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Review Article

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Review on Inspectional Observation and Warning Letters

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Abstract

The Food and Drug Administration (FDA) facilitates authority for inspection in foreign countries which supply pharmaceutical products to the USA. So, the pharmaceutical companies in India must follow CGMP as per the FDA guidelines for the supply of pharma products. After the completion of inspection, FDA issues form 483, if it finds any deviations from CGMP as per the FDA guidelines. The main reason for form 483 observation is procedures are not fully followed in accordance with cGMP. In addition to FDA, regulatory body of India i.e., Central Drugs Standard Control Organization (CDSCO) also inspects manufacturing facilities in local and multinational companies, those inspection reports are released only in one of form 483 but not released on its websites publicly and it is reviewed by CDSCO representatives. The companies should respond to observations in form 483 within 15 working days. If the management fails to respond to observations within specified period of time, the FDA issues warning letters. If the response is unsatisfactory to the warning letters it may lead to further actions like suspension/cancellation of the manufacturing license, refuse to give product approval, import refusal of the products. Such an individual may be liable for a violation of the Act and, if found guilty, be subject to the penalties specified by the law.

Keywords: USFDA, Warning Letters, FDA Form 483, Inspectional observation, Enforcement actions

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1. Introduction

1.1 Regulatory actions

The objective of FDA regulatory program is to assure compliance with the FFDCA. Specific enforcement activities include actions to correct and prevent the violations, remove violative products or goods from the market and punish offenders.

It divided into two categories;

a) Inspectional Observation
b) Enforcement Actions

1.1.1 Inspectional Observations

FDA's Office of Regulatory Affairs (ORA) is the lead office for all field activities, including inspections and enforcement. During an inspection, ORA investigators may observe conditions they deem to be objectionable. These observations, are listed on an FDA Form 483 when, in an investigator's judgment, the observed conditions or practices indicate that an FDA-regulated product may be in violation of FDA's requirements. Not all Form FDA 483s are generated by these tools as some 483s are manually prepared.

The Product and Program Areas include the following:

- Biologics
- Drugs
- Devices
- Human Tissue for Transplantation
- Radiological Health
- Parts 1240 and 1250
- Foods (includes Dietary Supplements)
- Veterinary Medicine
- Bioresearch Monitoring
- Special Requirements (1)

1.1.2 Enforcement Actions

The objective of FDA regulatory programs is to assure compliance with the Federal Food, Drug, and Cosmetic Act (the Act). Specific enforcement activities include actions to correct and prevent violations, remove violative products or goods from the market, and punish offenders. The type of enforcement activity FDA uses will depend on the nature of the violation. The range of enforcement activities include issuing a letter notifying the individual or firm of a violation and requesting correction, to criminal prosecution of the individual or

firm. Such an individual may be liable for a violation of the Act and, if found guilty, be subject to the penalties specified by the law.

The types of enforcement actions;

- Warning letters
- Seizures
- Injunctions
- Recall
- Criminal prosecution
- Criminal Fines for Food Drug and Cosmetic Act Violations (1,2)

2. FDA form 483

The FDA facilitates authority for inspection in foreign countries which supply pharmaceutical products to the U.S., so the companies in India must follow cGMP as per FDA guidelines. The Form 483 is issued by the FDA to the pharmaceutical companies/management after the completion of the inspection if it finds any deviations from cGMP as per FDA guidelines and any other specific guidelines. The form 483 officially known as "Notice of Inspectional Observations". sometimes, along with the form 483 FDA also issues Establishment Inspection Report (EIR) it specifies whether action is to be taken or not. The companies should respond to observations within 15 working days. If the management fails to respond to observations within specified period of time, the FDA issues warning letters.

FDA – 483 may be issued to the company is mainly due to:

- Inadequate training of staff members
- Inadequate maintenance of product quality standards
- Recurring problems due to poor corrective and preventative actions
- Improper investigations of an events
- Deviations / investigational results that remain undocumented
- Inappropriate reporting
- Failure to adhere cGMP guidelines (1,2)

2.1 FDA Form 483 statistical data

Table 1. No. of form 483 issue in various categories in FY2016-FY2021 (3)

No.	Category	2016	2017	2018	2019	2020	2021
1.	Foods	2196	2662	2583	2540	1749	1751
2.	Devices	934	1030	966	822	422	191
3.	Drugs	691	694	716	779	349	215
4.	Incidental text	0	0	0	0	0	0
5.	Biologics	84	115	89	116	28	17
6.	Bioresearch monitoring	215	243.	216	190	98	133
7.	Parts 1240 and 1250	97	75	70	47	9	3
8.	Veterinary medicines	281	244	206	229	100	105
9.	Human tissue for translation	92	61	97	109	47	51
10.	Special requirements	0	0	0	0	0	0
11.	Radiological health	32	31	26	17	9	6

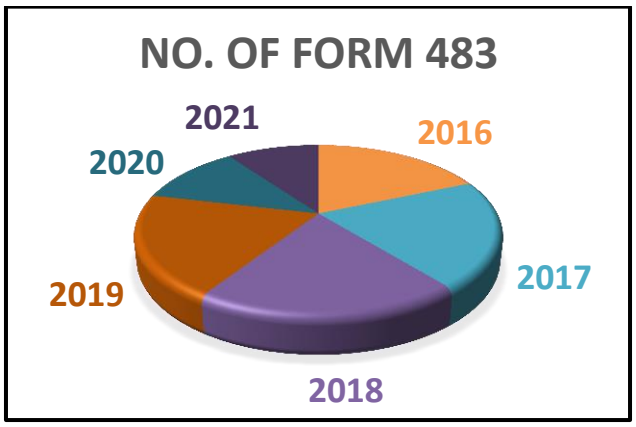

Figure 1. Number of FDA form 483 issue in Fiscal Year 2016-2021 (4)

- The top most category to issue FDA form 483 through Fiscal Year that is the FOOD, DUGS and MEDICAL DEVICE compare to other categories.

2.2 Steps of FDA form 483 response:

1. Establish a timeline for response activities
2. Identify the root cause
3. Issuing CAPA
4. Establish a timeline for addressing 483s
5. Draft initial response letter
6. Consistent follow up
7. Get ready for re-inspection (5)

3. Warning Letters

- A WLs notifies a responsible individual or firm that the agency considers one or more products, practices, processes or other activities to be in violation of the Federal Food, Drug and Cosmetic Act, its implementing regulations and other federal statutes.
- A WLs is one of the agency's principal means of achieving prompt voluntary compliance with the act.
- The agency has a computer application called the Compliance Management System (CMS) that district offices use to electronically submit warning letter recommendations to FDA centres.
- Most of the WL issued by the FDA has the quality or cGMP issues.
- Both FDA Form 483 and Warning Letters are public notifications and these can be viewed on the FDA's website because these are published immediately publicly on fda.gov. (3)

3.1 FDA WLs are issued by different offices

Table 2. No. of WLs issue in FY2018 to FY2021 by FDA centres (4)

No.	Issuance office	2018	2019	2020	2021
1.	CTP	124	117	139	295
2.	CDER	90	83	184	109
3.	CDRH	17	15	32	56
4.	CFSAN	42	59	49	38
5.	DPQO	1	66	44	21
6.	DHAFO	3	48	70	20
7.	CBER	90	1	6	1
8.	CVM	5	2	7	2
9.	DNI	0	1	13	29
10.	OMD & RHO	0	7	5	6

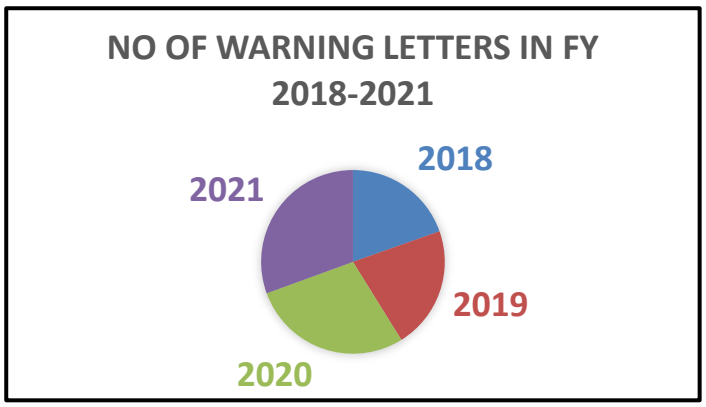

Figure 2. No. of WLs issue in FY2018 to FY2021 by FDA centres

3.2 How to respond WLs

a) The FDA ends a warning letter by indicating what the firm should do next.

b) The agency also will give the recipient a specific period of time during which a response is required. Most often this is around fifteen days. Maybe a few weeks.

c) If the recipient of the letter has one or more FDA compliance experts on staff, they should develop a plan to respond to the letter.

d) While the FDA can be slow in taking the possible next steps for persistent non-compliance issues after a warning letter, the ultimate response could be serious. In rare cases, it could lead to an injunction effort.

e) The key steps needed in addressing an FDA warning letter:

- Review the Warning Letter Thoroughly
- Conduct an Internal Investigation
- Define an Initial Response to the FDA
- Respond within the Deadline Indicated in the Warning Letter
- Define Accurate Next Steps
- Rectify Any Misguided Conclusions
- Take Further Preventive Action
- Take Internal Corrective Action
- Evaluate Any Possible Risk for Enforcement Action
- Gather a Defence Strategy (6,7)

4. Conclusion

- The main reason for form 483 observations is procedures are not fully followed in accordance with the FDA guidelines. In These instances, it mainly focuses on deviations from Good Manufacturing Process (GMP) regulations.
- The observed lack of adequate written procedures and responsibilities for the quality unit has remained a trending issue throughout recent history and its recent uptick has resulted in numerous warning letters.
- So, to decrease the number of inspectional observation and enforcement actions plan and conduct effective internal quality audits to ensure your quality system is completely aligned with all documentation and operations that is critical part of any internal audit.
- Moreover, to make the necessary improvements to ensure regulatory expectations are met across all functions of any organization.

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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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