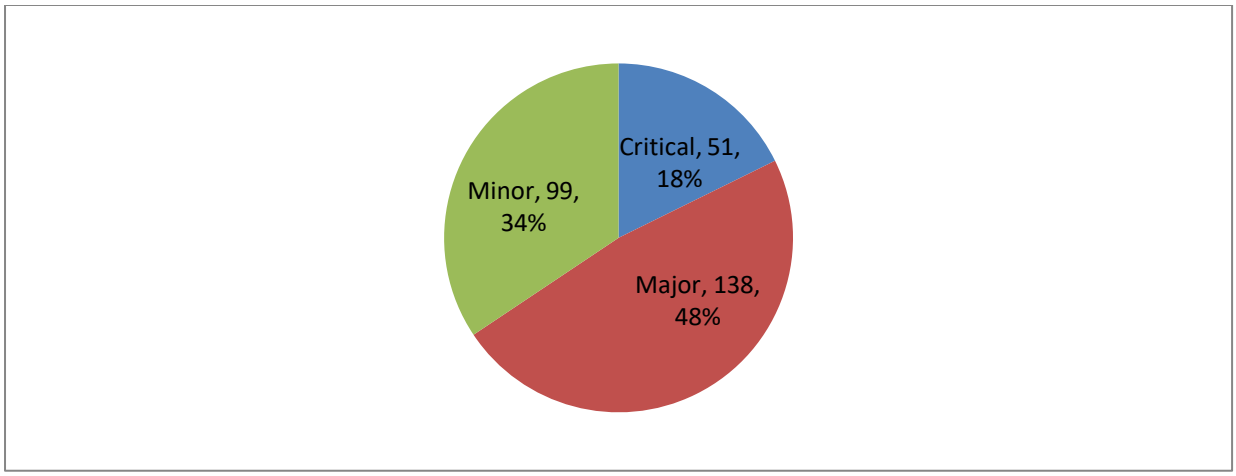


Figure 4: Frequency of type of deficiencies, Local Inspection (2019 – 2025).

Figure 5 compares the mean and maximum number of deficiencies identified per inspection across the three deficiency categories during 2019 – 2025 EFDA local GMP inspections. There was an average of 1.5 and maximum of 7 critical deficiencies per inspection. Similarly, there were an average of 4.2 and a maximum of 9 major deficiencies per inspection. And there were an average of 3 and a maximum of 6 minor deficiencies per inspection. This shows that the most common deficiency types found were major in each of the inspections.

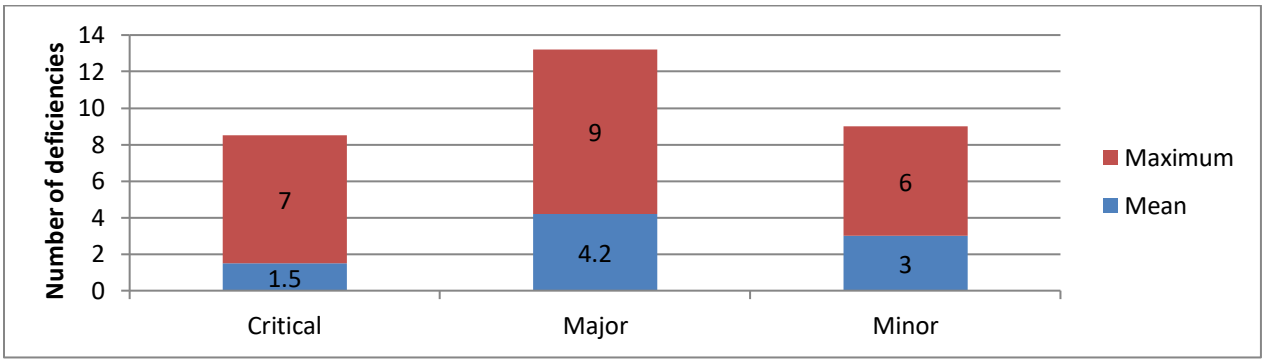


Figure 5: Mean and maximum number of deficiencies, Local Inspection (2019 – 2025).

Table 3 below shows the frequency and proportion of deficiencies found across the different chapters of the EFDA GMP guidelines. The data shows that deficiencies were most frequently identified in Chapter 1 - Quality Management, with deficiencies found in 90.9% of inspections. Chapter 12 - Validation and Qualification is second with deficiencies in 81.8% of the inspections. Chapter 3 - Premise, Chapter 8 - Good Practice in Quality Control, and Chapter 15 - HVAC had deficiencies in 72.7% of inspections. In terms of the total number of deficiencies, Chapter 1 again leads with 40 deficiencies, which account for 13.9% (40) of the deficiencies reported. This is followed by Chapter 3 - Premise with 32 deficiencies (11.1%), Chapter 12 - Validation and Qualification with 31 deficiencies (10.8%), and Chapter 15 - HVAC with 29 deficiencies (10.1%).

Table 3: Distribution of deficiencies found per EFDA GMP chapters, Local Inspections (2019 – 2025).

Chapter	**Inspections with deficiency (% of inspection)**	**Number of Deficiencies (% total of deficiencies)**
Chapter 1 - Quality Management	30 (90.9%)	40 (13.9%)
Chapter 2 - Sanitation and Hygiene	6 (18.2%)	6 (2.1%)
Chapter 3 – Premise	24 (72.7%)	32 (11.1%)
Chapter 4 - Equipment	9 (27.3%)	10 (3.5%)
Chapter 5 - Materials	15 (45.5%)	15 (5.2%)
Chapter 6 – Personnel	15 (45.5.4%)	16 (5.6%)
Chapter 7- Production	21 (63.6%)	26 (9.0%)
Chapter 8 - Quality Control	24 (72.7%)	28 (9.7%)
Chapter 9 - Contract Production and Analysis	6 (18.2%)	6 (2.1%)
Chapter 10 - Complaints and Product Recall	9 (27.3%)	9 (3.5%)
Chapter 11 - Self-inspection and Quality Audits	3 (9.1%)	3 (1.0%)
Chapter 12 - Validation and Qualification	27 (81.8%)	31 (10.8%)
Chapter 13 - Documentation	12 (36.4%)	12 (4.2%)
Chapter 14 - Water for Pharmaceutical Use	18 (54.6%)	25 (8.7%)
Chapter 15 - Heating, Ventilation and Air Conditioning Systems (HVAC)	24 (72.7%)	29 (10.1%)

Figure 6 presents an analysis of the top 10 EFDA GMP guideline chapters with the highest percentage of deficiencies across all inspected local medicine manufacturing facilities during this period. QMS has the highest deficiency, followed by qualification and validation, and Good practice in Pharmaceutical QC. The data indicates where local manufacturers most frequently deviate from GMP requirements. This indicates these ten GMP areas require greater attention and adherence by the local manufacturers.

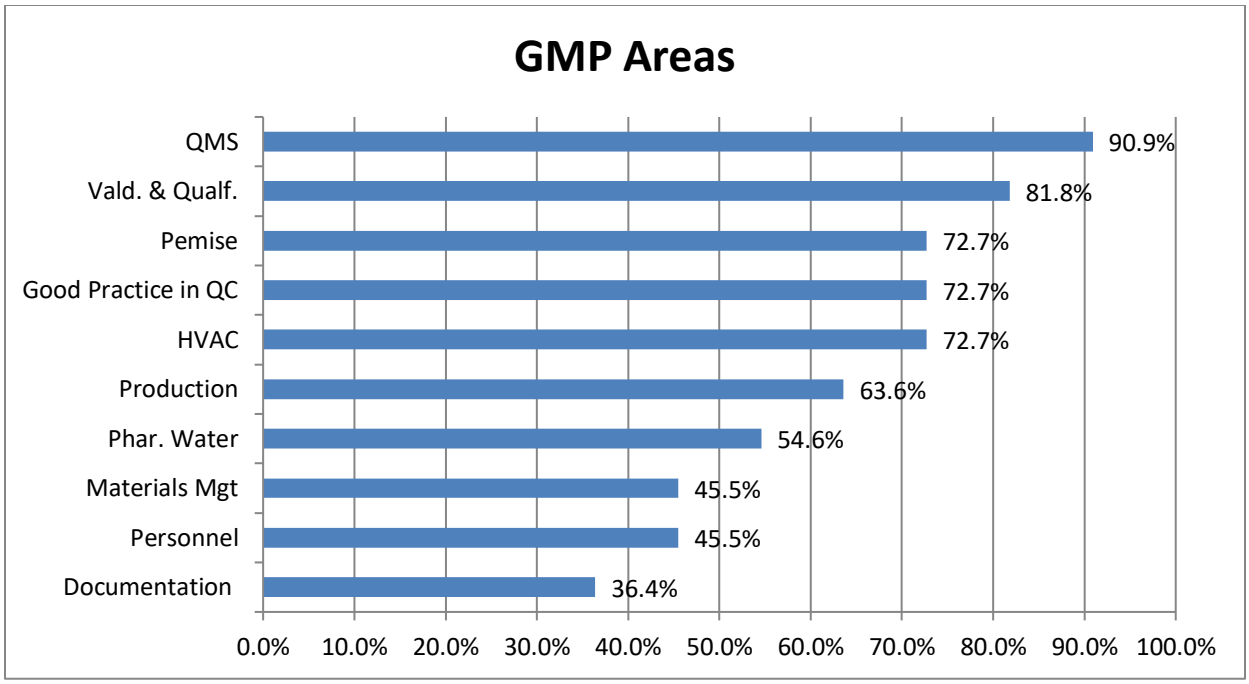


Figure 6: The top 10 EFDA GMP guideline chapters that exhibited the highest percentage of deficiencies, Local Inspection (2019 – 2025).

Table 4 shows the frequency of common deficiencies identified across all the inspected local manufacturing facilities. The data only considered critical and major deficiency types. The most common deficiency is that products were not consistently produced and controlled to the quality standards appropriate to their intended use, with a frequency of 26.7%. Production areas not have air treatment systems appropriate for the products manufactured, operations made, and external environment to prevent contamination and cross-contamination comes second with 11.7% and documentation do not cover all aspects of GMP, for example do not ensure that authorized person have all the information necessary to decide to release a batch of a drug for sale, did not provide traceability that will permit investigation or the availability of the data needed for validation, review, and statistical analysis is third with 10.0%.

Table 4: The most common deficiencies found among local inspections (2019 – 2025).

Deficiency	**Frequency (% of inspection found)**
Products are not consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization	48 (26.67)
Production areas do not have air treatment systems appropriate for the products manufactured, operations made, and external environment (including air filtration) to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity and	21 (11.67)

differential pressures	
Documentation does not cover all aspects of GMP, for example does not ensure that authorized person have all the information necessary to decide to release a batch of a drug for sale, does not provide traceability that will permit investigation or the availability of the data needed for validation, review, and statistical analysis	21 (11.67)
Validation of processes and systems does not establish confidence that the manufactured products will consistently meet their product specifications.	12 (6.67)
Analytical test methods, automated systems, or cleaning procedures not validated	12 (6.67)
Premises are not located, designed, constructed, adapted, or maintained to suit the operations to be carried out	12 (6.67)
Quality control does not properly evaluate the quality and stability of finished pharmaceutical products or, when necessary, of starting materials and intermediate products	9 (5.0)
Equipment, utility, or system not maintained, monitored, and calibrated according to a regular schedule	9 (5.0)
The quality control department does not have adequate resources to ensure that all the quality control arrangements are effectively and reliably carried out	9 (5.0)
Water systems (purified water and water for injection) not reviewed at appropriate regular intervals or not all the relevant topics considered	6 (3.33)
Quality assurance system is inappropriate for the manufacturing of pharmaceutical products. For example, does not ensure that deviations are reported, investigated, and recorded	6 (3.33)
Qualification and validation considered as one-off exercises. There is no on-going monitoring program based on a periodic review	3 (1.67)
Sampling not being conducted in such a way as to prevent contamination or cross-contamination	3 (1.67)
Personnel are not were trained or qualified to do their task properly	3 (1.67)

Note: The list of common deficiencies were taken from a similar study conducted on the GMP inspection reports of ANVISA (Geyer ARC, 2018)

Foreign Inspections (2015 – 2024)

Between September 2015 and July 2024 a total of 478 foreign GMP inspections, in 31 countries, were conducted by EFDA. Since there was no inspection in 2020, it was not included in the study period. Table 5 presents the total number of inspections conducted each year and the total number of deficiencies recorded in that year. Table 6 summarizes the details of the inspections per country, and includes the results along with the percentage of each result category. Data was aggregated under an "Other" category for countries with fewer inspections ($n < 4$): Cote D'Ivoire, Jordan, Kuwait, Lebanon, Malaysia, Mexico, Oman, Pakistan, Palestine, Philippines, Russia, Tanzania, Thailand, Ukraine, and Vietnam.

Of the total inspections, a significant majority, 363 (75.4%), were initial (first-time) inspections. The remaining 115 (24.6%) of the inspections were conducted at facilities with a prior inspection history (re-inspection), most of which were re-renewal inspections.

Table 5: The most common deficiencies found among foreign inspections (2015 – 2024).

Year of Inspection	**Number of Inspections conducted**	**Total No. of Deficiencies Found**
2015	13	218
2016	47	635
2017	78	919
2018	42	528
2019	63	583
2021	91	682
2022	34	236
2023	78	622
2024	32	177
Total	**478**	**4600**

Table 6: Number of inspections per country and outcomes per production line among foreign inspections (2015 – 2024)

Country	**Inspections**	**Acceptable***	**Partially Acceptable****	**Unacceptable*****
India	324 (67.8%)	368 (65.2%)	23(4.1%)	173 (30.7%)
China	52 (10.0%)	36 (45.0%)	3(3.8%)	41 (51.3%)
Egypt	25 (4.8%)	37 (67.3%)	1 (1.8%)	17 (30.9%)
Bangladesh	17 (3.6%)	33 (66.0%)	2 (4.05%)	15 (30.0%)
Turkey	10 (2.1%)	17 (65.4%)	-	9 (34.6%)
Saudi Arabia	8 (1.7%)	16 (76.2%)	2 (9.5%)	3 (14.3%)
South Korea	7 (1.5%)	7 (63.6%)	-	4 (36.4%)
Indonesia	7 (1.5%)	9 (75.0%)	-	3 (25.0%)
Kenya	5 (1.0%)	6 (46.2%)	-	7 (53.8%)
U.A.E	4 (0.8%)	14 (87.5%)	-	2 (12.5%)
Malaysia	4 (0.8%)	13 (76.5%)	-	4 (23.5%)
Others	16 (4.6%)	24 (49.0%)	1 (2.0%)	24 (49.0%
Total	478			

***** All inspected lines were acceptable **–** met the cGMP requirements of EFDA.

****** Some of the lines were acceptable and some were not.

*******All inspected lines were acceptable – did not meet the cGMP requirements of EFDA.

Table 7 below shows the distribution of inspections across different product types. General oral solid dosage forms were inspected most frequently, with 271 inspections (56.7%). General sterile products were inspected 188 times (39.3%), general liquids, nasal, and inhalation products came third with 137 inspections (28.7%), and topical product lines were inspected in 124 instances

(25.9%). It is important to note that a single inspection could encompass multiple production lines, and the GMP compliance outcome could vary across these lines. In cases where an inspection covered more than one production line and resulted in differing outcomes, the overall inspection was categorized as "partially acceptable."

Table 7: Production line inspection frequency and outcomes, Foreign Inspection (2015 – 2024)

	Number of Lines Inspected	**Acceptable**	**Partially Acceptable**	**Unacceptable**
General Oral Solids	271	166 (61.3%)	13 (4.8%)	92 (33.9%)
General Oral Liquids & Inhalations	137	86 (62.8%)	-	51 (37.2%)
General Sterile	188	104 (55.3%)	8 (4.3%)	76 (40.4%)
Topical Preparations	124	83 (66.9%)	3 (2.4%)	38 (30.6%)
Beta-lactam non-sterile	94	68 (72.3%)	4 (4.3%)	22 (23.4%)
Beta-lactam Sterile	39	29 (74.4%)	3 (7.7%)	7 (17.9%)
Vaccines and Biologicals	22	14 (63.6%)	-	7 (31.8%)
Hormonal formulations	30	21 (70.0%)	1 (1.3%)	8 (26.7%)
Anticancer Products	11	11 (100%)	-	-
Total	916	582 (63.6%)	32 (3.5%)	301 (32.9%)

The analysis of the foreign GMP inspection reports reveals a total of 4600 deficiencies. The analysis of the distribution of these deficiencies shows that there was an average of 9.62 deficiencies per inspection with a standard deviation of 7.94, indicating considerable variability in the number of deficiencies found in different inspections (manufacturing facilities). The median number of deficiencies was 7, indicating that in only a few inspections, a high number of deficiencies were found – a positively skewed distribution, which was further evidenced by the range of deficiencies found from 0 to 47.

Figure 7 shows the category of deficiencies based on severity. There were critical deficiencies in 216 of the inspections (45.2%), major deficiencies in 446 of the inspections (93.3%), and minor deficiencies in 380 of the inspections (79.5%). The figure indicates that major deficiencies are the most common deficiencies found during foreign inspection. There were a total of 4600 deficiencies, among the reported deficiencies, a breakdown into severity levels: 1204 (26.2%) were classified as critical, 2099 (45.6%) as major and 1297 (28.2%) as minor.

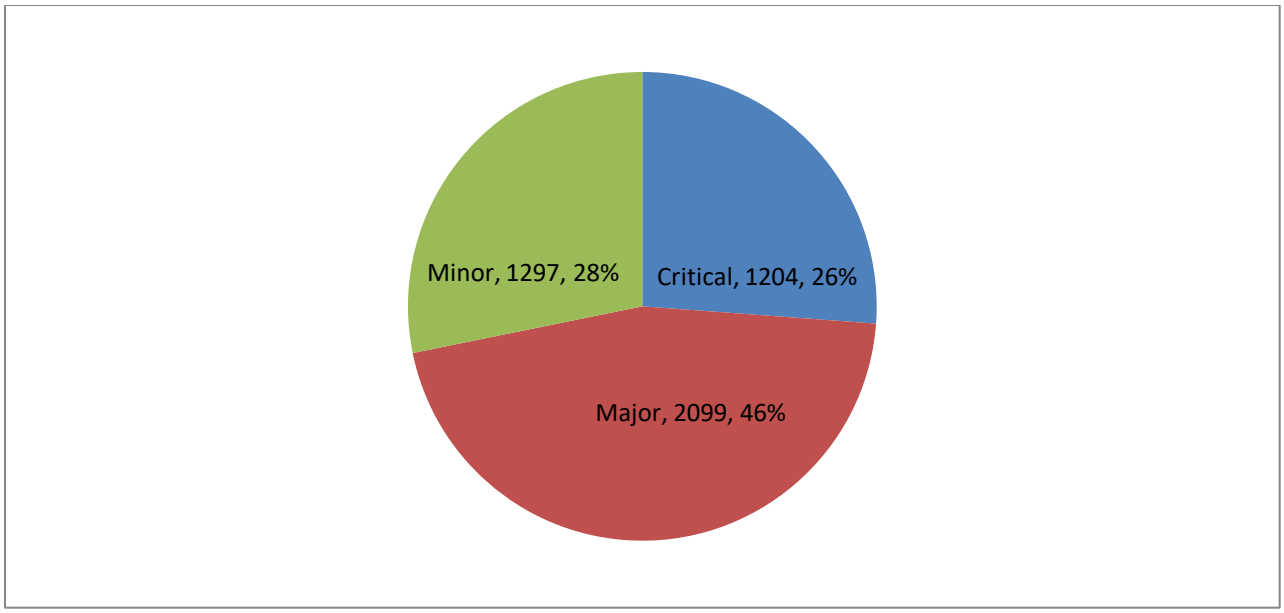


Figure 7: Frequency of type of deficiencies among foreign inspections (2015 – 2024).

Figure 8 indicates the mean and maximum number of each deficiency type found during foreign inspection. The mean of major deficiencies was 4.4. The maximum number of deficiencies found per inspection was 34 for both critical and major type deficiencies.

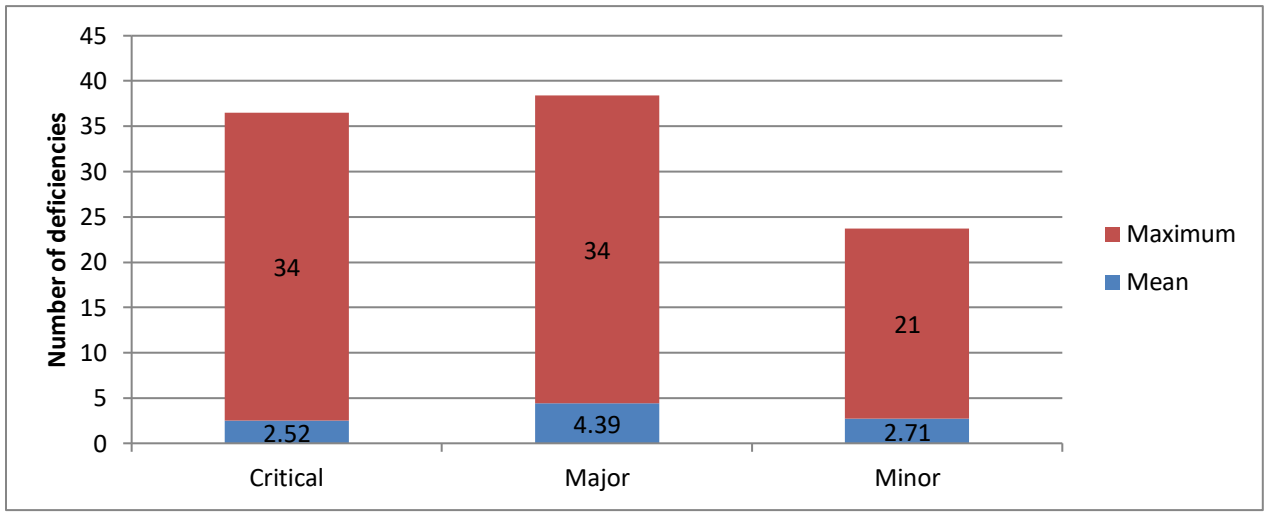


Figure 8: Mean and maximum number of deficiencies among foreign inspections (2015 – 2024).

Figure 9 presents the top 10 EFDA GMP guideline chapters with the highest percentage of deficiencies found across all inspected foreign medicine manufacturing facilities. The Good Practice in Quality Control (QC) chapter has the highest percentage of deficiencies, followed by Materials Management, HVAC (Heating, Ventilation, and Air conditioning), and production with 63.8%, 62.6%, 55.2% and 53.3% respectively. These GMP areas are where manufacturers most frequently deviate from the requirements of GMP and require greater attention and adherence by pharmaceutical manufacturers.

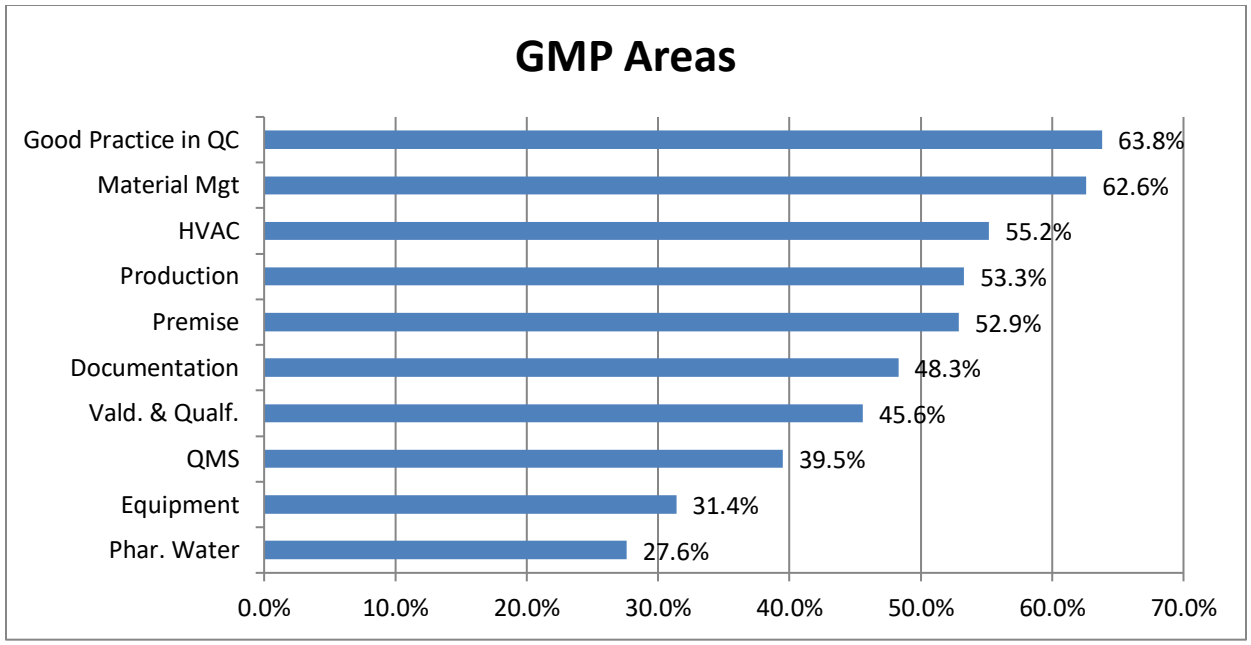


Figure 9: The top 10 EFDA GMP guideline chapters that exhibited the highest percentage of deficiencies among foreign inspections (2015 – 2024).

Figure 10 illustrates the trends in regulatory outcomes following EFDA foreign GMP inspections from 2015 to 2024. The outcomes of the inspection are acceptable, partially acceptable, and unacceptable. When all the production lines inspected fulfill the requirements of cGMP, the outcome will be "acceptable"; when some lines fulfill the requirements, the outcome will be "Partially acceptable"; and when all the inspected lines fail to meet the requirements, the outcome will be "Unacceptable. The outcomes are important for decision-making, such as the issuance of GMP certificates, the need for re-inspections, or other regulatory measures. The graph shows that the "Acceptable" trend is increasing, especially from 2018, and the "Unacceptable" outcome is decreasing from 2018.

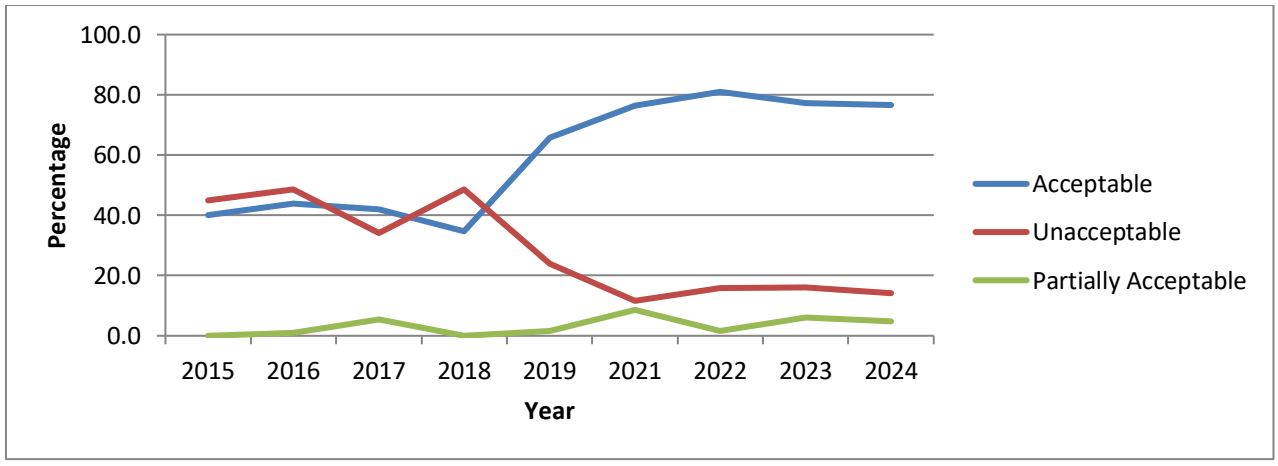


Figure 10: Trends in Regulatory Outcomes among foreign inspections (2015-2024).

Table 8 presents the number and proportion of deficiencies found across the different chapters of the EFDA GMP guidelines during foreign inspection. The data shows that Good Practice in Quality Control (QC) has the most deficiencies (63.8%), followed by Materials Management (62.6%), as per the inspections conducted. HVAC (55.2%), Production (53.3%), and Premise (52.9%) are the other chapters that have a high number of deficiencies as per the inspections conducted. Similarly, QC has the highest 630 deficiencies (13.3%) out of the total deficiencies found. Followed by Materials Management with 538 deficiencies (11.3%), Premise with 524 deficiencies (11.0%), and HVAC with 589 deficiencies (12.4%) out of the total deficiencies found. The chapters with the fewest deficiencies were Contract Production and Analysis, which accounted for just 0.3% of all deficiencies and were found in only 2.5% of inspections.

Table 8: Distribution of deficiencies found per EFDA GMP chapters among foreign inspections (2015-2024).

Chapter	**Inspections with deficiency found (% of inspection)**	**Number of Deficiencies (% total of deficiencies)**
Chapter 1 - Quality Management	189 (39.5%)	286 (6.0%)
Chapter 2 - Sanitation and Hygiene	130 (27.2%)	207 (4.4%)
Chapter 3 - Premise	253 (52.9%)	524 (11.0%)
Chapter 4 - Equipment	150 (31.4%)	232 (4.9%)
Chapter 5 - Materials	299 (62.6%)	538 (11.3%)
Chapter 6 - Personnel	101 (21.1%)	119 (2.5%)
Chapter 7- Production	255 (53.3%)	504 (10.6%)
Chapter 8 - Quality Control	305 (63.8%)	630 (13.3%)
Chapter 9 - Contract Production and Analysis	12 (2.5%)	13 (0.3%)
Chapter 10 - Complaints and Product Recall	44 (9.2%)	49 (1.0%)
Chapter 11 - Self-inspection and Quality Audits	37 (7.7%)	39 (0.8%)
Chapter 12 - Validation and Qualification	218 (45.6%)	425 (8.9%)
Chapter 13 - Documentation	231 (48.3%)	424 (8.9%)
Chapter 14 - Water for Pharmaceutical Use	132 (27.6%)	173 (3.6%)
Chapter 15 - Heating, Ventilation and Air Conditioning Systems (HVAC)	264 (55.2%)	589 (12.4%)

Table 9 below presents the top ten EFDA GMP guideline chapters with the highest deficiencies in a year across the study period in foreign inspections. The GMP chapters with the highest total deficiencies are Good Practice in QC with 305 deficiencies, Material Management with 299 deficiencies and HVAC with 264 deficiencies. The highest deficiencies in a year are Materials Management 66 (2021), followed by QC 56 (2017) and HVAC 54 (2017). Other GMP chapters with moderate deficiencies that still require regulatory attention are documentation practices (231 deficiencies), equipment compliance (150), and facility standards (Premises: 253).

Table 9: Distribution of Top 10 EFDA GMP chapters with highest deficiencies per year among foreign inspections (2015 – 2024)

Year /Chapters	**QMS**	**Prem.**	**Equip.**	**Mat.**	**Prod.**	**QC**	**Doc**	**V & Q**	**Ph.W.**	**HVAC**
2015	4	9	6	10	9	11	8	7	4	10
2016	16	34	18	26	23	34	32	31	14	38
2017	31	46	23	52	46	56	48	42	32	54
2018	17	21	14	28	29	30	25	27	16	27
2019	26	25	20	39	31	40	32	26	15	36
2021	36	48	25	66	41	47	33	30	20	39
2022	11	18	10	20	15	20	15	11	9	21
2023	32	36	28	43	43	52	28	39	11	28
2024	16	16	6	15	18	15	10	5	11	11
Total	**189**	**253**	**150**	**299**	**255**	**305**	**231**	**218**	**132**	**264**

Table 10 shows the frequency of common deficiencies identified across all the inspected foreign manufacturing facilities in the study period. The most common deficiency is that production areas do not have air treatment systems appropriate for the products manufactured, operations made, and external environment (including to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity and differential pressures with 12.6% frequency. Storage areas not designed or adapted to ensure good storage conditions, e.g., temperature and humidity not provided, controlled, monitored, and recorded where appropriate, is the second, with, 12.5% and the third is premises are not located, designed, constructed, adapted, or maintained to suit the operations to be carried out, with 10.5%.

Table 10: The most common deficiencies found among foreign inspections (2015 – 2024).

Deficiency	Frequency (% of inspection found)
Production areas do not have air treatment systems appropriate for the products manufactured, operations made, and external environment (including air filtration) to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity and	391 (12.58)

differential pressures	
Storage areas not designed or adapted to ensure good storage conditions, e.g., temperature and humidity not provided, controlled, monitored, and recorded where appropriate	388 (12.49)
Premises are not located, designed, constructed, adapted, or maintained to suit the operations to be carried out	327 (10.52)
Equipment, utility, or system not maintained, monitored, and calibrated according to a regular schedule	294 (9.46)
Validation of processes and systems does not establish confidence that the manufactured products will consistently meet their product specifications	257 (8.27)
Quality control does not properly evaluate the quality and stability of finished pharmaceutical products or, when necessary, of starting materials and intermediate products	254 (8.18)
Products are not consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization	206 (6.63)
Sampling and dispensing not being conducted in such a way as to prevent contamination or cross-contamination	125 (4.02)
Quality assurance system is inappropriate for the manufacturing of pharmaceutical products. For example, does not ensure that deviations are reported, investigated, and recorded	121 (3.89)
Water systems (purified water and water for injection) not reviewed at appropriate regular intervals or not all the relevant topics considered	100 (3.22)
Documents are not complete, accurate, reviewed regularly, contain all the required information or updated regularly.	97 (3.12)
There is no documentary evidence of design qualification, installation qualification, operational qualification, performance qualification, or process validation	94 (3.03)
The quality control department does not have adequate resources to ensure that all the quality control arrangements are effectively and reliably carried out.	88 (2.83)
Analytical test methods, automated systems, or cleaning procedures not validated	85 (2.74)
Where dust is generated, e.g., during sampling, weighing, mixing and processing operations, and packaging of powder, measures are not taken to avoid cross-contamination and facilitate cleaning	65 (2.09)
Identity test not conducted on a sample from each container of starting material	50 (1.61)
There is poor documentation practice	48 (1.54)
Documentation does not cover all aspects of GMP, for example does not	43 (1.38)

ensure that authorized person have all the information necessary to decide to release a batch of a drug for sale, does not provide traceability that will permit investigation or the availability of the data needed for validation, review, and statistical analysis	
Qualification and validation considered as one-off exercises. There is no on-going monitoring program based on a periodic review	30 (0.97)
Time limits for storage of equipment before and after cleaning not stated or based on data validation	16 (0.51)
The heads of the production and quality control and quality assurance do not share, or jointly exercise, responsibilities relating to quality, such as monitoring and control of the manufacturing environment, process validation and calibration of analytical apparatus, approval and monitoring of suppliers of materials, or approval and monitoring of contract manufacturers	14 (0.45)
Personnel are not were trained or qualified to do their task properly	14 (0.45%)

Note: The list of common deficiencies were taken from a similar study conducted on the GMP inspection reports of ANVISA (Geyer ARC, 2018)

Figure 11 displays the Pearson correlation analysis performed on the top five deficient GMP areas from the foreign inspection. The data are based on Table 9 (top ten EFDA GMP guideline chapters with the highest deficiencies in a year across the study period in foreign inspections). There was a significant correlation, specifically between QC and Production, which had the strongest correlation ($R^2 = 0.940$). While QC and Documentation ($R^2 = 0.836$), Materials and Production ($R^2 = 0.830$), and Premises and HVAC Systems ($R^2 = 0.757$) all showed positive correlation. This indicates that deficiencies in one GMP chapter may impact (cause a deficiency) in other GMP areas, e.g., deficiencies in Quality Control systems tend to also have non-compliance in production-related GMP areas.

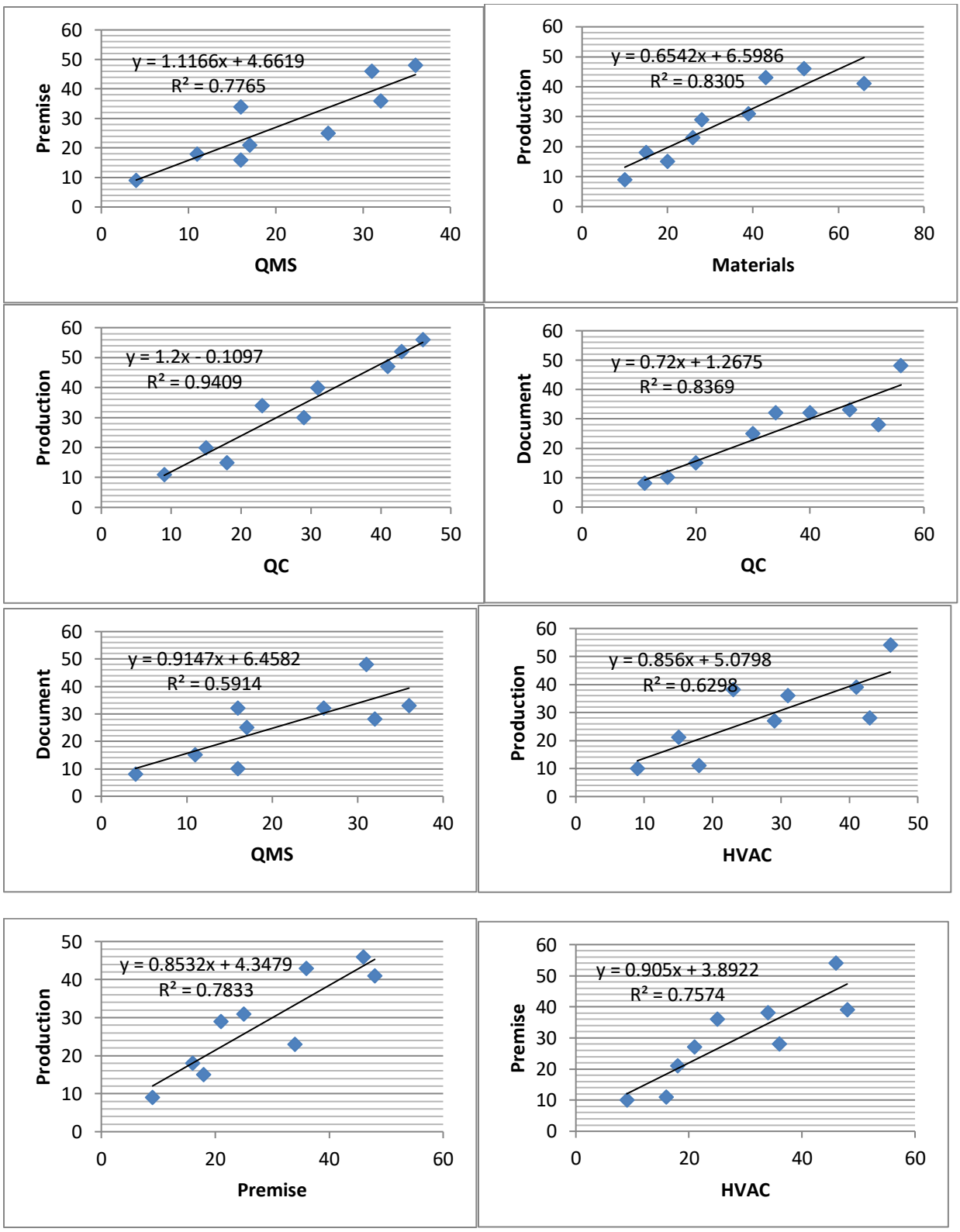


Figure 11: Relationship between the top five GMP areas with highest deficiencies, foreign inspection (2015 – 2025).

6. Discussion

Classification of Deficiencies

Evaluation of GMP inspection findings has considerable importance to regulatory authorities. It helps to identify recurring cGMP issues, recognize non-compliant manufacturers, and assess the overall level of adherence to quality standards within the pharmaceutical industry (Lebanova H, 2024). This information is crucial for targeted interventions, risk-based inspection planning, and the development of effective regulatory strategies to ensure the quality of medicines.

Based on EFDA's Directive 1055/2025 (Medicine Good Manufacturing Practice Inspection Procedure), deficiencies are classified as critical, major, and minor (EFDA, 2025), and as per PIC/S guidance, GMP inspection deficiencies are also classified as critical, major, and minor/other (PIC/S, 2019). Critical deficiency is defined as a deficiency that has produced, or leads to a significant risk of producing, a product that is harmful to the patient. A "Critical" deficiency also occurs when it is observed that the manufacturer has engaged in fraud, misrepresentation, or falsification of products or data. A "Critical" deficiency may consist of several related deficiencies, none of which on its own may be "Critical", but which may together represent a "Critical" deficiency, or systems' failure where a risk of harm was identified and should be explained and reported as such. A major deficiency is defined as a deficiency that is not a "Critical" deficiency, but which:

- has produced or may produce a product which does not comply with its Marketing Authorization, Clinical Trial Authorization, product specification, pharmacopoeial requirements, or dossier;
- does not ensure effective implementation of the required GMP control measures;
- indicates a major deviation from the terms of the manufacturing authorization;
- indicates a failure to carry out satisfactory procedures for the release of batches or failure of the authorized person to fulfill his/her duties;
- Consists of several "Other" related deficiencies, none of which on its own may be "Major", but which may together represent a "Major" deficiency or systems failure and should be explained and reported as such.

If the deficiency cannot be classified as either Critical or Major, but it is a deviation from the GMP, it also classified as Minor/Other. A deficiency may be minor either because it is Minor or because there is insufficient information to classify it as Major or Critical (PIC/S, 2019). GMP deficiencies show systemic challenges in the quality systems of manufacturers. This discussion compares GMP deficiency classes (critical, major, and minor) reported by the EFDA with data

from other NMRAs, including the EMA (EU), MHRA (UK), and ANVISA (Brazil), which classify deficiencies as per PIC/S guidance.

EFDA's critical deficiencies (14–26%, as indicated in figures 2, 4, and 7) are significantly higher than those of MHRA (2–3%) (Sandle, 2021), ANVISA (2.48%) (Geyer ARC, 2018), and EMA (5%) (Lebanova H, 2024). This is consistent with the most common deficiencies found during local inspection - products are not consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization (table-5) and foreign inspection - production areas do not have air treatment systems appropriate for the products manufactured, operations made, and external environment (including air filtration) to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity and differential pressures (table-10) indicating the presence of critical deficiencies. The EFDA's major deficiencies (36–48%) are similar to global trends (MHRA: 38–39%; ANVISA: 40.31%; EMA: 50%). Lower rates of minor deficiencies (28–50%) are reported by EFDA than MHRA (59–60%) and ANVISA (57.22%), which indicates either underreporting of minor issues or prioritization of critical/major findings during inspections.

EFDA has reported a high rate of critical and major deficiencies, while SRAs have reported a very high rate of minor deficiencies with a lower rate in major and critical deficiencies, which can be attributed to the difference in the facilities inspected. Manufacturing facilities inspected by SRAs (FDA, EMA, or MHRA) often show more robust pharmaceutical quality systems because of the very stringent global standards faced, advanced manufacturing technology, and proactive compliance measures. In contrast, countries in Africa inspect facilities with less mature pharmaceutical quality systems (Samunda BT, 2023) and places much more focus on high-risk facilities and production lines, leading to higher observed critical deficiencies at 14–26% compared to SRA benchmarks such as MHRA at 2–3%, EMA at 5%, and other PIC/S member NRAs like ANVISA at 2.48%.

When comparing the critical deficiencies from local EFDA inspections, there is an increase from 14% during baseline assessments (2016 – 2018) to 18% during the second period (2019 – 2025) inspections. This can be attributed to (1) during the second period (2019 – 2025) EFDA aligned more closely with international best practices, including revisions to GMP guideline & directive and more frequent follow-up inspection. This could result in identifying more critical issues under heightened criteria that were not as rigorously applied during the 2016-2018 baselines. (2) An increase in local manufacturing facilities and production lines inspected leading to a higher proportion of deficiencies compared to the baseline period. And (3) some manufacturers may not have kept pace with evolving GMP expectations. In contrast, in mature agencies like the MHRA and EMA, there are negligible critical deficiencies, and these agencies prioritize minor deficiencies. Compared to the local facilities, EFDA's inspections have relatively higher critical deficiency rates from foreign inspections (26%). This can be attributed to EFDA inspection processes are more stringent (stricter) for export-oriented facilities, compared to less stringent local inspections. The other contributing for the high rate of critical deficiencies, especially for

local manufacturing facilities, is that Ethiopia's limited access to advanced manufacturing technologies and inadequate qualified personnel exacerbate critical gaps (Hassen HK, 2025), whereas countries like Brazil report higher major deficiencies, likely due to rapid pharmaceutical industry growth outpacing the development of robust quality management systems.

Inspections Conducted and Outcomes

The EFDA Directive on Medicine Good Manufacturing Practice Inspection Procedure (1055/2025) also states that medicine manufacturers with a single critical finding or several major deficiencies (≥6) shall be refused acceptance for a GMP Compliance. A letter of non-compliance will be sent to the manufacturer in not more than 20 working days. However, corrective and preventive action may be required for re-inspection. When there is no deficiency, good manufacturing practice compliance certificate will be submitted to the manufacturer not more than 10 working days after the last date of the inspection. EFDA writes official letters to the inspected facilities addressing the inspected lines as "Acceptable," "Partially Acceptable," and "Not Acceptable." International medicine regulatory authorities use varying systems (e.g., NAI/VAI/OAI by US FDA, Compliant/Non-Compliant by EU, Satisfactory/On Demand/Non-Compliant by ANVISA, and a focus on deficiency types by MHRA).

Table 11: Conclusion of Local and Foreign inspections, EFDA (2015 – 2025)

Type of Inspection	No of Inspection conducted	Acceptable	Partially Acceptable	Not Acceptable
Local (2016 – 2018)	7	1 (16.7%)	4 (66.7%)	1 (16.7%)
Local (2019 – 2025)	33	18 (54.5%)	3 (9.1%)	12 (36.4%)
Foreign (2015 – 2024)	478	265 (55.4%)	87 (18.2%)	126 (26.4%)

Compliance with cGMP is a critical component of pharmaceutical quality assurance, ensuring that medicines are manufactured to meet the predefined standards of safety, efficacy, and quality. Analyzing the deficiencies found during inspections and the compliance rates to cGMP for both local and foreign manufacturing facilities provides insight into EFDA's regulatory capacity and performance in terms of cGMP enforcement. The number of GMP inspections conducted among different NRAs vary significantly, due to differences in their mandates, the size of the pharmaceutical industry they oversight, and the resource capacities they have.

Significant shift in compliance of local manufacturers was observed from the initial assessment (2016-2018) period and the later period (2019 – 2025). During the initial assessment, out of the 7

inspections conducted, one manufacturing facility (16.7%) was satisfactory (category A) with GMP requirements, four manufacturing facilities (66.7%) were partially satisfactory (category B), and one manufacturing facility (16.7%) was not satisfactory (category C). These findings during the baseline assessment indicate that a substantial proportion of local manufacturers were in the process of meeting GMP standards but had not yet fully achieved them. In contrast, the results from the latter period (2019-2025) show a marked improvement in compliance rate, with 6 out of 11 facilities (54.5%) meeting all GMP requirements. The number of facilities found not to comply was 36.5%.

In the latter phase of the local inspection, the total number of inspections increased from 7 to 33. This marks an improvement in the (frequency of) regulatory oversight by EFDA, as a result of stricter enforcement, increase in the number of pharmaceutical manufacturers, increased frequency of inspection as part of the WHO GBT benchmarking requirement, and follow-up inspections. Despite the increase in the number of inspections, the total number of deficiencies decreased from 380 to 288 signifying a decrease in the mean deficiency per manufacturing facility inspected, indicating improvement in compliance and also inspections became more focused (e.g., follow-up inspections). Among the inspected GMP areas, Sanitation and Hygiene, Equipment, Materials Management, Production, Pharmaceutical water, Good Practice in Quality Control, and Documentation show significant reductions in both the number of inspections with deficiencies and the proportion of deficiencies of the total deficiencies. QMS had small reductions in inspection coverage, but their proportion of total deficiencies remained stable or slightly increased, indicating partial progress. Validation and Qualification demonstrated regression with increased proportions of deficiencies indicating ongoing systemic issues in those areas which are critically important.

In the later period, which ranges from 2019 to 2025, 6 out of the 11 local facilities inspected achieved cGMP compliance, 54.5%. This indeed reflects that significant progress has been made by the local manufacturers in achieving GMP compliance, as opposed to the previous situation of 1 to 6 compliant manufacturers. However, 45.4% (5) of manufacturing still faced significant challenges in meeting the required cGMP standards.

EFDA has also conducted 478 foreign GMP inspections during the study period (2015 – 2024). 265 (55.4%) of the inspected manufacturing facilities complied with GMP requirements – Acceptable, 87 (18.2%) were partially compliant – Partially Acceptable, and 128 facilities (26.8%) were not compliant – Unacceptable. As presented in Table 6, analyses of these foreign inspections by country show variations in compliance rates. 324 manufacturing facilities with 524 production lines were inspected in India. Of which 65.2% of lines were Acceptable, 4.1% were Partially Acceptable, and 30.7 were Unacceptable. 52 manufacturing facilities with 80 production lines were inspected in China. Of which 45% were Acceptable, 3.8% were Partially Acceptable, and 51.3% were Unacceptable. 25 manufacturing facilities with 55 production lines were inspected in Egypt. Among the inspected facilities, 67.3% compliant, 1.8% partially

compliant, and 30.9% non-compliant production lines. These data indicate that manufacturers in China have a higher non-compliance rate compared to manufacturers in India and Egypt.

Following the GMP inspection, the US FDA investigator initially classifies the facility's compliance level as NAI, VAI, or OAI. No action indicated (NAI) classification indicates a facility is in an acceptable state of compliance. The facility, usually, was not issued a Form FDA 483 at the conclusion of the inspection. Voluntary action indicated (VAI) classification indicates the inspection found objectionable conditions or practices, but the agency has determined the facility can voluntarily correct its deficiencies and will not recommend any action. Usually, the facility was issued a Form FDA 483 at the conclusion of the inspection. Official action indicated (OAI) classification indicates a facility is not in compliance and must take preventative or corrective actions. A Form FDA 483 is issued at the inspection's conclusion. The facility receives a letter detailing the classification (e.g., NAI, VAI, or OAI), and this information is usually published on the data dashboard (Alam, 2024).

Analysis of data from the US FDA inspection dashboard from 2015-2024 indicated a fluctuating number of inspections. A total of 2765 inspections were conducted in 2015, 2565 in 2016, 2873 in 2017, 2665 in 2018, 2554 in 2019, 646 in 2020, 1335 in 2021, 1474 in 2022, 1577 in 2023, and 1648 in 2024. From 2554 to 646 in 2020, the number of inspections conducted reduced significantly. This was due to the COVID-19 pandemic, which highlighted the vulnerability of onsite GMP inspection to any health crisis. After COVID-19, the trend of the number of inspections conducted depicts a reduction relative to the pre-COVID-19 inspections. This could be attributed to a shift to desk reviews and remote inspections, which were used during the pandemic. Alongside the number of inspections, the US FDA also tracks the issuance of Form 483s, which document observed violations. The total number of Form 483s issued for drug inspections between 2015 and 2024 was 678 (2015), 691 (2016), 694 (2017), 716 (2018), 779 (2019), 349 (2020), 232 (2021), 527 (2022), 555 (2023), and 610 (2024) (FDA, 2024). The trend in Form 483 issuance indicates the frequency with which the US FDA identifies GMP deficiencies during its inspections.

Analysis of the Form 483s issued by the US FDA, to medicine manufacturers from January 1, 2023, to May 31, 2024 (17 months) indicates that 18.2% the inspections resulted in an NAI, 64.6% in a VAI, and 17.2% in an OAI in 2023. The same study indicates that there were 17.0% NAIs, 64.7% VAIs, and 18.3% OAIs in 2024. About 65% of the Form 483s issued were VAIs, indicating that the majority of the manufacturing facilities manage the deficiencies themselves without official enforcement. Approximately 17 to 18% OAIs were issued by the US FDA, indicating more serious cGMP non-compliance issues that require official enforcement. 59.5% Form 483s issued were for manufacturing facilities in the US, 10.4% in India, and 8.7% in Canada (Ajay Pazhayattil, 2024), indicating the majority of non-conformance occurs from the manufacturing facilities located in the US. When reviewing the pre-Covid-19 era, the study conducted between 2014 and 2018 on US FDA inspection database revealed that in 2016, 19.7%

of the inspections resulted in form 480s issuance, in 2017 20.8% of the inspections resulted in form 480s issuance and in 2018 21.4% of the inspections resulted in form 480s – the highest across the study period (Ajay Babu Pazhayattil M. I., 2019)

The EMA performance report from 2019 to 2023 was reviewed. The cGMP compliance rate of manufacturing facilities inspected in a given year was analysed. In 2019, 2626 (99.4%) of the facilities inspected were GMP compliant, and 16 facilities (0.6%) were non-compliant. In 2020, 1843 (99.9%) of the facilities were GMP compliant, with only 1 facility (0.1%) identified as non-compliant. In 2021, 1982 (99.7%) of the inspected facilities were GMP compliant, and 5 (0.3%) were non-compliant. In 2022, 2131 (99.7%) of the inspected facilities were GMP compliant and 6 facilities (0.3%) were non-compliant. In 2023, 2388 (99.7%) of the facilities were GMP compliant and 7 facilities (0.3%) were non-compliant. The data indicates that inspected facilities inspected by EMA have a high level of cGMP compliance rate across the reporting period. These figures suggest a robust level of adherence to GMP standards within the European Union (EMA, 2023).

The report was also reviewed for the compliance rates of manufacturing facilities inspected in foreign countries under EU GMP. All of the facilities inspected in the US were compliant with the cGMP requirement: USA [127 (2019), 35 (2020), 52 (2021), 118 (2022), 155 (2023)]. For India, the EU GMP inspections found a high number of compliant facilities [105 (2019), 64 (2020), 29 (2021), 81 (2022), 101 (2023)], but also identified some non-compliant companies [1 (2019), 2 (2022), and 4 (2023)]. China had 51 (2019), 11 (2020), 24 (2021), 15 (2022), and 44 (2023) compliant facilities, with 4 non-compliant companies reported in 2019 (EMA, 2023).

Comparing these EU GMP findings with EFDA's results for the same countries reveals some notable differences. The EU GMP data indicates a substantially higher overall compliance rate, compared to EFDA’s India (30.7%) and China (51.3%) non-compliance rate, to the EU's finding of India (1.8%) and China (2.8%) non-compliant companies out of the total inspected. The main reason for this discrepancy might be the difference in the type of facilities inspected by each authority.

The MHRA also classifies GMP inspections as critical, major, and minor. The MHRA conducted 303 inspections in 2015, 324 in 2016 (MHRA, 2016); no data is available for 2017 (not published by the authority), 286 in 2018, and 258 in 2019. Of these, a significant majority was conducted in the UK: 224 (74%) in 2015, 242 (75%) in 2016, 228 (80%) in 2018, and 228 (88%) in 2019. For overseas inspections in 2018, 43 (15%) were in India, 5 (2%) in China, and 5 (2%) in the US. The non-compliance rates found during these inspections were 5.2% in 2018 and 5.4% in 2019 for all inspected facilities (local and overseas combined). The non-compliance rates specifically for inspections conducted in the UK were higher, ranging from 26% in 2015 to 12% in 2019 (Unger, 2021).

Comparing the non-compliance rate (12 – 26%) found by MHRA for local inspections conducted in the UK is slightly comparable to the non-compliance rate (36.4%) reported by EFDA for local manufacturing facilities in Ethiopia inspected from 2019 to 2025. However, the non-compliance rates reported by MHRA for foreign inspections in 2018 (5.2% overall, with India at 15% of foreign inspections) and 2019 (5.4% overall) appear generally lower than EFDA's reported non-compliance rates for India (30.7%) and China (51.3%) across the entire 2015-2024 period (Unger, 2021). The difference in the non-compliance rate is mainly attributed to the difference in the types of manufacturing facilities inspected. The foreign manufacturing facilities inspected by the EFDA have inherent compliance gaps due to less mature PQS (Hassen HK, 2025).

An analysis done on the ANVISA outcomes of foreign GMP inspections in 2015 and 2016 showed a total of 255 inspections were conducted. The review classified 62.75% of the inspected companies as GMP satisfactory, 24.71% as having "on demand" status, and 12.55% as non-compliant with Brazilian GMP regulations. Among the inspected countries, France has the highest compliance rate (26.09%), followed by Ireland (25%) and China (20%) (Geyer et al., 2018). The ANVISA report indicates manufacturing facilities in China have a better cGMP compliance rate (20%) compared to the non-compliance rate (51.3%) reported by EFDA for Chinese manufacturing facilities during a wider time frame (2015 – 2024). ANVISA has a unique classification for compliance as “on demand” in addition to “acceptable” and “unacceptable,” indicating facilities requiring further monitoring or specific actions to achieve satisfactory GMP compliance (Geyer ARC, 2018).

The Tanzania Medicines and Medical Devices Authority (TMDA) classify deficiencies as critical, major, and minor. TMDA inspected 179 medicine manufacturing facilities in 2018 and 2019. Of the inspected companies, 43% complied, 39.6% were on demand, and 16.8% were non-compliant to the GMP requirements (Raphael Zozimus Sangeda, 2024). Of these facilities inspected, 128 (65.3%) were in India, 13 (6.6%) in China, and 9 (4.6%) in Kenya. The non-compliance rate (16.8%) reported by TDMA for foreign manufacturing facilities are moderately lower than the compliance rate (26.8%) reported by EFDA during 2015 – 2024. Of the 128 inspected companies in India, 61 complied, 45 on demand and 22 not compliant (17.2%). The non-compliance rate for India found by TMDA is lower than the 30.7% reported by EFDA for the broader 2015-2024 period.

The comparison of compliance rates between local and foreign manufacturers inspected by EFDA reveals those international facilities had a slightly higher rate of compliance (55.4%) compared to the local facilities in the latter period (54.5%). This trend is somewhat different from what is observed with EU GMP, where local inspections within EU member countries also show very high compliance rates (around 99.7%).

India and China are the main sources of imported pharmaceutical products to Ethiopia. Manufacturing facilities in India and China show variable cGMP compliance rates among

different regulatory authorities. The EFDA reported a 65.2% compliance rate for Indian manufacturing facilities. The EMA has a very high compliance rate. The highest non-compliance rate reported by EMA in 2020 was 3.1%. However, MHRA and TMDA reported a lower compliance rate for India. Reasons for the variations in compliance include the type of inspection followed (line-based Vs product-based), the type of manufacturing facilities inspected (with mature PQS Vs less mature PQS), and the study period. The EFDA reported a 48.7% compliance rate for Chinese manufacturing facilities. Chinese manufacturing facilities have a higher compliance rate with the EMA, MHRA and the ANVISA. The EMA reported 7.8% non-compliant companies from China in 2019. All of the inspected companies were compliant from 2020- 2023 by EMA. MHRA reported a 98% compliance rate in 2018. ANVISA reported a compliance rate of 80% in China from 2015 to 2016. The difference may be due to several factors, including language constraints and differences in the type of companies that were inspected.

Types and Frequency of Inspections

According to EFDA Directive 1055/2025, the frequency of inspection shall not exceed three years. All medicine manufacturing facilities are subject to GMP inspection; however, based on risk evaluation, different modalities of inspection—such as onsite inspection, remote inspection, desk review, and others—may be applied. In line with the directive, inspections are classified as routine, concise, follow-up, and special inspections.

A manufacturer approved by Reference Regulatory Authorities (RRA) and World Health Organization prequalified product shall be subjected to Good Manufacturing Practice inspection based on related documents. EFDA may waive the onsite inspection of RRA-approved companies based on required Good Manufacturing Practice-related documents for desk review, as per the authority update list of reference regulatory authority. EFDA may also conduct remote inspections without going in person, considering different scenarios when necessary.

The current analysis only evaluates the onsite inspections (first time and re-inspections) EFDA did over the defined time period, with other regional and international inspection reports. During the first period (2016 to 2018), only one facility was re-inspected among the inspected local manufacturers. During the second period (2019 – 2025), 28 (84.8%) were re-inspected. From the foreign inspections, 75.4% were first-time (pre-registration) inspections which are higher than that of ANVISA (60.4%) and TMDA (50.5%). The possible reasons are that EFDA prioritizes to conducting first-time inspections (high risk) compared to re-inspections. The remaining 24.6% of the inspections conducted by EFDA were re-inspections (routine renewals and follow-ups), which is lower than inspections conducted by TMDA (49.5%) and ANVISA (39.4%).

Production Lines and Outcomes

In pharmaceutical manufacturing, a production line or manufacturing line refers to the integrated sequences of equipment, workstations, and processes employed to formulate raw materials - active ingredient/s and excipients - into finished pharmaceutical products. All the stages of production, from mixing through formulation to packaging, are designed in a linear or modular flow for efficiency and proper control. Different types of products with the same dosage form can be manufactured on one production line. Similarly, there may be a number of production lines for one dosage form. During GMP inspections, inspectors assess production lines as part site inspection to assess overall compliance (EMA, 2023). The analysis of production line GMP inspection outcomes indicates that there are clear trends in the compliance rates of different product categories, reflecting variability in GMP standards application. These findings fall in line with broad global trends in regulatory inspections while highlighting region-specific challenges.

For the locally inspected manufacturing facilities in Ethiopia, the Beta-lactam Sterile Production Lines scored 100% acceptance. The General Sterile also scored moderately at 50.0% acceptance. The other two product lines scored equally at 66.7% acceptance. The Topical Preparation scored the highest in non-compliance from 30.6 (foreign inspection) to 100% (2nd phase local inspection). This can be attributed to the fact that 36.4% of the locally inspected plants were found to be non-compliant under GMP.

Foreign inspections conducted by the EFDA found more variations in compliance outcomes, incorporating the concept of a partially acceptable category. Beta-lactam sterile production lines (74.4% acceptable) and Non-Sterile production lines (72.3% acceptable) show higher compliance, consistent with stringent controls for beta-lactam products (Petrelli F, 2019). General Sterile production lines reflect the lowest compliance (55.3% acceptable, 40.4% unacceptable), similar to the challenges noted in EFDA's local inspections and aligning with sterility assurance deficiency as the main cause of recalls for sterile products (Kolluru, 2017). Vaccines and Biologicals demonstrated moderate compliance (63.6% acceptable), contrasting with the EU's near-perfect compliance rates for biologics, which may reflect differences in manufacturing facility infrastructure and types (EMA, 2023).

Across the four production lines inspected by ANVISA, Non-sterile solids accounted for the highest number of inspections, totaling 131. This category also exhibited the highest percentage of satisfactory outcomes at 70.99%, with 19.85% classified as On Demand and 9.16% as Unsatisfactory. Sterile products were the second most frequently inspected production line, with 125 inspections. Among these, 60.00% were Satisfactory, 27.20% were On Demand, and 12.80% were Unsatisfactory. Sterile products had the highest percentage of unsatisfactory outcomes among the production lines. The production line for Non-sterile liquids underwent 25 inspections. Of these, 52.00% were Satisfactory, 36.00% were On Demand, and 12.00% were Unsatisfactory. Non-sterile semisolids had the fewest inspections, with only 10 conducted. The

outcomes for this category were 30.00% Satisfactory, 50.00% On Demand, and 20.00% Unsatisfactory. This production line had the highest percentage of On Demand and Unsatisfactory classifications (Geyer ARC, 2018).

Among TMDA's inspections, general products underwent the highest number of inspections, with a total of 128 line inspections. A combination of general and beta-lactam antibiotics accounted for 20 lines. Beta-lactam antibiotics come third with 17 lines. There were 9 hormone lines inspected in the reporting period (Raphael Zozimus Sangeda, 2024). When the results obtained from the production line inspection in the three regulatory authorities are compared, the following important observations can be made:

- **Sterile Products:** Both EFDA and ANVISA show moderate compliance rates for sterile product manufacturing, with EFDA reporting 50.0% acceptable for local general sterile and 55.3% for foreign general sterile, and ANVISA reporting 60.00% satisfactory. This suggests that maintaining sterility remains a significant challenge in pharmaceutical manufacturing globally.

- **Non-Sterile Products:** The acceptance rate of 72.3% for the foreign non-sterile products was recorded by EFDA. Higher rates of acceptance were observed for the non-sterile solid products (70.9%) than the non-sterile liquids (52.00%) at the ANVISA. The regulatory agency TMDA carried out numerous inspections for non-sterile products, of which 44.5% were found to comply. This indicates the disparity among the acceptance rates of non-sterile products based on their type.

- **Biological Products:** EFDA's moderate compliance rate of 63.6% for foreign vaccines and biological is comparable to 42.9% compliance rate of TMDA for similar category of products which contrasts with the EU's reported near-perfect compliance. The differences can be attributed to variations in regulatory harmonization and stringency, where the EU benefits from a unified, resource-rich system under the EMA, while African authorities like EFDA often face challenges in capacity and enforcement for product approval and post-market surveillance. Additionally, factors such as the higher volume and diversity of sourced products in lower- and middle-income countries may contribute to lower compliance detection and consistency (Kirti Narsai, 2025).

The differences in the results of inspections per production line reflect the relevance of targeted regulatory enforcement and the fact that companies must concentrate their efforts on their respective GMP regulations for their product type. This can depend on the complexity of the production process involved in the manufacture of the product, the risk level attributed to the product type (sterile versus non-sterile products), as well as the regulatory body's specific GMP regulations.

Deficiencies found per EFDA's GMP chapters

The EFDA GMP Guideline for Pharmaceutical Products Second Edition (issued June 2023) was used for the analysis. The guideline has 15 chapters: Quality Management System, Sanitation and Hygiene, Premises, Equipment, Materials, Personnel, Production, Quality Control, Contract Production and Analysis, Complaints and Product Recall, Self Inspection and Quality Audit, Validation and Qualification, Documentation, Water for Pharmaceutical Use and Heating, Ventilation and Air Conditioning Systems (HVAC). Analysis of the GMP deficiencies identified under their corresponding chapters will enable understanding of the challenges that exist and are prevalent from the perspective of the pharmaceutical industry. This approach facilitates a more comprehensive understanding of the GMP areas that require focused improvement efforts.

The first phase of local inspections (2016–2018) revealed numerous deficits in the areas of QMS (100%), Materials Management (100%), Production (100%), Good Practices in Quality Control (QC) (100%), and Pharmaceutical Water (100%), and indicating non-compliance were found in every inspection for these chapters. This indicates that the main early challenges in the Ethiopian pharmaceutical industry these areas. Sanitization and Hygiene, Premise, Documentation, and HVAC were also each show significant deficiencies with 86.7% of the inspections were with a deficiency in these GMP areas.

There has been a notable change in the pattern of deficiencies observed during the following local inspection period (2019-2025). Though the issues related to QMS remain high (90.9%), progress have been made in Premise (72.7%), Good Practice in QC (72.7%) and HVAC (72.7%). Significant progress is observed with Pharmaceutical water (54.6) and Materials management (45.5). The most notable source of concern shifted to the area of Validation and Qualification (81.8%). This indicates the possible development of maturity in the basic level of manufacturing processes, as the concern of the EFDA has shifted towards the higher-order systems influencing the quality of pharmaceuticals.

The inspection of foreign manufacturing facilities that supplied Ethiopia, conducted by EFDA, had a different set of deficiencies. Higher percentages were found in the aspects of Material Management (63.8%), HVAC (62.6%), and Production (55.2%). This indicates that the inspection conducted by EFDA on the foreign manufacturers could be more strict or rigorous, especially when related to aspects that directly influence the product quality. These include the environment-related factor of HVAC systems and the actual product manufacturing aspect.

The comparison between the local and foreign deficiencies reported by the EFDA shows that the QMS, validation and qualification, premises, good practice in QC, and HVAC have been identified as serious deficiencies during the local inspections. The deficits in good practice in QC, HVAC, and production are comparable to the foreign inspections. Deficiencies in the QMS chapter remain high during the second period of local inspections (90.9%), indicating that both regulators and industry must continue to focus on quality systems.

The contrast in Material Management deficiencies between EFDA (45.5–100%) and other authorities such as ANVISA (18.04%), US FDA (6.1%), and TMDA (3.0%) suggests a unique challenge within the context of Ethiopia's pharmaceutical manufacturing sector. Factors such as inadequate storage facilities and insufficient inventory management practices can be attributed to local pharmaceutical manufacturing facilities in Ethiopia.

The higher deficiency rates recorded in the Premises category, noticed by EFDA (52.9 – 86.7%), TDMA (45.5%), and ANVISA (28.63%), compared to the MHRA (top five in 2018 and 2019) and US FDA (16.1%), might relate to the infrastructure issues commonly noticed in developing countries. This indicates that companies in the concerned countries might find more complications in ensuring that the infrastructure requirements following strict GMP norms related to cleanliness and maintenance are maintained.

The high deficiencies in Pharmaceutical Water Systems chapter (27.6%: international inspection, 100%: 1st phase of local inspection) as a significant deficiency during the first period of local inspections conducted by EFDA is substantially higher compared to that of TDMA's (15.2%). Access to potable water represents a vital service used during pharmaceutical production. This frequency clearly indicates the existence of specific issues during the design, operation, and validation of water systems for manufacturing facilities in Ethiopia.

Below follows a detailed breakdown of the top ten chapters of GMP deficiencies identified by the EFDA (as per the findings of the second period of the local inspection), compared to the findings of the GMP inspection conducted by ANVISA, MHRA, TMDA, and USFDA. While looking at each chapter separately, we can get a closer view of the particular challenges the pharmaceutical industry faces in both Ethiopia and worldwide.

Quality Management Systems (QMS)

The high rate QMS deficiencies reported by EFDA in foreign inspections (39.5% for 2015–2024), are somewhat consistent with those of US FDA (26.2%) and TDMA (12.1%), underscoring a fundamental global challenge in establishing and maintaining robust quality governance. The difference may arise from EFDA's frequent inspections following the WHO GBT benchmarking that uncovered several issues in local facilities, such as inadequate documentation and risk management gaps.

However, there is a significant difference in the magnitude of the QMS deficiency in pharmaceutical industries in Ethiopia (90.9% during the second phase) and those authorities listed above. This can be attributed to several reasons: the MHRA and US FDA regulate (inspect) well-established, better-resourced manufacturers that have a proactive compliance culture, and the TMDA has achieved ML3 status earlier (since 2018) and undergone harmonization with East African countries' efforts, enabling more efficient detection and pre-inspection improvements, reducing reported rates. As discussed above, several other factors that pharmaceutical manufacturers in Ethiopia face (Hassen HK, 2025; Tune Tibesso D, 2024) may

exacerbate the QMS deficiencies.

These QMS related deficiencies show systemic failures in critical areas such as corrective and preventive actions (CAPA), risk management, and overall quality management oversight leading to recurrent non-compliance, product quality risks, and a potential harm to patients (Tarranco, 2025). For local pharmaceutical industry in Ethiopia, addressing these deficiencies is crucial for building a sustainable QMS implementation and quality culture.

Premises

Deficiencies related to premises are also common findings during EFDA GMP inspections. There were 86.7% and 72.7% deficiencies recorded during the first and second period local inspections, respectively. In 52.9% international inspections, there were deficiencies related to premises. These deficiencies are attributed to poor facility design and maintenance. TMDA's (45.5%) and ANVISA's (26.3%) highest deficiency rate in this category further emphasizes the premises' limitations that can affect developing economies. The MHRA reported lower (top 5th in 2018 & 2019), deficiencies related to premises. The European GMP guideline – Annex 1 has stringent requirements for facility design, especially for a sterile manufacturing facility (EMA, 2022), indicating its critical nature. For local manufacturers in Ethiopia, investment in infrastructure and adherence to the EFDA and WHO cGMP guidelines for facility design and maintenance are imperative to address premises-related deficiencies.

Pharmaceutical Water Systems

EFDA's local inspections recorded a high proportion (86.7%) of deficiencies related to HVAC systems during the first phase. This was reduced to 72.7% during the second phase of local inspections. The data is higher than that reported by TMDA, with 15.2%. Pharmaceutical water systems are one of the most frequently cited deficiency areas in GMP inspection. Common findings include failure to properly validate the water system, inadequate sanitization procedures and insufficient monitoring (WHO, 2012). The findings of local manufacturing facilities are unique and critical. Local manufacturing facilities in Ethiopia should adhere to the EFDA and international cGMP standards to address pharmaceutical water-related GMP issues.

Validation and Qualification

The other common deficiencies reported by EFDA are related to validation and qualification. During the local inspection (2019 – 2025), validation and qualification-related deficiencies were the top 2, with 81.8% deficiencies, and the top 7 for international inspection with 45.6% deficiencies. Lower proportions of deficiencies were reported by TMDA (24.2%), ANVISA (20.8%), and MHRA (top 4th both in 2018 & 2019); however, the data indicate a global challenge in this critical area. Deficiencies in validation and qualification occur when there are inadequate processes and procedures to confirm that equipment, systems, facilities, and manufacturing methods consistently produce products meeting predetermined quality standards (May, 2022). Local manufacturers in Ethiopia rely on imported equipment and computerized systems, which exacerbates the challenges related to validation and qualification. In addition,

there are shortage of qualified experts on validation and qualification in the local pharmaceutical industry.

Good Practice in Quality Control

Quality Control (QC) is another area of GMP with common deficiencies. 100% and 72.7% deficiencies were reported by EFDA inspectors from local inspections, during 2016–2018 and 2019 – 2025, respectively. There was a significant improvement in compliance with cGMP requirements related to QC activities during the second period of local inspection. A comparable 63.8% deficiency in the findings to the local inspections reported from a foreign inspection by EFDA. The data is consistent with those of TMDA (48.5%), US FDA (26.2%), and ANVISA (23.53%). Challenges in ensuring the reliability and accuracy of test results and the poor handling of out-of-specification (OOS) results contribute to deficiencies related to QC. The MHRA reported lower (7^{th} top in 2018 and 8^{th} top in 2019) rates of QC-related deficiencies. Addressing issues related to calibration and verification, personnel competency, data integrity, and adopting/following recognized pharmacopoeial standards is important to improve QC-related GMP compliance of local facilities.

Production

Production is the other GMP element with a high number of deficiencies. The EFDA the first period (2016 – 2018) inspections have the highest proportion of deficiencies (100%), followed by the second period (2019 – 2025) local inspection (63.6%), and the foreign inspections (53.3%). These figures indicate an ongoing challenge in ensuring consistent and controlled manufacturing processes. TDMA reported 36.4%, US FDA 27.4%, and ANVISA 18.8% deficiencies related to production. Production-related deficiencies were the 3^{rd} top reported by MHRA in 2018 and 2019. These figures show production-related deficiencies are common across the pharmaceutical industries worldwide. For local pharmaceutical manufacturing sector in Ethiopia, strengthening process validation practices and in-process controls could mitigate production-related gaps and ensure product quality.

HVAC Systems

EFDA's local inspection recorded a high proportion (86.7%) of deficiencies related to HVAC Systems during the 1^{st} phase of local inspection. It was reduced to 72.7% during the 2^{nd} phase of the local inspection. The foreign inspection recorded 55.2% deficiencies which is comparable with deficiencies reported by the TMDA (42.4%) from its foreign inspection conducted between 2018 and 2019 (Raphael Zozimus Sangeda, 2024). This indicates significant challenges in maintaining appropriate environmental conditions in manufacturing facilities. This is particularly critical for sterile product manufacturing, as emphasized by the WHO guideline for sterile products (WHO, 2022). Inadequate environmental monitoring and control can lead to contamination risks. Addressing these deficiencies requires investments in HVAC system upgrades and maintenance, and comprehensive staff training on environmental monitoring procedures. This especially critical local pharmaceutical manufacturing facilities.

Equipment

As a GMP requirement, equipment shall be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. Equipment is another GMP area that has a high number of deficiencies in both local and foreign inspections conducted by EFDA. There was a notable reduction in the proportion of deficiencies from 71.4% to 27.3% found in local inspections during the 2016 – 2018 and 2019 – 2025 periods, respectively. Foreign inspections resulted in higher deficiencies (31.4%) compared to the later phase of local inspections. Most of these are attributed to poor qualifications and inadequate maintenance. TMDA has a comparable deficiency rate for equipment (21.2%) (Raphael Zozimus Sangeda, 2024). These data indicate that the infrastructure limitations commonly affect developing economies. The MHRA reported lower rates for equipment deficiencies (though it remained the top-five deficiency in both 2018 and 2019). For Ethiopian local manufacturers, improving qualification, maintaining critical manufacturing equipment and adhering to EFDA and WHO GMP guidelines regarding qualification and maintenance of equipment are paramount in addressing the deficiencies and producing safe and quality products.

Personnel

Deficiencies related to personnel are persistent and important challenges found during GMP inspections. EFDA's local inspections revealed personnel deficiencies as a significant presence, accounting for 71.4% (2016 – 2018) and 45.5% (2019 – 2025). The data is higher than ANVISA's findings, which reported 14.5% deficiencies (Geyer ARC, 2018). In contrast, personnel-related deficiencies are generally not listed as top-ten findings by stringent regulatory authorities such as the UK's MHRA, the US FDA, or those adhering to EU GMP standards. The disparity can be attributed to personnel competency and associated deficiencies. The competency of personnel in Ethiopia and South America may have limitations that directly manifest as inspection deficiencies. More mature regulatory systems might classify personnel issues as a root cause for other deficiencies (e.g., poor documentation due to inadequate training); however, in regions like Ethiopia and Brazil, personnel performance or training is a primary non-compliance.

Material Management

As a GMP requirement, all materials must be purchased from approved suppliers, handled, stored, sampled, tested, and released under controlled conditions to prevent the use of defective items. Material management was one of the most significant challenges for local manufacturers from 2016 to 2018, with 100% deficiencies. There was a significant reduction in deficiencies during the second period (2019 – 2025), with 45.5%. Foreign inspections recorded comparable deficiencies to those of the second period of local inspection, with 62.6%. These data indicate challenges in the supply chain and proper storage of raw materials. Other regulatory authorities reported a lower proportion of deficiencies related to materials management. ANVISA (18.04%) and MHRA (not listed in the top ten deficiencies both in 2018 and 2019), US FDA (4.1%), and TMDA (3.0%). The data show manufacturing facilities inspected by such NRAs have a more robust and well-regulated supply chain and material management. Local manufacturing facilities

in Ethiopia should address supplier qualification and inventory management gaps to improve material management practices and ensure product quality.

Common Deficiencies Found

Tables 4 and 10 present the most frequent major and critical deficiencies reported during the local (2019 – 2025) and foreign GMP inspections, respectively. In 26.6% of the local inspections, products were not consistently produced to meet quality standards as required by marketing authorization. Indicating challenges in maintaining consistent manufacturing quality products. Inadequate HVAC systems (11.67%) for contamination control emerged as the second most common issue, particularly concerning temperature, humidity, and differential pressure controls in production areas during the local inspections. Many local facilities (10.0%) lacked comprehensive GMP documentation that ensures proper batch release decisions and maintains necessary traceability for investigations and validation. Multiple validation-related issues in the top deficiencies, including process validation failures (6.67%), non-validated analytical methods and/or cleaning procedures (6.67%), and one-off validation approaches without ongoing monitoring (1.67%). Local manufacturing facilities were not properly designed or maintained (6.67%) for their intended pharmaceutical operations.

The foreign inspection shows a broader distribution of deficiencies with some notable differences. The top three deficiencies identified were related to environmental control and physical facilities: an inadequate air treatment system (12.58%), poor storage conditions (12.49%), and improper premise design (10.52%). Calibration and maintenance-related deficiencies accounted for 9.46%. While still important, validation issues ranked lower (8.27%) than local inspections. Similar to the local findings, quality control accounted for 8.18% which is a slightly higher frequency. Issues related to product consistency were much lower (6.63%) than those of the local inspection.

Comparison of GMP inspection observations shows similarities and differences between deficiencies found at local and foreign facilities. Local inspections generally identified product consistency as a major concern; foreign inspections demonstrated more balanced results when considering a range of manufacturing facility aspects, including air handling system, storage areas, and premises. Documentation practices reflect a key comparable difference; documentation issues ranked as the third most occurring issue in local inspections (10%) but significantly lower at eighteenth of all elements presented in foreign inspections (1.38%). This difference may indicate better documentation systems at foreign manufacturing facilities.

In both local and foreign inspections, validation was identified as a challenge. Local manufacturers have a slightly higher deficiency (1.67%) related to validation, considered as a one-off exercise, compared to foreign findings (0.97%). Personnel training emerged as a relatively minor issue in both inspections, appearing with similar low frequencies, suggesting it is less problematic than technical and facility-related issues. Finally, quality assurance system

failures were present in both local (3.33%) and foreign (3.89%) inspections, indicating a universal challenge. Nevertheless, issues related to inadequate quality control resources in terms of equipment, materials, etc. were more common in local inspections (5%) than in foreign inspections (2.83%).

Comparing these results with other foreign inspections reveals comparative findings. For example, analysis of ANVISA's international inspection reports indicated that the majority (14.90%) of the inspections found that products were not consistently produced to meet quality standards required by marketing authorization, which is similar to the local inspection findings of EFDA. The same study indicated issues related to the water system came in second position (8.63%), and issues related to documentation were observed in 8.24% of the inspections (Geyer ARC, 2018). Documentation found by the local inspection, 10.0%, was comparable with the third-highest deficiency findings of ANVISA.

Analysis of the US FDA Warning Letters, from 2019-2021 identified inadequate written procedure as a highly cited deficiency, followed by poor quality system, and inadequate investigation (Ashok B. Patel, 2022). A similar study carried out in Saudi Arabia revealed that the biggest deficiency was related to facility design and maintenance. This was followed by issues in the design and maintenance of equipment, with environmental monitoring and control issues coming third (Ali M Alhomaidan, 2023).

Deficiencies of various types and frequencies were found by different regulatory authorities during GMP inspections. This may be due to a difference in the priorities of regulatory bodies, inspection methodology, or an actual compliance status at various facility types. These findings are consistent with similar studies from US FDA and the Saudi Food and Drug Authority (SFDA) (Ali M Alhomaidan, 2023; May, 2022), yet reflecting region-specific challenges as well. To pharmaceutical manufacturers, this means understanding both the international GMP standards and local regulatory requirements.

GMP Standards

Strict adherence to cGMP is a critical requirement for pharmaceutical manufacturing companies to ensure the safety, efficacy, and quality of medicines. Regulatory harmonization has emerged as a strategy to mitigate international trade barriers and enhance global public health outcomes, particularly benefiting developing nations. The EFDA GMP standards (guidelines) are fundamentally aligned with the WHO guidelines.

However, noticeable differences exist between EFDA's regulatory framework and those enforced by leading international agencies, including the US FDA, the EMA, and members of the Pharmaceutical Inspection Co-operation Scheme (PIC/S). A comparative analysis of the EFDA GMP standard against these established international benchmarks is imperative, considering the following conditions:

Risk Based Approach to GMP Inspection

A risk-based approach to GMP inspections represents an internationally recognized strategy for regulatory authorities to concentrate their resources and focus attention on those facilities presenting the highest risk to product quality and patient safety. In such a way, it helps authorities to concentrate their efforts regarding those facilities and products that represent more risks in order to make their oversight as effective as possible (FDA, 2017).

In 2005, the US FDA adopted a risk-based approach to GMP inspections. The agency uses a Site Selection Model (SSM) to prioritize inspections of both domestic and foreign medical product manufacturing facilities. This model considers various risk factors, including: Facility type (e.g., manufacturer, control laboratory), compliance history, including the time since the last inspection, record of recalls linked to the facility, inherent risks of the product (e.g., dosage form, route of administration, sterility) and whether the facility has been inspected by a foreign regulatory partner. Based on these criteria the US FDA prioritizes facilities as high- or low-risk to use resources effectively to address public health risks (FDA, 2023).

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) is an informal, non-binding co-operative arrangement between regulatory authorities in the field of GMP for medicines. PIC/S recommended a model for risk-based inspection planning in 2012. This model involves a simple Quality Risk Management tool to rate manufacturing sites based on the estimated risk they may pose to patients and product quality. The risk assessment considers (PIC/S, 2012):

- Intrinsic Risk: Based on the complexity of the site, its processes, and products, as well as the criticality of the products or services provided.
- Compliance-related Risk**:** Assessed based on the deficiency profile from the last inspection (e.g., number and severity of deficiencies).

These two risk factors are combined to generate a relative risk rating, which then informs the suggested inspection frequency. PIC/S recommends that every manufacturer should be inspected at least once every three years (PIC/S, 2012).

A risk-based approach to regulation is one of the pillars of EFDA. Article 19 sub-article 1 of Proclamation No.1112/2019 states that “the rigor of regulatory assessment of medicines shall be commensurate with the product’s type, nature, and potential risk to human health” (EFDA, 2019). This mandate covers all types of regulatory functions, including GMP inspection. The EFDA’s Medicine GMP Inspection Procedure Directive, Directive No. 1055/2025, is itself a mechanism through which EFDA implements its risk-based approach to GMP enforcement. This directive has limited the re-inspection interval to not more than three years, a regulatory decision based on re-evaluating the acceptable level of risk over time and aligning with international practice. This directive has rules for inspection scheduling – indicating how EFDA prioritizes which facilities to inspect, and reliance and wavier – desk review is used for companies from SRA-listed or WHO-prequalified.

The EFDA's Guideline on Reliance for GMP inspection is a critical document for the risk-based regulatory strategy. It leverages external trust for efficiency. It outlines the process by which EFDA can rely on the GMP inspection outcomes and certificates issued by trusted, highly matured (WHO-listed) NRAS and the WHO pre-qualification program. (EFDA, 2024). EFDA also uses risk-based factors for reliance and recognition, including the type and complexity of products manufactured, the strength of the regulatory system of the national regulatory authority, the regulatory compliance history of the manufacturing facility, and the level of GMP harmonization (EFDA, 2024). Using this approach, EFDA, instead of conducting on-site inspections for every foreign manufacturing facility, transfers the compliance verification to a trusted third party. This is a risk-based approach that saves EFDA's resources for higher-risk products and facilities without prior trusted approval. However, EFDA remains independent, responsible, and accountable for its final regulatory decision.

The EFDA's approach to risk-based inspection is aligned with international best practices established by PIC/S, the WHO, and SRAs like the US FDA and EMA. Especially the recent directive and reliance guidelines show the inspection approaches are shifting from routine, fixed-interval to a systemic, risk-prioritizing enforcement. The risk assessment criteria and weighing of risks used by EFDA are not as transparent as those of mature regulatory authorities, which have a methodology quantifying and public disclosure of risk weighting.

The African Medicines Agency (AMA) is established with a mandate to promote regulatory reliance, harmonization, and collaboration among African nations. Its risk-based approach to GMP is built on work-sharing models of African Regional Economic Communities (RECs). The African Medicines Regulatory Harmonization (AMRH) initiative is a flagship program of the African Union (AU. A risk-based approach to GMP inspections is one of the harmonization areas. Work-sharing through joint inspections and reliance on the works of trusted authorities are the approaches used (SAHPRA, 2023). A cooperative agreement is established between PIC/S and AUDA-NEPAD to share information on GMP and enhance capacity building among African NRAs. This collaboration includes facilitating the accession of African NRAs under the African Medicines Agency (AMA) to PIC/S and providing training for inspectors (IPQ, 2025).

Disclosure of GMP Inspections Findings

The disclosure of GMP inspection findings is a critical component of the global pharmaceutical quality system, which serves as a mechanism to drive industry-wide quality improvement, regulatory efficiency, and public health protection. Disclosure and regulatory sharing among regulatory authorities are essential for global oversight of the complex regulatory system. Disclosure and regulatory sharing enable regulatory reliance and work-sharing, facilitate a risk-based approach, and lead to harmonization and uniform interpretation of GMP standards (EPIFA, 2014). Disclosure of common GMP inspection deficiencies also provides insight to regulators into prevalent cGMP challenges, which aids in planning risk-based GMP inspections, providing targeted training for inspectors. For the pharmaceutical industry, disclosure of

observed deficiencies, especially publication of common or critical observations by regulatory agencies, allows the pharmaceutical industry to learn from other failures and implement voluntary improvements to its PQS and process (PMDA, 2024). Different regulatory authorities worldwide have adopted various approaches to publicizing the results of their GMP inspections.

The US FDA uses Form 483s and Warning Letters to notify inspected facilities of compliance issues. The Form 483, formally called "Inspectional observations," is an initial list of findings made by the inspector, containing a list of objectionable conditions. It is issued at the end of an inspection process. They are not officially public immediately (FDA, 2024). A warning Letter is more serious, escalated regulatory action issued when there is a significant violation of the regulatory laws. Warning Letters are publicly disclosed. The US FDA posts all Warning Letters on its public website shortly after they are issued to the company (FDA, 2023). In addition, the US FDA provides access to inspection classification data (No Action Indicated, Voluntary Action Indicated, and Official Action Indicated) through its data dashboard (FDA, 2024). This ensures transparency and alerts the public and other stakeholders.

The European Union Drug Regulating Authorities Good Manufacturing and Distribution Practice (EudraGMDP) is the official, publicly accessible European repository for information on the compliance status of pharmaceutical companies operating within or supplying the EU. EudraGMDP makes compliance certificates and non-compliance reports publicly available. This allows all EU NRAs to immediately access and verify the compliance status of a drug manufacturer or distributor. For pharmaceutical companies, it is a mandatory resource for supplier qualification. For patients and healthcare providers, it builds trust that medicines on the market are regulated and safe (EMA, 2011).

Public disclosure of GMP inspection findings is limited in many African NMRAs. Resource constraints and regulatory maturity are cited as the main reasons. However, there is progress. For example, the TMDA analyzed GMP conformance of foreign pharmaceutical industries and reported aggregated data on non-conformances (Raphael Zozimus Sangeda, 2024). The AMRH initiative, with participation from various African NRAs, aims to enhance GMP standards and inspection practices across the continent. PIC/S has also established a cooperative agreement with AUDA-NEPAD to share information on GMP and enhance capacity building for GMPs among African NRAs (Eglovitch, 2025).

PIC recommends that all PIC/S participating Regulatory Authorities collect, analyze, and trend GMP inspection deficiency data to improve the quality system of inspectorates and to inform the pharmaceutical industry. All PIC/S participating Authorities should analyze and trend deficiencies annually to identify common specific GMP areas that require focused attention. The results of the annual deficiency assessment should be used as a key input for risk-based inspection planning (PIC/S, 2019).

The EFDA does not have a mechanism for disclosing GMP inspection findings to the public.

Disclosing common GMP deficiencies is considered a best practice in the current regulatory landscape. As discussed above, public disclosure of deficiencies enhance transparency, accountability, and public health protection. EFDA should consider the following recommendations, as per the practices of international and African regulatory authorities (Sachdeva, 2024):

- Development of Targeted Guidance Documents: Based on the analysis of common deficiencies, develop and disseminate specific guidance documents or best practice recommendations to the pharmaceutical industry, focusing on areas where non-compliance is prevalent.
- Utilization of the EFDA Website: Leverage the EFDA website to publish summary reports and potentially even anonymous examples of common deficiencies, making this information easily accessible to pharmaceutical industry and other stakeholders.
- Engagement with AMRH: Actively share information on common GMP deficiencies identified in Ethiopia with other African NRAs through the AMRH platform to contribute to regional knowledge sharing and harmonization.

Mature regulatory authorities use databases and information management systems to manage and analyze GMP inspection data. Using such platforms, they share findings internally and with other regulatory authorities. This enhances understanding of GMP compliance across the pharmaceutical industry and regions (Sachdeva, 2024). In Africa, there are initiatives such as AMRH that intend to facilitate information sharing among the African NRAs. This will improve decision-making and reduce reliance on onsite inspection. EFDA should prioritize strengthening its systems for collecting, analyzing, and sharing GMP inspection findings internally and to the public.

Working in collaboration with other NRAs to share information on GMP deficiencies can contribute to early detection of potential quality issues in marketed products. EFDA should explore opportunities to participate in regional and international networks for information sharing related to GMP inspection findings and their implication for product quality (EMA, 2017).

Relationship between Major GMP Areas of Non-Compliance

Table 8 presents the top ten GMP chapters with the highest deficiencies of EFDA foreign inspections (2015–2024). A Pearson correlation analysis was conducted among the top five GMP areas to assess the potential relationships between them. The results show significant interdependencies between these chapters. Quality Control and Production exhibited the strongest correlation (R^2 = 0.940), as indicated in Figure 11. This relation indicates that deficiencies in QC systems frequently coincide with production-related non-compliance, due to shared root causes such as inadequate process validation or deviation during manufacturing that may result QC failures or out of specification (OOS) results (Pazhayatil, 2019).

Quality Control and Documentation also have a significant correlation ($R^2 = 0.836$). This emphasizes the critical role of good documentation in ensuring the accuracy and validity of QC activities, as incomplete documentation can inhibit traceability and investigation of deviations or OOS (Wang, 2021). Materials and Production also have a strong correlation ($R^2 = 0.830$). This reflects the impact of raw material issues on production consistency, which continues as a common deficiency in US FDA Warning Letters (The FDA Group, 2023). Premises and HVAC Systems also have a high correlation ($R^2 = 0.757$). This highlights the link between facility design (e.g., Cleanroom controls) and contamination risks, which are a key, focus in both US FDA and EMA inspections (Buendia, 2025).

A quantitative analysis of FDA Form 483 observations similarly identified strong correlations between: Laboratory Controls (21 CFR 211 Subpart I) and Records/Reports (Subpart J) (*R^2 = 0.78*), indicating that data integrity lapses often accompany inadequate lab controls. Production Controls (Subpart F) and Equipment (Subpart D) ($R^2 = 0.52$), reinforcing the relationship between process validation failures and equipment maintenance gaps (Ajay Babu Pazhayattil M. I., 2019).

7. Conclusion and Recommendations

Conclusion

The analysis of EFDA GMP inspection findings across local and foreign manufacturers during different time periods revealed recurring deficiencies in key GMP elements, such as quality management, quality control, premises, material management and production. The local GMP compliance rate appears to be improving over time. However, significant proportions still face challenges in meeting all of the GMP requirements. When the findings of EFDA are compared to the findings of other international regulatory authorities, the US FDA, EMA, MHRA, and ANVISA, similarities and notable differences are observed. Possible reasons for differences in the inspection findings include the type of manufacturing facilities inspected, inspection approaches (line-based Vs product-based), and the scope of inspection. The GMP inspection findings of EFDA indicate that a high number of pharmaceutical manufacturing facilities, local and foreign, are not operating in adherence to GMP standards. Therefore, robust regulatory oversight and continuous improvement efforts by manufacturing facilities are required to ensure the quality of medicines.

EFDA has made good progress in adopting a risk-based approach towards GMP inspections. EFDA has formulated a directive and guidelines on this matter, keeping pace with regional and international best practices, thereby emphasizing reliance on trusted authorities. By pursuing further improvements in the risk assessment criteria, transparency, and international cooperation, EFDA could achieve optimal control of its GMP, thereby ensuring that all drugs circulating in Ethiopia are safe and quality, and may lead to more recognition, such as through membership of PIC/S.

To effectively regulate the pharmaceutical industry, in a globalized environment, EFDA needs to harmonize GMP inspection standards (requirements), participate actively in regional and international inspection processes (such as through PIC/S), and establish mutual recognition agreements with regional or international regulators. By leveraging its present strength and implementing, in a strategic way, the recommendations provided in this research, EFDA can enhance its capability in GMP oversight and, as a result, can itself assure the quality of drugs supplied within Ethiopia, while facilitating more international cooperation in this most essential sector of public health.

Public disclosure of GMP deficiencies is an important step toward regulatory transparency and trust from the public. The EFDA, through the adoption of this international best practice and consideration of recommendations by PIC/S, improves its practice in this regard. Regular assessment and trending of GMP deficiencies, coupled with public disclosure, build a robust pharmaceutical quality system in Ethiopian local pharmaceutical industries that contributes to improved public health.

Recommendations

To further strengthen the GMP compliance and ensure the quality of pharmaceutical products in Ethiopia, the following recommendations are proposed:

1. **For EFDA:**
    - **Annual Review of GMP Deficiencies:** An annual review of GMP inspection findings for both local and foreign pharmaceutical manufacturers will assist EFDA in identifying recurring issues and trends. Adopting PIC/S recommendation for annual review will also align EFDA with international best practices, ensuring consistency in identifying and addressing non-compliance.
    - **Public Summary Reports of Common Deficiencies**: To facilitate transparency, summary reports of common deficiencies can be made available on EFDA's online platform, thereby enabling EFDA's regulated community to learn about GMP components that have potential room for improvement on the part of manufacturers through other people's mistakes, thereby helping them enhance their pharmaceutical quality system. EFDA can develop a database system that facilitates easier accessibility of this information, thereby enabling better stakeholder engagement.
    - **Engagement with AMRH:** Sharing GMP deficiencies on the AMRH platform with other African NMRAs will promote regional sharing of knowledge and harmonization. Local manufacturers will get information on best practices across the content. Foreign manufacturers will benefit from a harmonized regulatory environment, reducing compliance costs and improving market access across Africa.
    - **Refine Risk Assessment Criteria**: Continuously improving risk assessment criteria based on available data and international best practices can help inspections focus on high risk products of facilities effectively.
2. **For Ethiopian Pharmaceutical Manufacturers:**
    - **Strengthen Pharmaceutical Quality Systems (PQS):** PQS is a comprehensive, overarching system that ensures and manages adherence to GMP principles. Therefore, establishing a robust PQS facilitates continuous improvement through the CAPA system, change management, risk management, and management review. These result in GMP compliance, which ensures product quality and patient safety.
    - **Improve Documentation Practices:** Good documentation practice (GDocP) is the backbone of the PQS. GDocP is essential for maintaining GMP compliance as it provides the evidence that medicines are manufactured correctly, safely, and consistently as required by law. Therefore, a comprehensive documentation practice is critical for GMP compliance.
    - **Focus on Facility and Equipment Maintenance:** Facility maintenance ensures the manufacturing environment itself does not compromise product quality. Equipment maintenance ensures that machinery functions as designed and qualified, consistently producing a quality product. Proper and regular maintenance of the manufacturing facility and equipment is critical for GMP compliance and to manufacture safe and

quality products at all times.

- **Ensure Robust Quality Control Services:** Quality Control (QC) serves as the final safeguard for patient safety by providing the documented evidence that every batch of a pharmaceutical product meets the required specification before its release to the market. Establishing and maintaining a robust QC service is critical for GMP compliance and verifying product quality at all manufacturing stages.
- **Effective Material Management:** Materials must be protected from deterioration, contamination, and mix-ups throughout their time in the facility. Effective materials management ensures that components of a medicine are correct, uncontaminated, and handled correctly at all times. Implementing effective material management is critical to GMP compliance and ensuring safe and quality products.
- **Increase Local Production:** Local production strengthens quality and safety through several key mechanisms. Local facilities allow for better regulatory oversight (easier inspection) and enforcement (in case of non-compliance, the authority can take immediate actions, close relationships). Increased local production results in improved supply chain control (shorter supply chain) and traceability. Therefore, booting local production capacity can facilitate GMP compliance and ensure the availability of safe and quality products.

3. **For Further Research:**
   - Conduct more detailed studies to identify the specific root causes of GMP non-compliance within the Ethiopian pharmaceutical manufacturing sector.
   - Evaluate the impact and effectiveness of EFDA's regulatory interventions on the quality of locally manufactured medicines across different product categories.
   - Explore the feasibility of adopting more stringent GMP standards for high-risk product categories like sterile pharmaceuticals and biologicals in alignment with international best practices.

8. Limitation of the Study

The analysis presented in this study utilized the EFDA's GMP inspection reports between 2015 and 2025, alongside publicly available information regarding the inspection activities and findings of other regulatory authorities. It is important to acknowledge that direct comparisons between these agencies may be subject to certain limitations due to variations in reporting periods, differences in the definitions and classifications of compliance, and the specific focus and scope of inspections conducted by each authority.

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Annex I: Data Collection Tool

The data collection tool was an MS-Excel with four sections.

Section 1: Types of Inspection

Blind ID	Year of Inspection	Country/Region	Type of Inspection	Number of deficiencies per inspection	Deficiency Type		
					Critical	Major	Other /minor
1001							
1002							

Section 2: Production Lines and Conclusion (Outcomes)

Blind ID	General Oral Solid DFs	General Oral Liquid DFs	Topical/ Semisolid DFs	Sterile Products	Beta-Lactam / Penicillin Oral DFs	Beta-Lactam/ Penicillin Oral Liquid DFS	Hormonal Oral DFS	Vaccines/ Biological/ Hormonal Products
1001								
1002								

Section 3: Deficiencies observed Per EFDA GMP Chapters

Blind ID	Quality Management	Sanitation and Hygiene	Premise	Equipment	Materials	Personnel	Production	Quality Control	Contract Production and	Complaints and Product Recall	Self-inspection and Quality Audits	Validation and Qualification	Documentation	Water for Pharmaceutical Use	Heating, Ventilation and Air Conditioning Systems (HVAC)
1001															
1002															

Section 4: Common critical and major deficiencies found as per the following areas

1002	1001	Blind ID
		Products are not consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization
		Water systems (purified water and water for injection) not reviewed at appropriate regular intervals or not all the relevant topics considered
		Documentation does not cover all aspects of GMP, for example does not ensure that authorized person have all the information necessary to decide to release a batch of a drug for sale, does not provide traceability that will permit investigation or the availability of the data needed for validation, review, and statistical analysis
		Time limits for storage of equipment before and after cleaning not stated or based on data validation
		Qualification and validation considered as one-off exercises. There is no on-going monitoring program based on a periodic review
		Quality assurance system is inappropriate for the manufacturing of pharmaceutical products. For example, does not ensure that deviations are reported, investigated, and recorded
		Storage areas not designed or adapted to ensure good storage conditions, e.g., temperature and humidity not provided, controlled, monitored, and recorded where appropriate
		Validation of processes and systems does not establish confidence that the manufactured products will consistently meet their product specifications.
		Analytical test methods, automated systems, or cleaning procedures not validated
		Quality control does not properly evaluate the quality and stability of finished pharmaceutical products or, when necessary, of starting materials and intermediate products
		Equipment, utility, or system not maintained, monitored, and calibrated according to a regular schedule
		Sampling not being conducted in such a way as to prevent contamination or cross-contamination
		Documents are not complete, accurate, reviewed regularly, contain all the required information or updated regularly.
		The quality control department does not have adequate resources to ensure that all the quality control arrangements are effectively and reliably carried out.
		Identity test not conducted on a sample from each container of starting material
		There is no documentary evidence of design qualification, installation qualification, operational qualification, performance qualification, or process validation
		The heads of the production and quality control and quality assurance do not share, or jointly exercise, responsibilities relating to quality, such as monitoring and control of the manufacturing environment, process validation and calibration of analytical apparatus, approval and monitoring of suppliers of materials, or approval and monitoring of contract manufacturers
		Production areas do not have air treatment systems appropriate for the products manufactured, operations made, and external environment (including air filtration) to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity and differential
		There is poor documentation practice
		Premises are not located, designed, constructed, adapted, or maintained to suit the operations to be carried out
		Where dust is generated, e.g., during sampling, weighing, mixing and processing operations, and packaging of powder, measures are not taken to avoid cross-contamination and facilitate cleaning