RESEARCH ARTICLE

A Retrospective Study of Documentation Shortfalls Mentioned in USFDA Warning Letters Issued to India Pharmaceutical Industries

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ABSTRACT

The pharmaceutical industry is an indispensable sector that ensures patients have access to safe and effective medications. Therefore, it is essential that companies comply with regulatory standards and maintain accurate and complete documentation practices. This study will investigate the documentation violations cited in warning letters sent to Indian pharmaceutical companies between 2010 and 2022. The analysis will focus on identifying the most common documentation deficiencies and the impact they have on the pharmaceutical industry in India. The findings of this research will provide Indian pharmaceutical firms with valuable insights. to improve their documentation practices and ensure compliance with regulatory standards. This information will be useful for stakeholders in the pharmaceutical industry, including regulatory agencies, pharmaceutical companies, healthcare professionals, and patients. By understanding common documentation violations, companies can take proactive steps to prevent them and avoid regulatory penalties. The findings of this study will aid policymakers and regulatory agencies in devising strategies to enhance the integrity of pharmaceutical industry documentation practices. The findings will also inform the development of educational and training programs for pharmaceutical companies, which can help them enhance their documentation practices and ensure compliance with regulatory standards.

Keywords: Good documentation practices, United states food and drug administration, Pharmaceutical industries, Warning letters.

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INTRODUCTION

Good documentation practice (GDP) is essential for the integrity of data collection and reporting in the pharmaceutical industry to support the development, registration, commercialization, and life-cycle management of pharmaceutical products.[1] Documentation control and administration are essential components of the organization's good manufacturing practice (GMP) program. Facilities must have documented systems based on specifications, manufacturing and packaging instructions, procedures, and records for GMP compliance. Specifically, batch-specific manufacturing documentation must be present. These documents must enable the history of each shipment to be traced. Traceability must be possible for a minimum defined period, typically one year after batch expiration.[2]

GDP refers to the principles and processes that ensure that documents related to a product, process, or system are accurate, complete, and consistent. Here are some guidelines for GDP.[3]

Clarity and conciseness, consistency, accuracy, relevance, approval and sign-off, version control, accessibility and training.

Guidelines for good documentation practices:

- United states food and drug administration Guidelines: Industry guidance on the standardization of data and documentation practices for product tracing.[4]
- WHO Guidelines: Guidelines for effective data and record management.[5]
- ICH Guidelines: Guide to good manufacturing practice for pharmaceutical active ingredients.[6]

Indian Pharmaceutical Market in the United States

The supply of Indian pharmaceuticals to the United States is significant, as India is a major supplier of generic drugs to the US market.[7] According to data from the US FDA, India is the second-largest exporter of drugs to the US, accounting for approximately 12% of the US drug market.[8]

Indian pharmaceutical companies supply a wide range of drugs to the US market, including generic versions of popular brand-name drugs used to treat a variety of medical conditions such as diabetes, heart disease, and cancer.[9] These generic drugs are often more affordable than their brand-name counterparts, making them an important option for patients seeking lower-cost alternatives.[10]

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However, the supply of Indian pharmaceuticals to the US market has faced some regulatory challenges in recent years. The US FDA has increased its scrutiny of the quality and safety of drugs manufactured in India, leading to a number of warning letters and import alerts for Indian pharmaceutical companies. This has led to increased regulatory compliance costs for Indian companies and has also impacted their reputation in the US market.[11]

USFDA Warning Letters

During inspections or investigations, the US FDA issues warning letters to pharmaceutical companies when it discovers significant violations of regulatory requirements. These warning letters are formal notices to the company that it is in violation of the law and must take corrective action.[12]

The procedure for issuing warning letters by US FDA typically follows these steps:

- Inspection or investigation
- Inspection report (form 483)
- Response from the company
- Warning letter
- Follow-up

It's important to note that warning letters are serious regulatory actions and can have significant consequences for the company's reputation and business. Companies that receive warning letters are expected to take prompt and effective corrective action to address the violations identified by the FDA.[13]

Impact of USFDA Warning Letters

USFDA warning letters have significant impacts on pharmaceutical companies.[14] Here are some of the impacts of USFDA warning letters: Reputational damage, sales decline, regulatory scrutiny, compliance costs and legal action.

MATERIALS AND METHODS

A comprehensive literature evaluation will be conducted to identify the most frequent documentation deficiencies cited in USFDA warning letters sent to the Indian pharmaceutical industry.[15] This will provide a framework for the investigation and ensure that all relevant issues are addressed. From the USFDA's publicly accessible website, warning letters issued to Indian pharmaceutical industries during the study period were compiled. The warning letters will be analyzed to identify the specific documentation shortfalls cited in each letter. The quantitative data collected from USFDA warning letters will be analyzed using statistical tools, and the results of the data analysis will be presented in tables and graphs to provide a comprehensive overview of the most frequently cited documentation deficiencies in USFDA warning letters issued to Indian pharmaceutical industries. The discussion will focus on identifying the root causes of documentation shortfalls and providing recommendations for improving documentation practices in Indian pharmaceutical industries.[16]

RESULTS AND DISCUSSION

Warning letters can be issued by various offices depending on the context and the nature of the warning. Warning letters issued offices to drugs during the study period were categorized (Figure 1) and analyzed for a number of warning letters issued by the individual office.

The above data illustrate during the research period, the Centre for Drug Evaluation and Research [CDER] issued the majority of warning letters.

US FDA inspections on Indian pharmaceutical industries is gradually increasing till 2019 and there is a gradual decrease in the number of inspections due to the pandemic years (2020-2022) and number of inspections in 2022 increased when compared to the pandemic years (Figure 2) and it is expected to increase in forthcoming years (Table 1).

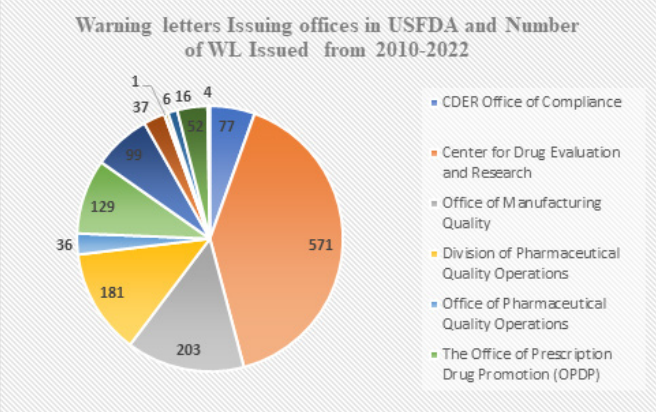

Figure 1: Warning letters issuing offices in USFDA

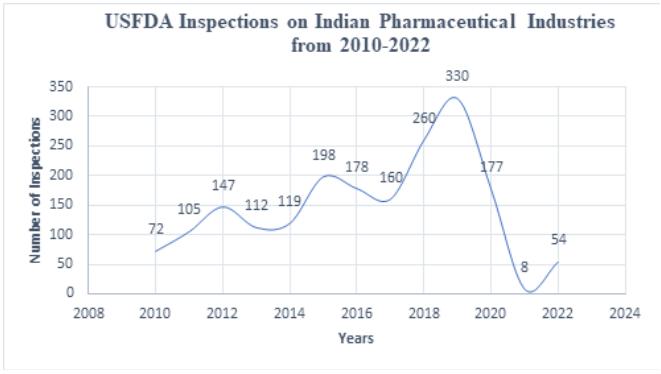

Figure 2: Number of USFDA inspections held at indian pharmaceutical industries from 2010-2022

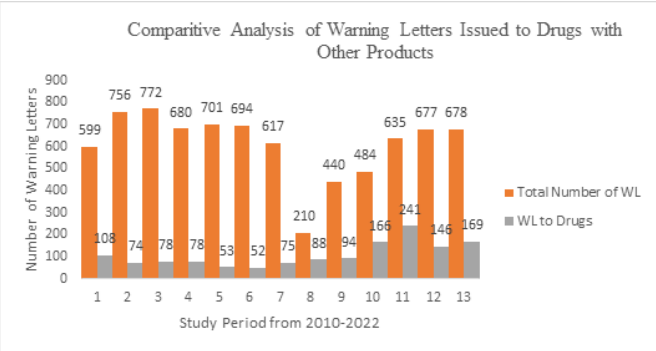

Figure 3: Comparative analysis of warning letters issued to drugs with other products

Table 1: Classification of USFDA inspection outcomes on Indian pharmaceutical industries

Total number of USFDA Inspections on indian pharmaceutical industries from 2010-2022	No actions indicated (NAI)	Official action indicated (OAI)	Voluntary action indicated (VAI)
1920	704	209	1007

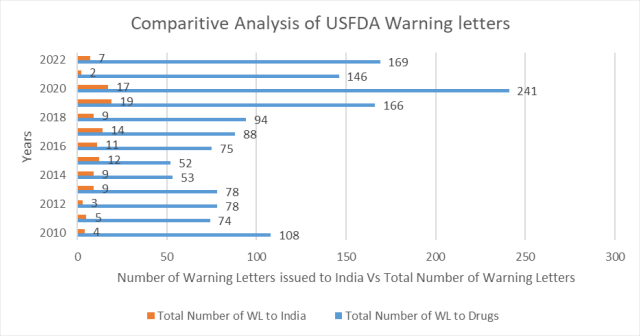

Figure 4: Comparative analysis of USFDA warning letters

Table 2: Frequency of Documentation Violation Observations cited in USFDA warning Letters Issued to Indian Pharmaceutical Industries

S. No	*Observation*	*Frequency*	*Cum*	*%Cum*
1	Destroy/delete raw data	21	21	29.1
2	Raw data missing	7	28	38.8
3	In adequate BMR	6	34	47.2
4	Unofficial batch record forms	4	38	52.7
5	Uncontrolled batch records	4	42	58.3
6	Use of unofficial notebook and paper	4	46	63.8
7	No adequate documentation	4	50	69.4
8	No documentation- MFG	4	54	75
9	Maintain production and control records	3	57	79.1
10	Incomplete raw data	3	60	83.3
11	No Documentation- Test sample	2	62	86.1
12	Data not traceable	2	64	88.8
13	Destroying original BMR	2	66	91.6
14	No Retention of raw data	1	67	93
15	Use of duplicate records	1	68	94.4
16	Destruction/ Incineration of Documents	1	69	95.8
17	Not maintaining log books	1	70	97.2
18	Inadequate cleaning record	1	71	98.6
19	No records for equipment maintenance	1	72	100

The majority of Indian pharmaceutical industries were asked to take voluntary actions against violations cited during the Inspections.

A comparative analysis was performed between the number of warning letters issued for drugs and other products and a progressive rise in the number of warning letters for drugs was observed (Figure 3).

A comparative analysis of warning letters issued to Indian pharmaceutical industries and the total number of warning letters issued revealed that USFDA auditors are paying more attention to Indian pharmaceutical industries and that Indian pharmaceutical industries received the most warning letters in 2019 (Figure 4).

From the above data destruction or deletion of data, missing of raw data and inadequate BMR are the frequently cited observations in warning letters (Table 2).

The objective of the Pareto Analysis was to identify 20% of the reasons for 80% of the documentation deficiencies cited in warning letters (Figure 5).

Table 3: Possible solutions to overcome Documentation shortfalls cited in USFDA Warning letters to Indian Pharmaceutical Industries.

S.No	*Documentation violations cited in warning Letters*	*Possible solutions to overcome documentation shortfalls*
01	Destroying or deletion of data	Institute a data disposal and destruction Policy Digitize records Use records management software[17]
02	Lacking in-depth data	Validity confirmed Preserving the necessary data to ensure the quality, accuracy, and timeliness of the user of the data.[18]
03	Inadequate BMR	Identify the gaps associated in Batch Manufacturing Records with the manufacturing process Pharmaceutical Industries.[19] Initiate change control for the change in Batch manufacturing record and associated SOPs.[20] Train the personnel involved in handling BMR and revise the BMR as on when required in compliance with regulatory requirements.[21]

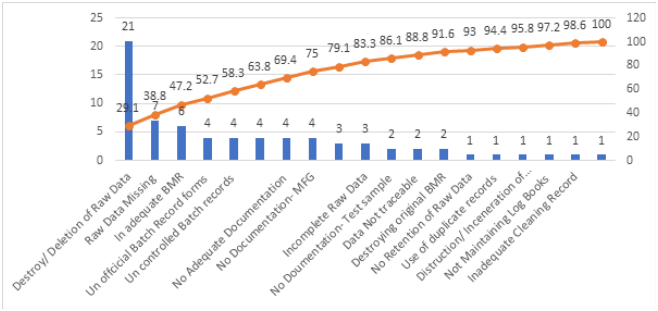

Figure 5: Pareto analysis of documentation shortfalls cited in USFDA Warning letters issued to Indian pharmaceutical industries

CONCLUSION

Documentation deficiencies identified in USFDA warning letters to Indian pharmaceutical companies were analyzed and found destruction of documents, missing of raw data, and inadequate batch manufacturing records (BMR) are frequently

mentioned as the top reasons. These issues can have serious implications for the safety and efficacy of pharmaceutical products, as well as for regulatory compliance. It is crucial for pharmaceutical companies to address these documentation shortfalls and take necessary steps to ensure the completeness, accuracy, and integrity of their records (Table 3). Failure to do so can result in warning letters, regulatory sanctions, and reputational damage. Overall, improving documentation practices is essential for the Indian pharmaceutical industry to maintain its position as a key player in the global market.

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AUTHOR CONTRIBUTION

All the authors are equally contributed for the preparation of the manuscript, proofreading and docking work.

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