Ind. J. Pharm. Edu. Res., 2023; 57(3s):s758-s765.
https://www.ijper.org

Original Article

Understanding the Trending of Laboratory Investigations as Part of Quality Management Systems-A Quality Assurance Perspective

Anupriya Naduparambil Reji[1], Marina Koland[2,*], Sandeep Divate Satyanarayana[2]

[1]Department of Pharmaceutical Quality Assurance, NITTE (Deemed to be University), NGSM Institute of Pharmaceutical Sciences, Mangaluru, Karnataka, INDIA.
[2]Department of Pharmaceutics, NITTE (Deemed to be University), NGSM Institute of Pharmaceutical Sciences, Mangaluru, Karnataka, INDIA.

ABSTRACT

Background: In the pharmaceutical sector, the effectiveness of the laboratory and its compliance with regulatory standards is critical in establishing an effective Quality Management System (QMS). **Objectives:** The present study was undertaken to carry out the laboratory investigation which is an integral aspect of a QMS, and is often used to investigate non-conformity in results in order to determine the most possible root cause. **Materials and Methods:** Laboratory investigation data is retrieved from a successful company involved in pharmaceutical product R&D which was used to identify the critical root causes by using 5 M method of root cause analysis. CAPA strategies were implemented based on trending results to prevent their recurrence. **Results:** From the root cause analysis it was found that manpower was found to be the potential root cause (47%) among the 5Ms. Sinceall these events resulted from human error, identification of the analysts responsible for these errors was important for finding out effective CAPA. The trending of the analysts involved in the potential error assisted in identifying the person who committed the same type of event several times. **Conclusion:** HPLC and GC are well-known instruments that are sensitive to a number of problems. As a result, analysts must exercise extreme caution while employing these instruments. In comparison to manpower and machine, method, material, and measurement errors are shown to be less frequent.

Keywords: Laboratory investigations, Quality management system, CAPA, HPLC, GC.

Correspondence:
Dr. Marina Koland
Professor and HOD Department of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences, NITTE (Deemed to be University), Mangalore-575018, Karnataka, INDIA.
Email: marinakol@nitte.edu.in

Received: 13-06-2022;
Revised: 10-11-2022;
Accepted: 08-06-2023.

INTRODUCTION

Pharmaceutical companies are the most strongly regulated ones and the quality management system ultimately determines the quality of its finished product. The basis behind the conceptualization of pharmaceutical Quality Management System (QMS) is the Internationally Harmonized Guidance 'ICH Q10' since it describes a model for a pharmaceutical quality system. The objective of the QMS stands for the establishment, implementation, and maintenance of a system that allows the product delivery with the desired quality attributes.[1,2] Laboratory investigation is considered as a comprehensive part of the Quality management system. Failures are inevitable in any organization, and it refers to the state or condition of not meeting a desirable or predetermined specification. However, performing a detailed investigation in order to identify the root cause for the reported non-compliance or failure to take an appropriate corrective action is important for the organization to avoid recurrence.[3]

During inspection of quality control laboratories of pharmaceutical industries, the non-conformity result investigation continues to be one of the most commonly observed cGMP deficiencies. Since the release of non-conforming products may result in potential public safety issues, handling of non-conformity results is considered critical.[4] The evaluation of each individual case and the analysis of data for trends in order to detect potential problems and implement relevant corrective and preventive actions should be included in the management of non-conformity results. The use of trending for a holistic evaluation of processes is considered as a comprehensive approach towards quality issues.[5,6]

Trending is considered as a regulatory requirement. FDA has released a number of warning letters to the pharmaceutical industries for not having a trending procedure. Continual improvement can be implemented by the trending process.[7] Tracking the log of investigation record is the important step towards trending. Training should be imparted on users for data

DOI: 10.5530/ijper.57.3s.86

tracking and is necessary for performing trending. As a second key step the development of smart root cause and sub-causes are recommended for the users. Due to the potentiality, the non-conformity related data which resulted from analysis should be reported periodically and reviewed by the management to recognize and implement appropriate actions. Trends should be defined, identified timely and actions implemented since trending is intended to be a proactive approach.[8]

Most of the organizations use an electronic database system for tracking and trending purposes. Some popular systems are Track wise, Microsoft access, and SAP (Systems Applications and Products in Data Processing). These systems help to produce reports which are useful for management review as well as trends. They are also helpful to the auditors for reviewing purposes.[9]

MATERIALS AND METHODS

This work is done based on the data gathered from a successful company related to Research and Development (R&D) of a pharmaceutical product. The study comprises of a thorough understanding of the Laboratory Investigation process and trending of the investigation reports based on the reported root causes. The critical root causes were identified using the data gathered.

Laboratory Investigation

Laboratory testing is required by the cGMP regulations for the conformation of the developed methods to meet the specifications and validation parameters. If any non-conformity was identified during the laboratory testing, an investigation was initiated for the determination of the most probable root cause. Non-conformity occurs when the analysis test result falls out of the specified limit mentioned in the official compendia, drug master file or drug application. The reason behind the non-conforming result may be, for example, errors in the testing process, malfunctioning of the equipment, contamination of the components or test method discrepancy.[10]

Laboratory investigation process

Immediately upon discovering an aberrant result, the analyst notified an analytical team leader, analytical manager or designee. All the solutions and reagents used for the testing had to be retained for the investigation until the final conclusion of the investigation. The analyst verified that the results were calculated correctly. If errors found in the results calculated previously and the correct calculation gave the satisfactory result, that result was documented. If the calculation error was not the cause of the suspect result, the analyst and analytical team leader, analytical manager or designee determined whether the result is expected. The criticality of the data was taken into account in deciding whether the result should be treated as expected. If the suspected result was not expected, laboratory investigation record was to be initiated by the QA department within one day.[10]

Initial investigation

If the suspect result was found to be not expected, the investigation team began the initial investigation. As a first step the investigation team should ensure that the analyst had the proper training to execute the investigation. Discussions were carried out with the analyst, to confirm that the correct method was used and was adequately and properly executed. Confirmation was made that the correct glassware and pipettes were utilized, correct filter was used, and correct filter volume was discarded prior to the analysis. An evaluation was made to find out whether the method of grinding was manual or mechanical where applicable. It was also confirmed that the correct HPLC/GC column and correct flow rate were used, and the correct volume was injected into the instrument. Checks were made to determine the presence of any baseline noise during the analysis, and that the integration of the peak was optimal. In case of UV-spectrophotometric analysis, it was ensured that the sample cell used was clean and bubble free. The reference standard and reagents were validated.

The method was reviewed and it was confirmed that the steps were executed correctly as per the current method. The data associated chromatograms and the sample and standard solutions were examined to determine that an obvious discrepancy existed such as discoloration of the solution, incorrect volume, un-dissolved material etc. It was also confirmed that there was no system suitability failure, no air bubble in the injector or detector flow cell and the instrument parameters were utilized properly. The scheme of initial investigation is represented in Figure 1. It was ensured that all the data has been checked or reviewed by the investigator or supervisor. If an obvious laboratory error was identified as an assignable cause, the original data was declared invalid and the analysis was repeated for the recordable results. In case of any instrument malfunction or system suitability failure, the analysis was repeated using another instrument to generate a reportable result.[10,11]

Laboratory actions

If no assignable cause was identified from the initial investigation, laboratory action experiments were carried out to investigate the potential causes of aberrant results. Laboratory actions were cauterized into three phases:

Phase 1: Reassessment experiment.

Phase 2A: Expansion of investigation to operations or manufacturing.

Phase 2B: Extended investigation of laboratory error.

Phase 3: Resampling.

Phase1 Laboratory actions: Reassessment experiment

Phase 1 laboratory actions involve reassessment of the original test sample and standard stock solution in order to investigate the assignable cause for the suspect result e.g., dilution error, improper mixing, standard/sample preparation error, contamination etc. Phase 1 investigation did not involve retesting of the sample. The result from the reassessment experiment was not used to replace the original aberrant result. The scheme for Phase 1 laboratory action is described in Figure 2. If the assignable cause could be identifiable from the Phase 1 investigation, this was documented in the Phase 1 laboratory action. Repeat testing was carried out to generate the reportable result. If the assignable cause was identified to be a method deficiency, additional method optimization was performed. Retesting was carried out using a separate method, alternative methodology or variants of an original methodology. If no assignable cause is identified from the Phase 1 investigation, Phase 2A investigation was performed concurrently with phase 2B investigation.[11]

Phase 2A Laboratory actions: Manufacturing process review

The manufacturing investigations include the review of the batch records and deviations associated with the lot to determine, if there is an assignable manufacturing cause for aberrant data. If there is a manufacturing deviation, the manufacturing investigation was closed and the findings were reported at the conclusion of the laboratory investigation and the original result was also reported. If no deviation had been noted, the manufacturing investigations remained open, pending conclusion. The laboratory investigations then progressed to retesting, using original methodology.[11]

Phase 2B Laboratory actions: Retesting using original sample or composite

Phase 2B investigation involved retesting using a part of the original sample. It was collected from the same homogenous lot that the original samples were removed, and the Out of Specification (OOS) result was obtained. In case of a liquid, the sample was taken from the original unit liquid product or from composite liquid product. For a solid, the same sample composite prepared for the original test was weighed. The identification of instrument malfunction or the identification of the sample handling problems was done by the retesting of the original sample, for e.g., Dilution error. Decision for the retesting was based on the objectives and sound scientific judgment. The analyst performing the retesting must be other than the one who performed the original test and should be experienced and qualified in the method.[11]

Phase 3 Laboratory action: Resampling

While retesting refers to the analysis of the original sample material, the resampling involves analysis of the sample from additional units collected by the original sampling procedure or a new sample collected from the batch. The original sample was sufficiently large to accommodate retesting in case of OOS results. However, in some situations it became necessary to proceed with resampling, when sampling error was suspected or there was insufficient sample for further laboratory actions, or if the original sample did not seem to be a representative of the batch or the original sample was subjected to extreme environmental conditions.

Retesting using original methodology

If no analytical or manufacturing assignable cause for the aberrant result had been identified from the investigation thus far, the original sample or composite (Phase 2B) or a new sample (Phase 3) was retested using original methodology or it was established whether the original result was representative of the lot. All of these results were considered for the disposition of the batch. For quantitative retesting, the number of the sample preparations for retest was six unless otherwise documented in the investigation. For a qualitative retesting a minimum of two retests were equired.[11]

The scheme for Phase 2a and 2b laboratory actions is depicted in Figure 3.

Investigation conclusion

For a conformed Out-of-Trend (OOT) result, an impact assessment including intended use of the product was documented in the final conclusion tab. The assessment included results and sound scientific rationale to justify why there was no impact to the product, process and data quality. If the assessment determines there was an impact to product, process, data quality or shelf-life assignment, an incident report child record was raised. For OOS/OOT results which were not confirmed, the manufacturing investigation was closed. If the investigation confirmed an OOS for stability results at the intended storage conditions, the analytical team discussed the issue with the Quality Assurance (QA) department. If the data impacted current shelf life/retest date/expiration or it was deemed that further investigation was required, then an incident report was initiated by the analytical team. If the current data did not impact upon current inventory supplies or the current shelf life/retest date/expiration and no further investigation was required, the rationale was documented in the final conclusion tab. If the investigation conclusion highlighted deficiencies in the analytical methodology or process which required corrective action, CAPA was initiated as a child record to the LIR to track these further actions. Once the investigation conclusion tab was completed, the investigation was approved by analytical team leader, analytical manager or designee as technical reviewer. The technical reviewer ensured that an incident report had been raised if required and that CAPA had been raised. If senior management report was required, the record was approved by a second analytical team leader, analytical

Table 1: Examples for Laboratory Investigation Records.

Sl. No	Event Description	Data Assessment	Final Conclusion	Primary Root Cause	Sub-Cause
1	Accuracy at LOQ not meeting the acceptance criteria.	Due to dilution error during sample preparation.	Repeated the experiment with new sample.	Human error	Dilution error
2	In mobile phase stability RT of drug not met the acceptance criteria.	Due to poor performance of the column.	Repeated the experiment using another column.	Machine	Column performance/ Leakage
3	% Recovery of elemental impurity was not within acceptance criteria.	Due to sample matrix interference.	Modified the sample preparation procedure.	Method	Interference of reagents
4	Carry over impurity peak was observed during qualification of reference standard.	Due to contamination of sample.	Requested for new sample for reference standard qualification.	Material	Contamination
5	Recovery results was not meeting the acceptance criteria.	Analyst was overlooked the integration of peak.	Optimized integration of the peak.	Measurement	Improper integration

manager or designee. The laboratory investigation was completed and approved within 45 calendar days from initiation. If the investigation was not complete, then an extension justification was detailed in the extension request tab.[10]

Laboratory Investigation Records (LIR)

The laboratory investigation record was mentioned as invalid if the reason for the non-conformity was identified during the initial investigation. In such cases the original results became invalid and the record type was selected as invalid. If the assignable cause was not identifiable from the initial investigation the analyst initiated a LIR record type. It includes Phase1, Phase 2 and Phase 3 investigations. The LIR with different examples and other details is shown in Table 1.

Trend Analysis in Laboratory Investigation

Even after the organization concluded and implemented the CAPA system, the work doesn't complete. It was important for the organization to track the investigation results to identify its location, type, frequency and whether they were representing a new problem, or it was a recurrence of an old one. Organizations can also track those events which were not classified previously, because they can be used for getting a baseline information which could be used for the future trend. Some investigations were denoted as invalid, which did not require further investigation. However, tracking of such investigation also eased the recording and documentation process. The trending was considered as a tool for the continual improvement of the quality system as it was helpful in tracking the recurrence of the events. This data was helpful in identifying preventive actions for reducing future recurrence of such events.[8]

Trending classification

The 5M Method of root cause investigation is a useful tool for trending of the laboratory investigation data. As mentioned earlier in 5M method the root causes are given as 5Ms: man, method, material, machine, and measurement. These are considered as the primary root cause of the problem and from each of these primary root causes, we can find out the sub-cause or sub-code.[12,13]

The 5M methods of root cause analysis fish bone diagram is depicted in Figure 4.

The implementation and evaluation of the effectiveness of corrective actions and preventive actions can be done using the trending based on 5M method and its sub-code. Application of the preventive action is the backbone to the quality systems, since it is intended for avoiding the recurrence of the events. For the effective implementation of the preventive action, we have to focus on the sub-causes for the identified events.[14]

RESULTS AND DISCUSSION

Identification of the potential root causes was done by trending of the laboratory investigation reports using 5M method of root cause analysis. Man power was found to be the potential root cause (47%) among the 5Ms.The trending of primary root causes is shown in Figure 5 and the trending of sub causes in man power is depicted in Figure 6.

The trending of equipment type errors was illustrated in Table 2 which describe the different factors to contribute the errors in the analytical results of different types of instruments.

The percentage of other types of errors associated with different instruments is represented in pie charts as shown in Figure 7.

Table 2: Trending of equipment/instrument (QIA).

Type of error	Type of instrument				
	HPLC	LC-MS	GC-MS	ICP-MS	UPLC
Instrument malfunction	54%	13%	27%	3%	--
Baseline drift	82%	--	--	--	18%
Chromatographic artifact	89%	--	--	--	11%
Carousel malfunction	67%	--	--	--	33%
System suitability	43%	15%	14%	14%	14%
Column leakage	100%	--	--	--	--
Detector	67%	--	9%	8%	8%
System pressure malfunction	75%	--	--	--	25%

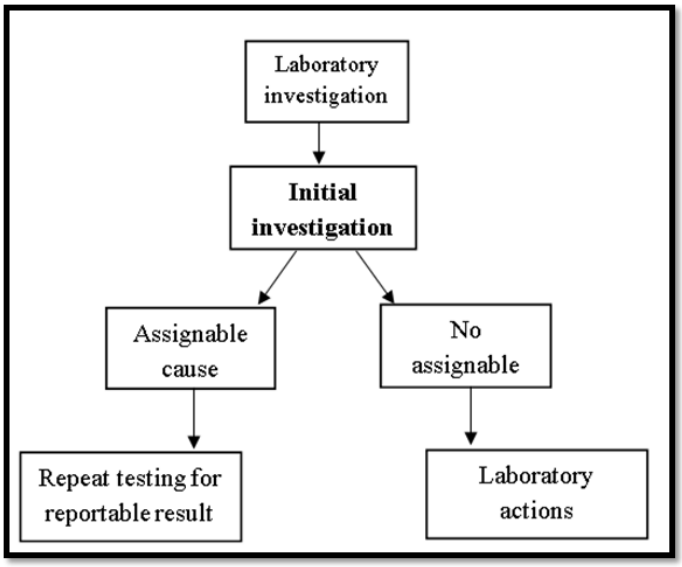

Figure 1: Scheme for initial investigation.

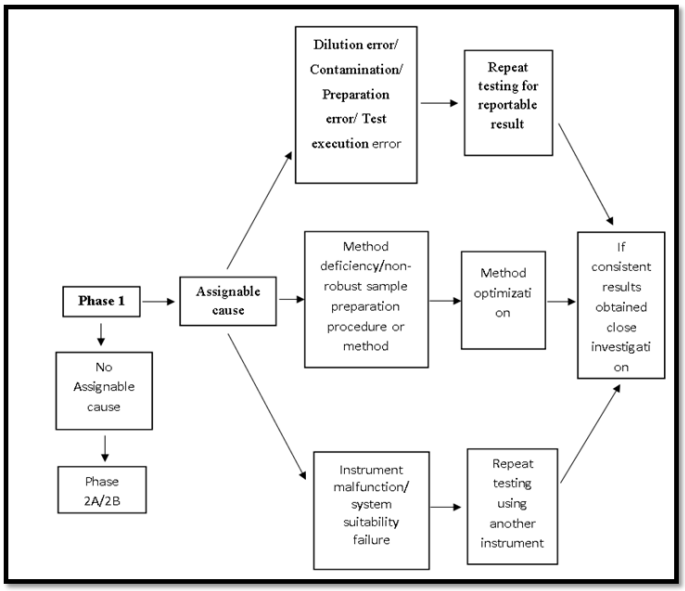

Figure 2: Scheme representing Phase 1 Laboratory action.

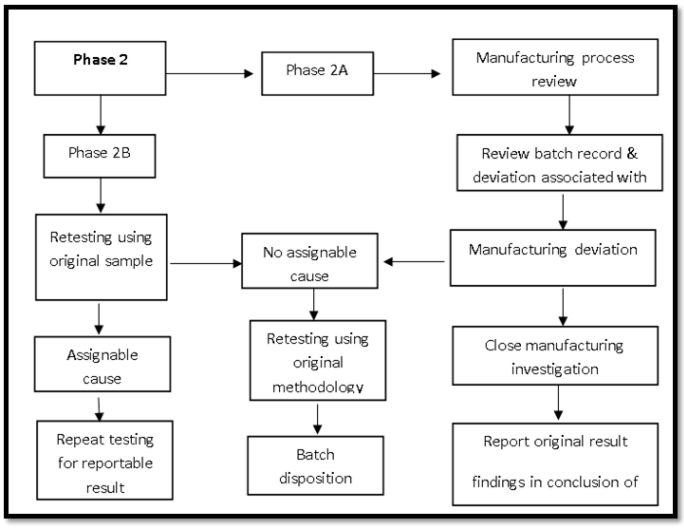

Figure 3: Scheme for Phase 2A and 2B Laboratory actions.

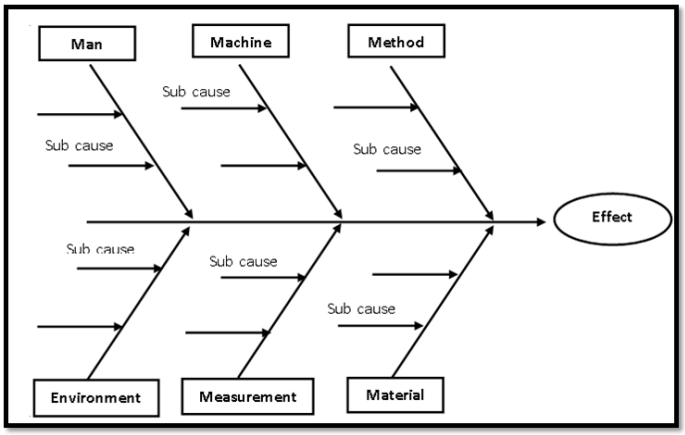

Figure 4: 5M Method of Root Cause Analysis.

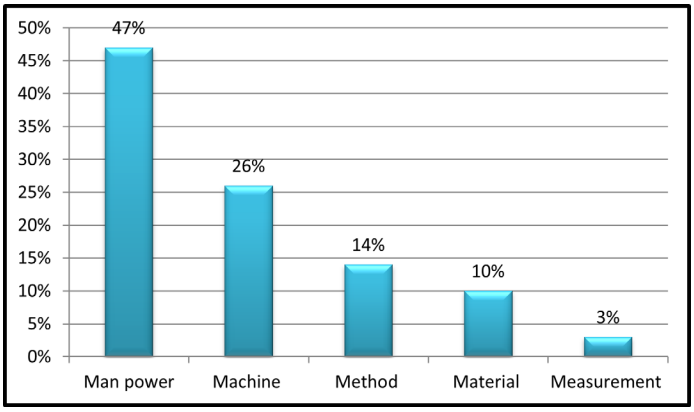

Figure 5: Trending of primary root causes.

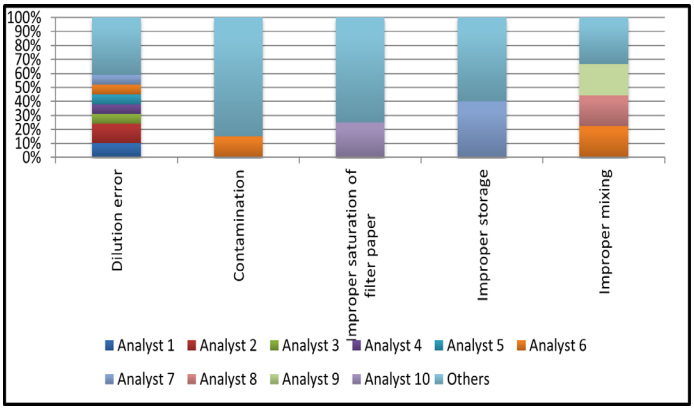

Figure 8: Trending of the analyst involved in the event.

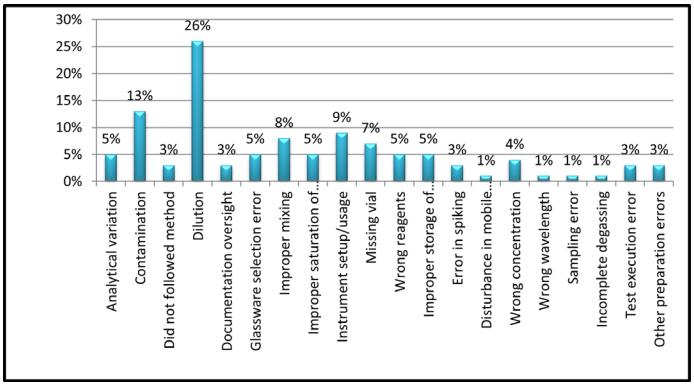

Figure 6: Trending of sub-causes in man power.

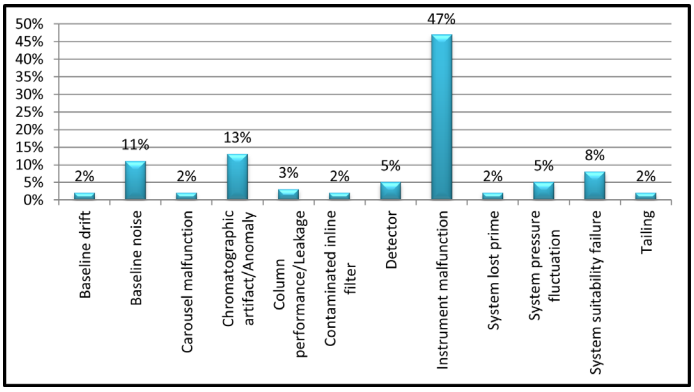

Figure 9: Trending of sub-causes in machine.

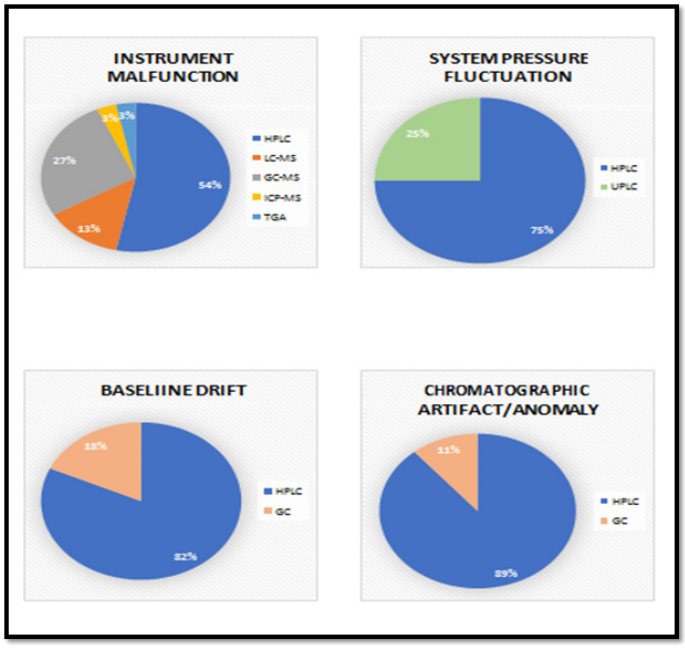

Figure 7: Percentage of different errors with different types of equipments.

Comparison, the percentage of errors contributed by human were more when compared to equipment's and all such events resulted from human error, identification of the analysts responsible for these errors was important for finding out effective CAPA. Trending of the analysts involved in the potential error helps to identify the person repeatedly committing the same kind of event and also in multiple events.

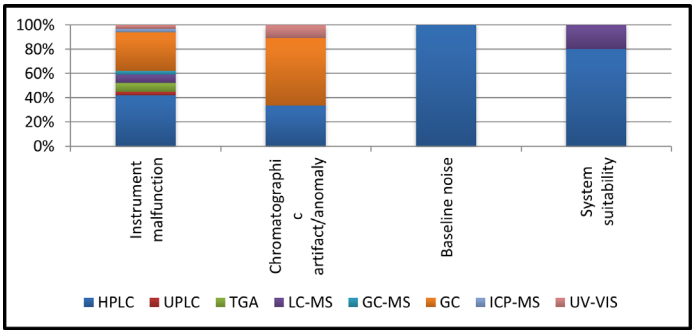

Figure 10: Trending of Equipment/Instrument type.

Figure 8 represents the analysts who committed the potential errors repeatedly and the percentage of involvement in that particular event. Brilliant analytical chemists with good qualification are required to avoid man power errors. In order to make them efficient, a comprehensive method was required for ensuring that they qualify. Training needs to be provided on analytical methods, general SOPs, and Performance Verification/ Calibration of Equipment/Instrument along with evaluation before entering into regular analysis. An annual Good Manufacturing Practices (GMP) training and retraining programs on relevant Standard Operating Procedures (SOP) will help to improve their capability. Events regarding machines also need a strong recognition. Figure

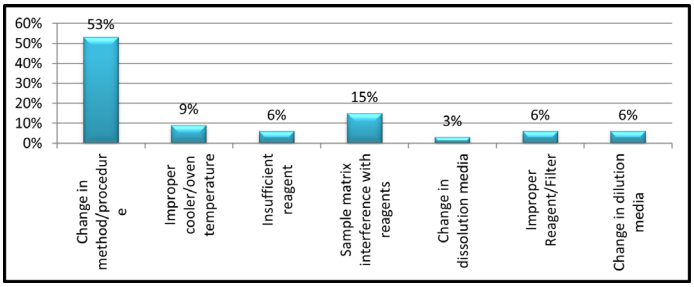

Figure 11: Trending of sub-causes in method.

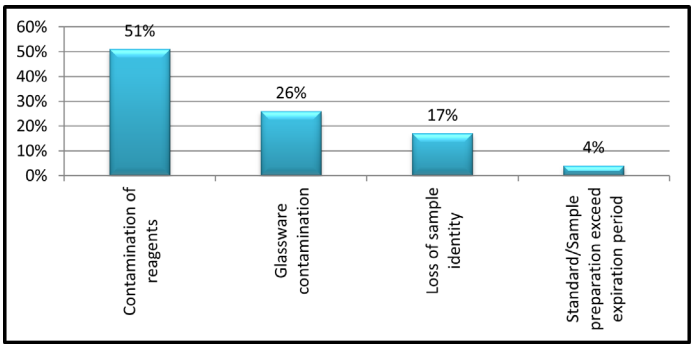

Figure 12: Trending of sub-causes in material.

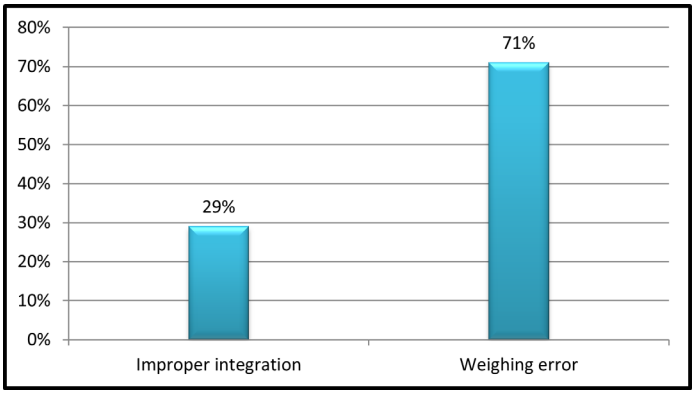

Figure 13: Trending of sub-causes in measurement.

8 illustrates the events caused by the machine and their frequency of occurrence.

A regular preventive maintenance program will be helpful in preventing recurrent non conformity results due to various machine errors. In order to find out the equipment's/instruments which frequently undergo the potential events specified in Figure 9, trending has been performed regarding them and the results are shown in Figure 10.

From the results, it was understood that HPLC and GC are instruments that frequently undergo various issues. So, analysts need to be very careful regarding the usage of these instruments. The identification of critical and consumable parts of the instrument and a period or criteria for change of these parts is important to assemble the activities in timely and cost-effective manner. Method, material and measurement errors are found to occur to a lesser extent as compared to man power and machine.

Optimization procedure for the newly developed methods should be performed by well qualified scientists and should be validated to prevent non-conformities due to methods. The trending of sub causes in method and in material are represented in Figures 11 and 12.

A comprehensive method for the storage and handling of materials are required to prevent errors regarding materials. Measurement error is rare and negligible. Improper integration and weighing errors are usually considered under measurement errors. The trending of sub causes in measurement is shown in Figure 13.

CONCLUSION

Compliance of Analytical Laboratory with regulatory requirements is one of the essential needs to be fulfilled by a pharmaceutical company. The equipment/instruments which are sophisticated with secured software and smart and efficient analytical chemists with good qualifications brought reliability and best quality into the results. A continuous effort to find out the weakest points for improvement will help to bring out a strongest quality management system in pharma industries. Laboratory investigation is considered as a comprehensive part of the Quality management system which is intended to find out the most probable root cause of the non-conformity events in pharma industries. Trending of laboratory investigation has a strong recognition in regulatory auditing process, and it is an effective method to identify the weakest points in the analytical laboratory which leads to the frequent uncertainty results in the laboratories. The use of 5M method of root cause analysis is a robust method which can be relied on to bring out effective trending methodology. The initiation of trend based CAPA process is an upcoming step to be focused on. Identification, implementation and the continuous effectiveness evaluation of CAPA is capable of bring out continuous improvement to the quality management system.

ACKNOWLEDGEMENT

The authors thank NGSM Institute of Pharmaceutical Sciences and authorities of NITTE (Deemed to be University) for the necessary support.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

QMS: Quality Management System; **CAPA:** Corrective and Preventive Action; **ICH:** International Conference on Harmonization; **FDA:** Food and Drug Administration; **SAP:** Systems application and products in data processing; **cGMP:** Current Good Manufacturing Practices; **HPLC:** High performance liquid chromatography; **GC:** Gas chromatography;

OOS: Out of specification; **OOT:** Out of trend; **LIR:** Laboratory investigation report/record; **LOQ:** Limit of quantitation; **SOP:** Standard operating procedures.

SUMMARY

- The present work was done to determine the efficacy of laboratory and its compliance to bring out an effective Quality Management System (QMS).
- Laboratory investigation is considered as a comprehensive part of the QMS which is intended to find out the most probable root cause of the non-conformity events in pharma industries.
- The use of 5M method of root cause analysis is a robust method which can be relied on to bring out effective trending methodology.
- CAPA can help to improve the quality management system by identifying, implementing, and evaluating its performance over time.

REFERENCES

1. Dubey N, Gupta H, RKS, Dubey N, Dubey N. Pharmaceutical quality management system: Current concept. J Adv Pharm Edu Res. 2011;2(1):120-24.
2. ICH Official web site. ICH. Available from: https://www.ich.org/page/quality-guidelines.
3. Jadaun Singh GP, Saklani V, Dixit S, Jain R, Singh S. Implementing quality management system in pharmaceutical laboratories. J Anal Pharm Res. 2016;2(1):1-5.
4. Out-of-specification laboratory investigations: New Look at an Old Issue; 2018. Available from: http://www.ivtnetwork.com/article/out-specification-laboratory-investigations-new-look-old-issue.
5. Kumar Jain S, Kumar Jain R. Investigations and CAPA: Quality system for continual improvement in pharmaceutical industry. Int J Res Pharm Pharm Sci. 2017;2(6):47-54.
6. Do you have confidence in your data? considerations for minimizing Out-of-Specification (OOS) results in pharmaceutical qc; 2018. Available from:https://www.waters.com/webassets/cms/library/docs/local_seminar_presentations/GE_Events/GE%20Pharma%20and%20Biopharma%20Forum%202018/Addressing%20OOS%20and%20OOT%20results%20in%20Pharmaceutical%20QC_Boiteux_Waters.pdf.
7. OOS data trending; 2018. Available from:http://www.labcompliance.com/seminars/audio/201/default.aspx.
8. The importance of trending during laboratory investigations. 2018. Available from:https://www.lachmanconsultants.com/2018/10/the-importance-of-trending-during-laboratory-investigations/?_sm_au_=iVVH96sRVJcJCJnQ.
9. Ravi GN, Gupta NV. FDA guidelines-for Out of Specifications (OOS) in industries. Int J Pharm Tech Res.2013;5(3):943-8.
10. Investigating Out-of-Specification (OOS) test results for pharmaceutical production;2006 [citedOct252018]. Available from: https://www.fda.gov/media/71001/download.
11. Ravi Kiran SN, Ravi G. Management of Out of Specification (OOS) for finished product. Int J Pharm Clin Res.2017;9(3):221-32.
12. Root cause analysis for drugmakers; 2013. Available from:https://www.fdanews.com/ext/resources/files/archives/1011301/Root%20Cause%20Analysis%20for%20Drugmakers-ExecSeries.pdf.
13. Root cause analysis. Available from:https://www.msdprevention.com/userContent/documents/Resource%20Pool/Basic%20and%20Comprehensive/Root%20Cause%20Analysis.pdf.
14. Venkatesh MP, Philip A, Gangadharappa HV. Corrective action and preventive action: Management and applications in pharmaceutical industry. Int J Pharm Sci Rev Res.2017;46(2):184-89.

Cite this article: Anupriya NR, Koland M, Sandeep DS. Understanding the Trending of Laboratory Investigations as Part of Quality Management Systems-A Quality Assurance Perspective. Indian J of Pharmaceutical Education and Research. 2023;57(3s):s758-s765.