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Review Article

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Technical reasons for delay and denial of regulatory approval of Initial applications for (Abbreviated) New Drugs filed by Indian Companies by USFDA, 2005-2022

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Abstract

Indian pharmaceutical companies are one of the leading sources of generic medicine to the United States. The US Food and Drug Administration (US FDA) conduct regular inspections and assessments of manufacturing facilities in order to confer product quality and to ensure a firm's compliance with applicable laws and regulations, such as the Food, Drug and Cosmetic Act and related Acts. Identified regulatory violations and noncompliance are notified by US FDA to the manufacturer in the form of 483s and warning letter. Warning letters led to the unfavourable consequences to the company such as loss of trust, reputation and affects their financial stability. A trend analysis of warning letters may help Indian pharmaceutical manufacturing companies to adopt cGMP practices as per the requirement of US FDA and thus will result in reduced number and frequency of warning letters. Therefore, a trend analysis of warning letters issued to Indian Pharmaceutical sector between 2005 till 2022 by US FDA was carried out by extracting the information from publicly available FDA archives and dashboard. There is an increasing trend in number of US FDA inspections in India post 2012 which could be due to the new regulations, updated laws, also the changed expectations and mindset of FDA inspectors. The FDA major findings included inadequate investigations systems, lack of authoritative quality units, product contamination and inadequate documentation practices. The study reported here enlists the expectations of US FDA from Indian Pharmaceutical sector. This will help Indian pharmaceutical manufacturers to adopt the strategies to minimize US FDA warning letters.

Keywords: Indian Pharmaceutical Industry, GMP, warning letter, trend analysis, US FDA, CAPA, CFR.

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1. Introduction

Good manufacturing practices (GMP) is part of quality assurance which are particularly a set of guidelines including basic control measure and procedures to be followed to meet standard specification of product which are safe to consume by human. These regulations address a variety of areas, including cleanliness, personnel qualifications, and record-keeping, all to ensure safety in the manufacture and care of FDA-regulated products by minimizing the chance of contamination or human error. As the product being manufactured in manufacturing units is meant to be used by critically ill patients, GMP environment while manufacturing is a must for pharmaceutical companies. This helps to ensure the consistent, acceptable product quality and safety.

Only way to determine how well GMP is being implemented is to conduct planned and periodic audits. Audits can be internally held to ensure GMP compliance by in house audits or external audits can be conducted by external bodies such as FDA etc. The Centre for Drug Evaluation Research (CDER) under the USFDA's Office of Manufacturing Quality (OMQ) evaluates compliance with cGMP for drugs based on inspection reports and evidence gathered by investigators. When FDA finds a manufacturer has significantly violated the regulations, they notify the manufacturer in the form of a 483s and warning letter. The firms are issued Form-483s which details the observations and expectations. They are then given time to rectify the errors and respond to FDA. Warning letters are issued if the firms still fail to comply with the observations after the repeated inspections. Warning letters are made public which is detrimental to the reputation of the manufacturer or company. This ultimately leads to the loss of time, cost and resources.

The trends in the pharmaceutical-related regulatory letters (warning letters, notice of violations) released by the FDA during the period 1997-2011were analysed and the differences were assessed in the average number and type of regulatory letters released during that period by four federal administrations. This study was the first to assess differences in regulatory letters issued by four different federal administrations including the Obama

administration. It was concluded that the annual number of pharmaceutical related regulatory letters issued by the FDA and specifically CDER headquarters and district offices was related to the federal administration. The number of regulatory letters was highest during the second Clinton administration, diminished during the Bush administrations, and increased again during the Obama administration. (1) Most regulatory letters released by FDA headquarters were related to marketing and advertising activities of pharmaceutical companies.

The impact of changes in federal administration on the enforcement policy of the FDA was also highlighted in the subsequent trend analysis done by multiple authors.

The warning letters from 2007 to 2014 issued to medical products, viz. medical devices, biological products, pharmacy compounding, finished pharmaceuticals and APIs about current good manufacturing practices (cGMP) violations were evaluated. It was concluded during the study, that the issuance number of warning letters increased during 2009-2011. Medical device manufacturers received the largest numbers of letters. The issuance number and type of warning letters were greatly influenced by changes in FDA's internal enforcement procedures, drug policies and regulations, as well as other departments' regulations. Hence, recommended that manufacturers should comply with regulations voluntarily and respond promptly to policy changes. (2)

This observation was also made during the analysis of warning letters issued by US FDA in 2019. The detailed summary of the drug GMP warning letters issued in FY2019, as well as a comparison of trends since FY2013, holistically were done. The major observation was that the warning letters issued to firms in the US constituted a majority of the drug GMP warning letters, far outpacing India and China combined. This could be the result of the changes in FDA's internal enforcement areas. (3)

In another study, the warning letters issued to Indian pharmaceutical companies from January 1, 2005, to December 31, 2018 were studied. There was a gradual increase in the number of warning letters issued to Indian pharmaceutical and medical device manufacturers, during this period. It was discussed that the primary reason of all the violations was the failure of compliance with the cGMP guidelines. Out of which majority of these warning letters were not followed by a close-out warning, which indicated that the violations listed in these warning letters could not be resolved. (4)

2. Objective

The objective of this research was to analyse the trend of warning letters issued by USFDA to Indian Pharmaceutical and Manufacturing Industry about current good manufacturing practices (CGMP) violations during 2005-2022. In addition, this paper also provides a checklist of US FDA's expectation from Indian manufacturers which can help them to reduce the number of 483s and warning letters.

3. Materials and methods

The method adopted in this research is exploratory, where the data about the inspections was extracted from US FDA data dashboard with the appropriate filters primarily: "Country/Area: India". Retrospectively, warning letters issued to Indian pharmaceutical and manufacturing industry by USFDA for the period 2005-2022 were extracted from publicly available FDA archives and dashboard. (5-7)

FDA data dashboard is created by US FDA to increase transparency and accountability by displaying and allowing the analysis of public FDA data through easy to use, visually accessible, customizable, and understandable graphics. (8)

The sources of data used to generate the dashboard graphs includes:

- Transparency datasets including Inspection Database
- Data already available to the public through the FDA.gov website
- Selected data elements from the compliance and enforcement related information on FDA.gov
- Recall data based upon the Enforcement Reports.

However, it does not include all inspections in the database. Inspections conducted by States, pre-approval inspections, inspections waiting for a final enforcement action, and inspections of nonclinical labs are not included.

4. Result and Discussion

Results

Of the 1259 warning letters (WL) issued by US FDA globally, 113 (9%) were issued to Indian Pharmaceutical Industry (Finished Product and Active Pharmaceutical Ingredient).

Table 1. Year-wise distribution of Warning letters

Year	Total No. of WLs issued by US FDA, globally	WLs issued to Indian Pharmaceutical Industry	% age of WLs issued to Indian Pharmaceutical Industry
2005	42	0	0
2006	36	2	6
2007	58	0	0
2008	43	2	5
2009	122	0	0
2010	108	3	3
2011	20	5	25

2012	22	1	5
2013	21	9	43
2014	19	8	42
2015	14	8	57
2016	84	10	12
2017	103	17	17
2018	90	10	11
2019	83	21	25
2020	184	11	6
2021	109	1	1
2022	101	5	5
TOTAL	**1259**	**113**	**9**

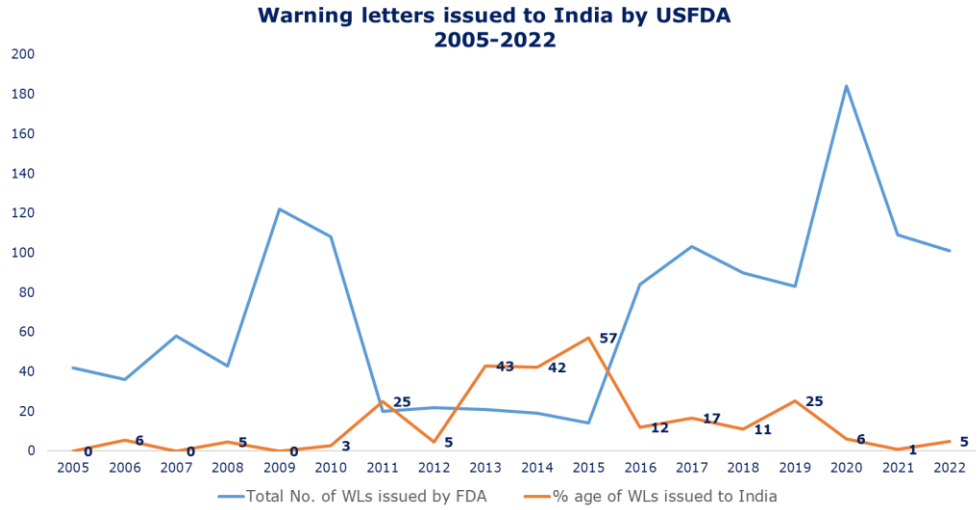

Figure 1. Graphical representation of Warning Letters issued to Indian Pharmaceutical Industry by US FDA

Table 2. Top CFR citations

S.No.	Program Area-Citation	Citation Id	Count
1	Investigations of discrepancies, failures	21 CFR 211.192	30
2	Incomplete laboratory records	21 CFR 211.194	17
3	Inadequate Quality Control unit	21 CFR 211. 22 and 22(a)	16
4	Inappropriate controls over computer or related systems	21 CFR 211. 68(b)	14
5	Control of microbiological contamination for sterile products	21 CFR 211.113(b)	14
6	Incomplete batch production and control records	21 CFR 211.188	11
7	Inappropriate equipment cleaning and maintenance to prevent contamination	21 CFR 211. 67(a)	10
8	Inadequate system for monitoring environmental conditions in aseptic processing	21 CFR 211. 42(c)(10)(iv)	9
9	Inadequate written procedures for production and process control	21 CFR 211.100(a)	9
10	Inadequate sample testing of components with all appropriate written specifications for identity, purity, strength, and quality	21 CFR 211. 84(d)(1) and (2)	8
11	Inappropriate laboratory determination of satisfactory conformance to final specifications for the drug product, prior to release	21 CFR 211. 165(a)	5
12	Inappropriate Equipment design, size, and location.	21 CFR 211. 63	4

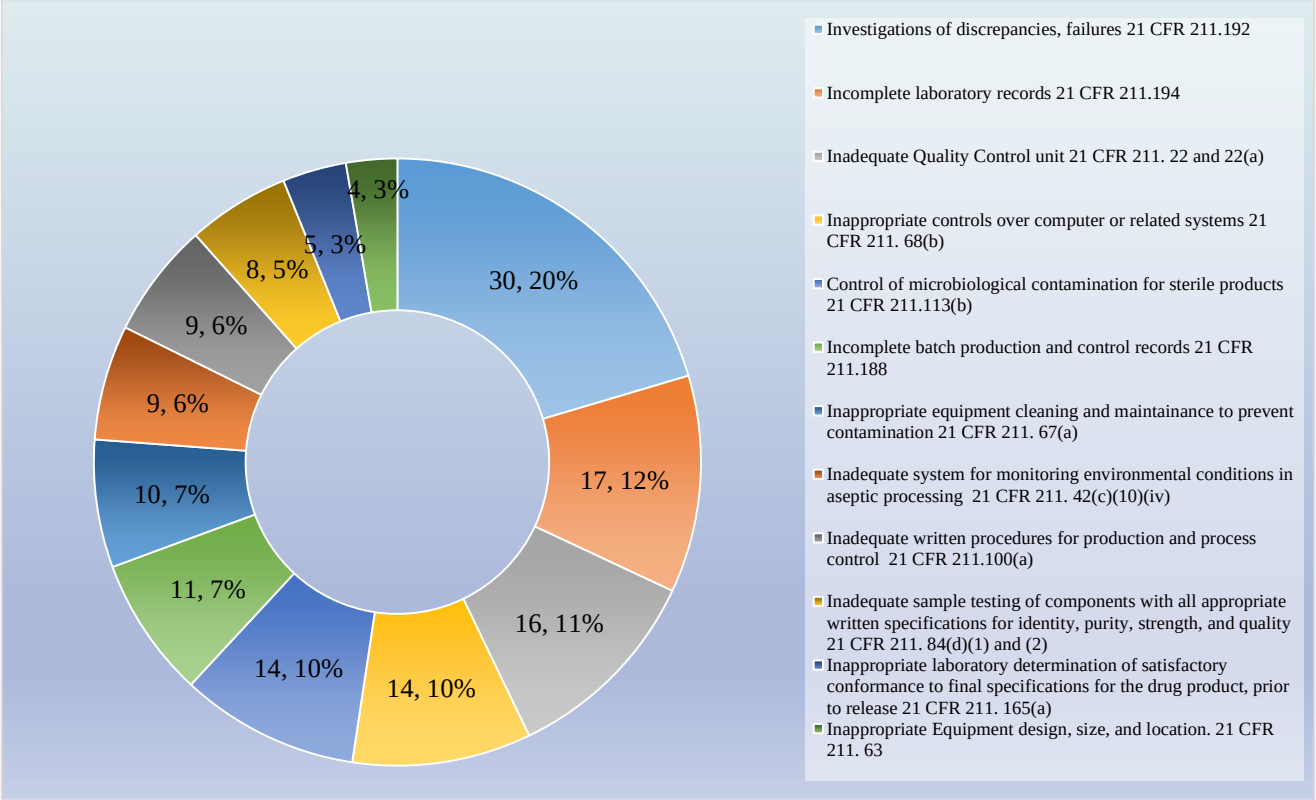

Figure 2. Top CFR citations

The FDA observations are listed in warning letters in accordance with the cited Code of Federal Regulation (CFR). 21 CFR Part 210 and 211 deals with current GMP in Manufacturing, Processing, Packing, or Holding of Drugs and GMP for Finished Pharmaceuticals, respectively. (9) The top 12 CFR citations in the warning letters issued to Indian Pharmaceutical Industry during the period 2005-2022 are tabulated in table 2 and represented in figure 2.

Based on the literature and critical analysis of warning letters issued to Indian Pharmaceutical industry, recommended is a *checklist* which provides a list of minimum documentation that should be available prior to inspection in order to avoid and/or minimize rejections or 483's issued by USFDA.

Table 3. Checklist of minimum documentation

Top CFR Citations	Citation Description	Documentation	Availability (Yes or No)
21 CFR 211.192	Investigations of discrepancies, failures	Independent assessment of the overall system for investigating deviations, discrepancies, complaints, OOS results, and failures	
		A detailed action plan to remediate this system with root cause evaluation, CAPA effectiveness, quality assurance unit oversight, and written procedures.	
		An independent review of all invalidated laboratory incidents and OOS (including in-process and release/stability testing)	
21 CFR 211.194	Incomplete laboratory records	A retrospective, independent, assessment of the OOS investigation	
		A comprehensive, independent assessment of laboratory practices, procedures, methods, equipment, documentation, and analyst competencies and its remediation plan	
		Corrective action and preventive action (CAPA) plan to implement routine quality checks of laboratory equipment.	
21 CFR 211. 22 and 22(a)	Inadequate Quality Control unit	A comprehensive assessment and remediation plan to ensure Quality Unit is	

		given the authority and resources to effectively function	
		How top management empowers quality assurance	
		A complete assessment of documentation systems used throughout manufacturing and laboratory operations to identify the gaps	
21 CFR 211. 68 (b)	Inappropriate controls over computer or related systems	Provide an assessment of all computer systems used for CGMP activities at facility.	
		Ensure how audit trails are continually enabled	
21 CFR 211.113 (b)	Control of microbiological contamination for sterile products	Well defined plan to ensure appropriate aseptic practices and cleanroom behaviour during production.	
		A retrospective review and risk assessment of aseptic practices and cleanroom behaviour	
		A comprehensive review of media fill program and its remediation plan	
21 CFR 211.188	Incomplete batch production and control records	A comprehensive review and remediation plan that assures ongoing management oversight throughout the manufacturing lifecycle of all drug products.	
21 CFR 211. 67 (a)	Inappropriate equipment cleaning and maintenance to prevent contamination	A comprehensive, independent retrospective assessment of cleaning effectiveness to evaluate the scope of cross-contamination hazards and its remediation plan	
		An independent review of the investigations and complaints of foreign matter contamination in products.	
21 CFR 211. 42 (c)(10)(iv)	Inadequate system for monitoring environmental conditions in aseptic processing	A comprehensive, independent risk assessment of all contamination hazards with respect to aseptic processes, equipment, and facilities	
		A comprehensive, independent review of personnel and environmental monitoring programs	
21 CFR 211.100 (a)	Inadequate written procedures for production and process control	A detailed qualification, manufacturing and validation program for each of the manufacturing processes that includes vigilant monitoring of intra-batch and inter-batch variation to ensure an ongoing state of control	
21 CFR 211. 84 (d)(1) and (2)	Inadequate sample testing of components with all appropriate written specifications for identity, purity, strength, and quality	An independent review of the material system to check the list of qualified suppliers and the materials are assigned appropriate expiration or retest dates. It should also determine whether incoming material controls are adequate to exclude the use of unsuitable materials.	
		The chemical and microbiological quality control specifications, methods and validations used to test and release each incoming lot of component for use in manufacturing along with its certificate of analysis	
		A summary of the program for qualifying and overseeing contract laboratory facilities that test the active ingredients used in the drug products that are being manufactured.	
21 CFR 211. 165(a)	Inappropriate laboratory determination of satisfactory conformance to final	A list of chemical and microbial specifications, including test methods, used	

	specifications for the drug product, prior to release	to analyze each lot of drug products before a lot disposition decision.	
		A comprehensive, independent assessment of the laboratory practices, procedures, methods, equipment, documentation, and analyst competencies.	
21 CFR 211. 63	Inappropriate Equipment design, size, and location	CAPA plan to implement routine quality checks of facilities and equipment.	
		A thorough evaluation and risk assessment that addresses the suitability of the equipment for its intended use.	
		An independent retrospective review of all complaints and investigations	
		An independent, comprehensive review of the complaint system that identifies deficiencies in the system and corresponding CAPA that are needed.	
		A comprehensive, independent assessment of the change management system.	

Discussion

According to table 1 and figure 1, there has been an increase in the issuance of warning letters to Indian Pharmaceutical and Manufacturing Industry. The increasing trend, post year 2012 could be due to the new regulations, implementation of Generic Drug User Fee Amendments (GDUFA), updated laws, also the changed expectations, changed focus of inspection to sterile manufacturing units, and mindset of FDA inspectors. (10)

As per table 2 and figure 2, the FDA major CFR citations during inspections included inadequate quality control units, contaminated environment, inadequate root cause analysis, incomplete written procedures for production and process control. While these violations represent serious deficiencies, some of them can be relatively easy to identify and resolve.

When FDA sends the warning letters, they specify their expectations from the companies as a response to their inspection observations. Basis the data available for the period 2005-2022, Agency's expectations and as against the top CFR citations, identified in table 2, a checklist of minimum documentation has been proposed in this paper. Manufacturing units should be prepared with the quality documentation, risk assessments, complete and adequate investigations and remediation plan, prior to the US FDA inspection, to avoid the issuance of warning letter.

5. Conclusions

Warning letters are not a respectable sign for any inspection. Indian Pharmaceutical industry should acknowledge the existence of an authoritative and strong quality assurance unit which can further build a quality culture in the organisation. Due to similar, repeated observations of inspections of different manufacturing units by US FDA, the industry should take the advantage of the checklist proposed in this research paper.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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