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IN-DEPTH ANALYSIS OF USFDA WARNING LETTERS: A COMPARATIVE STUDY BETWEEN PRE-COVID AND POST-COVID PHASES – A REVIEW

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ABSTRACT

In recent time, the pharmaceutical industry, among others, has been markedly influenced by the COVID-19 pandemic. The current review article conducts a comprehensive analysis of USFDA warning letters and their impact on the pharmaceutical industry, making a comparison between the pre-COVID and post-COVID periods for Indian manufacturers. These warning letters serve as official notices of violations and errors found during inspections, requesting companies to correct them promptly. This analysis covers a range of factors, including non-compliance with Current Good Manufacturing Practices, quality control concerns, data integrity issues, product safety, packaging and labelling violations and also emphasizes the importance of addressing the new challenges arising from the pandemic and ensuring the resilience and safety of the pharmaceutical supply chain. Overall, this comprehensive examination of USFDA warning letters reveals the dynamic nature of regulatory compliance and the need for continuous evaluation and adaptation within the pharmaceutical industry.

Keywords: United State Food and Drug Administration (USFDA), Warning letters, Inspection, pre-covid scenario, post-covid scenario, Out-of-specification

INTRODUCTION

A federal government agency called the US Food and Drug Administration (US FDA), protects the nation's health by maintaining the safety of pharmaceuticals, medical

equipment, animal medications, food additives, cosmetics, and items that produce radiation **[1]**. FDA checks the companies for their adherence to regulatory compliance in order to ensure the safety and quality of items launched into the US market. The FDA performs four main kinds of inspections: pre-approval inspections, post-approval inspection, Routine inspection and for-cause inspections **[2]**. When the FDA finds problems during an inspection, the manufacturer receives a warning letter from the agency. "A correspondence that notifies regulated industry about violations that FDA has documented during its inspections or investigations" is the definition of a warning letter **[3]**. The FDA asks the producer to address issues that are generally noted in form 483 before sending out a warning letter **[3]**.

Forms 483 provide advice to the organization regarding conditions that may be deemed disagreeable and potentially violate the Act, but they are not regarded as final FDA decisions for filing infractions. FDA may issue a notification if the regulatory body determines that the Form 483 addressing both planned and true corrections was satisfactorily answered, or if an infraction is considered to be of a serious nature. In contrast to Form 483, warning letters describe the relevant regulation for each and every infringement **[4]**.

After receiving a warning letter, the company has fifteen days to report to the issuing office with a detailed report outlining the corrective actions taken to address the previously mentioned infractions. If the violation cannot be resolved within that time frame, the company must also provide an action plan to prevent the violation from happening in the future. No warning letter contains an exhaustive list of violations related to the company's pharmaceutical product. The organization is going to investigate and evaluate other infractions. The FDA carries out a follow-up inspection to evaluate how effectively the changes that were made worked **[5]**.

Since the majority of Warning Letters caused by adulteration also had cGMP-related infractions, it may be assumed that the main factor in identifying the product as adulterated was a cGMP violation. After assessing the corrective activity, FDA may issue a warning letter close-out letter, also known as a close-out letter. Reliability of a close-out letter depends on the Corrective action plan of the company. If the violation cannot be corrected, a close-out letter will not be sent. Still, the FDA may take legal action if an organization does not immediately correct the infractions **[5]**.

Overview of warning letter

Company inspections or FDA investigations are the first steps in the Warning Letter

procedure. Following the inspection, the inspector will send the establishment inspection report (EIR) to the FDA for review before forwarding it to the organization. Additionally, the inspector will provide the inspection comments on form 483 to the company **[6]**. The following **Figure 1** could be interpreted as a flow process of warning letter, represented below:

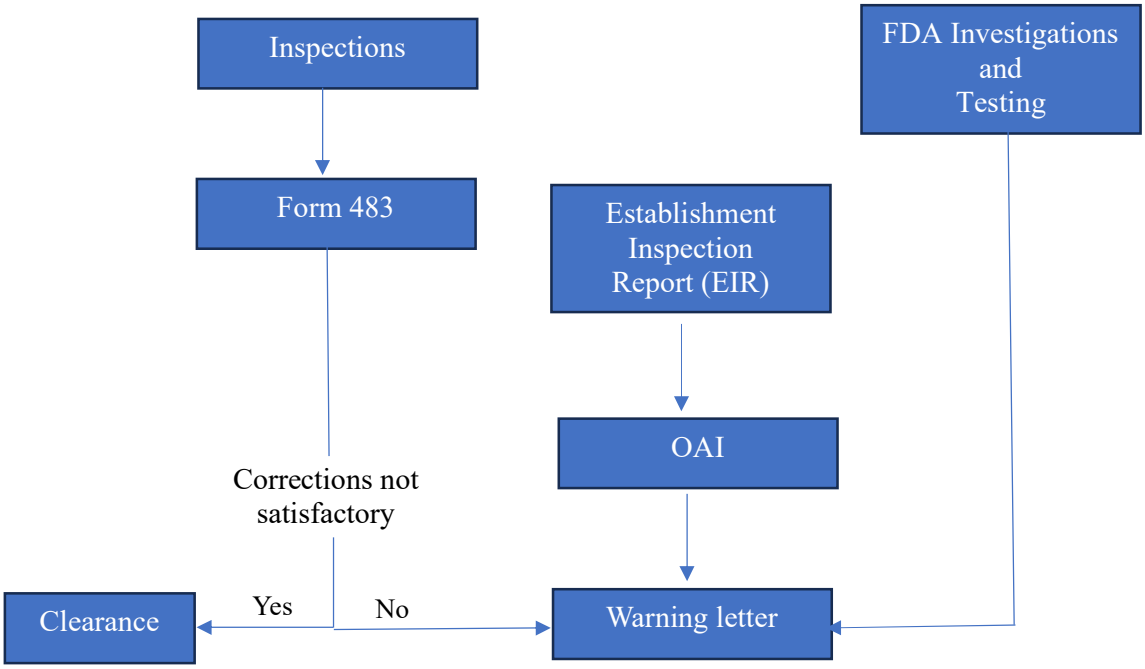

Figure 1: Flow process of Warning Letter

Inspection

The FDA surveys and inspects controlled facilities to see whether companies comply with all applicable rules and laws. Production facilities, clinical testing sites, labs that test animals or microorganisms, and imported restricted commodities are all subject to border inspections by the FDA. Foreign facilities that manufacture or process FDA items for export to the US are also subject to inspections **[7]**. Inspections may be conducted as follows, for any of the reasons.

Types of Inspections in Pharmaceutical Industries

1. **Pre-approval inspections [8]**

Following an organization's application to sell a novel component, these inspections take occur. The US Food and Drug Administration (US FDA) can only approve a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA), according to the Food, Drug, and Cosmetic Act, if the procedures followed in manufacture of the medicinal product, conducting, packing, and examination,

along with its control facilities, are sufficient to verify the identity, potency, stability, and purity of the medication. Consequently, the FDA reviewed organizations through a company listed in the CMC's on-site inspection and file review process. portion of the application before to approving any applicant.

2. Post-approval inspections [9]

Specific to a given product, post-approval inspections are designed to evaluate components of a facility that:

- Might not have been prepared for the pre-approval inspection
- Are more crucial in ensuring quality

Usually, eight to twelve months after approving the pre-market application, the FDA will carry out a post-approval inspection. This happens after the product is sold in markets.

3. Routine inspections [9]

cGMP inspections are conducted. The US Food and Drug Administration (US FDA) requires that production companies verify conformity every 2 years, even after the application has been accepted; however, this requirement may change based on the risk. cGMP inspections might take a long time or little time. Full inspections are carried out when a structure is freshly constructed, when flaws have been found, or when significant enhancements have been made since the last examination.

4. For cause inspections [10]

This inspection is started when an agency receives information that leads it to assume that a facility is having quality issues, investigates complaints, or assesses the changes made to address previous violations. There is a very specific objective for these examinations. These audits examine data pertaining to certain issues, including client complaints or reminders.

Form 483 [11] - Form 483 Observation

Indian enterprises must adhere to cGMP in accordance with FDA requirements, as the FDA facilitates authority for inspection in foreign nations that export pharmaceutical items to the U.S. After the inspection is over, the FDA sends Form 483 to the pharmaceutical companies and management if it discovers any deviations from cGMP in accordance with FDA regulations and any other particular requirements. Form 483 formally known as the "Notice of Inspectional Observations,". In addition to the Form 483, the FDA occasionally provides Establishment Inspection Reports (EIRs), which indicate whether or not action is necessary. Observations should receive a response from the companies within 15 working days. The FDA sends warning letters to management when they fail to respond to observations within the allotted time.

Classification of inspections [12]

The classification of inspections categorizes various types of assessments based on their specific purposes and criteria.

1. **No action indicated (NAI):** This indicates that the examination identified no unfavorable circumstances or behaviors.
2. **Voluntary action indicated (VAI):** It signifies that although the agency has discovered undesirable conditions or behaviors, it is not yet ready to implement administrative or regulating actions.
3. **Official action indicated (OAI):** which signifies that it is advised to take regulatory and/or administrative action.

Summary of the warning letters:

The tables below contain a summary of warning letters issued before and after the COVID-19 pandemic.

- **Pre-Covid Warning letters:** A summary of pre-COVID warning letters is provided in the **Table 1** given below.
- **Post-Covid Warning Letters:** A summary of post-COVID warning letters is provided in the **Table 2** as represented below:

Table 1: Warning letters issued by USFDA during Pre-Covid - Scenario

Sr. No.	Name of Company	Issued Date	Letter Summary
1.	Private Ltd. Company based on API production located in Baroda [13]	January 2019	The company received notification from the FDA regarding significant changes in active pharmaceutical ingredients (API) in accordance with current good manufacturing practices (CGMP). The warning letter outlines the major issues observed during the inspection. 1. The company did not share all quality or regulatory information from the API manufacturer with clients. 2. The company did not have procedures in place to guarantee that the production of active pharmaceutical ingredients (APIs) at their facility adhered to stringent quality and purity standards. 3. The company did not have appropriate written procedures for cleaning and releasing equipment utilized in the production of active pharmaceutical ingredients (API). 4. The company failed to ensure that the water used in producing their active pharmaceutical ingredients (API) is suitable for its intended purpose.
2.	Private Pharmaceutical company located in Navi Mumbai [14]	February 2019	The FDA found major violations in manufacturing practices, making the pharmaceutical products adulterated and unapproved. Despite prior reviews, the violations were discovered during an inspection. 1. The company lacks a proper stability program for drugs, with issues in testing methods. The FDA requires a plan to address these problems, including SOPs, stability studies, and risk assessments for market drugs. 2. Production procedures lacked quality control unit approval, violating regulations. Absence of validation studies led to inadequate control and variability in product characteristics. 3. The company did not implement appropriate equipment cleaning methods and lacked a sufficient cleaning validation program. Reports highlighted excessive

			chemicals and inadequate investigation of failed water samples.
3.	**Private pharmaceutical Laboratories located in Gujarat [15]**	**May 2019**	**The FDA identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceutical products.** **1. The FDA found the company neglected to keep accurate laboratory records. Damaged documents from stability studies were improperly discarded, with some official records contradicting the discarded data. Additionally, blank stability study forms were pre-signed before recording test results.** **2. The organization does not have adequate controls for the computer systems utilized in laboratory equipment for batch release and stability testing.** **3. The company neglected proper cleaning and maintenance of equipment, raising concerns about cross-contamination and product variability.**
4.	**Private Homeopathy company located in Hyderabad [16]**	**June 2019**	**The FDA discovered significant violations of current good manufacturing practices (CGMP) for finished pharmaceutical products.** **1. The FDA found quality control issues in a drug manufacturing company, involving failure to test incoming components, purchasing potentially toxic materials, lacking testing procedures, and insufficient manufacturing plan details.** **2. The FDA found deficiencies in a drug manufacturing company's batch production and control records, lacking essential details such as line clearance, equipment, components, test results, and more.** **3. The FDA identified quality control unit (QU) failures in a drug manufacturing company, including oversight gaps in manufacturing processes, labelling control issues, and a lack of procedures for essential quality and production operations."**
5.	**Pharma Limited Company based on API & Generic drug located in Hyderabad [17]**	**June 2019**	**The warning notice highlights significant deviations from current good manufacturing practices (CGMP) for active pharmaceutical ingredients (API), prompting concerns about the facility's compliance with regulatory standards.** **1. The company carried out inadequate investigations into impurities in their active pharmaceutical ingredients (APIs) and failed to expand these inquiries to potentially affected batches.** ***2.* The company's investigations into poor equipment maintenance were found to be inadequate.**
6.	**Private Life-science Company based on API located in Surat [18]**	**July 2019**	**The warning notice highlights significant deviations from current good manufacturing practices (CGMP) for active pharmaceutical ingredients (API), prompting concerns about the facility's compliance with regulatory standards.** **1. Water Quality Monitoring Failure: The facility inadequately monitored and controlled water quality for manufacturing non-sterile APIs intended for sterile drug products, including oversight for endotoxins, objectionable organisms, and overall microbial counts.** **2. Inadequate Investigation of Out-of-Specification Results: The company invalidated an out-of-specification (OOS) test result for a batch of APIs without sufficient scientific support. The investigation lacked a thorough examination of potential causes for an unknown impurity.**
7.	**Private Pharmaceutical Company based on Finished dosage forms located in Mumbai [19]**	**July 2019**	**The warning letter issued by the FDA addresses significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals.** **1. The organization inadequately maintained batch manufacturing and control records for (b)(4) mg tablets. The recorded values for compression machine process control in batch records did not match those logged by**

			the programmable logic controller (PLC) on the machine. **2. The company's investigation into batch record discrepancies regarding compression force values for (b)(4) mg tablets was inadequate, lacking thorough reviews of data integrity, extension to other products and strengths, a substantive root cause analysis, and a corrective action plan.**
8.	**A Pharmaceutical Company located in Pune [20]**	**August 2019**	**The FDA discovered significant violations of current good manufacturing practices (CGMP) for finished pharmaceutical products.** **The letter highlights the following key points:** **1. The FDA found the company neglected to thoroughly assess disparities or sterility failures in two drug product batches, one exhibiting Bacillus cereus growth and the other lysinbacillus fusiformis growth. The investigations primarily targeted laboratory errors, overlooking potential manufacturing causes**
9.	**Private pharmaceutical company based on API & Generic drugs located in Mumbai [21]**	**September 2019**	**Major deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).** 1. **The company failed to conduct thorough investigations into unexplained discrepancies or batch failures to meet specifications, as required by FDA regulations.** 2. **The company lacked adequate written processes for production and process control to ensure medication goods met claimed specifications for purity, strength, quality, and identification.** 3. **The company failed to properly clean and maintain equipment, risking contamination and quality issues in drug products**
10.	**Global Pharmaceutical company based on Generic drugs located in Mumbai [22]**	**October 2019**	**The FDA discovered significant violations of current good manufacturing practices (CGMP) for finished pharmaceutical products.** **1. In November 2017, the company insufficiently addressed multiple complaints about grittiness in their cream. Despite rejecting 20 batches and receiving 38 complaints, the problem persisted since 2010 and was previously highlighted in a facility inspection. The company's November 2018 response lacked adequate data to validate the proposed remedy, asserting resolution through reformulation. Although a recall was initiated in July 2019, it was not promptly executed.** **2. The company insufficiently addressed drug products exposed to improper temperatures during transit to the U.S., despite facility inspection deficiencies. Although plans for improvement and additional studies were in place, they were not promptly executed. Additionally, their response lacked a satisfactory evaluation of the risks posed by products in the market exposed to incorrect temperatures.** **3. The company inadequately investigated out-of-specification test results for critical product attributes, leading to batch rejections.** **4. The company inadequately investigated 70+ customer complaints about container defects in various drug products, failing to address the extent, cause, or evaluate similar issues in other products from the same supplier.**
11.	**Pharmaceutical Company based on Generic drugs & API located in Ahmedabad [23]**	**October 2019**	**The company received a warning notification from the FDA, highlighting significant violations of cGMP rules for finished pharmaceuticals.** **1. The FD&C Act considers the pharmaceutical products are adulterated as a result of these violation.** **2. Lack of Written Procedure Adherence: The company strayed from established processes for ensuring the identification, strength, quality, and purity of pharmaceutical items. When using a different active pharmaceutical ingredient (API) for Losartan**

			Potassium Tablets, they disregarded the approved process validation protocol, resulting in the production of multiple batches with quality issues, including elevated nitrosamine impurity levels. **3. Poor investigation of Out-of-Specification (OOS) Results: The company closed OOS cases without identifying root causes or providing scientific justification. Batches were released based on retested results without addressing initial failing OOS results. A significant percentage of invalidated initial OOS test results was attributed to errors, without a comprehensive review of all drug products for root causes and corrective actions.** **4. Repeat Observations and Inadequate Executive Management Oversight: The FDA noted that the inadequate investigations and CGMP violations were repeat observations in the company.**

Table 2: Warning letters issued by USFDA during Post-Covid - Scenario

Sr. No.	Name of Company	Issued Date	Letter Summary
1.	**Private Pharma company located in Hyderabad [24]**	**January 2022**	**Major deviations from current good manufacturing practises (CGMP) for active pharmaceutical ingredients (API) are the subject of this warning letter.** **1. The company increased acceptable limits for impurities in their API starting material without assessing the potential impact, relying on lab-scale studies that did not comprehensively consider all potential impurities.** **2. The company's quality unit inadequately addressed critical deviations in a gas chromatography-mass spectrometry method transfer. They attributed a failing result to a column issue without proper investigation, and no controls were established to prevent similar issues**
2.	**Private Chemical company located in Vadodara [25]**	**February 2022**	**Major deviations from current good manufacturing practises (CGMP) for active pharmaceutical ingredients (API) are the subject of this warning letter.** **1. The USFDA issued a warning letter to a pharmaceutical facility for not maintaining equipment according to specifications, citing issues such as rust-like residues, the use of tape to prevent contamination, and a lack of equipment qualification procedures.** **2. The company did not validate the manufacturing process for a particular pharmaceutical ingredient (API). They implemented uncontrolled process changes and neglected to establish equipment qualification procedures.** **3. The company inadequately validated equipment cleaning procedures and lacked written guidelines for cleaning non-dedicated equipment. Insufficient cleaning instructions were provided for certain equipment, and operators cleaned without following a procedure, raising concerns about cross-contamination.** **4. The company lacks a proper stability testing program for their (b)(4) Active Pharmaceutical Ingredient (API). They determined the API's retest date based on a single, improperly stored 2016 batch and destroyed essential batch records while the batch was still in distribution.** **5. The USFDA issued a warning letter to a pharmaceutical manufacturer for lacking a Quality Unit with sufficient authority and oversight, leading to unreliable operations and poor documentation practices.**
3.	**Generic Pharma company located in Maharashtra [26]**	**September 2022**	**Major deviations from current good manufacturing practises (CGMP) for active pharmaceutical ingredients (API) are the subject of this warning letter. The letter highlights deviations found during the inspection, signalling non-compliance with CGMP** **1. The warning letter underscores major violations in the company's cleaning procedures and cross-contamination**

			controls for manufacturing intermediates and API. Risk assessments lacked supporting data, and cleaning effectiveness was insufficient to prevent cross-contamination. Conflicting data was reported, and the response was deemed inadequate. **2. The organization lacked monitoring and control protocols for processing stages affecting component and API quality. The (b)(4) process for manufacturing (b)(4) and (b)(4) API exhibited irregular frequencies of quantifiable levels of (b)(4) Impurity (b)(4). Benchtop studies suggested effective disinfection of genotoxic impurities, but commercial manufacturing data showed inconsistency.** **3. The company neglected to identify and investigate all critical deviations, including limit excursions. Despite an out-of-specification (OOS) result in cleaning verification, the final report concluded that equipment cleaning was validated, dismissing the failure data.**
4.	**Private Pharmaceutical company located in Mumbai [27]**	**November 2022**	**The company received a warning notification from the FDA, highlighting significant violations of cGMP rules for finished pharmaceuticals.** **1. The warning letter highlights the company's insufficient investigation of discrepancies and batch failures, especially with desmopressin acetate tablets. Rejected batch investigations were inadequate, lacking attention to related batches. Although the company acknowledged the issues in its response, it failed to address timely assay failure investigations.** **2. The organization lacked adequate documented protocols for process and production control, notably in the manufacturing process for a gel product, leading to validation issues and concerns about inter-batch and intra-batch variability.** **3. The company failed to establish and sustain essential laboratory control systems, particularly concerning chromatographic data processing. The FDA noted instances of manual entry of integration events and identified inadequate procedures.** **4. The company failed to properly document batch production and control records, specifically in establishing tablet compression machine reject limits. The FDA observed production operators using default rejection values instead of calculating batch-specific limits, leading to incomplete records.**
5.	**Private Indian Pharmaceuticals company based on API & Finished dosage forms located in Punjab [28]**	**December 2022**	**Major deviations from current good manufacturing practises (CGMP) for active pharmaceutical ingredients (API) are the subject of this warning letter.** **1. A Quality Unit (QU) neglected its duty to ensure CGMP compliance, particularly due to inadequate document control practices for both paper and electronic records. Issues include uncontrolled logbooks, blank forms, and an information shredder labelled for "emergency use," containing destroyed information employees cannot identify.** **2. The company failed to ensure scientifically sound test procedures for pharmaceutical ingredients, specifically related to beta-lactam containment. Inadequate validation and procedure compliance posed risks to patient safety.** **3. The organization failed to establish and follow protocols for investigating critical deviations or API batch failures. Notably, they inadequately addressed black particles in API batches and failed to identify their root cause, providing an unsatisfactory response.**

CONCLUSION

The current study provides, the comprehensive examination of USFDA warning letters. This study compares pre-COVID and post-COVID periods, providing valuable insights into the evolving regulatory compliance in pharmaceutical and healthcare industries. This study has identified a significant difference in the total number of warning letters issued during the pre-COVID and post-COVID phases. The study reveals notable variations in the issuance of warning letters before and after the COVID-19 pandemic, notably highlighting a decrease in the number of post-COVID warning letters.

In the pre-COVID phase, more warning letters were issued due to non-compliance with Good Manufacturing Practices, misbranding, and adulterated drugs. Post-COVID, critical deviations were noted in a gas chromatography-mass spectrometry method transfer, equipment maintenance issues, and the absence of written cleaning procedures for non-dedicated equipment. Common issues in both phases encompass inadequate equipment maintenance, ineffective cleaning procedures, failure to follow documented procedures, the absence of a Quality Unit and a lack of adherence to laboratory requirements.

This observation holds vital implications for industry professionals and regulators. Professionals can benefit from a discerning grasp of the evolving compliance landscape, enabling prioritization and addressing specific concerns. The decrease in post-COVID warning letters suggests potential improvement in industry practices, reflecting heightened awareness, revised protocols, or increased regulatory preparedness. For regulators, the study provides insights into the effectiveness of measures, guiding strategies for enhanced compliance and streamlined industry practices.

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