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# Strategic Analysis of Warning Letters Issued by United State Food and Drug Administration to Pharmaceutical Companies Globally

Tiwaskar G. H.<sup>1</sup>, Pise A. G.<sup>1</sup>, Pise S. A.<sup>1</sup>, Bhardwaj P<sup>2</sup>

<sup>1</sup>Dadasaheb Balpande College of Pharmacy, Besa, Nagpur – 34, India; <sup>2</sup>Department of Regulatory affairs, Anushakti Nagar, Mumbai, Maharashtra, India.

## ABSTRACT

In pharmaceutical companies, the term “Quality” has special importance. It deals with the patient’s healthcare as well as their safety. To maintain this “Quality” there are various regulatory authorities around the world and these are according to the different countries such as the United States Food & Drug Administration (USFDA) for the US, Medicine & Healthcare Products Regulatory Agency (MHRA) for the UK, Therapeutic Good Administration (TGA) for Australia, etc. These regulatory authorities conduct an audit to identify the common issues that arise in pharmaceutical companies in a variety of sectors such as manufacturing quality, prescription drug promotion, immediate office, etc. and the authorities are responsible for giving a detailed report of violations of regulations in the form of CODE OF FEDERAL REGULATIONS (CFR) in the form of Warning letters. In this paper, we will mainly focus on the manufacturing quality and the common issues that arise in FDA483 for the U.S.A.

**Keywords:** Audit, FDA483, Quality, Regulatory affairs, Warning letters, Guidelines

## INTRODUCTION

### Quality:

A product that is fit for use can be described as which meets its established quality imputes and standards and has been manufactured by following cGMP regulations.<sup>1</sup> According to ISO, the International Standards Organization, in “ISO 9000:2005 – Fundamentals & Vocabulary”, defines quality as “the degree to which a set of characteristics fulfils requirements”.<sup>2</sup>

### Quality Audit:

Quality audit is defined as a structured and self-sufficient examination to determine whether activities and related results comply with planned arrangements. These arrangements are executed effectively and are suitable to achieve objectives.<sup>3</sup> there are three main types of audit which are as follows:

1. Internal Audit
2. External Audit
3. Regulatory Audit.

To verify the efficacy of a quality management system the quality audit is performed.<sup>4,5</sup>

1. **Internal Audit:** This is also known as a First-Party Audit or self-audit. Those auditing and those being audited are all held accountable by the same organization. It consists of counselling organizations on how to reach their goals in a better way.
2. **External Audit:** This is also known as a Second-Party Audit. And or as customer/customers running an audit on a supplier or contractor. It is important to examine the competence of the contractors in which we developed our products or perform the analysis of our products or any other activity according to GMP.
3. **Regulatory Audit:** This type of audit is also known as a Third-Party Audit. A regulatory agency or independent body manage a third-party audit for compliance/certification/registration purposes.

There is a team to perform the audit; it must include audit inspectors and a multidisciplinary company team. The company team consists of members from each of the following departments such as production, quality control, warehousing, maintenance, and administration, personnel, marketing and sales. These audits can be conducted without warning as manufacturers are required to always comply with GMPs. International regulatory bodies such as “Medicines and Healthcare products regulatory agency (MHRA) the UK,

### Corresponding Author:

Tiwaskar Gayatri H., Dadasaheb Balpande College of Pharmacy, Besa, Nagpur – 34, India.  
Email: [gtiwaskar073@gmail.com](mailto:gtiwaskar073@gmail.com)

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United States food and drug administration (USFDA), Therapeutic goods administration (TGA) Australia, Medicines control council (MCC) South Africa and other organizations worldwide are responsible for carrying out these checks.<sup>6</sup>

### Regulatory Audit Report:

A regulatory audit aims to analyze that a project is compliant with regulations and standards. National Emergency Management Executive Academy (NEMEA) Compliance Centre describes the regulatory audit as “must be accurate, objective, and independent while providing accuracy and assurance to the organization”.<sup>5</sup>

Audit Report means a report that figures the audit process and provides a summary of the audit findings. Regulatory Audit Plan means the annual plan of scheduled audits planned to measure the level of an organization’s uniformity.

**Regulatory Audit Program (RAP)** refers to examining programs and ensuring that the procedures and compensation mechanism comply with the contractual and regulatory requirements.<sup>7</sup>

**Regulatory Compliance** deals with the importance of observing rules or regulations. The theory has implications regarding all rules, regulations and standards development for human services and economic domains. The research is being designed from the human services field.<sup>8</sup>

### Office of manufacturing Quality:

The office of Manufacturing Quality (OMQ) evaluates concurrence with manufacturing requirements for drugs based on inspection reports and evidence gathered by FDA inspection. OMQ develops and allows the compliance policy and takes risk-based actions to preserve the public from adulterated drugs in the U.S. market.<sup>9</sup> The OMQ has outlined its mission as follows:

Develop and implement compliance, impose policies, and take actions to protect patients from products that result in a risk to public health. Work to bring inspected facilities with significant violations of federal law and regulations into compliance through warning letters and other actions. Work with Food Drug Administration (FDA) investigators to make certain that the consistent application of risk-based, patient-focused compliance and enforcement policies and actions. Evaluate manufacturing and product quality issues to diminish the drug shortages.

The organization of OMQ follows<sup>10</sup>

- Division of Drug Quality I
- Division of Drug Quality II
- Manufacturing Quality Guidance and Policy Staff.

### Regulatory Authority of USA

The United States Food Drug Administration was established in 1848. This is an agency under the U.S. department

of health and human services to control the quality of food.<sup>11</sup> It comprises the Office of the Commissioner and four heads of directors regulate the main functions of the agency such as Medical Products and Tobacco, Foods and Veterinary Medicine, Global Regulatory Operations and Policy, and Operations.<sup>12</sup> It ensures that the product is a safe supply of food and/or an effective drug to the public.<sup>13</sup> The products are affordable and consumers have to purchase the new products. They are also responsible for making sure that the product should be of high quality.<sup>14</sup> FDA also helps develop the innovation speed that further helps build the medical product as more effective, safer, and more affordable.<sup>15</sup> The FDA usually comes for inspection in pharmaceuticals companies. And inspections are observed for three main reasons i.e., pre-approval inspection before approval of drug products, Regular cGMP inspection, and for the audit causes.<sup>16</sup> during the inspection, if noncompliance is observed, the investigator issues the observations on the 483 forms. Form 483 is used by U.S. FDA to communicate the inspection observation.

### FDA483:

The FDA Form 483. It is officially known as “Notice of Inspectional Observations,” or just 483. The 483 is issued at the end of a field-based inspection if the FDA onsite investigator observed inaccuracy in your quality system or conditions that violate the Food, Drug, or Cosmetic Act. It is issued at manufacturing sites after the completion of the FDA audit.<sup>17</sup> you must respond to the 483 or a Warning Letter promptly within 15 days. Following this identify your steps of action to improve the findings within the FDA’s specified timeframe. A detailed response to each observation or violation should be noted. The quality and punctuality of response to this letter are very crucial.

1. Analyze the findings of the FDA Form 483 and/or Warning Letter.
2. Suggest an appropriate timeline to satisfy the FDA.
3. Assist your company in charting a course of action.
4. Propose “Corrective Actions” to be made to your quality system.
5. Assist in implementing corrective actions in response to FDA Form 483.
6. be available to answer all questions from you or the FDA during your efforts to correct the noted deficiencies or violations.<sup>18</sup>

### Guidelines of FDA:

The most important guidelines are the Code of Federal Regulation 210, 211.

CODE OF FEDERAL REGULATIONS (CFR) Part 210: The regulations contain the minimum current good manufacturing practice for methods to be used in the facilities or controls to be used for manufacturing, processing, packaging, and holding of a drug to convince that the drug meets the requirements

of the act to safety and has the identity and strength to meet its quality and purity characteristics that it claims to possess.

Part 211: The regulations in this part contain the least cGMP for the preparation of drug products for administration to humans or animals.<sup>19</sup>

**Common issues that have appeared in FDA483:**

The most common violations of regulations occur specifically in different sections of 21 CFR part 210 and 211 which are as follows (Table 1)<sup>20, 21, 22</sup>

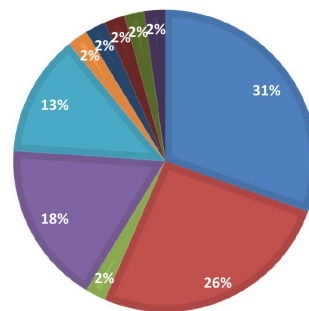
Section 501 (a) (2) (B) FD&C Act, 21 U.S.C. 351 (a) (2) (B), 21 U.S.C. 351 (a) (2) (B), Section 505 (a) FD&C Act, 21 U.S.C. 355(a), 301 (d) of FD&C Act, 21 U.S.C. 331 (d), section 502 (c) and (x) FD&C act, 21 U.S.C 352 (c) and (x), section 301 (a) of FD&C act, 21 U.S.C 331 (a).

**Table 1: different Issues found in some companies**

Sr. No.	Company Name	Issues
1.	Panacea Biotec Limited MARCS-CMS 607837 SEPTEMBER 24, 2020	<ol style="list-style-type: none"> <li>The firm failed to establish laboratory controls.</li> <li>The firm did not establish an adequate system for monitoring environmental conditions in aseptic processing areas.<sup>23</sup></li> </ol>
2.	Mayon's Pharmaceuticals Pvt Ltd MARCS-CMS 607388 SEPTEMBER 04, 2020	<ol style="list-style-type: none"> <li>The firm failed to carry out at least one test to verify the identity of an individual component of a drug product.</li> <li>The firm did not test each component for conformity with all appropriate specifications for purity, strength, and quality.</li> <li>The firm failed to establish written procedures for production and process control.</li> <li>The firm failed to Accomplish the cleanliness of the equipment and utensils and to prevent them from contamination or carry-over of a material that would affect and change the quality of the API beyond the official or other established specifications.<sup>24</sup></li> </ol>

Sr. No.	Company Name	Issues
3.	Windlass Healthcare Private Limited- MARCS-CMS595494 MARCH 10, 2020	<ol style="list-style-type: none"> <li>The firm failed to assure laboratory records which included complete data derived from all tests.</li> <li>The firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components.<sup>25</sup></li> </ol>
4.	Yibin Lihao Bio-technical Co., Ltd. MARCS-CMS 592503 FEBRUARY 13, 2020	<ol style="list-style-type: none"> <li>The firm failed to prepare and use the production and control records for each intermediate and API batch.</li> <li>The firm does not establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.<sup>26</sup></li> </ol>
5.	Sunstar Guangzhou Ltd. MARCS-CMS 592906 JANUARY 22, 2020	The firm failed to perform, for each batch of a drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product. <sup>27</sup>

- failed to maintain the written procedure of testing/production/manufacturing/raw materials/microbial contaminations
- failed to meet the final product specifications
- failed to use the equipments
- failure of quality control unit
- failed to clean and maintain the nature of drug
- failed to sanitize or sterile the equipments
- failure of laboratory control
- failed to assure drug expiration date



**Figure 1:** Diagrammatic representation of a variety of failures that occurs in various pharmaceutical companies in the year 2019.

Result and Discussion: In these cases of manufacturing quality, the FDA483 announced to the firms, the firms failed to accomplish the criteria given by the regulatory authority. The solutions for all these issues can be considered as the guidelines, rules, and regulations of the USFDA to be followed by the firm. If the pharmaceutical industries follow the guidelines strictly on a day-to-day basis in all aspects of their manufacturing, testing, and documentation, etc. the ratio of the failure of firms can be easily decreased. They can apply CAPA to the problems and make sure that it does not repeat.

As represented in figure 1, the year 2019 had the highest number of warning letters including failures of maintaining the written procedures of testing, production, manufacturing, raw materials, and microbial contaminations. The least number of issues found, related to the failure to sanitize or sterile the equipment, failure in laboratory control (related to the testing), failure to give the assurance of the expiration date of the raw material as well as product, failure to establish the monitoring of environmental conditions, failed to investigate out of specification (OOS) documents, and failure to use the equipment. The second-highest ratio is related to the failure to meet the final product specification. Relatively the failure of the quality control unit in the testing of raw material, final product, and microbial estimation shows the efficient number of warning letters. The last common issue found is related to the failure to clean and maintain the nature of the drug. In this, all common issues some are interrelated with each other such as failure of the quality control, laboratory control directly affects the documentation. Failure to use the equipment and clean or maintain the nature of the drug, failure to sanitize or sterile the equipment directly affects the final specification of the product and also leads to failure in the result of testing procedures.

In the year 2020, the highest number of warning letters include the two common violations adulteration violation and unapproved new drug and misbranding violation. As compared to 2019, in 2020 the ratio of other issues was less. The minimum number is related to the failure to written procedures of handling of written and oral complaints, testing procedures for production, process control, and manufacturing, testing procedures, stability testing, storage conditions and expiration date, and written responsibilities and procedure apply to the quality control unit.

In 2021, the highest numbers of warning letters include adulteration violation is relatively more than the unapproved new drug and misleading violation. The minimum numbers of issues related to the failure to written procedures related to responsibilities and procedures apply to the quality control unit, testing procedures, stability testing, storage condition, and expiration date. Other issues were failure to identify the component of the drug, failure to meet with the final specification, adulteration and misbranding, and misbranding due

to misleading labeling of the drug product, failure in receipt of the adulterated drug, failure in the supply chain with a history of non-compliance.



Figure 2: Diagrammatic representation of problems found in FDA483 in the year 2020.

As per the common problems found in 2019, 2020 and 2021 the highest numbers of warning letters were issued in 2019. And they all are related to the written procedures, use of the equipment, and meeting with the final specification. Then equipment-related problems such as sanitization, sterilization, and use of equipment were found in a lesser frequency. In 2020, fewer problems are found related to sanitization, sterilization, and use of equipment. And another noticeable

issue was the failure to meet the final specification. In 2020 and 2021, adulteration violations and unapproved new drug and misbranding violations were found in a higher number.

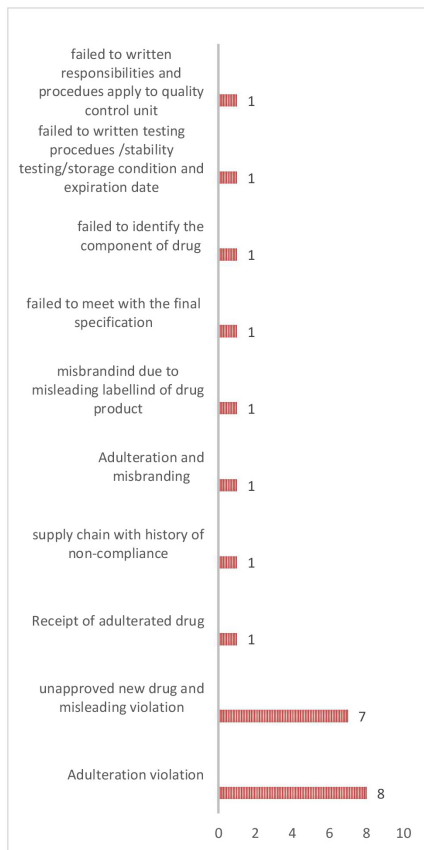


Figure 3: Diagrammatic representation of problems that arises in 2021.

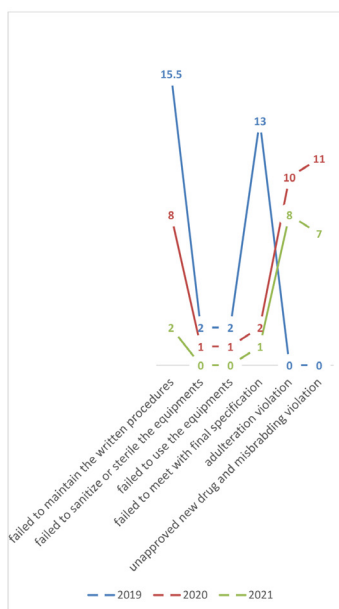


Figure 4: common issues found in 2019, 2020 and 2021.

## CONCLUSION

From the above overall information about the manufacturing quality and the problems that arise from them, depending on the guidelines given by the USFDA, the solutions exist in following set protocols. Such as maintaining the drug quality, safety, and efficacy. The common problems which occurred are related to the documentation, handling the procedures, cleanliness. And the reasons seem to be manual misconduct of the guidelines. FDA483 gives details information about the violation in the form of CFR and solutions are already present in the CFR as guidelines. In many of the pharmaceutical industries, material failure was related to the specifications for purity, and the process. These firms were unable to match the expectations of the regulatory authorities. For example, the violations such as adulteration, misleading, mislabeling and misbranding related to the warning letters issued to the companies of hand sanitizers and antiseptic hand rubs. Form 483 is generally issued in the case of insufficient training of staff members related to the use of equipment, testing protocol, and written procedures. Poor corrective and preventive actions. Deficient investigation of unexplained error or events, deviation in the result and their documentations.

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### Author's Contribution:

Dr. Pise A.; Designed and evaluate the data and supervised the review.

Bhardwaj P.; Designed and evaluate the data.

Tiwaskar G.; Collected the data and wrote the paper.

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