CROSS-SECTIONAL ANALYSIS OF INVESTIGATION FAILURES CITED IN USFDA WARNING LETTERS AND ITS IMPACT ON INDIAN PHARMACEUTICAL INDUSTRIES

Dr. Raju Kamaraj[a]*, T.Sudheer Kumar[a]

Article History: **Received**: 27.05.2022 **Revised**: 26.06.2022 **Accepted**: 09.07.2022

Abstract: Indian manufacturing plants manufacturing for the United States should comply with the regulations of USFDA, Indian Pharmaceutical Industries are the major suppliers of generic drugs to the US Market. USFDA has the right to inspect manufacturing plants periodically to ensure manufacturing site compliance with the regulations. USFDA inspectors may issue form483 about their findings and unjustified observations may turn into Warning letters. Investigation failures and Insufficient corrective actions to Customer complaints, OOS and Deviations are grabbing more attention from USFDA auditors during their manufacturing site inspection and these observations were turning into form 483 and Warning letters for Indian Pharmaceutical Industries. A cross-sectional analysis was performed for the warning letters issued from 2010 to 2021 and all Warning letters issued from Indian Pharmaceutical Industries during the study period and the Data has collected from UDFDA publically accessible database. About 114 USFDA issued Indian Pharmaceutical industries warning letters 211 CFR citations & 595 observations were analysed and categorised based on the violation theme. Insufficient Corrective actions of Out of specifications, Consumer / Market complaint and deviation marks the primary reason for the issue of warning letters under cGMP non-compliance violation.

Keywords: CAPA, Deviation, Out of Specification, Customer Complaint, USFDA.

[a]. SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, 603 203, Kanchipuram, TN, India

***Corresponding author**

Email : moishakamaraj@gmail.com

DOI: 10.31838/ecb/2022.11.04.007

INTRODUCTION

Investigating an Out of specifications, Deviation Investigation and Customer complaint investigations has concurrently become the most challenging function in pharmaceutical Industries[1]. USFDA inspectors are concerned about the Improper Investigation during their visit to Pharmaceutical Industries and these observations may also lead to the issue of Warning Letters to the concerned Manufacturing Plant.

Deviation Investigation: Deviation is a departure from the approved internal written procedure or established standards. Deviations can be categorized into planned and unplanned deviations. Based on the impact on product quality unplanned deviations can be classified into three types: Critical, Major and Minor deviations. An Incident cannot be classified under the same category because Incidence is an event that may affect product quality and cGMP compliance. Any significant deviations from a pre-defined procedure and instructions shall be fully recorded and investigated[2]. Any deviations should be avoided as far as possible if a deviation occurs, deviated batches should undergo investigation pertaining to their impact on quality and measures shall be taken to correct and the batches shall be reviewed should be approved by a Quality Assurance person. Potential deviations are identified and avoided by implementing risk control measures and preventive actions[3]. USFDA has issued a Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations which includes guidance for handling Deviations in Pharmaceutical Industry[4].

Out-of-specification (OOS): test results of any analysis that fall outside the specifications or acceptance criteria established in the pharmaceutical industry, or do not comply with regulatory, legislative, or specification limits in Pharmaceutical. The guidance established an empirical organizational approach to investigation and decisions, which can be utilized at the different stages of the investigation. When an OOS test result is identified, it is important to determine the root causes of the event and to avoid the reoccurrence of such results[5]. USFDA has issued a guidance document for handling and Investigating out of Specification (OOS) test results for Pharmaceutical Production. As per the guidance document all the OOS investigation, the results should be evaluated, the batch quality should be determined, and a release decision should be made by the Quality Control Unit. Once a batch has been rejected, there is no limit to further testing to determine the cause of the failure so that corrective action can be taken[6].

Consumer Complaint Investigation: If any Pharmaceutical Product which is not meet the customer requirement or with the presence of any critical defect in the market may receive a market complaint from the customer[7]. Market complaints need to be investigated with well-defined procedures on higher priority. If the complaint is genuine, then a root cause analysis performed to rectify the problem and the product should be recalled from the market if it is necessary[8]. USFDA Expects all consumer/ Market Complaints need to be investigated in a timely manner[9]. USFDA has issued a guidance document for handling consumer/ Market complaints in 21 CFR 211 § 820.198.

According to the above regulation, the manufacturer shall review and evaluate all complaints to determine whether an investigation is necessary. When no investigation is made, the manufacturer shall maintain a record that includes the reason no investigation was made and the name of the individual responsible for the decision not to investigate[10]. Corrective and preventive action subsystems should be initiated soon after receiving OOS, Deviation and Consumer complaints, CAPA includes collecting information, analyze information, identify and investigate product and quality problems, and take appropriate and effective corrective and/or preventive action to prevent their recurrence. Verifying or validating corrective and preventive actions, communicating corrective and preventive action activities to responsible people, providing relevant information for management review, and documenting these activities are essential in dealing effectively with product and quality problems, preventing their recurrence, and preventing or minimizing device failures[11]. Improper investigation/ Insufficient Corrective action is grabbing regulatory attention during audits and this may lead to regulatory actions like form 483 and Warning letters.

METHODOLOGY

USFDA Warning Letters issued from 2010 to 2021 were collected from USFDA Publically accessible database and analysed based on the following variables.

- Cross-Sectional analysis was performed for Warning letters issued to Indian Pharmaceutical Industries by comparing with US and China.
- CFR cited from 2010-2021.
- OOS Investigation failure Observations cited from 2010 to 2021
- Deviation Investigation failure observations cited from 2010 to 2021
- Consumer complaint/ Market complaint investigation failure observations cited from 2010-2021

RESULTS & DISCUSSION

USFDA has issued 7265 Warning Letters issued from 2010 to 2021, among 7265 Warning letters 1253 were issued to Pharmaceutical Industries. US Pharmaceutical Industries had received the highest number of warning letters followed by China and India.

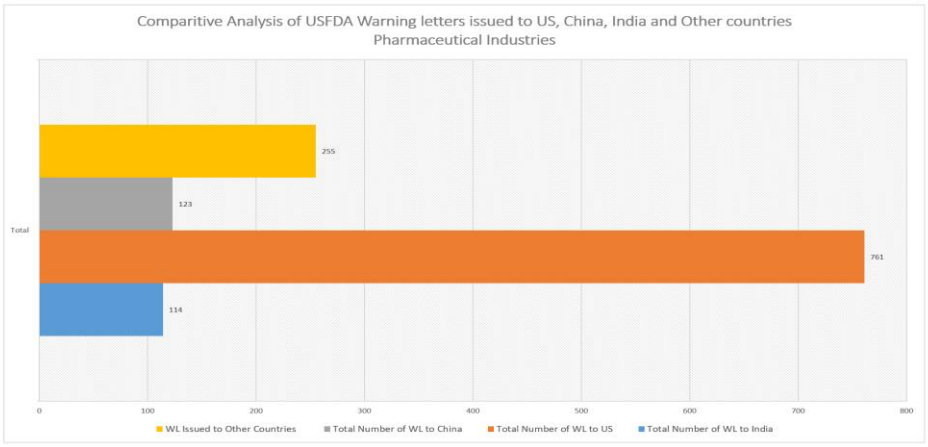

Figure 1: Cross-Sectional analysis of USFDA Warning letters issued to Pharmaceutical Industries of US, China, India and other counties from 2010-2021

USFDA has inspected nearly 1890 Indian manufacturing plants and were issued with 114 Warning letters from 2010 to 2021.

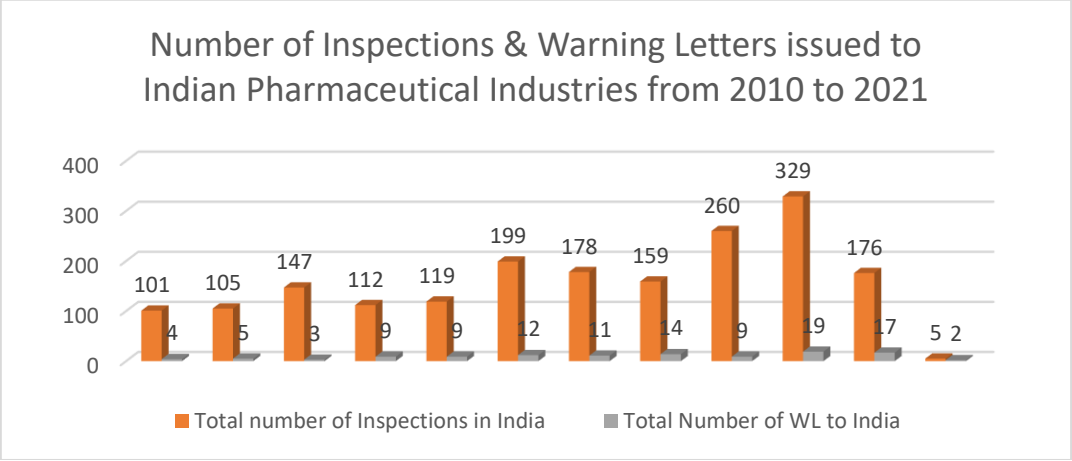

Figure 2. Cross-Sectional analysis of Inspections and Warning Letters issued to Indian Pharmaceutical Industries

USFDA have issued 114 Warning Letter to Indian Manufacturing Plants and 211 CFR's violations and 595 observations were cited in warning letters issued from 2010 to 2021.

Table 1. Number of CFR and Observations Cited from 2010 to 2021

Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
Total No.of WL to India	4	5	3	9	9	12	11	14	9	19	17	2	114
CFR cited	10	4	3	21	11	25	20	20	16	40	34	6	211
Observations	20	19	5	57	70	97	81	65	35	73	64	9	595

Observations cited in Warning Letters of Indian Pharmaceutical Industries were categorized based on the violation theme with the aim of identifying frequency of violations from 2010-2021 from the above study we found that cGMP violations occupy major portion in Indian Warning Letters.

Table 2. CFR cited in Indian Pharmaceutical Manufacturers USFDAWarning letters Issued from 2010 to 2021

CFR Cited in Warning Letters	Violation Theme	Frequency of violation
21 C.F.R. § 211.192	Production Record Review/ Investigation	29
21 C.F.R. § 211.194 (a)	Laboratory Records	19
21 C.F.R. § 211.113(b)	Control of Microbial Contamination	17
21 C.F.R. § 211.22	Quality Control Unit	17
21 C.F.R. § 211.68	Automatic, Mechanical & Electronic Equipment	15
21 C.F.R. § 211.100	Written Procedures; Deviations	13
21 C.F.R. § 211.84(d)	Testing & Approval or Rejection of Components	13
21 C.F.R. § 211.67(a)	Equipment Cleaning & Maintenance	15
21 C.F.R. § 211.42(C)	Design & Construction Features	12
21 C.F.R. § 211.160	General Requirements	10
21 C.F.R. § 211.165 (e)	Testing and release for distribution.	10
21 C.F.R. § 211.188	Batch production and control records.	8
21 C.F.R. § 211.25(a)	Personnel Qualification	4
21 C.F.R. § 211.198	Complaint files.	4
21 C.F.R. § 211.56(a)	Sanitation	3
21 C.F.R. § 211.180	Records & Reports General Requirement	3
21 C.F.R. § 211.63	Equipment Design, Size & Location	3
21 C.F.R. § 211.166 (a)	Stability Testing	3
21 C.F.R. § 211.52	Washing & Toilet facilities	2
21 C.F.R. § 211.111	Time Limitations on Production	2
21 C.F.R. § 211.110	Sampling and testing of in-process materials and DP	2
21 C.F.R. § 211.58	Maintenance	2
21 C.F.R. § 211.182	Equipment cleaning and use log.	2
21 C.F.R. § 211.142	Warehousing procedures.	1
21 C.F.R. § 211.28 (a)	Personnel Responsibilities	1
21 C.F.R. § 211.186 (a)	Master production and control records.	1

Table 3. Categorization of Observations received from 2010 to 2021

Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
cGMP	13	10	3	22	18	47	39	36	23	54	42	6	313
GLP	5	1	0	11	20	12	6	5	2	7	3	0	72
GDP	1	3	0	9	8	8	14	12	3	5	9	3	74
DI	1	5	2	7	14	7	13	3	3	3	3	0	61
GALP	0	0	0	7	9	20	9	4	2	4	5	0	60
Others	0	0	0	1	0	1	0	5	2	0	0	0	9

66 observations related OOS Investigation failure cited in Warning letters issued to Indian Pharmaceutical Industries from 2010-2021 and these observations occupy major portion in cGMP violations.

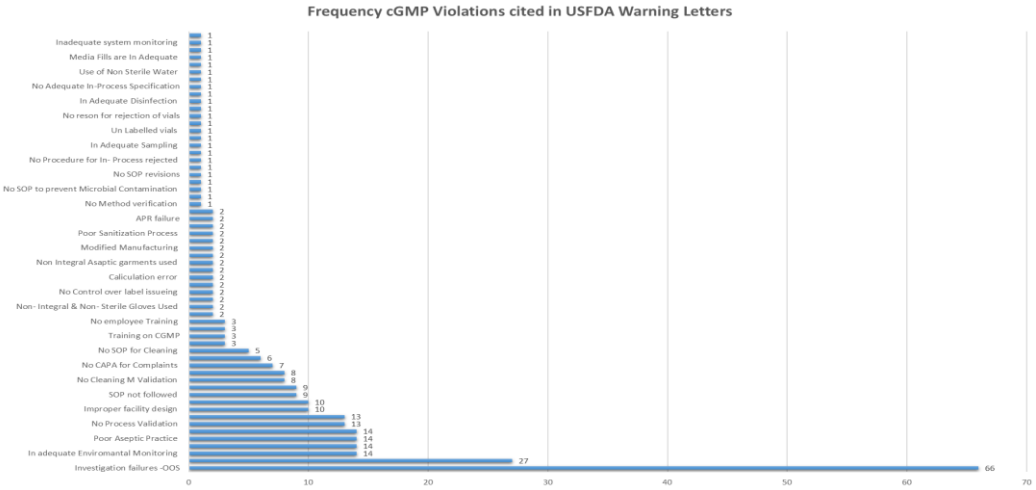

Fig.No. 3: Cross-Sectional analysis of cGMP observations cited in Warning Letters

Cross-Sectional analysis was performed among the Investigation failures with the aim of identifying highest number investigation failures cited in Indian Pharmaceutical Manufacturers complaint and found out of Specifications Investigation failures occupy major portion followed by Deviation Investigation & Consumer/ Market Complaint Investigation failures.

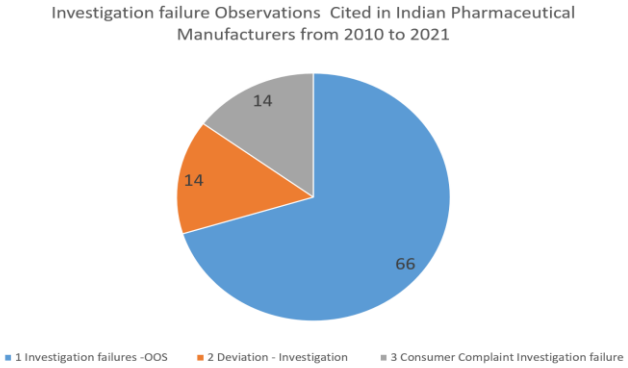

Figure 4. Investigation failure observations cited in USFDA Warning letters

CONCLUSION

A cross-sectional analysis of warning letters issued to Indian Pharmaceutical Manufacturers by china and US manufacturers was performed and found US manufacturers have received the highest number of warning letters than China & India. Further warning letters issued to Indian Pharmaceutical Industries were evaluated to identify the frequency of violation theme and found cGMP violations occupy a major portion and it becomes clear that Investigation failures like OOS investigation, Deviation Investigation and Customer / Market Complaint Investigations failures are the most frequent deficiencies cited in warning letters issued to Indian Manufacturers. According to these analyses, Indian companies are not giving adequate attention to investigating discrepancies/failures and it's remained the dominant theme in the FDA warning letters.

ACKNOWLEDGEMENT

I would like to extend our gratitude to the management of SRM College of Pharmacy for providing us with all the facilities that were required. We are also thankful to the Prof. Raju Kamaraj for his excellent research guidance and support.

Compliance and Ethical standard

I. Ethical approval - NA

II. Funding details (In case of Funding) - NA

III. Conflict of interest - No conflict of interest

IV. Informed Consent – NA

Author's contribution

T. Sudheer Kumar collected and analysed all the Warning letters issued to Indian Pharmaceutical Industry and Prepared manuscript, corrections were done by Prof. Raju Kamaraj

REFERENCES

i. Ali H, Talreja P, Hajela R. Investigating an Out of Specifications results (OOS): The most challenging function in pharmaceutical industries. Drug Invention Today. 2011 Apr 1;3(4).

ii. Eu GMP requirement [https://www.ema.europa.eu/Accessed on 01/03/2022]

iii. WHO guidelines for Deviation handling and quality risk management [https://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/ Accessed on 21/02/2022]

iv. Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations[https://www.fda.gov/media/71023/download Acessed on 10/05/2022]

v. Kuselman, I. and Fajgelj, A., 2013. Human errors and out-of-specification test results. Chem. Int, 35(3), pp.30-31.

vi. USFDA Guidelines on Guidance for Industry Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production [https://www.fda.gov/media/71001/download Accessed on 10/07/2022]

vii. Krishna, T.V., Kumar, L., Reddy, M.S., Muddukrishna, B.S. and Pai, K.G., 2013. Market Complaints in Pharmaceuticals: A Brief Review on its Handling, Investigation and Reporting. Research Journal of Pharmacy and Technology, 6(11), pp.1314-1316.

viii. Shashikant, G.S., Chhabra, G. and Nayan, G., 2018. HANDLING OF MARKET COMPLAINTS AND RECALLS, REVIEW OF FDA-483 FORM. *Asian Journal of Pharmaceutical Research and Development*, *6*(3), pp.55-59.

ix. Shearer, G.L., 2003. Contaminant identification in pharmaceutical products. MICROSCOPE-LONDON THEN CHICAGO-, 51(1), pp.3-10.

x. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-820 Accessed on 10-02-2022

xi. https://www.fda.gov/corrective-and-preventive-actions-capa Accessed on 12-04-2022