GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS IN ETHIOPIA:

RETROSPECTIVE ANALYSIS OF REGULATORY INSPECTION FINDINGS

Ethiopian Food and Drug Authority

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FIGURES AND TABLES

!Unexpected End of Formula

ACRONYMS

EFDA	Ethiopia Food and Drug Authority
GMP	good manufacturing practice
PQM +	Promoting the Quality of Medicines plus program
QMS	quality management system
SRA	Stringent Regulatory Authority
USP	United States Pharmacopeia
USAID	United States Agency for International Development
WHO	World Health Organization

DEFINITIONS OF KEY TERMS

GOOD MANUFACTURING PRACTICE: The part of quality assurance that ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization or product specification.

CRITICAL DEFICIENCY: A deficiency that has produced, or leads to, a significant risk of producing a harmful product or that results in a product that endangers the patient or poses a significant risk to the patient.

MAJOR DEFICIENCY: A deficiency that indicates a major deviation from good manufacturing practice.

MINOR DEFICIENCIES: Deficiencies that do not correspond to the definition of the two previous categories but indicate a departure from good manufacturing practice.

QUALITY MANAGEMENT SYSTEM: A set of policies, processes, and procedures required for planning and execution (production/development/service) in the core business area of an organization (i.e., areas that can impact the organization's ability to meet customer requirements).

QUALIFICATION: A process that establishes documented evidence that a specific equipment, facility, or system is fit and ready for its intended use and that ensures the satisfaction of critical requirements necessary for related product quality.

PHARMACEUTICAL INSPECTION: An aspect of the universal drug quality assurance system aimed at enforcing good manufacturing practice compliance or providing a license for the manufacture of pharmaceutical products. This inspection focuses mainly on a request by applicants of drug product registration for marketing authorization (WHO, Provisional Guidelines on the Inspection of Pharmaceutical Manufacturers 1992).

REGULATORY SYSTEM: A framework of legal provisions on good manufacturing practices, inspections, and enforcements that safeguard the public health.

THE AUTHORITY: Ethiopia Food and Drug Authority.

ACKNOWLEDGMENT

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1. INTRODUCTION

Good manufacturing practice (GMP) is the part of quality management which ensures that products are produced and controlled in conformance with quality standards appropriate to their intended use and as required by marketing authorization. Adherence to the GMP regulations contributes to reaching key quality attributes, including but not limited to the identity, strength, quality, and purity of drug products.

The primary objective of GMP is to manage and minimize the inherent risks in pharmaceutical manufacturing to guarantee the quality, safety, and efficacy of products. Achieving that objective will assure the highest standards of efficacy, quality, and safety in any process that involves the manufacture of health products.

GMP regulations address all aspects of manufacturing, packaging, and labeling, including cleanliness and sanitation, equipment function and use, recordkeeping, personnel, operations and processes, product testing, and addressing errors and complaints.

The circulation of poor-quality medicines, especially in developing countries, is a public health concern. Compliance with GMP is essential to ensure the quality, efficacy, and safety of medicines.

Food and Medicine Administration Proclamation No.1112/2019, Article 20 Sub-article 4, states that every medicine or medical device shall be produced in accordance with the appropriate GMP.

The Ethiopian Food and Drug Authority (EFDA) is mandated to perform an on-site inspection of foreign manufacturers as per the Food and Drug Administration Proclamation No.1112/2019. But due to resource limitations, the Authority designed strategies for reliance on GMP inspection certificates and reports of stringent Regulatory Authority (SRA) and the World Health Organization (WHO). The Authority's objective is , after conducting its own desk review of their inspection report, is to boost access to safe, high-quality, and efficacious medicines through the expedited market authorization process.

Although the Authority implemented the aforementioned strategy, it continues to conduct on-site inspections for those manufacturers that are not approved by the SRA countries or inspected by WHO. Even though the Authority has tried to minimize the risk of substandard and falsified medicines through its strategy of utilizing data from SRA/WHO inspections, so far there are not enough data or an effective system available to implement risk-based inspections to utilize the limited resources effectively.

The study's relevance to implementation of a risk-based inspection approach centers on its ability to use the gathered facts and findings to build on the limited data available on documented GMP inspection reports. The evidence-based data will strengthen the EFDA approach for implementing risk-based inspections. The assessment findings will help the Authority to identify areas of deficiencies and distribution of GMP non-compliance by country/facility and recognize gaps in inspection procedures to design a better risk-based inspection strategy in the future.

2. SCOPE

This assessment included pharmaceutical manufacturers' foreign GMP inspection reports that were inspected by the Authority during 2016, 2017, 2018, 2019, and 2021.

3. OBJECTIVE

3.1. Main Objective

The main objective of the assessment is to present an analysis of regulatory compliance following GMP inspections by the EFDA in foreign companies conducted in five years (2016, 2017, 2018, 2019, and 2021) to provide evidence for the Authority to propose future inspection strategies.

3.2 Specific Objectives

- To review the GMP deficiencies observed during the inspection periods
- To review consistency of inspectors for implementing the GMP guidelines and checklist
- To identify countries of distribution that are non-compliant with EFDA GMP requirements
- To identify gaps that need to be tackled to assure quality improvement of GMP inspection practices
- To suggest future inspection strategies based on recently observed trend data analysis

4. METHODOLOGY AND METHODS

EFDA in collaboration with PQM plus carried out a retrospective assessment by reviewing the full GMP inspection reports of all foreign manufacturers inspected by the EFDA in 2016, 2017, 2018, 2019, and 2021. The analysis included 277 inspection reports from five years of inspections. The team prepared the inspection reports according to the EFDA's GMP guideline requirements and other applicable local legislations. The team analyzed the reports by examining the scope of inspections, type of companies within product categories, dosage forms manufactured, deficiencies, and regulatory compliance and classified the inspection deficiencies as critical, major, and minor. A critical GMP failure occurs when a practice could give rise to a product that could or would be harmful to the patient or has produced a harmful product. A combination of major deficiencies indicating a serious system failure may also be considered as a critical deficiency according to the EFDA GMP Inspection Procedure Directive. All deficiencies found during the foreign GMP inspections are recorded, classified, and listed in the GMP inspection report as critical, major, or minor in the compliance conclusion.

5. DATA COLLECTION AND ANALYSIS

In collaboration with the Promoting the Quality of Medicines Plus (PQM+) program funded by United States Agency for International Development (USAID) and implemented by United States Pharmacopeia (USP), the Authority conducted data entry on a designed Excel spreadsheet from April to May 2022. This spreadsheet, used which is designed based on the EFDA standard content of the report, was used for the purpose of collecting data from GMP inspection reports and preparing the data for further analysis to propose a relevant strategy.

Prior to the main data entry and analysis, the Authority conducted a pilot test to validate the agreed-upon Excel sheet for data entry. Based on the results of this pilot test, the team made modifications to make it a better fit for its intended purpose.

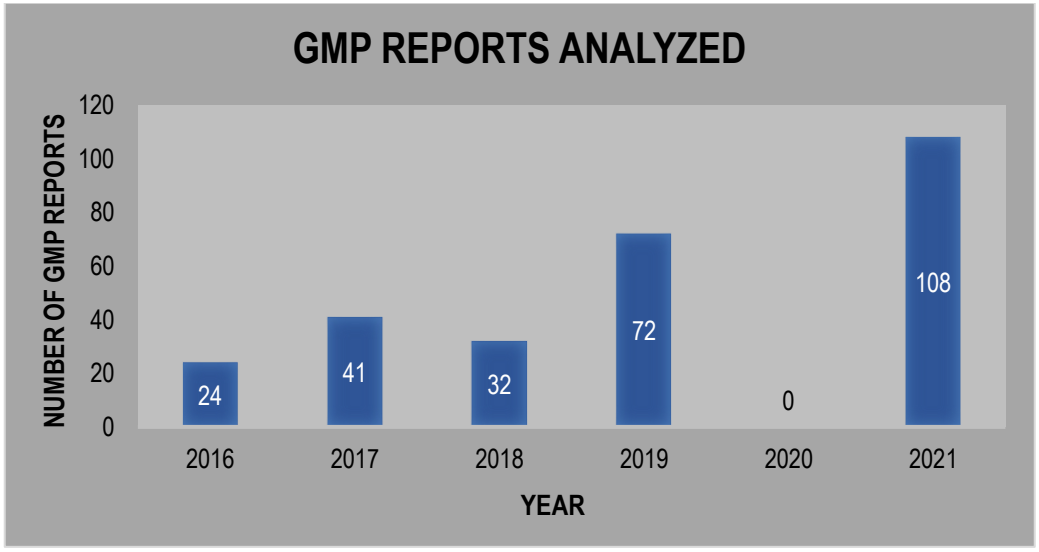
The GMP data included 277 foreign companies that manufacture medicinal products. The team entered the data into the Excel database for analysis and interpretation. The findings are summarized below using different data presentation formats, including figures, tables, and graphs.

6. RESULTS

6.1. Trend of inspected medicine manufacturing companies

All inspected foreign manufacturers covered in this trend analysis were companies inspected in 2016, 2017, 2018, 2019, and 2021. Figure 1 illustrates the distribution of GMP reports with year of inspection. The results show that the total number of inspected manufacturers increased from year to year. N = 277.

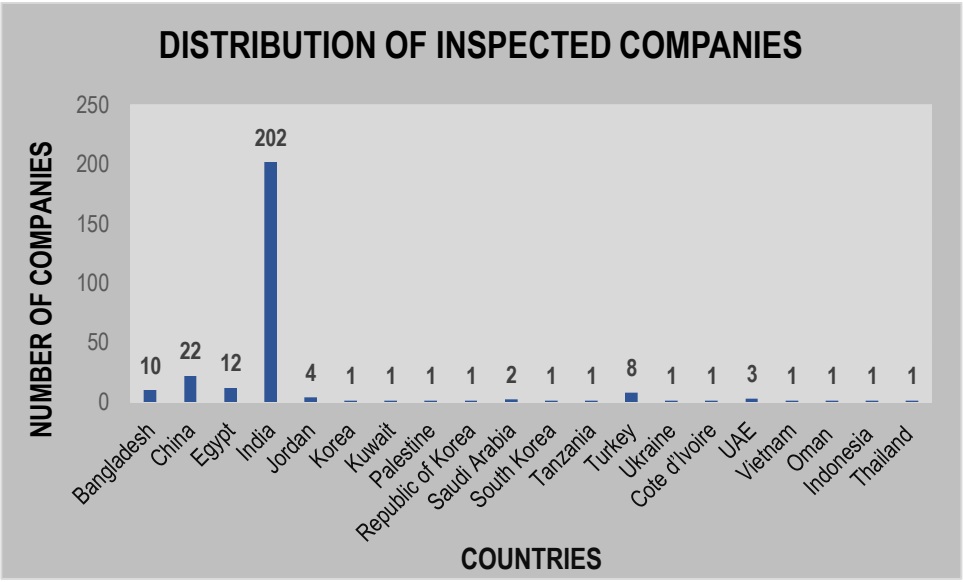
FIGURE 1. DISTRIBUTION PROFILE OF INSPECTED COMPANIES BY YEAR



6.2. Geographical coverage of inspected medicine manufacturing companies with respect to country

EFDA analyzed the distribution pattern of the inspected companies with respect to location. The largest proportion of the 277 companies by site were in India, 202 (72.9%); China, 22 (7.9%); and Egypt, 12 (4.9%). The majority of on-site inspections occurred in India and China. Figure 2 illustrates the distribution of inspected foreign pharmaceutical sites by location. N = 277.

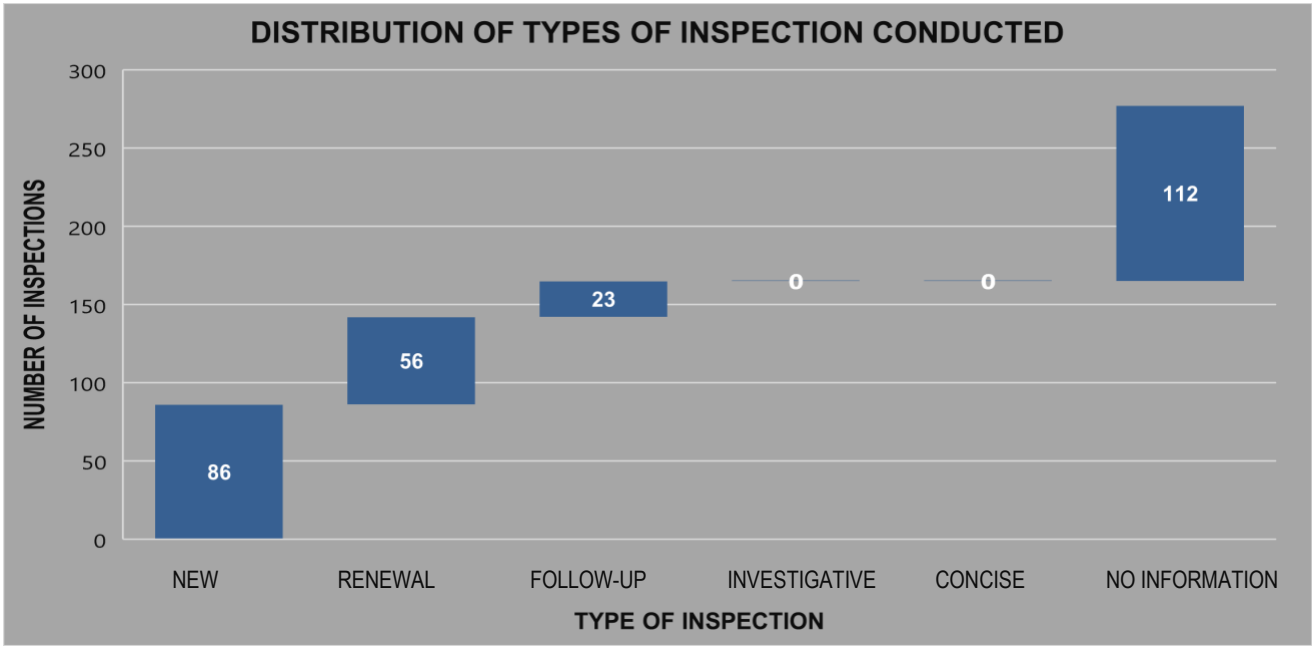
FIGURE 2. DISTRIBUTION OF INSPECTED FOREIGN PHARMACEUTICAL COMPANIES BY LOCATION



6.3. Profile of inspected medicine manufacturing companies with respect to country.

EFDA analyzed the type of inspection conducted based on Medicine Inspection Procedure Directive No. 830/2021. The data analysis shows that for 112 companies, the type of inspections was not indicated in the report, and 56 companies were designated as new inspection sites. The results in Figure 3 illustrate the type of inspections conducted by the Authority. N = 277.

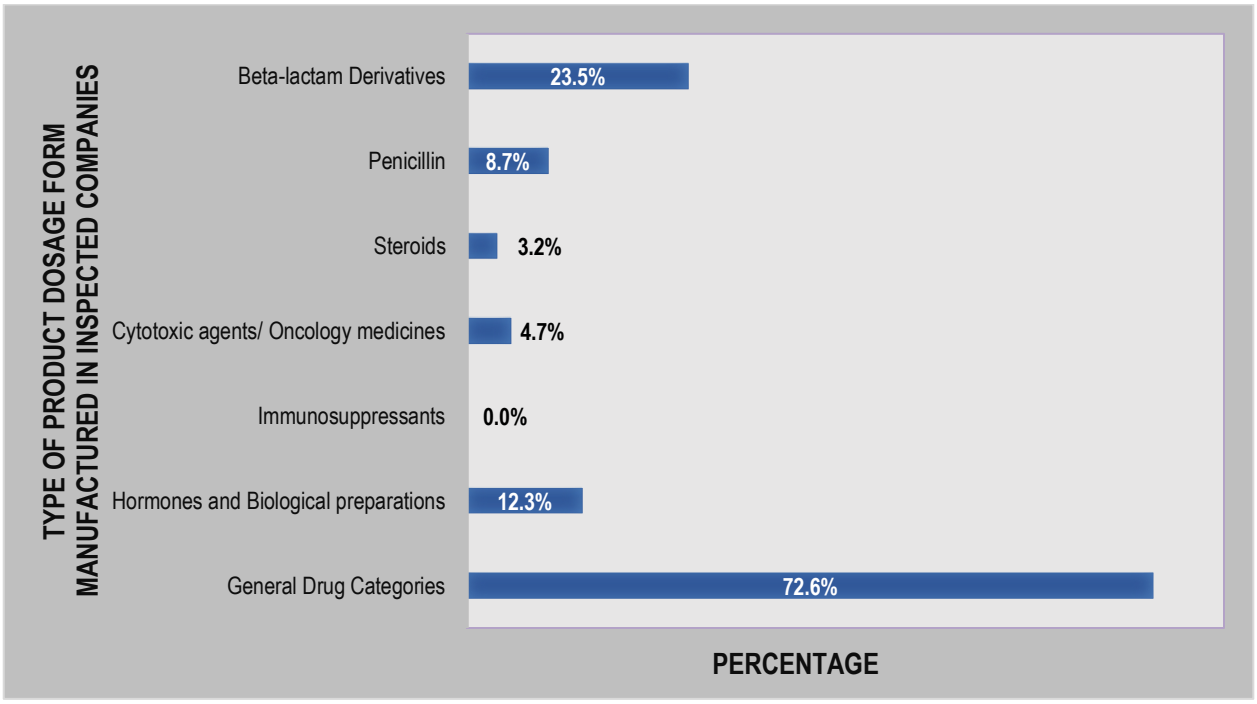
FIGURE 3. TYPE OF INSPECTION CONDUCTED BY THE AUTHORITY IN FOREIGN COMPANIES



6.4. Types of products manufactured in inspected foreign companies

EFDA analyzed the product categories manufactured by inspected foreign companies and found that more than 72 percent of the inspected products were in general drug categories. No pharmaceutical companies that manufactured immunosuppressants were inspected within the time period. The assessment results show that the Authority did not consider other low-use product categories. Figure 4 shows the distribution of inspected product categories manufactured by inspected foreign companies. N = 277.

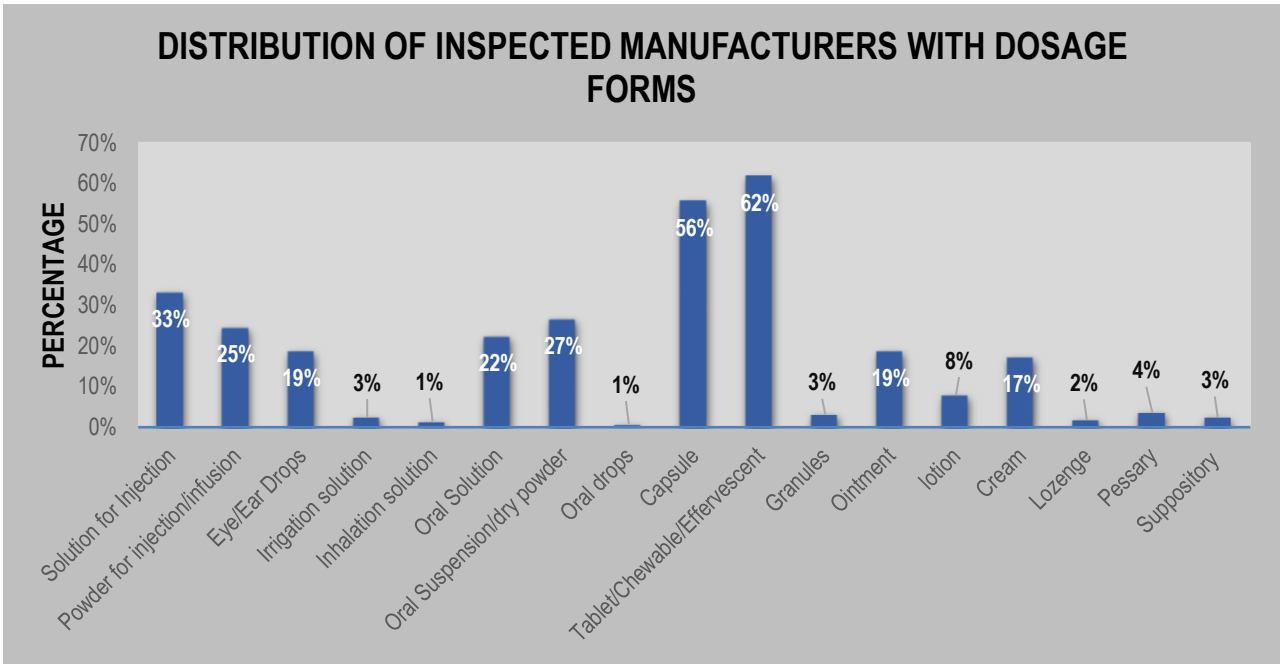
FIGURE 4. DISTRIBUTION OF INSPECTED PRODUCT CATEGORIES MANUFACTURED BY INSPECTED FOREIGN COMPANIES



6.5. Distribution of inspected manufacturer with their manufacturing dosage form

EFDA analyzed the type of dosage forms manufactured in the inspected companies. The results indicate 171 (62%) manufactured tablets (chewable and effervescent) and 154 (56%) manufactured capsule dosage forms. Figure 5 shows the distribution of inspected manufacturers with manufactured dosage forms. N = 277.

FIGURE 5. DISTRIBUTION OF INSPECTED MANUFACTURER WITH THEIR MANUFACTURING DOSAGE FORM



6.6. Coverage of the quality management system by inspectors during the inspection

As per the requirements of the EFDA's GMP Inspection Procedure Directive, all elements of the quality management system (QMS) shall be assessed by inspectors as per the checklist. The results show that all elements of the QMS were not covered during inspection. This could indicate that the inspectors were not using the inspection checklist consistently. Table 1 shows the coverage of the QMS elements during the inspection. N = 181.

TABLE 1. COVERAGE OF THE QUALITY MANAGEMENT SYSTEM ELEMENTS

Quality Management System Audit	Companies inspected	
	Number (N)	Percentage (%)
Audit or self-inspection management	155	86%
CAPA management	113	62%
Change control management	140	77%
Risk management	138	76%
Quality management review	99	55%
Training control/management	158	87%
Annual product quality review	130	72%
Handling of non-conformances	106	59%
Out of specification handling	139	77%
Complaint handling system	119	66%
Product recall system	139	77%

Quality Management System Audit	Companies inspected	
	Number (N)	Percentage (%)
Vendor Qualification	110	61%
Contract Agreement	120	66%

6.7. Coverage of GMP elements inspected for warehouse as per the checklist

According to the EFDA inspection checklist, inspectors shall evaluate the raw materials, packaging materials, finished product storage area, and sampling areas of the warehouse. The assessment results show that in 22 percent (39) of 181 inspected companies, the inspectors did not inspect the packaging materials. This assessment also shows that the inspectors did not follow the same procedure and checklist to inspect foreign companies. Table 2 shows the overage of the warehouse GMP elements during the inspection. N = 18.

TABLE 2. COVERAGE OF THE WAREHOUSE GMP ELEMENTS DURING INSPECTION

Warehouse Audit	Companies inspected	
	Number (N)	Percentage (%)
Raw materials	178	98%
Packaging materials	142	78%
Finished product	163	90%
Sampling room	177	98%
Dispensing room	175	97%

6.8. Coverage of GMP elements inspected for quality control as per the checklist

The inspector shall audit the GMP and good laboratory practice areas of the quality control based on the checklist, including method validation, sampling, instrumentation qualification, and preparation of the analytical solution. Out of 181 inspected companies, 131 were not inspected for method validation, and 96 were not inspected on reference standard usage. The results show that the inspectors were not consistent in using the inspection checklist as per the requirement. Table 3 shows the coverage of the quality control GMP elements during inspection. N = 181.

TABLE 3. COVERAGE OF THE QUALITY CONTROL GMP ELEMENTS DURING INSPECTION

Quality Control Audit	Companies inspected	
	Number(N)	Percentage (%)
Methods of validation	50	28%
Sampling	132	73%
Instrumentation qualification	125	69%
Physico-chemical	132	73%
Microbiology	158	87%
Analytic solution	94	52%
Retention sample	129	71%

Quality Control Audit	Companies inspected	
	Number(N)	Percentage (%)
Reference standard	85	47%
Stability studies	157	87%

6.9. Coverage of GMP elements inspected for production operation as per the checklist

The production operation GMP elements should consider qualification of facility/equipment/systems, process validation systems, cleaning validation systems, and environmental monitoring as per the EFDA's GMP guidelines. Analysis of data from 181 inspections carried out in 2016, 2017, 2018, 2019, and 2021 shows that in 59 (of 181) inspected companies, the qualifications of facility/equipment/systems were not audited, and in 146 inspected companies, the computer systems were not inspected. This assessment result shows that the inspectors were not using the same procedure to inspect all the companies. Table 4 shows the coverage of the production operations GMP elements during inspection. N = 181.

TABLE 4. COVERAGE OF GMP ELEMENTS INSPECTED FOR PRODUCTION OPERATION AS PER THE CHECKLIST

Production Operation Audit	Companies inspected	
	Number(N)	Percentage (%)
Qualification of facility/equipment/systems	122	67%
Process validation systems	131	72%
Cleaning validation system	129	71%
Environmental monitoring	104	57%
Personal hygiene/key personnel/training	118	65%
Computerized system	35	19%
Preventive and emergency maintenance	69	38%

6.10. Coverage of GMP elements inspected for utilities as per the checklist

The EFDA GMP guidelines state the requirements in pharmaceutical manufacturing industries. The inspector checklist requires that inspectors to audit the HVAC system, water system, and steam system to assure the quality of water and air used for production operations. EFDA inspected data from 181 inspections carried out in 2016, 2017, 2018, 2019, and 2021. The results show that 156 (86%) of the inspected pharmaceutical companies' steam systems and 56 (31%) of the inspected pharmaceutical companies' compressed air systems were not inspected. Table 5 shows coverage of the production operations GMP elements during the inspections. N = 181.

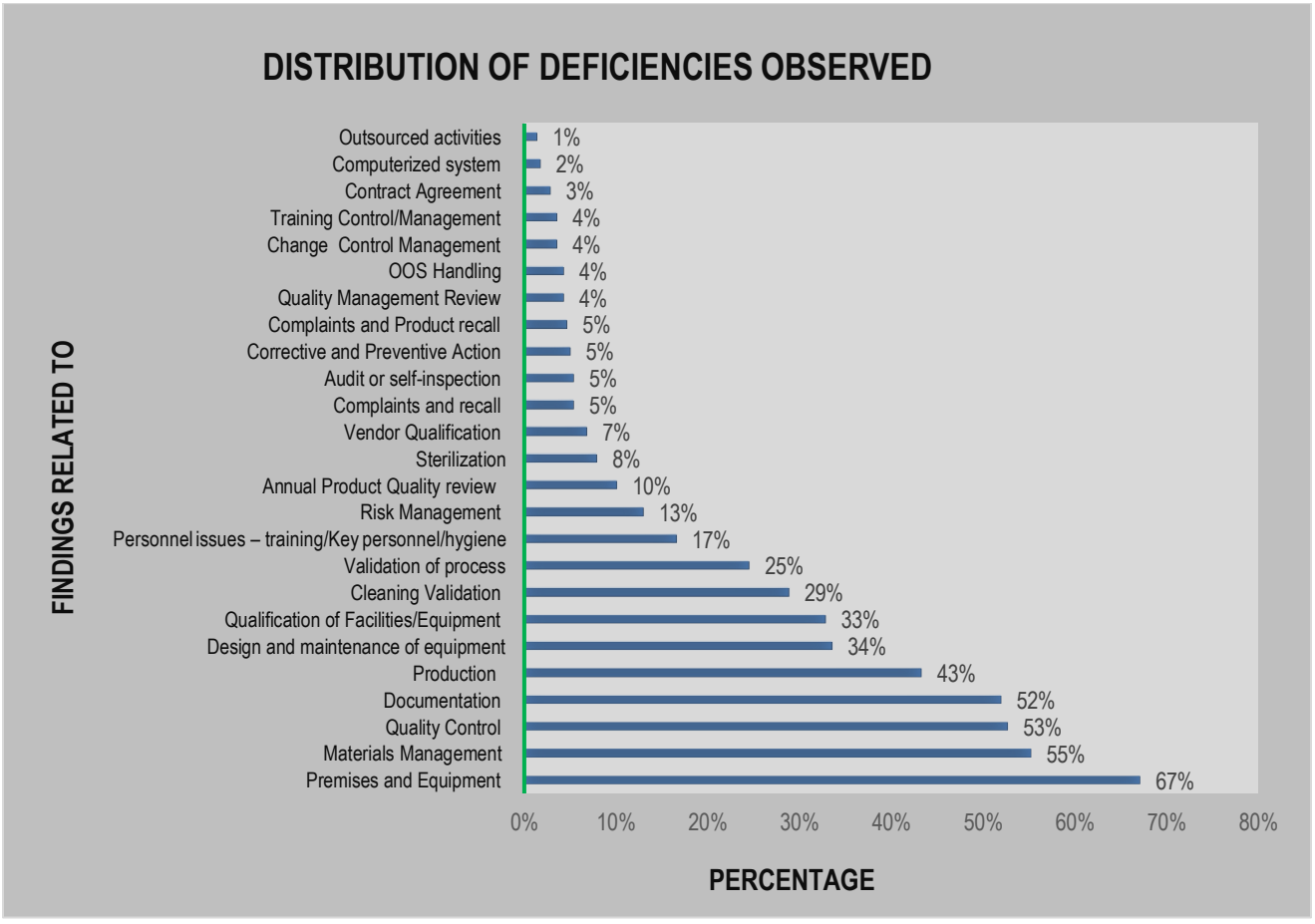
TABLE 5. COVERAGE OF THE PRODUCTION OPERATIONS GMP ELEMENTS DURING INSPECTION

Utilities Audit	Companies inspected	
	Number (N)	Percentage (%)
HVAC system	178	98%
Water quality testing and treatment systems	176	97%
Steam system	25	14%
Nitrogen (N2)	35	19%
Compressed air system	125	69%
Emergency power/stand-by generator	3	2%

6.11. GMP deficiencies documented by EFDA in in 2016, 2017, 2018, 2019, and 2021

[EFDA] analyzed data from 277 inspections carried out in 2016, 2017, 2018, 2019, and 2021 and tabulated the deficiencies found during the inspections. Those deficiencies are as follows: related to premises and equipment (67%), related to material management (55%), related to quality control (53%), and related to documentation (52%). Figure 6 shows the GMP deficiencies during inspection. N = 277.

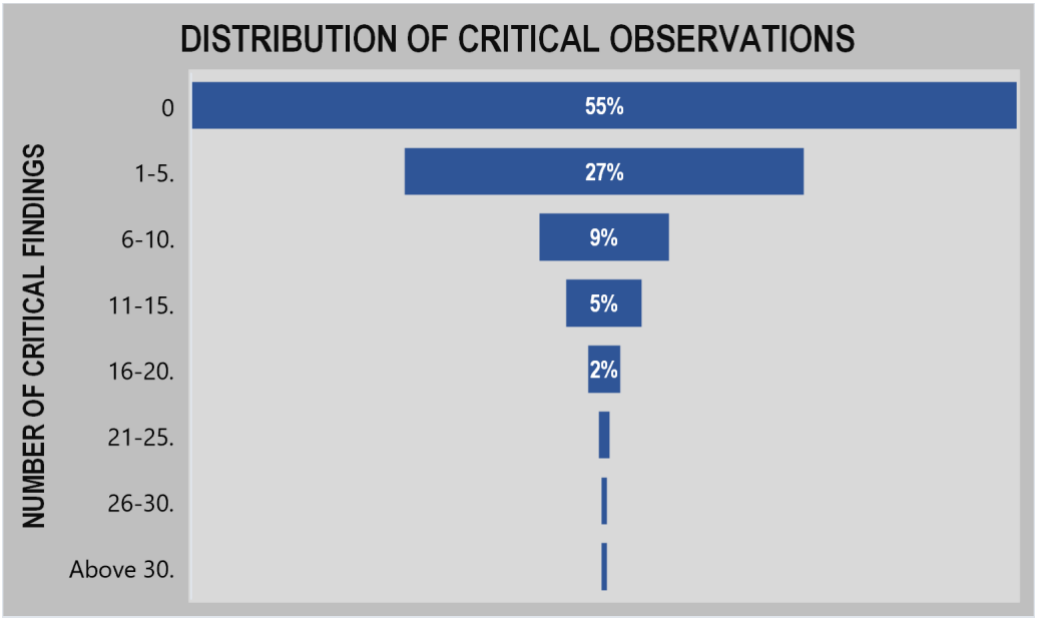
FIGURE 6 GMP DEFICIENCIES DURING INSPECTION



6.12. Critical deficiencies documented by EFDA in in 2016, 2017, 2018, 2019, and 2021

The EFDA Inspection Procedure Directive states that a company is considered non-compliant if it has one or more critical findings. Analysis of data from 277 inspections carried out in 2016, 2017, 2018, 2019, and 2021 shows the number of critical findings. Figure 7 illustrates the critical deficiencies found during inspection. The results show one or more critical findings among the inspected companies greater than 45 percent of the total inspected companies.

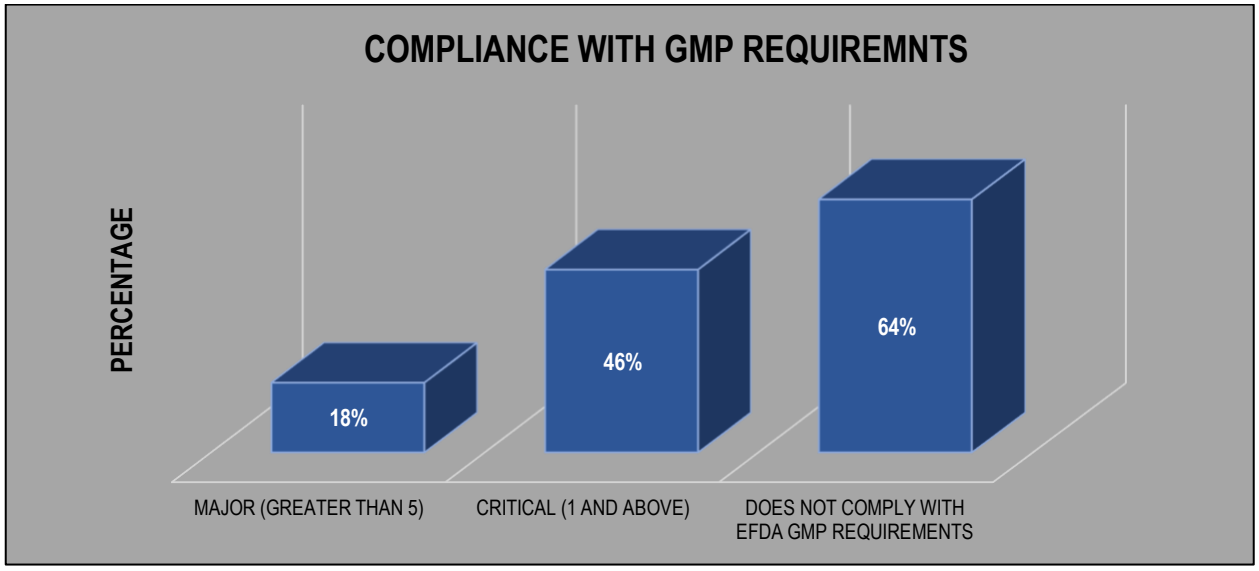
FIGURE 7. CRITICAL DEFICIENCIES DISTRIBUTION IN INSPECTED MANUFACTURER



6.13. Regulatory compliance as per the GMP Inspection Procedure Directive

The EFDA Inspection Procedure Directive states that a company is considered non-compliant if it has at least one critical finding and more than six major findings. [please fill in] analyzed data from 277 inspections carried out in 2016, 2017, 2018, 2019, and 2021 and found that 64 percent of the inspected pharmaceutical manufacturers will be non-compliant according to EFDA GMP guidelines. Figure 8 illustrates the GMP deficiencies by category (major, critical, and non-compliant).

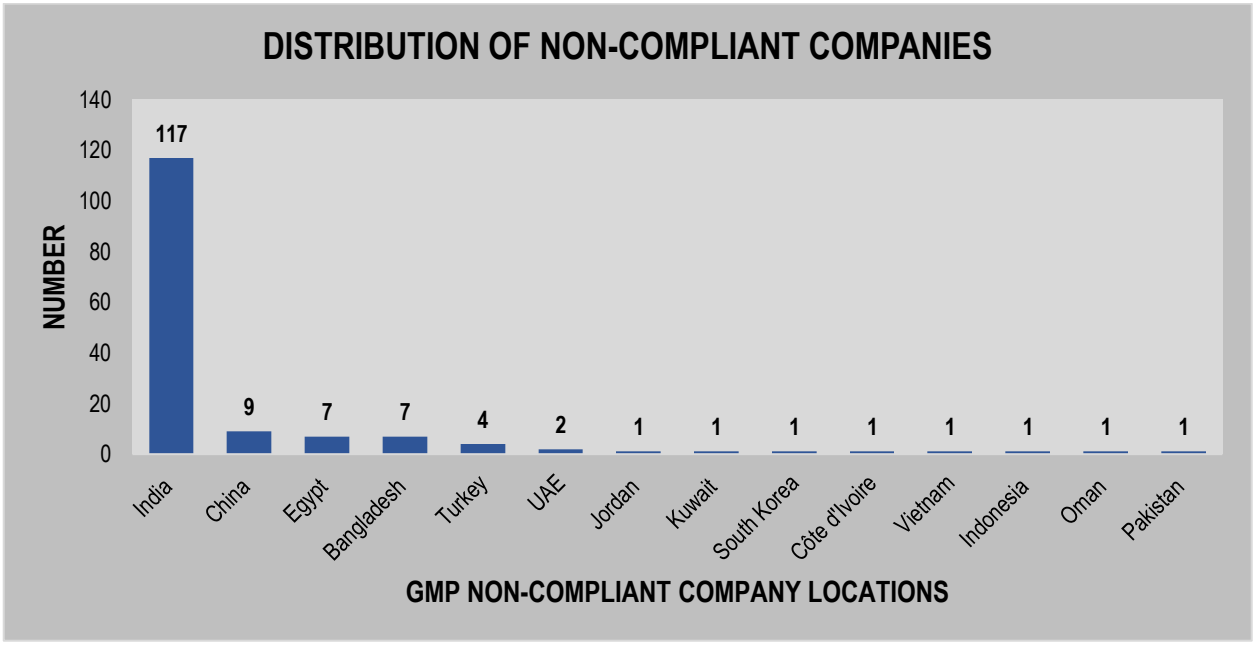
FIGURE 8. REGULATORY COMPLIANCE AS PER THE EFDA GMP PROCEDURE DIRECTIVE



6.14. Distribution of non-compliant manufacturing companies with respect to location

[EFDA] analyzed data from 277 inspections carried out in 2016, 2017, 2018, 2019, and 2021 and found that 154 (56%) were non-compliant with EFDA GMP requirements. Among the non-compliant manufacturers, 117 (76%) were located in India. Figure 9 illustrates the distribution of non-compliant companies with respect to the country of location. N = 277.

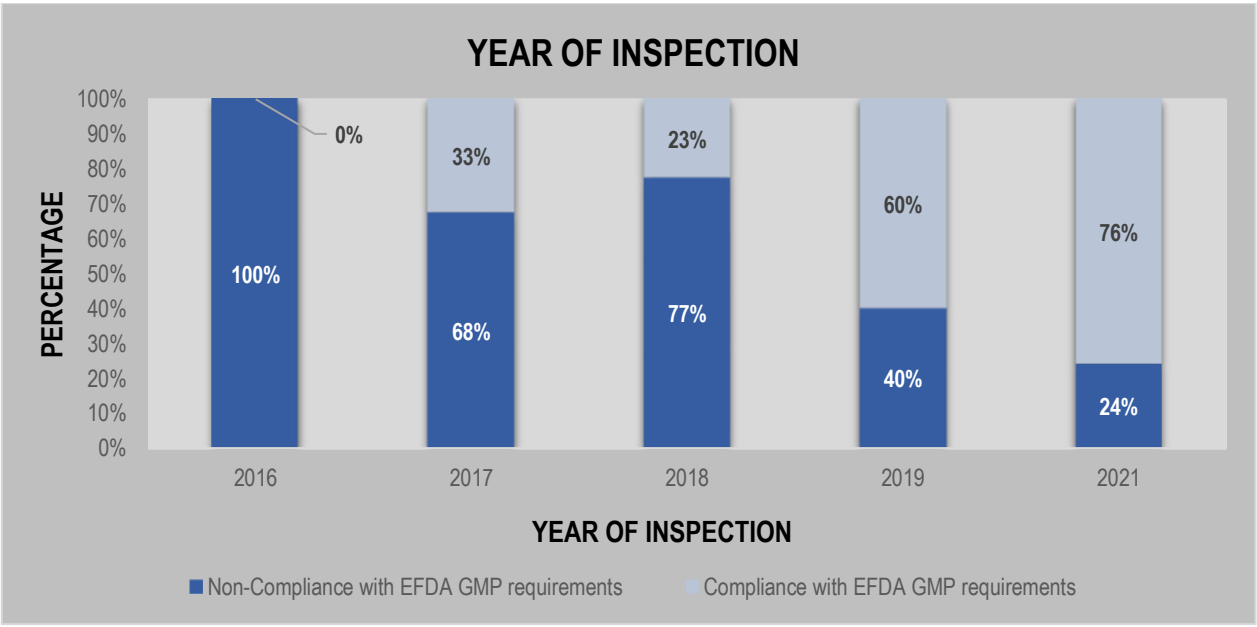
FIGURE 9. DISTRIBUTION OF NON-COMPLIANT COMPANIES WITH RESPECT TO THE COUNTRY OF LOCATION



6.15. Trend analysis with non-compliance with EFDA GMP requirements

[EFDA analyzed data with respect to years of non-compliance and compliance with EFDA GMP requirements. Of the inspected companies, 77 percent in 2018, 40 percent in 2019, and 24 percent in 2021 failed Ethiopian GMP requirements. The study result illustrates that the trend for non-compliance with GMP requirements is decreasing from year to year. Figure 10 shows the trend of GMP compliance for EFDA GMP requirements.

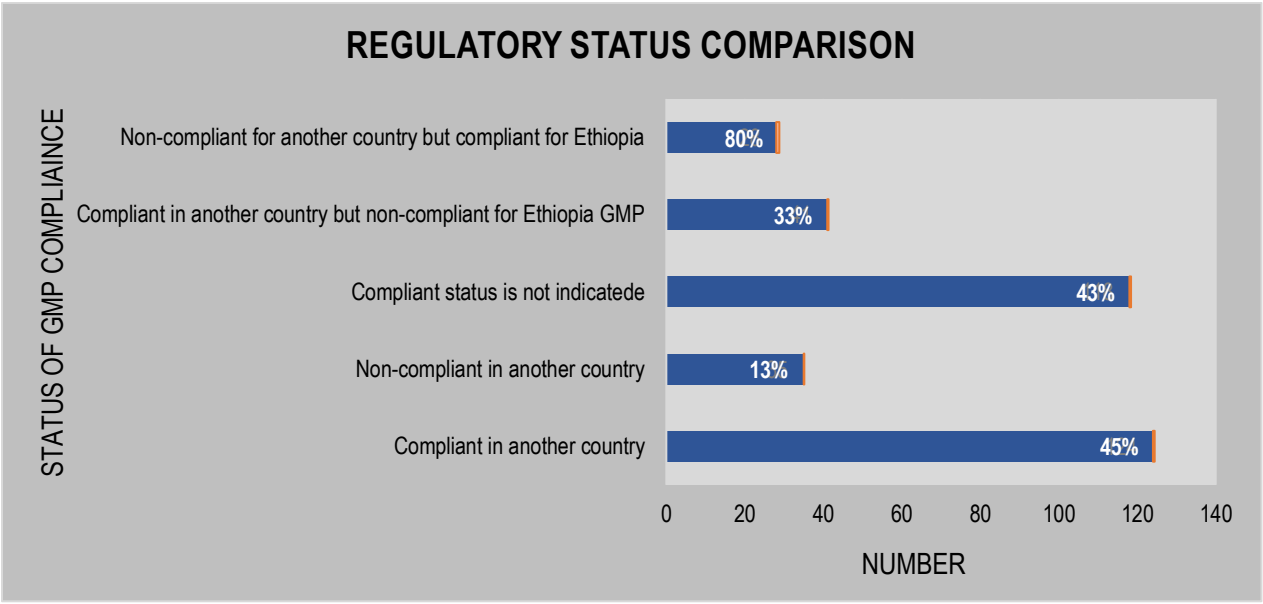
FIGURE 10. TREND OF GMP COMPLIANCE FOR EFDA GMP REQUIREMENTS PER INSPECTION YEARS



6.16. Regulatory status comparison

EFDA analyzed data from 277 inspections carried out per the regulatory compliance by other foreign regulatory Authorities and the EFDA. The results show that 80 percent of manufacturers that were non-compliant with other countries' GMP requirements and applied for EFDA GMP certification met compliance standards for the EFDA GMP requirements. Figure 11 shows the regulatory compliance of inspected manufacturers.

FIGURE 11. COMPARISON OF MANUFACTURES COMPLAINTS FOR GMP



7. CONCLUSIONS

This assessment represents a retrospective study of 277 foreign GMP inspection reports (2016, 2017, 2018, 2019, and 2021). In view of the findings made in this assessment, the conclusions reached are as follows:

1. In terms of compliance with the Authority's GMP guidelines, the results of assessment showed that 54 percent of the inspected companies were not in compliance with the Ethiopian GMP requirements. Observed manufacturers' deficiencies were noted for proper corrective actions.

2. The frequency of non-compliant observations was assessed to identify the gap areas for inspectors as well as for manufacturers. The most common areas of deficiencies found on documented GMP report data analyses were premises and equipment related (67%), material management related (55%), quality control related (53%), and documentation related (52%). These deficiencies contribute to the manufacturers' non-compliance.

3. The analysis of the GMP inspection findings shows that among the inspected manufacturers in the stated years, the majority of on-site inspected manufacturers were located in India (72%), and the most (117) GMP non-conformities were also located within India (76%) followed by China (9%), Egypt (7%), and Bangladesh (7%).

4. From the data analysis, the study results showed that the degree of manufacturers' non-compliance decreases from time to time (100% in 2016 and 24% in 2021) by implementing the same guidelines and procedures. The reason for the decrease could be related to the experience of inspectors and preparedness of the manufacturer as per the EFDA requirements.

5. EFDA made comparisons with respect to GMP compliance with other countries and EFDA. The comparison shows that 80 percent of manufacturers that were GMP non-compliant in other countries

were compliant for Ethiopia's GMP requirements, and 33 percent of manufacturers compliant in other countries were non-compliant for Ethiopian GMP requirements.

8. RECOMMENDATIONS

The Authority's management should apply strong regulatory requirements for those countries with a high prevalence rate for non-compliance; revise the requirements for reliance-based (risk-based) strategies for acceptance of the SRA GMP report; and assign experienced inspectors for those countries.

The management of the Authority should provide training for inspectors on the most commonly observed deficiencies and prepare a GMP guideline interpretation document for premises and equipment-related issues.

The Medicines Facility and Inspection Directorate shall strictly follow the implementation of EFDA guidelines, checklists and procedures, and common technical report writing format by all inspectorates for improving the consistency of GMP reports.

There should be periodic reassessments of the inspectors' competence to improve their performance in report writing and to have sufficient knowledge of GMP requirements.

The observed deficiencies reported reflected non-uniformity in classifying as critical, major, and minor, and the classification of the findings on non-conformities shall be based on their risks to product and patient.

Periodically publishing the results from GMP inspections reports performed by the EFDA will assist with knowledge surrounding the trend of deficiencies and non-compliant manufacturers' locations so that the strategies and regulations can be revised.

9. REFERENCES

1. European Medicines Agency. EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. EudraLex. 2012; 4: 1–8.

2. Food and Drug Administration. Facts about the Current Good Manufacturing Practices (cGMPs) [Internet]. 2015 [cited 28 May 2017] pp. 1–3. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm

3. Food and Medicine Administration Proclamation No.1112/2019.

4. Food, Medicine, and Health Care Administration and Control Authority. Expediting Medicine Market Authorization Strategy, 2007.

5. Good Manufacturing Practice Guideline for Pharmaceutical Products, 2014. http://www.rrfa.co.za/wp-content/uploads/2014/01/GMP-Guideline-for-pharmaceutical-products-2014.pdf

6. Pharmaceutical Inspection Co-operation Scheme (PIC/S). Guide to Good Manufacturing Practice for Medicinal Products. 2017.

7. Pharmaceutical Manufacturer GMP inspection Directive No338/2020. http://www.fmhaca.gov.et/publication/pharmaceutical_manufacturer_gmp_inspection_directive_no_338/

8. PLoS One. Quality of medicines: Deficiencies found by Brazilian Health Regulatory Agency (ANVISA) on good manufacturing practices international inspection, 2018.

9. WHO Expert Committee on Specifications for Pharmaceutical Preparations. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Tech Rep Ser. 2014; 986: 78–135.