Review Article

Findings and Regulatory Inspections of USFDA Form 483

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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. The FDA form 483 is officially called a "notice of inspectional observations". 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 .The companies may avoid getting form 483 if they have a strong internal audit procedures.

Keywords: cGMP, Inspection, Warning letters, Audit.

INTRODUCTION

Food and Drug Administration, agency of the United States Department of Health and Health services authorized by congress to test, inspect, approve and provide safety standard for foods, chemical, food additives, cosmetics, medical devices and household devices .The FDA obtain its regulatory power from four laws : Federal food, food, Drug and Cosmetic act established for safety and purity standard, Through court process FDA has the right to seize products and conduct legal proceedings against persons or organizations for legal violations.

Forms commonly used during FDA inspections[2]:

- Form 482 – Notice of inspection
- Form 483 – Inspectional observations
- Form 484 – Receipt for physical evidence (Eg: Samples), but not for documentary evidence.

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[3].

The form 483 officially known as "Notice of Inspectional Observations[4]" 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. 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.

Why it is important[3]?

In the country many pharma companies have made major investment in facilities for export growth to the U.S. Over the past years issue of form 483 to the companies has been increased which further led to warning letters. India received highest number of warning letters over the past 4 years. Quick satisfactory response to form 483 observations is mandatory to prevent Issue of warning letters .

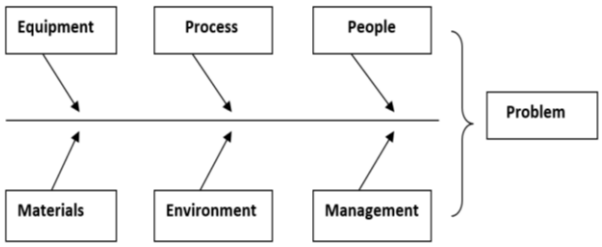
FDA – 483 may be issued to the company is mainly due to[5]:

- 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

How to respond to Form 483:

1. A timeline for response activities should be established: A response to the form 483 observations should be within 15 working days.
2. Identification of main cause: It is important to identify a main cause when issue of form 483 occurs. There are many techniques to identify the root cause. Some causes includes:



3. Issuing CAPAS : Once main cause for form 483 was identified, issue of corrective action plans (CAPAs) is recommended, it should specify
    - Description of the issue
    - Main cause analysis
    - Corrective action plans to prevent occurrence/recurrence
    - Assignment of CAPA owner
4. A timeline for addressing form 483 should be established: CAPA process should be followed and appropriate time should be taken to correct and prevent the recurrence of the form 483.
5. Draft initial response letter to FDA
6. Regular follow up
7. Ready for re – inspection

How to avoid getting form 483 [6]:

The main reason for form 483 observations is procedures are not fully followed in accordance with the FDA guidelines. This was noted in 160 separate form instances. In these instances it mainly focuses on deviations from Good Manufacturing Process (GMP) regulations.

Any pharmaceutical company to operate safely FDA requires a manufacturer's standard operating procedures (SOPs), should be clearly written, modified and should be maintained in a consistent timely manner.

The best approach for preventing human based errors is to establish a system in which each step has to be carefully followed by implementing an Enterprise Quality Management Software (EQMS) system. The best feature include it avoid mistakes which are common in manual data entry and manual document management.

EQM is an emerging software type of system able to handle all the types of files. Retrieving, maintaining, and searching for the audit documents can be simplified with configurable organizational functionality and search functionality. Audit trial functionality provides the detailed information who has changed which document and when the document was changed, ensuring that latest version of a document is in use.

By employing all these processes and best practices, the pharmaceutical company may avoid/prevent chances of issue of form 483 observations.

How to prepare for an FDA inspection[7] :

- Root analysis must be carried out and CAPA should be closed
- Monitor the data integrity regulations carefully and ensure that access is granted to right people
- It is important to check every single document is written properly including all the activities, procedures and protocol etc
- Paper – based system should be avoided because they can be lost and they are hard to update
- Standard operating procedures are in simplified manner and they are maintained, updated in timely manner
- Ensure that the staff members should be well trained on all aspects of company procedures and they must cGMP guidelines
- Maintain proper hygiene conditions at the site and the equipments should be cleaned properly
- At any time FDA inspector may ask to review any type of data, so it is important that every document is readily available on request
- The companies may avoid getting form 483 if they have a strong internal audit procedures.

Companies involved[8] :

All the Indian companies received FDA form 483, though the company sizes varies from small like Divis laboratories to large like Dr. Reddy's, Hospital and Wockhardt which has their manufacturing sites in other countries like US, UK, Ireland and France.

Other companies receiving the 483 review includes: Aurobindo, Aarti, Akorn India, Ajanta pharma, Apotex, Cipla, Emcure pharmaceuticals, Glenmark generics, Hetero, Ipca laboratories, Lupin, Nosch pharma, Sri Krishna pharmaceuticals etc.

At "Aarti drugs laboratory" during FDA review of batch manufacturing sector FDA inspector found that at the same time manual activities were performed for two different products which is quite impossible.

During FDA's review of manufacturing operators 'Training evaluation papers" the inspector found that one of the quality assurance officer answers 4 of 7 questions correctly and is considered to be satisfactory.

One of the "Sunsite" in Dandra, India inspector found that in the laboratory information management software system six "generic" user accounts were created which are not traceable to the employee using any software, so users may have chance to delete /change the values related to the particle size, sample weights, substance values and make any other changes.

Following inspection[9] in late September 2019, India based generic drug makers Lupin, Aurobindo and Cipla received form 483 by the USFDA posted last week for observations related to cleanliness, investigations into out of the specification results and for other deficiencies.

Lupin's site in Tarapur, India was inspected over five days in late September and 483 include three observations. The first question the company investigation into metal particle contamination, noting that quality team members did not include all the batches manufacturing during the operation for a risk evaluation.

FDA raised further questions about sites batch production and control records as they do not contain sufficient information relating to the production and control of each batch. The inspection was failed to cover the information regarding handling and storage of cleaned utensils to prevent contamination.

Aurobindo received form 483 for seven observations, following seven day inspection at the manufacturing Polepally, India based site in late September.

Investigations were found to be deficient in out of specification results which have been invalidated for various tests without identifying the main cause.

Aurobindo also failed to provide the entire requested document to the FDA or the documents which are provided either contain incomplete, inaccurate information or explained with misleading information throughout the inspection.

At Cipla's site Goa, India the inspection was carried out for total 11 days and resulted in 12 observations. A very big issue related to the cleaning activities makeup a large portion of the 38 page form 483.

Other observations which are related to the aseptic processing areas and the procedures which are designed to prevent the microbial contamination and specifications related to materials, it also failed to explain about the batch or any of its specifications whether the batch has been already distributed or not.

Since Indian Pharmaceutical Companies have secured USFDA ANDA approvals in the first six months of 2018, Indian Pharmaceutical Companies and their subsidiaries have continued their fine securing substantial number of final ANDA approval at USFDA. Aurobindo pharmaceuticals continues to lead.

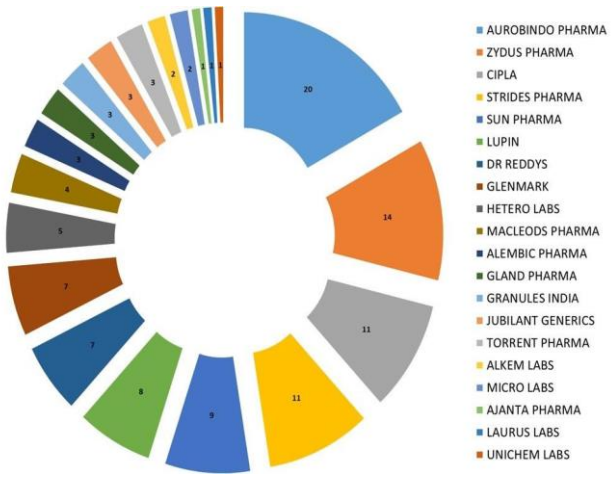


Figure 1: USFDA approvals for Indian Companies from Jan-June 2018[10]

483s and warning letters and import alerts[10] :

Form 483 is issued to management when an inspector has observed any conditions that in their judgment that in their judgment may constitute the violations of the Food Drug and Cosmetic Act and related act.

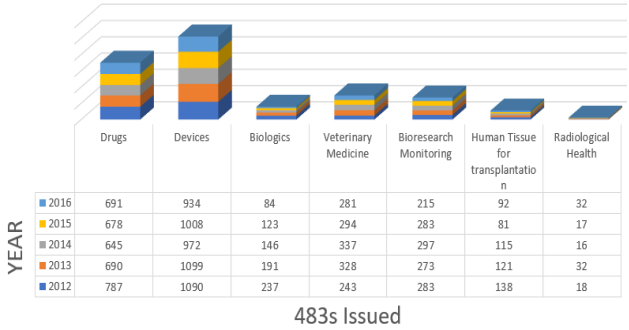


Figure 2: Total 483s issued by USFDA until 2016[10]

After a form 483 is issued and the inspector complete the establishment inspection report, the agency may issue warning letter. A warning letter indicate that a serious violation may exist and higher FDA officials have reviewed the observations.

While India received the highest number of warning letter issued to a single country (32 warning letter) over the 4 year time period, of 2013-2016.

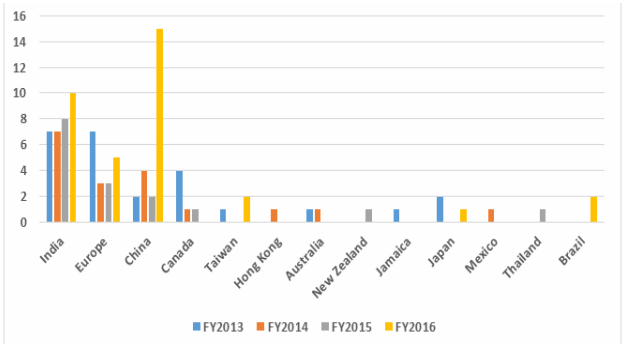


Figure 3: OUS Warning Letters by Geography[10]

Table 1: Drug GMP warning letters regarding sites outside the U.S.[10]

Country / Geography	FY2013	FY2014	FY2015	FY2016	Total
India	7	7	8	10	32
China	2	4	2	15	23
Europe	7	3	3	5	18
Canada	4	1	1		6
Taiwan	1			2	3
Japan	2			1	3
Hong Kong		1			1
Australia	1	1			2
Brazil				2	2
New Zealand			1		1
Jamaica	1				1
Mexico		1			1
Thailand			1		1

Out of the thirty – five warning letters that were issued regarding OUS (outside the U.S.), 17 of these were associated with import alerts for failure to comply with drug GMP's.

Table 2: Number of 483s from the system[11]

Inspections ending between 10/1/2016 and 9/30/2017

Center Name	483s Issued
Biologics	115
Bioresearch Monitoring	243
Devices	1030
Drugs	694
Foods	2662
Human Tissue for Transplantation	61
Parts 1240 and 1250	75
Radiological Health	31
Veterinary Medicine	244
Sum Product Area 483s from System*	**5155**

Summaries of the top five observation occurrences per sector are as follows[11] :

Observations reported by the Drug sector are:

- Procedures applicable to the quality control units are not fully followed / not in writing
- Laboratory controls are not scientifically appropriate
- Lack of written procedures for production and process controls
- Failure to thoroughly review
- Cleaning / maintenance of equipment and utensils are not followed

Observations reported by the Devices are:

- Procedures for corrective and preventative action have not been adequately established
- Procedures for receiving, reviewing and evaluating complaints have not been adequately established
- Process inspection and testing results not been adequately validated
- Failure to provide the procedures to ensure that all purchased / services

Observations reported by the Biological sector are:

- Written SOP's were not always established
- Failure to perform a thorough investigations
- Failure to maintain records that provides a complete information about the work performed
- Equipment used foe blood and components is not standardized / calibrated on a regularly scheduled basis

Observations reported by the Veterinary sector are:

- Failure to maintain treatment record
- Causing a residue of an approved human / animal drug above an establishment safe level
- Expired drugs observed in drug storage areas
- Lack of adequate inventory system for quantities of drugs used to medicate livestock
- Failure to maintain record used to identify the animals

Conclusion:

- The main reason for form 483 observations is procedures are not fully followed in accordance with the FDA guidelines. This was noted in 160 separate form instances. In These instances it mainly focuses on deviations from Good Manufacturing Process (GMP) regulations.
- Any pharmaceutical company to operate safely FDA requires a manufacturer's standard operating procedures (SOPs), should be clearly written, modified and should be maintained in a consistent timely manner.

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