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Review Article

Warning Letter: Cause and Remedy in Pharmaceutical Industry

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ABSTRACT

The abstract summarizes the critical findings and gaps identified in scholarly research concerning USFDA inspections and warning letters issued to pharmaceutical facilities in India over the past thirteen years. It highlights the lack of detailed explanation and understanding of the six-step inspection model employed by USFDA inspectors during facility audits. Additionally, the abstract points out a perceived increase in the expectations of USFDA inspectors, with a trend towards more thorough and in-depth scrutiny of pharmaceutical operations. However, there appears to be a lack of awareness among researchers regarding these heightened expectations. Furthermore, the abstract emphasizes a notable gap in understanding the root causes behind non-compliance with Good Manufacturing Practices (GMP) and data integrity standards, despite these being common reasons cited for warning letters. It suggests that further investigation is needed to uncover these underlying causes and propose effective remedies. Overall, the abstract underscores the importance of enhancing understanding of USFDA inspections, including the six-step model, evolving inspector expectations, and the reasons behind non-compliance, to improve compliance and quality standards within the Indian pharmaceutical industry.

INTRODUCTION

The pharmaceutical sector is the biggest sector in India. Day by day, so many new pharmaceuticals industries are established in India. The Indian pharmaceuticals companies are engaged in manufacturing of Drug Substance-API (Sterile and Non-Sterile), Drug (Finished) Products like oral solid dosage (Tablets, capsule, Sachet), Injection (IM & IV), IVs-Large Volume Parenteral and Small Volume Parental, Vaccine etc. These drugs are used as medication for human being with the aim to cure human. Indian Pharmaceutical companies are dealing in generic as well as in brand medications. The Indian pharmaceutical sector comprises five pivotal segments: contract research and manufacturing services (CRAMS),

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active pharmaceutical ingredients (APIs), formulations, biologics and biosimilars, and vaccines. Prominent pharmaceutical corporations in India are situated in Vadodara, Ahmedabad, Ankleshwar, Vapi, Baddi, Sikkim, Kolkata, Visakhapatnam, Hyderabad, Bangalore, Chennai, Margao, Navi Mumbai, Mumbai, Pune, and Aurangabad. India has been increased exports from 6.23 billion US $ to 8.7 billion US $ 8.7 from the year of 2006 2009 and it was noticed that it goes up as 8.7 billion US $ 11.7 billion in 2014 and in 2020 it was noted that around 20 billion US $, it shows increase of export of pharmaceuticals products in India.To sell the finished products or drug substance (API) in the US market, every manufacturer needs to have file DMF (in e-CTD) in US and must go under USFDA inspection. US regulatory takes time to review DMF and they send queries if found any. There are three types of inspection(audit) is being done by US, pre-approval inspection, routine inspection, for cause inspection(https://www.fda.gov/about-fda/fda-basics/what-does- fda-inspect). The inspection is generally for 05 days, if any discrepancy finds during audit, then it may extend and the number of days to extend it depend upon drugs inspector, it may vary person to person. On the last day of inspection, drugs officer or designee is being give his observation to manufacture as known as “Form 483”, it indicates that registered product in US may be in the violation of FDA’s requirements (21 CFR 210 & 211) and the firm must give response within next 15 working days. The Firm expects to receive establishment inspection report (EIR) from FDA, only after submission of complete and adequate compliance report with all required evidence against the 483 observations. If the response is inadequate or any critical observation that may have impact on product quality, safety & purity then firm may be received “Warning Letter”.

483 Observation and warning letter may harm the reputation of company and it may have impact on business of company. The Firm needs to take appropriate corrective and preventive action against observation and needs to submit a compliance report. After the verification of corrective and preventive action from FDA, which is executed by firm, FDA may give close out letter against warning letter.

Types of warning letter are mentioned below.

1. General FDA Warning Letters
2. Tobacco Retail Warning Letters
3. Drug Marketing and Advertising Warning Letters (and Untitled Letters to Pharmaceutical Companies)
4. Warning Letter Close-Out Letter Program (applies to letters issued on or after Sept. 1, 2009).

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/about-warning-and-close-out-letters

MATERIALS AND METHODS:

Researcher scholar has reviewed the number of articles, observations, the warning letters received by various Indian pharmaceuticals, journals, book by using different websites and surfed proposed research related site to gather the more information for review and to get knowledge in the same filed and to understand the thought process of researcher.

The below mentioned are the literatures:

Warning letters were discussed with its categorization issued in the year 2010 to 2020. A cumulative sum of 3777 warning letters were dispatched to pharmaceutical industries within that specified year. The major warning letters were issued due to non-compliance to cGMP and misbranding, data integrity. Approximately 18% warning letters were issued to the US industries, 65% to Asia country (most of are India and China) and 17% warning letter to the Europe country. The

six- step inspection model was shown by researchers (Rathore et al., 2022). Researcher presented the total 28143 number of inspections carried out by USFDA, out of which 1890 inspection was done in India from 2010-2021. A total 1253 warning letters were issued in which 114 was belong to Indian pharmaceuticals. Researcher shown the comparative study of warning letter of India with China and USA. In India, the major root cause to received warning letter is data integrity (Kamaraj & Kumar, 2022).

The number of warning letter was presented with subject, different nature of observation from the year 2019 to 2021 for different countries like India, China and US, Japan, Australia, and many more in the articles. The China and India received more warning letter after US in 2019 (Patel et al., 2022). The Form 483 and warning letter were issued due to data integrity to the pharmaceutical's companies. The author explained the ALCOA concept to avoid data integrity problems (Shah et al., 2022). The procedure was explained to get the warning letters and presented the consequence of warning letters and 483 observations with its categorized like VIA, NAI, OAI. Researchers also mentioned the number of warning letters and Form 483 issued in the year 2017 to 2020 to the pharmaceuticals industries (Saini et al., 2022). The ACOA concept were explained to avoid data integrity issues and represented the warning letter related to data integrity for 2008 to 2018 to different countries (James et al., 2021). Dr. Reddy's has trouble after receiving the warning letter in 2015 for 03 plants, 483 Observation to their different plant. Aurobindo, Lupin, Sun-Pharma also received Form 483 (Dash et al., 2021). The warning letter were issued because of inadequate or missing of Corrective and Preventive action (CAPA) in Quality system and reoccurring of similar or repetitive CAPA (Deshpande et al., 2019). The FDA Inspection system were discussed and how to avoid warning letters from USFDA (Jain & Jain, 2020). The information about warning letter issued to India, China, US for the year FY2013 to FY2019 was provided. India and China have the more warning letter received as compared to other countries. The major root cause was data integrity issue for warning letters (UNGER, 2020). Data integrity (ALOCA & ALCOA plus) was explained by scholar. The author represented the quantity of warning letters received in the FY 2017 and 2018, categorized by countries, due to issues related to data integrity. India as well as China received the greatest number of notifications in terms of warning letters. The Quality Control department received more warning letters as compared to other departments (Jaiswal et al., 2020). Dr. Reddy's faced problems in FY 2015 like falling profits due to warning letter received by USFDA to their three different manufacturing sites. The author discussed the history of Sun pharma, Lupin, Aurobindo Pharma companies (Abraham & Kumar, 2020). Dr. Nirali provided information about financial losses due to receiving warning letters from USFDA (Shah, 2020). A summary of the USFDA warning letters during the fiscal period from 2015 to 2019 concerning over the counter (OTC) products was presented and Rx Drugs was provided. The major Violation was observed in laboratory control for Rx and OTC drugs in the year 2015 to 2019 (Bai et al., 2020).

The total count of notifications dispatched to pharmaceutical entities during the calendar year of 2015 to 2017 to China and India was presented. Researchers also discussed the violation in pharmaceuticals (Anantha et al., 2018). Total 85 warning letters were issued to the API manufacturer and finished dosage manufacturer because of inadequate Quality control, QMS and data integrity and poor production control in the year 2014 to 2016. In 85 warning letters there were 580 observations were found and these warning letters were issued to Asia, Europe, and North

America. Researchers also discussed FDA investigation six system model, category of cause in warning letter and has given give recommendations to improved quality system (Jain & Jain, 2018). The 483 forms have impact on import and export business of manufacturer (Gavande et al., 2018).There is increased in number of warning letters to India pharmaceuticals from USFDA in FY2012-FY2017. 30% were related to quality, 10% OAI, 4% warning letters were issued because of drug recall to Indian Pharmaceuticals in the year FY2012-FY2017 (John et al., 2018). An overview was provided for the warning letter from the year 2008 to 2017. India has received the highest number of warning letters followed by China and US due to data integrity (Unger, 2018). Researcher explained the drugs products and drugs substance is being audited by USFDA to verify cGMP compliance, author said inadequate investigation and CAPA is always most common root cause, proactive organizations take preventive action to improve the system. This proactive approach will improve the quality metrics of the organization and reduce the frequency of regulatory audits (Jain & Jain, 2017). The history of Ranbaxy pharmaceuticals companies was explained with its achievement. The author explained the India biggest pharmaceutical's Ranbaxy collapsed due to warning letter issued by USFDA because of non-compliance to cGMP and Violation of cGMP in the years 2002, 2006 and 2009. In 2014, Ranbaxy received 483 Form along with a several observations. In 2014, Sun Pharma take over to Ranbaxy, approx. 64% (Agarwal et al., 2017).

The overview was provided for warning letter issued by USFDA in the year 2003-2008 because of misleading claims in US country (Chatterjee et al., 2012). The detailed review of Indian and US Pharmaceutical Manufacturer's warning letters provides insights into the FDA's systemic approach to assessing GMP compliance, additionally, he remarked that the USFDA has escalated its issuance of warning letters, import alerts, and seizures against manufacturers of drug products found in violation of GMP regulations. Researcher has given recommendations to develop compliance check lists/data/trends to enhance their GMP compliance and manage future FDA inspections (Patel, 2012). The guidance for avoiding receiving Form 483 and warning letter from USFDA explained (Winchell, 2011). The procedure for securing approval from the US FDA for a tablet manufacturing enterprise was deliberated upon, offering guidance to applicants in preparing the Common Technical Document (CTD) for pharmaceutical registration intended for human use submission to the FDA. Recommendations encompass approval modifications concerning components and composition, manufacturing sites, manufacturing processes, specifications, container closure systems, and labeling. The author said FDA can take action against companies if they fail to comply with regulations like warning can be issued (Gowtham et al., 2011) Details were provided regarding warning letters sent to manufacturers of drug products and substances for breaching current good manufacturing practice (cGMP) regulations. The FDA is employing a systematic and risk-focused strategy to evaluate compliance with GMP, with specific emphasis on aspects like the quality control unit, validation of manufacturing processes, and investigation of laboratory test results that fall outside specifications (OOS). Author suggests to the pharmaceutical companies to do carefully assess FDA GMP warning letters from the past year to enhance their quality systems and improve their manufacturing processes (Church and Mahoney, 2009). Details were disclosed regarding the issuance of 483 forms and the number of total warning letters issued during the fiscal year spanning from 2008 to 2009. The author also given

the 483 observation number along with its deficiencies. India has received high number of warning letters as compared to US and Canada. Companies should focus on risk analysis and be familiar with the product supply chain, API, excipients, and container/closure systems. This knowledge will help avoid potential FDA 483 observations and write valid procedures to manufacture products within the scope and intent of CGMPs (Poska and Graham, 2009).

RESULTS AND DISCUSSION:

There are too many facilities have been inspected in the India by USFDA for API as well as formulation unit by different US inspectors in last thirteen years. The scholar found that USFDA has six-step inspection models which are being used during inspections. No author or researcher has explained the six-step inspection model in detail, lack of explanation of six system model. Lack of understanding of six step inspection or system model. The scholar found that USFDA's drug inspector and officer's expectations are little high, and they are upgrading their requirements day by day and officer are going in-depth of each activity during inspection, which may be not the earlier practice and procedure of Audit has been changed by the USFDA. Lack of awareness of expectation of drug inspector and officers. Researcher scholar found, nobody is talking about actual root cause to receive 483 form and warning letter, all articles are said about warning letter issued because of non-compliance in GMP and data integrity, yet no one has talked about why non-compliance in GMP and data integrity occurred in pharmaceuticals company though there is guideline for GMP and on data integrity and hence scholar thought further study is require to find out the cause and want to give appropriate remedies based on finding.

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