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Review Article

Current Practices for Out of Specification in Indian Pharma

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ABSTRACT

Objectives: This study focuses on understanding why Out of Specification (OOS) results are commonly reported by the United State Food and Drug Administration (USFDA) in official letters given to Indian Drug companies. **Methodology**: The author reviewed several sources including USFDA Form 483 reports, official warning letters, and global regulatory guidelines such as those from the USFDA and World Health Organization (WHO). The study mainly analyzed letters from the years 2023 and 2024, while older data from 2019 to 2022 were reviewed for reference. **Results**: The analysis showed that many companies failed to properly investigate OOS results. Main reasons included lack of scientific justification, poor documentation, and failure to find the actual root cause. Some companies invalidated failing results without proper evidence and did not check other batches that could also be affected. The Quality Unit did not follow clear procedures for investigating failures. **Conclusion**: Data shows that training on OOS guidelines, better documentation, and strong investigation procedures are essential to avoid such issues. More research is needed to find why Indian companies struggle with OOS compliance and how it can be improved. A major limitation of the study was difficulty in reviewing all data.

Keywords: *Corrective and Preventive Actions, Good Manufacturing practice, Out of Specification, Quality Control, Standard Operating procedure, USFDA.*

INTRODUCTION

In the pharmaceutical sector, ensuring product quality, safety, and regulatory compliance is critical. Among the key focus areas during regulatory inspections is the management of Out of Specification (OOS) test results. An OOS result refers to any test outcome that fails to match the defined acceptance limits specified in pharmacopoeias, regulatory submissions, or internal standards. Such results can raise serious questions about the reliability of manufacturing processes and the uniformity of product quality (Abraham and Kumar, 2020; Agarwal et al., 2015; Ali et al., 2018; Ananth et al., 2018; Bai et al., 2021; Binnar and Bhalla, 2025; Church and Mahoney 2009; Hoinowski et al., 2002; Jain and Jain, 2017; Jain and Jain, 2018; Jain and Jain, 2020; Kamaraj and Kumar, 2022; McDowall, 2020; Kolekar and Bhagwat, 2021; Kumar and Gupta, 2015; Kuselman and Fajgelj, 2013; Kuselman *et al*., 2010; Kuselman et al., 2011; Neves et al., 2020; Patel et al., 2022; Patel, 2012; Ravi et al., 2013; Swartz and Krull, 2004; Unger, 2014; Winchell, 2011).

To address this, the United States Food and Drug Administration (USFDA) issued detailed guidance titled *"Investigating OOS Test Results for Pharmaceutical Production"* in October 2006 (USFDA Investigating Out of Specification Test Results, 2022). This paper still serves as a base reference for how companies should handle OOS findings. It emphasizes that every OOS result, whether ultimately confirmed or not, must be investigated thoroughly through a logical, science-based, and clearly documented approach (Abraham and Kumar, 2020; Agarwal et al., 2015; Ali et al., 2018; Kamaraj and Kumar, 2022; McDowall, 2020; Kolekar and Bhagwat, 2021; Kumar and Gupta, 2015; Kuselman and Fajgelj, 2013; Kuselman *et al*., 2010; Kuselman et al., 2011; Neves et al., 2020; Patel et al., 2022; Patel, 2012; Ravi et al., 2013; Swartz and Krull, 2004; Unger, 2014; Winchell, 2011).

As per the guidance, OOS investigations are conducted in two phases (Abraham and Kumar, 2020; Agarwal et al., 2015; Ali et al., 2018; Kamaraj and Kumar, 2022; McDowall, 2020; Kolekar and Bhagwat, 2021; Kumar and Gupta, 2015; Kuselman and Fajgelj, 2013; Kuselman *et al*., 2010; Kuselman et al., 2011; Neves et al., 2020; Patel et al., 2022; Patel, 2012; Ravi et al., 2013; Swartz and Krull, 2004; Unger, 2014; Winchell, 2011).

Phase I: Laboratory Investigation

The initial stage of investigating an OOS result focuses on determining whether the deviation may have been caused by errors within the laboratory. This includes reviewing all areas of testing to identify any mistakes, procedural lapses, or equipment-related issues.

Critical checkpoints in Phase I include:

- **Sample Handling:** Verifying if the sample was properly labelled, stored, and processed as per standard protocols.
- **Analyst Performance:** Assessing whether the analyst was adequately trained and followed correct procedures without making operational errors.
- **Instrument Condition:** Reviewing calibration records and operational status of instruments used during testing.
- **Method Execution:** Confirming that validated procedures were followed correctly, and all calculations were performed accurately.
- **Data Review:** Examining raw data, including chromatograms and reports, for completeness, accuracy, and consistency.
- **Reagents and Standards:** Ensuring that all chemicals and reference substances used were within validity and properly prepared.

When the examination reveals a clear mistake during laboratory testing, such as analytical error or equipment malfunction, the first outcome may be considered incorrect, and a justified retest can be performed. However, if no such error is found during the laboratory review, the investigation must move forward.

In such cases, Phase II involves a comprehensive assessment of the drug manufacturing activity. This includes evaluating factors for example, the standard of raw materials, equipment calibration status, any deviations in the batch manufacturing process, and potential environmental influences that could have impacted the product quality.

Phase II of the OOS investigation focuses on a detailed examination of the manufacturing activity to determine any underlying issues that may leading to the problem. Areas typically reviewed during this stage include:

- **Batch Records:** A thorough check of production documents to identify any deviations, skipped steps, or inconsistencies.
- **Raw Materials:** Verification that all components met their required specifications and were sourced from approved vendors.
- **Environmental Controls:** Review of conditions such as temperature, humidity, and cleanliness during the manufacturing lot. Equipment Usage Logs: Examination of calibration, maintenance, and cleaning records to confirm proper machine functioning.
- **Manufacturing Trends:** Evaluation of previous batch histories to detect any patterns or repeated concerns.
- **In-Process Checks:** Assessment of test results taken during production to highlight any signs of drift or unusual outcomes.
- **Personnel Qualifications:** Confirmation that the staff involved were adequately trained and followed established procedures.
- **Data Integrity:** Scrutiny of documentation accuracy, audit trails, and electronic record processes that help confirm data authenticity.

If a definite root cause is identified during the investigation, suitable Corrective and Preventive Actions (CAPA) must be implemented and documented thoroughly. However, in cases where no specific reason can be determined, the result must be treated as OOS, and the corresponding batch may either be rejected or placed on hold pending further evaluation.

Regulatory bodies like the USFDA clearly prohibit unethical practices such as retesting without scientific justification, ignoring unfavourable data, or selectively testing until a desired result is achieved commonly referred to as "testing into compliance." Such actions are considered serious breaches of data integrity. All test outcomes whether acceptable or not must be properly recorded and considered at the time of checking the problem. Even if a batch later produces results within specification, the original result that was out of limits cannot be disregarded and should be factored into the final assessment. Importantly, product release must only occur once a scientifically justified root cause has been confirmed and appropriate CAPAs are established to stop it from repeating. Figure 1 explain how to investigate when OOS occurred.

In India, regulatory oversight on OOS handling is enforced by the Central Drugs Standard Control Organization (CDSCO) under the framework of Good Manufacturing Practices (GMP) outlined in Schedule M of the Drugs and

Cosmetics Act, 1940. Pharmaceutical manufacturers are required to maintain comprehensive records, follow written OOS procedures, and uphold data integrity in alignment with the expectations of both the USFDA and the World Health Organization (WHO). The WHO Technical Report Series (TRS) 996, Annex 5 Guidelines on Good Data and Record Management Practices is frequently adopted by Indian firms to harmonize with global regulatory standards.

OOS related issues remain a leading cause of USFDA Form 483s and Warning Letters issued to Indian pharmaceutical companies. These typically arise from insufficient investigations, lack of finding the main reason for the problem, deviations from established Standard Operating Procedure (SOPs) or data manipulation to meet specifications.

Overall, effective OOS management is very important in maintaining the quality of the product and following the rules Both USFDA and CDSCO mandate a systematic, transparent, and science-based approach for handling OOS results. Adhering to these principles not only enhances audit readiness but also ensures that patients receive safe and effective medicines.

Regulatory Guidelines

Several international regulatory agencies have established well-defined procedures for managing OOS results encountered during pharmaceutical manufacturing and testing. One of the most widely referenced guidelines comes from the USFDA, initially published in 2006 and later clarified in 2022, titled *"Investigating OOS Test Results for Pharmaceutical Production"* (USFDA Investigating Out of Specification Test Results, 2022)**.** This guidance outlines a two-phase investigation approach, beginning with laboratory-related evaluations and extending to manufacturing level assessments when required. It strongly emphasizes traceability, valid scientific reason for doing the test again, and explicitly prohibits data manipulation or selective result reporting.

In the European Union, OOS expectations are embedded within EudraLex Volume 4 of Good Manufacturing Practices, especially in Chapter 1 (Pharmaceutical Quality System) and Chapter 6 Quality Control (QC) (EudraLex, Volume 4 - Good Manufacturing Practice, 2015) . These sections stress comprehensive documentation, evidence-based investigation of deviations, and robust root cause analysis with preventive action planning.

In India, regulatory oversight falls under Schedule M of the Drugs and Cosmetics Act, 1940, enforced by the Central Drugs Standard Control Organization (CDSCO). Although no standalone OOS guideline exists, Indian manufacturers are expected to align with WHO and USFDA standards, maintaining internal methods used to confirm thorough and timely evaluation of any unexpected results (WHO TRS 986, Annex-2, 2014).

The United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) has issued specific guidance addressing OOS investigations, which includes detailed flowcharts, decision trees, and distinctions between OOS, Out of Trend (OOT), and atypical results.

Although the Pharmaceutical Inspection Co-operation Scheme (PIC/S) has not released a dedicated OOS guideline, its GMP Guide (PE 009-17) sets out clear requirements for investigating abnormal results. It mandates immediate evaluation, risk-based decision-making, and coordinated actions before batch disposition.

Figure 2 provides a comparative overview of key regulatory agencies and their respective approaches to handling OOS results.

METHODOLOGY

In this review, the author performed a detailed examination of various sources, including peer-reviewed publications, USFDA Form 483 reports, and official warning letters sent to pharmaceutical manufacturers (USFDA Inspection Citation, 2009). Key regulatory documents addressing OOS investigations particularly those from the USFDA and the WHO Technical Report Series (TRS) were studied during the review process (WHO TRS 986, Annex-2, 2014). To strengthen the relevance of the analysis, official letters sent during 2023 and 2024 to Indian drug companies were specifically reviewed, while data from 2019 to 2022 was considered for context and comparison (USFDA Inspection Citation, 2009).

A visual an overview of the full research process from initiation to completion is illustrated in Figure 3. The primary aim of this work is to examine and summarize the OOS related findings noted by the USFDA in its communications to Indian drug manufacturers. It should be noted that the coverage of this study only focuses on pharmaceutical drug products, and any observations concerning medical devices, food items, or other regulated categories were deliberately excluded.

Table 1 provides an overview of the total number of Form 483s and warning letters sent to pharmaceutical companies between 2019 and 2024. Figure 4 visually represents this data in graphical format. All information presented has been sourced directly from the official USFDA database (USFDA Inspection Citation, 2009).

Table 2 presents the compiled data from USFDA warning letters provided in the years 2023 and 2024. The observations are categorized department wise, with each department's observation count and its corresponding percentage clearly indicated. Notably, the percentage of OOS observations has been calculated according to the total number of observations recorded during the period, which amounts to 51 for the financial years 2023 - 2024. In 2024, a total of 04 companies received OOS observation because of inadequate investigation, however in 2023 it is 09 (USFDA Investigating Out-of-Specification Test Results, 2022; USP General Chapter <1010>, 2021; USFDA Drug quality sampling and testing Programs, 2025; WHO Digital Publication, 2021; EMA's Data Integrity, 2016; WHO TRS 1033 - Annex 4, 2021; USFDA Warning Letters, 2023; 21 CFR Part 211, 2025; WHO TRS 986, Annex-2, 2014; USFDA 21 CFR Parts 11 & 210, 2025; FDA Form 483 Frequently Asked Questions, 2024).

Following is the main reason.
During regulatory reviews, it was found that the firm's investigations into product quality complaints were insufficient, primarily due to the absence of effective and timely CAPAs. Additionally, the scope of investigations was not extended to potentially impacted batches, representing a significant gap in quality assurance.

In violation of 21 Code of Federal Regulation (CFR) 211.192, the company did not thoroughly investigate unexplained discrepancies or failures of batches or their components, regardless of whether the batches had already been distributed. Endotoxin testing and assessments of the 100% automated visual inspection process were also found lacking in depth and scientific rigor.

The Quality Unit (QU) failed to address abnormal findings, such as unidentified peaks observed in dissolution testing of long-term stability samples using High Performance Liquid Chromatography (HPLC). Oversight of laboratory investigations was found to be deficient, as evidenced by the invalidation of multiple OOS results for USP products without appropriate scientific rationale.

From the start of 2020 to late 2022, hundreds of chromatographic sequences were aborted in Quality Control (QC) labs without proper documentation or justification. In addition, QU lacked well defined procedures outlining its responsibilities, particularly in areas like supplier qualification, change control, and handling of OOS investigations.

Ethical Consideration
This review is based entirely on publicly accessible regulatory sources and does not involve any experiments with human participants or animals. As a result, no ethical approval was necessary for conducting this study.

RESULTS
These evaluations uncovered several weaknesses in quality control systems. Key issues included incomplete handling of Investigation and delays in implementing important steps taken to correct the problem. In many instances, potential risks to other batches were not considered. The company was unable to completely investigate unexplained test results, which go against regulatory expectations (21 CFR 211.192). Processes such as endotoxin testing and automated visual inspection lacked depth and a scientific basis. Table 2 and Figure 5 Figure 6 indicate the total count of companies having observations because of inadequate investigation OOS. Data shows in quality control OOS investigation should be carried done thoroughly otherwise firm would have audit findings from regulatory body.

The QU did not succeed in managing lab related anomalies, including unidentified peaks in long term stability studies using High Performance Liquid Chromatography (HPLC). Several OOS findings were dismissed without valid reasoning. Additionally, from January 2020 to November 2022, numerous chromatographic runs were terminated without sufficient explanation. Clear procedures outlining the Quality Unit's responsibilities for supplier assessment, change control, and OOS handling were also missing. The data indicates that in quality control investigations were not done properly and thoroughly for OOS.

Table 1: Warning Letter and 483 Form.

For Indian Drugs Pharma Companies		
Year	**Number warning Letter provided**	**483 Form (Observation)**
2019	25	26
2020	14	5
2021	7	3
2022	3	13
2023	12	16
2024	8	19

Total	69	82

Table 2: OOS Observation for FY 2023 and FY 2024.

Year	Department	Total Number of Observation in warning letter	% of Observation	No, of observations due to OOS	% of OOS
2024	Quality Assurance	11	21.57	0	0.00
	Quality Control	20	39.22	4	7.84
	Production	17	33.33	0	0.00
	Warehouse	1	1.96	0	0
	Maintenance	2	3.92	0	0
	Total	51	100.00	4	7.84
2023	Quality Assurance	11	22.45	0	0.00
	Quality Control	15	30.61	9	18.37
	Production	20	40.82	0	0.00
	Warehouse	1	2.04	0	0
	Maintenance	2	4.08	0	0
	Total	49	100.00	9	18.37

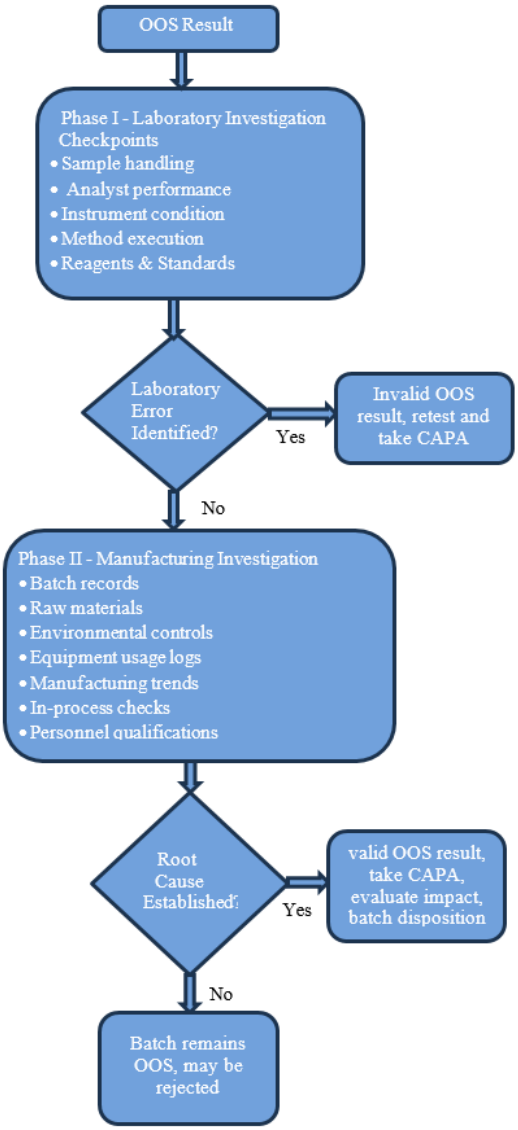

Figure 1: Flow Chart of OOS Invetsigation.[2]

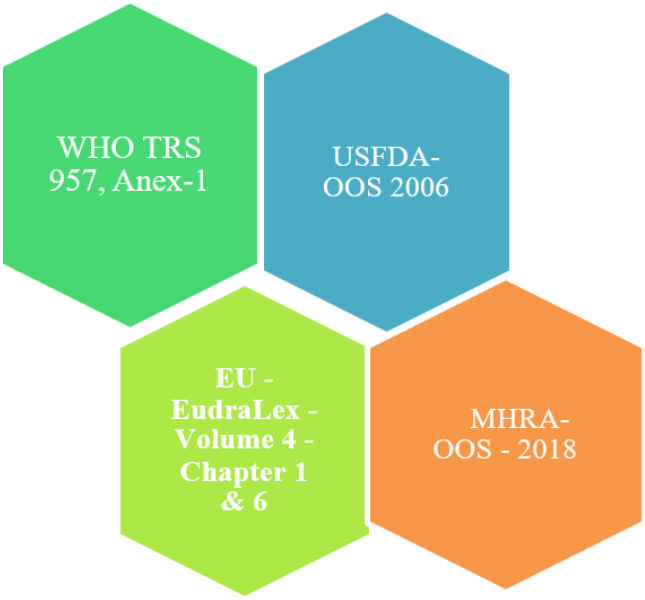

Figure 2: Major OOS Regulatory Guidelines.[2-6]

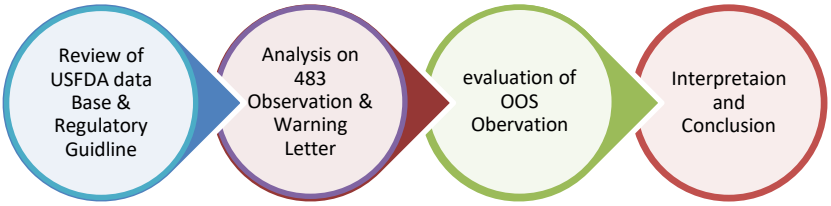

Figure 3: Review Methodology for OOS.

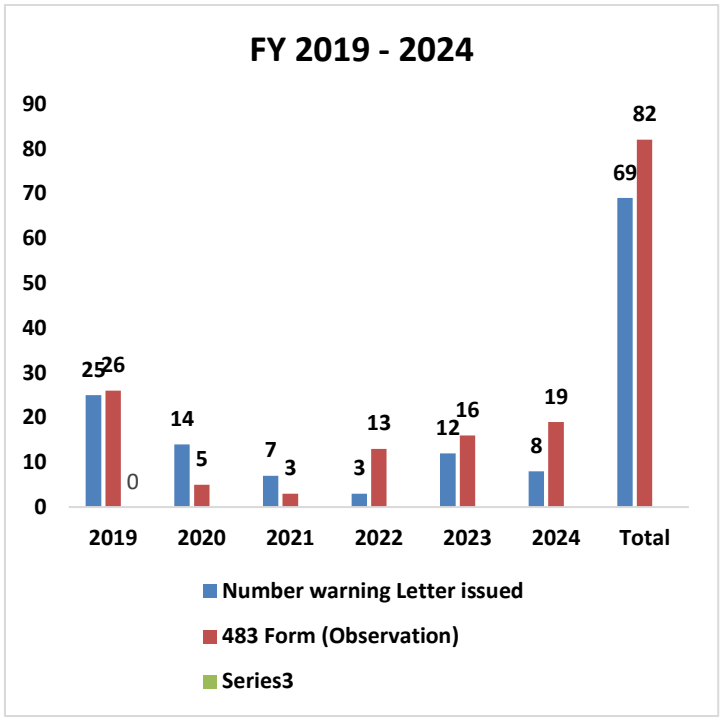

Figure 4: Graphical data FY 2019- FY 2024.

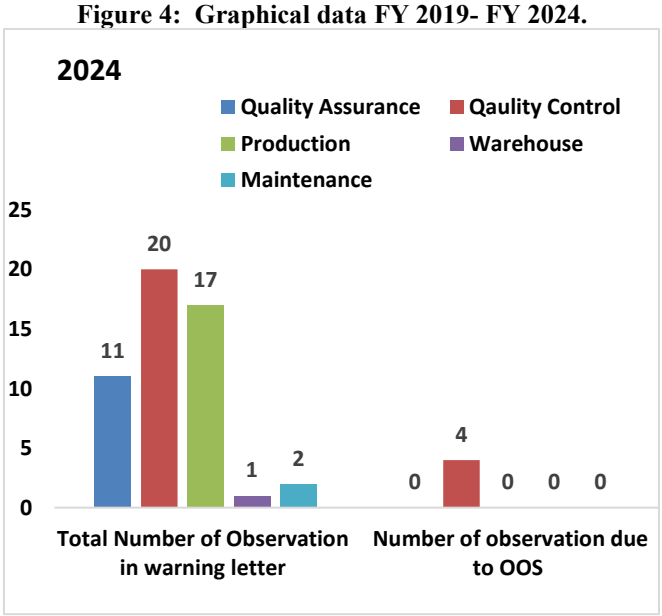

Figure 5: Graphical data FY 2024.

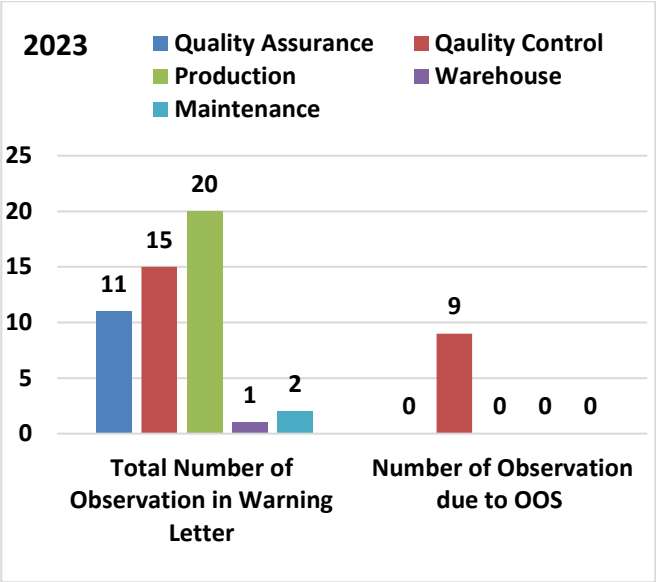

Figure 6: Graphical data FY 2023.

DISCUSSION

After reviewing USFDA warning letters and reports from 2023 and 2024, it was found that many Indian pharmaceutical companies are still facing issues in how they handle Out of Specification (OOS) test results. In several cases, companies did not carry out complete investigations. Some failed to find the actual reason for failure, while others rejected poor results without proper evidence. Many firms also did not check if other batches were affected, which shows weak follow-up actions.

These problems suggest that there is a need to improve quality systems and staff training in the industry. Although Indian pharma companies are strong in manufacturing, they need to focus more on proper documentation, investigation, and regulatory compliance.

This study could not include every report from the USFDA due to the large amount of data available. However, the selected documents clearly show repeated issues that need to be addressed.

CONCLUSION

Inadequate methods used to deal with OOS situations along with weak documentation result in incomplete investigations making it difficult to find the actual reason for failures. To address this, companies must provide proper resources and systematic training to ensure investigations are complete. The author concludes that the OOS procedure needs to be defined thoroughly, and adequate documentation shall be available for OOS. The firm shall impart adequate training in different regulatory guidelines to enhance the knowledge of OOS. Training shall be periodically. It can be done externally if required.

Every OOS incident should be fully investigated until the actual reason is determined. Further research is required to recognize the actual primary cause in Indian Pharma Companies why firm are not following the OOS guideline or what are the challenges for OOS investigation.

SUMMARY

This review article explores the current practices adopted by Indian pharmaceutical companies in handling Out of Specification (OOS) results, with a particular focus on observations made by the United States Food and Drug Administration (USFDA). Drawing from regulatory documents such as Form 483s and warning letters issued between 2019 and 2024, the study identifies recurring deficiencies in investigation procedures, documentation practices, and scientific justification during OOS handling.

The review highlights that many firms either fail to identify the root cause of deviations or inappropriately invalidate test results without adequate supporting data. The role of the Quality Unit in such failures is also examined, particularly in the context of inconsistent or poorly followed investigation protocols. Based on these findings, the article emphasizes the need for improved training, clearer SOPs, and a culture of accountability to align industry practices with global regulatory expectations. Limitations include restricted access to complete data from all firms.

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ABBREVIATIONS

USFDA: United State Food and Drug Administration; **WHO TRS:** World Heald Organization Technical Report Series; **OOS:** Out of Specification; **QC:** Quality Control; **CDSCO:** Central Drugs Standard Control Organization; **PIC/S:** Pharmaceutical Inspection Co-operation Scheme; **CAPA:** Corrective and Preventive Actions; **MHRA:** Medicines and Healthcare products Regulatory Agency; **CFR:** Code of Federal Regulation; **QU:** Quality Unit; **HPLC:** High Performance Liquid Chromatography; **GMP:** Good Manufacturing Practices; **OOT:** Out of Trend; **EU:** European Union; **SOPs:** Standard Operating Procedure.

Conflict Of Interest: The Authors Declare that there is no Conflict of Interest**.**

Financial Support and Sponsorship: This Study Was Carried Out Without any External Funding.

Ethics Approval and Consent to Participate: The Author and Co-Author Confirm that All Necessary Ethical Rules Were Followed During This Study**.**

Consent For Publication: The Author and Co-Author Confirm that All Ethical Steps Were Properly Followed, and No Such Special Consent Required for Collecting Any Data, it is Available in USFDA Database.

Availability Of Data and Materials: All Data Used in This Study Are Included in The Manuscript, And Any Extra Raw Data Can Be Shared by the Author if Requested Reasonably.

Author Contributions: This Review Article Was Successfully Completed Due to the Active Involvement of the Author and Co-Authors in Data Collection, Analysis, and Interpretation.

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