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REVIEW ARTICLE

Review of FDA Warning Letters to Pharmaceuticals : Cause and Effect Analysis

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ABSTRACT:

Purpose: The purpose of this paper is to identify the cause and effect of increased number of warning letters issued by the USFDA year after year in spite of clarity in the guidance issued by the agency. Increased number of warning letters is matter of concern for the manufacturer, drug authority and society. This review of the warning letters would help to identity the recurring observations and learning to other organizations to avoid similar non-compliances. **Methods:** 85 warning letters issued to the drug substance and drug product manufacturers for three years (2014 to 2016) were reviewed and causes were classified in categories based on nature of observations. Pareto analysis was performed to identify the 4 top categories. Further review and Pareto analysis identified the causes of the observations under these top 4 categories. **Results:** Total observations are 580 reported in 85 warning letters for last 3 years. Pareto analysis of the observations revealed that the top four issues among all categories of the plants are contributing 82% of the total observations. These are related to poor quality system (195, 34%), followed by breach of data integrity (142, 24%), poor laboratory controls (76, 13%) and poor production controls (65, 11%). For manufacturing with sterile operation where the risk is high w.r.t. product quality and patient safety, the highest issues were related to poor aseptic behaviour i.e. 31.5% of the total 130 observations cited in the warning letters. **Conclusions:** It is evident from the review of warning letters for last 3 years that pharmaceutical industry need to Improve quality systems specifically investigation system, CAPA system, adherence to SOP compliance and sound stability program. Authors suggest that other manufacturer involved in drug product and drug substance shall regularly review these warning letters to learn to be proactive and implement the preventive actions to avoid the occurrence in their organization. There is need for Paradigm shift in quality culture and transparency with regulators while interacting during the audits. Quality, compliance and integrity are the pillars for any pharmaceutical organization to be successful.

KEYWORDS: Warning Letter, FDA, 483 Observation, Import Alert, Data Integrity, cGMP