Original Article

The Significance of Quality Metrics in a Pharmaceutical Quality Management System – A Case Based Study

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ABSTRACT

Background: The pharmaceutical quality management system is a concept of management function that design and implement the "Quality policy". The pharmaceutical manufacturing industries all over the world have just begun to apply the United States Food and Drug Administration (USFDA) guidelines in the 21st century. The study tries to identify the quality metrics based on Quality Indicators for a pharmaceutical industry and to investigate the utilization of quality KPIs. **Methodology:** The work experience from a successfully working pharmaceutical organization related to Research and and Development (R&D) of pharmaceutical products are discussed here. Important areas were identified and analysed based on the data collected from the deviation reports of selected organization and other resources. The R&D centre uses a software system for Quality management system including, Deviation management, Change management, Laboratory investigation, Incident management and Corrective Action and Preventive Action (CAPA). **Results:** The primarily considered Quality indicator (QI) was the pharmaceutical deviation. A Among the deviations reported in the year of 2017-18, 214 cases were selected as sample. In this 171 were permanent deviations and 43 is temporary deviations. Secondarily, Pharmaceutical incidents are selected for the study as the QI in which 70% of the root cause is due to human related issues. Failure to meet acceptance criteria comes first with 48% and failure to follow procedure with 28%. **Conclusion:** A good quality metrics system supports both industries' profitability, GMP compliance and precludes overproduction of metrics; only measure what adds value to quality in the most efficient way.

Key words: Quality Metrics, CAPA, Key performance indicators, Deviation, Change control.

INTRODUCTION

The pharmaceutical manufacturing industry is one of the most sharply regulated manufacturing unit and Quality management system plays a major role in the ultimate quality of the final products. The perception of the existing quality management system is based on the International Conference for Harmonization of Technical Requirements for Registration known as ICH Q10 guidelines which is a science and risk-based approach and is applicable in different stages of the product life-cycle. It works in combination with the fundamentals of International Organisation for Standardisation (ISO). ICH Q10 is an interconnection between the pharmaceutical development and manufacturing activities, which paves the way for innovation and continuous improvement in a non-mandatory manner and also predominantly emphasizes on achieving global uniformity in the aspects of Quality, Safety and Effectiveness of pharmaceutical products.[1]

Q10 guidelines ensures the product quality and customer satisfaction. It provides guidance on the means to implement Quality Management System in the pharmaceutical industry.[2]

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Two basic elements of Quality Management System include:

- Quality system covers the organisational structure, procedures, processes and the resources.
- Systematic actions must be implemented to ensure the product will comply with the quality policies.

The combination of the elements are known as quality assurance and quality control.

Quality metrics and Q-KPI (Key Performance Indicators)

With an idea of developing stringent inspection procedures, USFDA introduced the term Quality Metrics.[3] It mainly focuses on the supervision of quality control process, which intern is interlinked to continuous improvement.[4] Quality- Key Performance Indicators helps to measure and maintain the quality health.[3]

The USFDA utilises the Quality metrics data in the following areas:

- To establish an indicator program to identify the products that may have significant risk to the customers.
- To recognise the conditions which are at high risk to drug supply disruption
- To provide effective inspection of establishments
- To improve FDAs inspection of drug manufactures

The following are the types of pharmaceutical quality metrics that FDA assess based on industrial performance data.

- Lot Acceptance Rate (LAR) used to measure the manufacturing process performance.
- Product Quality Complaint Rate (PQCR) used to measure the patient or customer feedback
- Invalidated Out-of-Specification (OOS) Rate (IOOSR) used to measure and understand the performance of laboratory activity.[4]

Key performance indicators are the measure of performance, which is based on standards determined through valuable evidences. According to the Joint Commission on Accreditation of Healthcare Organization (JCAHO) in the United States, KPIs are not direct measure of quality but instead act as warning signal to drug manufactures for the improvement of weak areas.[5]

There are some Quality KPIs identified for pharmaceutical operations: Deviation, Incidents, Investigation, Change control, Market complaint, Product recalls, Quality Risk Assessment, Training Program Internal, Audit Program, Product Mix-up and Corrective Action Preventive Action (CAPA).

The quality metrics program plays a major role in addressing risk-based inspection scheduling as well as in the detection and mitigation of drug shortages. The top priority of FDA is to take necessary actions against the drug shortages that pose a significant problem and threat to the public.[1]

Pharmaceutical deviation

The quality improvement became everyone's challenge and the department of quality control and quality assurance came into the picture very recently.[6]

Failure refers to the state or condition of not meeting a desirable or predetermined specification and is viewed as opposite of the compliance.[7]

The sec 211.100 of Code of Federal Regulations (CFR) states that; There shall be written procedures for production and process control designed to ensure that the drug products have the identity, strength, quality and purity they possess or are represented to possess. These written procedures, including any changes, shall be drafted, reviewed and approved by the appropriate organizational units and reviewed and approved by the quality control unit.[8]

Deviation Categorization

As a basic requirement of deviation management process, personnel should be aware and alert of possible changes in the existing procedures and to clearly know how to handle according to GMP requirements. The deviations are categorized as follows:

Minor Deviations

If a deviation doesn't have effects on a quality attributes, a critical process parameter or any instrument, can be considered as minor and treat with applicable procedures.

Major Deviations

If a deviation has an impact on any quality attributes, critical process parameter, or any instrument, equipment critical for the process control, can be considered as major deviation.

Critical Deviations

If a deviation effect any quality attributes, critical process parameter, or any instrument, equipment critical for the process control and also affect to the patients and

customers, including life-threatening situations, the deviation considered as critical.[9]

Overview of a Typical Quality Risk Management Process

The following three steps are considered as the basic elements of Quality risk management process.[9,10]

- Risk assessment
- Risk control
- Risk review

Risk Assessment

Risk assessment process consists of the identification of hazards the analysis and evaluation of risk associated with exposure to those hazards. Risk assessment consists of the below progressive process.

Identification of Hazards

It is a process of identification of possible hazards using adequate description and sources of information, nothing but "What might go wrong?" The details like historical data, description of possible consequences may consider for the detailed description.

Risk Analysis

Estimates the risk associated with the identified hazard/s. It is the process of linking the probability of occurrence and severity of harms.

Risk Evaluation

A process which compares the identified and analysed risk against given risk criteria.

Risk Control

Risk control considered as a risk management process in which the risk reduce to an acceptable level. It mainly consists of the following steps.

Risk Reduction

It is a process of reduction or elimination of risk associated with quality and applicable in certain conditions like risk at high or unacceptable level.

Risk Acceptance

It is formal procedure of decision making to accept a residual risk.

Risk Review

The review process is an essential element of QMS activities which is incorporated with overall product lifecycle and continuous improvements approaches conducted by the Quality assurance department.[10]

Change control

Change control is "A process that ensures the changes to material, methods, equipment and software are properly documented, validated, approved and traceable". The changes made to control the established processes must be recorded reviewed and approved by the quality assurance unit.[11]

When there is a requirement of a change in the existing system, a change control proposal will be initiated to report, record, categorize and assess/ evaluate the impact of changes relevant to existing system and procedures. USFDA-regulated pharmaceutical companies are expected to establish change management system in accordance with Current Good Manufacturing Practice (cGMP) regulations outlined in 21 CFR Part 2 11.160.[11,12]

Benefits of Change Control System

- A consistent and structured approach towards managing deviations
- Documenting the details of a deviations and changes
- Risk control and management
- Assessment of change requests through appropriate individuals for approvals
- Documentation of changes approvals and implementation by QA
- Maintenance of change history in easy retrieval manner
- Effective change tracking and provides an audit trail

Procedure for Change Control

A change control system manages the end to end changes through initiating, reviewing, approving, distributing and tracking change history. Following critical steps results in a robust change management system that can help an organization to manage change and implement continuous improvement.

Change Identification, Initiation and Description

The initiator individual/department identifies the change. On identification, initiator should initiate a change proposal. It consists of description, reason and justification for the proposed changes.

Risk Assessment

There is a need for evaluation and approval for every proposed change based on change initiated, impact on existing procedure and documents and identification of the affected system etc.

Coordinate

On consideration of type and evaluation of proposed change, propose a methodology for initiation and review process. The review process would coordinate with all concerned personnel /affected departments i.e., Quality assurance, Operation, Production, Analytical, Engineering and other ancillary departments.

Expected Timelines

An expected timeline should be fixed for the initiated actions. If for some reasons the process out of the fixed timeline an extension memo will be issued by Quality assurance department upon request by the initiator department.

Change Control Assessment

The assessment process of determining the impact of the proposed change on Product quality, Safety, Quality Management System, Operating procedures, Environment and Personnel based on the Risk Analysis. If the change possesses any impact on any of the mentioned factors, classify the change as critical, major or minor.

Critical

Applicable to those proposed change control which may have an impact on the final product quality in terms of chemical, physical attributes of the drug product and may result in adverse health consequences.

Major

Applicable to those proposed change control which may have an impact on the final product quality in terms of chemical and physical attributes of the drug product, but unlikely to cause any health consequences.

Minor

Applicable to those proposed change control which may not have any impact on final product quality.

Change Control Action Plan for Implementation

Based on the risk assessment a detail implementation plan will be prepared; it describes the details of action to be performed.

QA Approval

Based on the risk assessment and in consultation with the respective department the proposed change will be approved/ disapprove by QAD with justification.

Change Control Tracking and Change History

A system should be present to assess the completeness/ effectiveness of the Change proposed.[11]

Pharmaceutical incident

Any atypical event which occurs during the manufacturing, Packaging, testing, holding or release processes for cGxP materials / Environment.

Incident Report

The record used to document any deviation related to the receipt of material, sampling, manufacturing and packaging, testing and holding processes. This record serves as a precursor to an Investigation Report.

Quality Approver

Member(s) of the Quality Unit who perform(s) incident approvals and may help with the overall management of the Incident process.

Deviations are of two types:

- Planned deviation
- Unplanned deviations

Planned deviations are the deviation from the standard procedures that are planned and it's known before they occur. Change in calibration or validation schedule due to various reasons can be considered as an example for planned deviation. The unplanned deviations are the failure of procedure, utility, material, equipment or any system has been made with an intention for better process. The unplanned deviations may be critical, major or minor and can be categorized based on their impact on product quality.

Corrective action and preventive action (CAPA)

The CAPA defined as a systematic approach that includes actions needed to correct (correction), avoid recurrence (Corrective action) and eliminate the cause of potential nonconforming product and other quality problems (Preventive action). The Corrective action helps to eliminate the causes of a detected nonconformity or other undesirable situation and should avoid the reoccurrence of the same issues. Whereas the preventive action is to eliminate the cause of a, potential non-conformity or other undesired potential outcomes.[13,14]

CAPA Relationship with Quality Subsystems

The CAPA considered as important element of an effective QMS and it should have a close link with other quality subsystem as specified in the Figure 1.

Requirements for CAPA Procedure

Identification of Existing and Potential Causes of Quality Problems

The internal data are the primary sources for the identification of potential problems. Inspection and

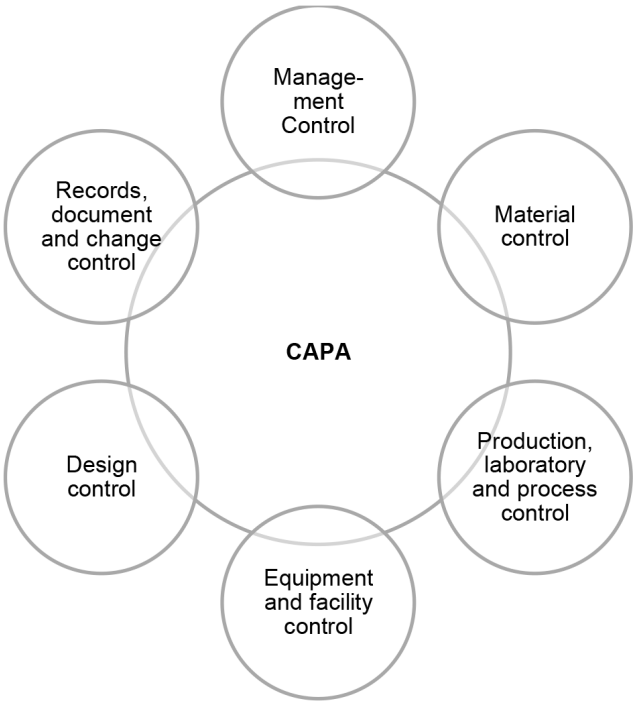

Figure 1: Relationship of CAPA with quality subsystems.

test results, process control information, equipment and instrument calibration results are the basic internal data sources. The external data are the secondary sources for the CAPA procedure. (eg., Post marketing reports, field service report, legal claims, product warranties etc.)

Failure Investigation

An effective investigation should be carried out based on established objectives to find out the quality problems. The check list of investigation process should ensure that all the procedures were followed. The risk associated with identified quality problems should correlate with the magnitude and results of investigation.

Determining Appropriate Corrective and Preventive Action

A well-defined corrective action is necessary to correct the undesired results and to prevent its reoccurrence. Similarly standard procedure should be in place to allow the identification and remedy for the same. All the CAPA actions should be verified by the quality assurance department before implementation to ensure the actions are effective.

Change Procedure

The standard operating procedure and methods should be changed according to the CAPA strategic plans. The employees directly responsible for the changes should be informed through written instructions to avoid any confusions.

Management Review

All the relevant information and actions taken based on CAPA plan should be submitted and reviewed by higher management and it should be documented.[13]

CAPA Procedures

Implementing an effective CAPA system that capable to assure satisfactory quality and regulatory requirements consist of the following basic steps which are as follows:

Identification

The primary step in the CAPA system is to define and identify the problems. This detailed description should include the sources of information, a detailed explanation of existing issues, information regarding available information's and evidence related to it.

Evaluation

The situation that has been explained and documented in the "Identification" section should be evaluated first and the need for action and then the level and the area of action required. The evaluation process also includes the assessment of potential impact of the issues and the risk to the organization or to the customers.

Investigation

In the investigation process, a written procedure should be present for investigating the problem. The procedures and written instructions should provide the primary objectives of action, the procedure to be followed, the personnel that who is responsible for the action implementation and other anticipated resources required.

Analysis

Mainly there are two goals in the analysis, primarily to determine the root cause of the problem described and to identify the other contributing causes. This step consist of collection of relevant data, investigation of all possible causes and determination of the cause of the problems using available information's.

Action Plan

Among the various steps of CAPA procedures the action plan consider as a fundamental one. By using the outcomes from the pre analysis, the optimum method for correcting the situation is determined and an action plan developed.

Follow Up

The follow up of actions is an evaluation of the action that were taken. The following questions need to be answered in follow up procedure,

- Have all the goals of the implemented actions been met? (Did the action correct the identified problem, the possibility of that the same situation will not happen again?)
- Have all recommended changes related to the system and documents been completed and verified by QA department?
- Have appropriate and relevant training given to employees? Or all the personnel are aware of changes?
- Does the implemented action have any adverse effect on the product or service?

Below are the few events given for which the suitable CAPA has been implemented explained in the Table 1.

Pharmaceutical investigations

Investigation of Out Of Specification

The two terms Out-of-Trend (OOT) and Out-of Specification (OOS) results are in many cases confused by pharmaceutical companies and regulatory agencies. OOT results are defined as a stability result that does not follow the expected trend, either in comparison with other stability batches or with respect to previous results collected during a stability study.[15]

The major goals of the investigation are to determine the root cause of existing potential problems. It also provides recommendations for solutions. A written plan should be present prior to the investigation and it should be define objectively.

In the year 2006, FDA established guidance "Investigating Out-of-Specification (OOS) test results for pharmaceutical production" which provides current trend of evaluation of out of specification test results. The out of specification results include all laboratory test results that falls outside the specifications or acceptance criteria established in drug applications, drug master file (DMF) or by the drug manufacturer.

Laboratory Investigation

The objective of the investigation is to determine the root cause of the OOS result. The source of each OOS result should be identified either as an aberration of the measurement process or an aberration of the manufacturing process. An investigation should be thorough, timely conducted and it should be unbiased, well-documented and scientifically sound.[13,16]

The laboratory investigation mainly consists of three parts:

- Phase I: Laboratory investigation (Identifying and assessing OOS test results)
- Phase II: Full-scale OOS investigation (Investigating OOS test results)
- Phase III: Investigation (Resampling)

The US FDA has issued a guidance document for GMP studies on conducting OOS investigations.

Phase I: Laboratory Investigation

cGMP Concept of Laboratory Investigations

Normally laboratory investigations are conducted when there are questionable results.

Pharmaceutical organizations conduct a review to identify a laboratory error or need for a full investigation. The step wise procedure is detailed in the Figure 2. In every investigation the following items that should be evaluated:

- Data-laboratory notebooks
- Methods
- Calculations
- Equipment's
- Sample integrity
- Reagents, standards used
- Training.[13]

Table 1: Examples for Corrective and Preventive actions (CAPA).

Sl.no	EVENT	CAPA
1	Calibration of UPLC related incident	SOP training was given to analyst on UPLC calibration. The incident occurred due to improper channel connections, hence there is no quality impact associated with this incident
2	Weighing print-out related incident	The CAPA has been initiated to list of the activities for handling such events and the procedures were incorporated in the respective SOP.
3	The sample bottle of tablets for testing was labelled using obsolete format.	Proposed to use a pre-printed label to avoid such observation in future.
4	The % assay results are on the higher side.	As a part of CAPA, instructions given to analyst to strictly adhere to the GLP practices.

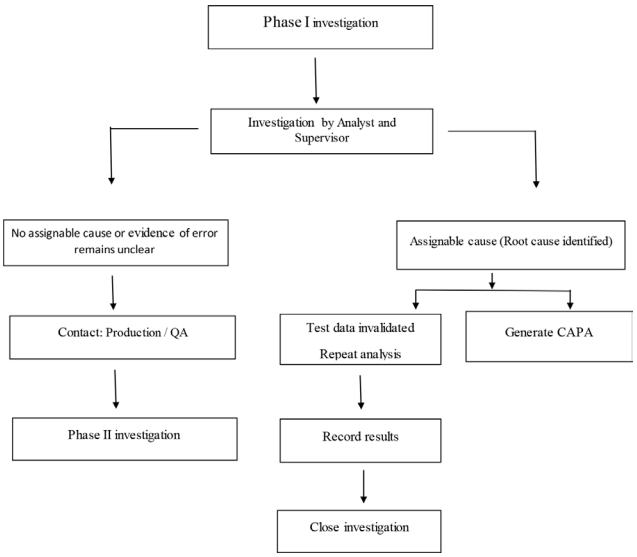

Figure 2: Procedure for phase I: laboratory investigation.

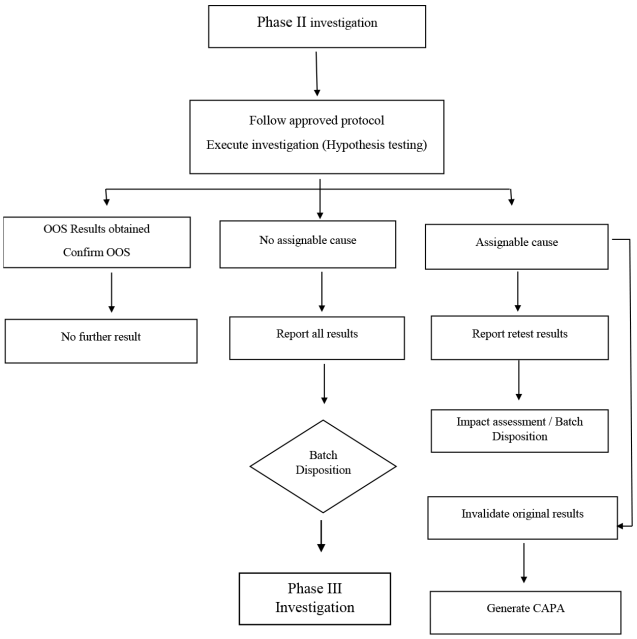

Figure 3: Procedure for phase II: laboratory investigation.

Phase II and III: Laboratory Investigation

Review of Production

The Quality control unit is responsible for the investigation procedure and should involve all other departments that could be impacted, including manufacturing, process development, maintenance and engineering. The step wise procedure for the phase II and phase III are detailed in the Figure 3 and Figure 4.

Additional Laboratory Testing

Additional laboratory testing is a part of full-scale OOS investigation. These investigations consist of several practices, such as, (1) Retesting a part of original sample and (2) resampling.

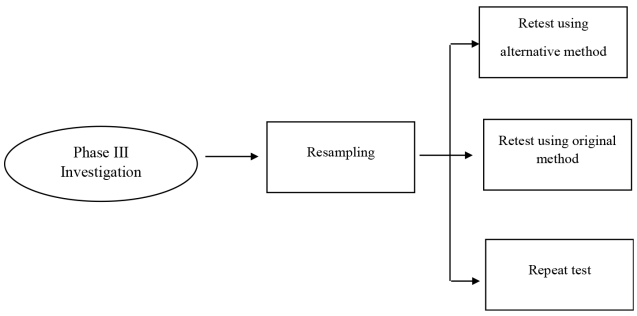

Figure 4: Procedure for phase III: laboratory investigation.

- Retesting

  The sample for the retesting should be taken from the same homogeneous material that was originally collected from the lot, tested and yielded the out of specification results.
- Resampling

  While retesting refers to the re-analysis of the original, homogenous sample, the resampling involves analysing a specimen from any additional units collected as part of the original sampling procedure or from a new sample collected from the batch.

Reporting of Test Results

Reporting and interpretation of laboratory test results include (1) averaging (2) outlier tests.

Concluding the Investigation

To conclude an investigation procedure, all the results should be evaluated and the batch quality should be determined. The standard operating procedures should be followed in arriving at this point of investigation. Once a batch has been rejected, there is no limit to further testing to determine the cause of the failure so that corrective action and preventive can be taken the quality control unit has the authority to review Production records to assure that no errors have occurred.[17,18]

RESULTS

Pharmaceutical deviation

Out of 214 deviation recorded during the time of study 171 deviations were categorized as permanent deviations which contributed to the 80% of total deviations. Remaining 20% of deviations as shown in the Figure 5 was contributed by 43 temporary deviations. The collected data were used for the analysis as shown in Figure 5.

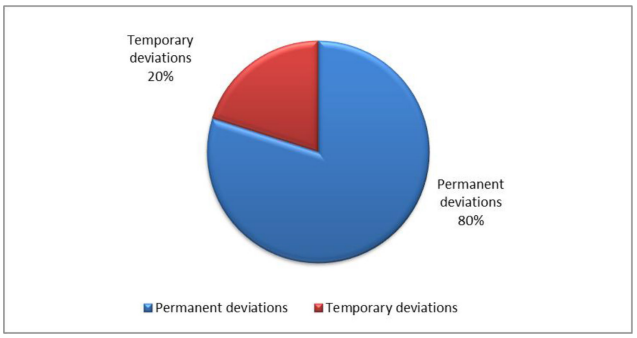

Figure 5: Overview of the pharmaceutical deviations for the year of 2017-2018.

Table 2: Overview of various root causes of incidents in pharmaceutical industry.

ROOT CAUSES	NO. OF INCIDENTS	PERCENTAGE
Man Power	153	70%
Machines	56	26%
Measurement	4	2%
Materials	3	1%
Method	2	1%
Total No. of Incidents	218	100%

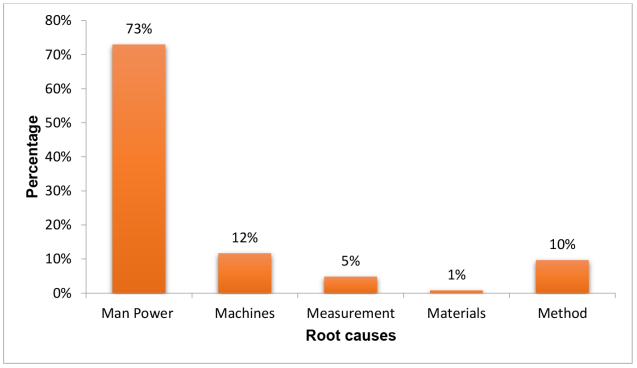

Figure 6: Overview of various root causes based on laboratory investigation report (LIRs).

Pharmaceutical incident

In the root cause analysis of pharmaceutical incidents reported human error is found to be the major cause followed my mechanical problems occurred with the machines. Measurement errors, faulty materials and method errors were revealed to be minor causes of incidents reported. The data is shown in Table 2.

Pharmaceutical investigations

Based on the laboratory investigation reports root cause analysis data for incidents are shown in the Figure 6. Manpower caused error remain major among

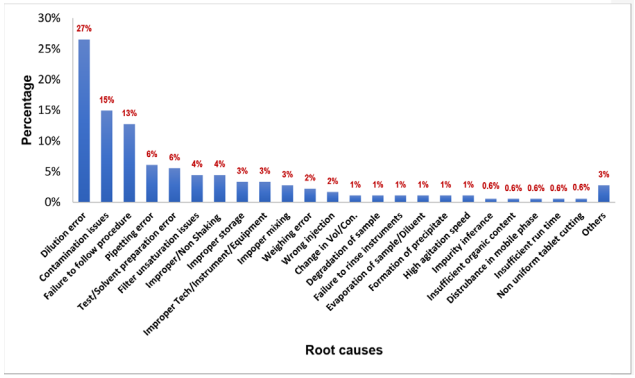

Figure 7: Overview of various types of root causes -based laboratory investigation report (LIRs) for the year of 2017-18.

Table 3: Overview of corrective and preventive actions (CAPAs).

TYPE OF ACTION	No. OF CAPAs
Total no. of CAPAs identified	13
CAPAs involved redesign and redevelopment of process	13 (100%)
CAPSs involved retraining of personnel	12 (92%)

all the root causes followed by machines and method errors. As the manpower based issues prevail up to 73% of the root causes for deviations and incidents they were further classified as shown in the Figure 7. Out of 181 selected manpower based root causes dilution errors were 47% resulting in analytical deviations and incidents. Contamination issues and failure to adhere to the SOP also remained critical among them.

Corrective action and preventive action

Effective CAPA planning and implementation was essential for the control of deviations and incidents reported. Various CAPA initiated on these incidents were classified into two based on their mode of implementation. As presented in Table 3, all the cases where CAPA was initiated involved the modification or redesign of process and 92% of them required retraining of the personnel associated with the process. The extent of redesign of the process may demand additional training for the personnel involved in.

DISCUSSION

The primarily considered Quality Indicator is the pharmaceutical deviation. Total 214 deviations from the year of 2017-18 were selected as sample. In this 171 are the permanent deviation and remaining 43 are temporary deviations i.e., 20% temporary deviations and 80% permanent deviations.

The temporary deviation again subcategorized based on the category and area involved, the due of excipients comes as the major deviation with 19% and relocation of equipment and instrument comes second with 16%. Also fine the percentage of each category of deviation as given below, due of calibration 12%, controlled batch execution 9%, use of booth under validation 9% and fabrication of controlled batch tablets 7%.

Also found the signing of partial report, SOP deviation 5% and manufacturing without CoA 5%, impurity reporting MFC not approved and use of old LNB comes with 2%.

The same method were followed for the permanent deviation were, the percentage of each category of deviation found as given below, the SOP revision 51%, Relocation of equipment 18%, installation of new equipment 8%, software related deviation and revision of guidelines 4%, revision of STP 3%.

Implementation of mew methodology, instrument from other site, retirement of equipment, guideline obsolete and allocation of new identification number comes 1%.

Secondarily, Pharmaceutical incidents are selected for the study as the quality indicator. 218 samples were taken and screening was done in order to find out the root cause. In this 70% of the root cause is due to human related issues. The major root cause is found to be human error and they are further screened to identify the actual errors. Failure to meet acceptance criteria comes first with 48% and failure to follow procedure with 28%.

Next Laboratory investigation reports (LIR) is chosen as the quality indicator. In this, 248 samples were selected from the year of 2017-18 and human error is found as the major root cause after screening. This human related issue are further screened for individual root causes.

The dilution error found the major human error with 27% and Contamination issues 15%, failure to follow procedure 13% and pipetting error 6%.

The same pattern of the case study was used for the identified Corrective action and Preventive actions (CAPA) in the year of 2017-18. The comprehensive CAPA program has been identified as a strong indicator of a robust quality. Continuous improvements of pharmaceutical manufacturing activities are based on preventive and corrective actions to the detected undesired results. The FDA has observed that less robust quality system often rely on preventing recurrence solely through personnel re-training (i.e., The same training has already been provided to the employees), while more robust quality systems consider re-design and redevelopment of the process.

From the collected data it was found that the CAPA procedures involved 100% of redesign and redevelopment of the process and 96% of personnel re-training. The quality metrics for each pharmaceutical indicators were calculated by using the above-mentioned data and reported the same.

CONCLUSION

To remain regulatory compliant and to assure the continuity of product supply in a cost effective way, the system and process must be evaluated and controlled. Important tools in this context are accurate Quality Metrics, Key Performance Indicators (KPIs) and Continuous Quality Improvement.

The pharmaceutical Quality Metrics (QM) has been used in the pharmaceutical industry for years – mainly to measure operational performance. But quality can be measured on different levels and for many processes. If performed in the right way, Quality metrics can enable companies to reach a high-quality performance. They will benefit for continuous improvement in both Operational Performance and GMP Compliance and are important for the continuity of business and product supply.

A good quality metrics system supports both industry's profitability, GMP Compliance and precludes over-production of metrics; only measure what adds value to quality in the most efficient way. This way the metric system is fit for purpose enables the pharmaceutical industry to maintain a high-quality standard and allows to lower the non-conformance. To make this happen, the industry must come together in courses like this to learn and discuss how to build a better-quality system using smart quality metrics.

In order to solve the quality related issues, every pharmaceutical organization must know how to implement quality metrics in an effective way.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

USFDA: United States Food and Drug Administration; **CAPA:** Corrective action and Preventive action; **QI:** Quality Indicators; **KPI:** Key performance indicator; **QAD:** Quality Assurance Department; **QMS:** Quality management Systems; **CFR:** Code of Federal Regulations; **OOS:** Out of specification; **QM:** Quality metrics; **MFC:** Master formula card; CoA- Certificate of analysis; **GMP:** Good Manufacturing Practices; **LNB:** Laboratory note book; **LIR:** Laboratory investigation report.

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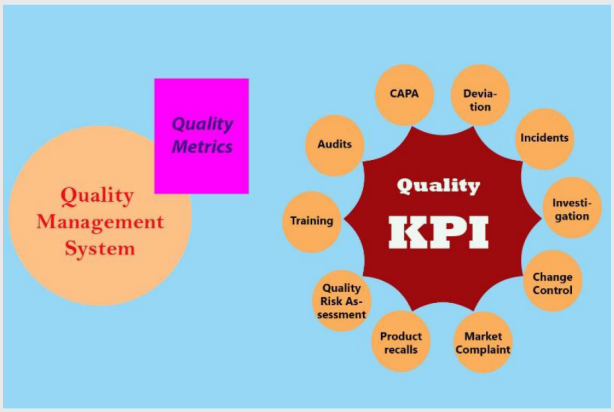
PICTORIAL ABSTRACT



SUMMARY

A pharmaceutical quality management system is an integral part of any pharmaceutical company which remains as the backbone of their business. Quality Metrics serves as a measuring tool for various aspects of quality making it possible to rate and quantify the quality system which is in place. Quality Key Performance Indicators (Q-KPI) serves as checkpoints for the measure of quality. The present study considered Pharmaceutical deviation, quality risk assesment, risk review, change control, pharmaceutical incidents and CAPA as Q-KPI for the evaluation of QMS in the company. Types of deviations, change control systems, risk review process and CAPA are carefully categorized and analyzed to reach a conclusion regarding their relevance in a Pharmaceutical Quality Management system. In a pharmaceutical quality control facility, the various analytical problems and their handling in a laboratory enviroment are thouroughly discussed.

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