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Review Article

CORRECTIVE AND PREVENTIVE ACTION - A ROUTE CAUSE ANALYSIS IN MANUFACTURING QUALITY SYSTEM: REVIEW

KIRAN KUMAR B*, PRAMOD KUMAR TM

Department of Pharmaceutics, Pharmaceutical Quality Assurance Group, JSS College of Pharmacy, JSS University, Sri Shivarathreeshwara Negara, Mysuru - 570 015, Karnataka, India. Email: bhandari.kiran.kumar6@gmail.com

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ABSTRACT

A well-designed and implemented corrective and preventive action (CAPA) offers a mechanism for obtaining critical quality data in a timely manner to enable quick response to out-of-specification (OOS), early warning of potential failures and redeployment of resources to problematic areas. This article presents the key features of CAPA program and provides the current thinking on how to evaluate OOS test results that can lead to detection and resolution of OOS test results for pharmaceutical production. To solve OOS, every organization must know how to conduct an effective investigation, identify root causes, and implement workable CA in a timely manner that can help prevent potential problems in the future.

Keywords: Corrective and preventive action, Out-of-specification, Fault tree analysis, Quality management system.

INTRODUCTION

Corrective and preventive action (CAPA) is a fundamental management tool that should be used in every quality system. This program provides a simple step by step process for completing and documenting CA or PA. The result will be a complete, well-documented investigation, and solution that will satisfy regulatory requirements and form the basis for an effective continuous improvement plan for any company. Properly documented actions provide important historical data for a continuous quality improvement plan and are essential for any product that must meet regulatory requirements demanded by FDA and ISO and other quality systems [1].

QUALITY MANAGEMENT SYSTEM (QMS)

The quality system is a set of formalized business practices that define management responsibilities for organizational structure, processes, procedures, and resources needed to fulfill product or service requirements, customer satisfaction, and continuous improvement. A QMS is a set of interrelated processes used to direct and control an organization with regard to quality.

Most companies have recognized that how the quality system is maintained and monitored is critical to its effectiveness. The risk-based CAPA requirements demand a well-documented system that determines the root cause of non-conformances, system failures or process problems, corrects the problems, and prevents them from recurring. The documentation must identify why something went wrong-or why it may go wrong-and what has been done to make sure it does not happen again.

Quality systems are regulated by the Food and Drug Administration (FDA) under 21 CFR Part 820 referred to as the "quality system regulation" (QSR). To provide FDA inspectors with guidelines on how to evaluate compliance with the issues outlined in the QSR, the FDA produced the Quality Systems Inspection Technique (QSIT). QSIT focuses on four key subsystems as primary indicators of QSR compliance and provides guidelines for evaluating each. These four subsystems are management controls, design controls, CAPA and production, and process controls and are considered the basic foundation of a quality system. The remaining three subsystems of the QSR (facilities and equipment controls, materials controls, and documents/records/ change controls) can be looked at while evaluating the other four [2,3].

CAPA

Many investigations carried out under CAPA result in the CA being retraining. However, non-specific recommendations normally indicate that the root cause of a problem has not been identified. Furthermore, as root causes are, in most cases, a reflection of a company or corporate policy and it is apparent that retraining is not a logical end of a CAPA. CA is one of the most important improvement activities. CAPA identifies actions needed to correct the causes of identified problems and seeks to eliminate permanently the causes of problems that have a negative impact on systems, processes, and products. CA involves finding the causes of some specific problem and then putting in place the necessary actions to avoid a reoccurrence. PAs are aimed at preventing the occurrence of potential problems.

CAPA DEFINITIONS

When it comes to CAPA we must segregate between three different subjects:

1. Correction or remedial action
2. CA
3. PA.

CORRECTION

In the first instance, correction or remedial action focuses on the immediate situation to eliminate an existing non-conformance or undesirable situation. It is very important to note that those actions that focus on the immediate situation do not tackle the root cause but just "fixes" the problem temporarily.

CA

The CA is a reaction to a non-conformity or undesirable situation that has already happened. It assumes that a non-conformance or problem exists and has been reported by either internal or external sources. The actions initiated are intended to prevent the recurrence, which included the following steps.

- Correct the problem
- Modify the quality system so that the process that caused it is monitored to prevent the recurrence
- The documentation for the CA provides evidence that the problem was
- Recognized
- Corrected
- Proper controls installed.

PA

The PA is a proactive approach and process for detecting non-conformances or undesirable situations that have not yet happened and prevents them before occurring. The process includes:

- Identify potential problems or non-conformances
- Find the cause of the potential problem/non-conformance
- Develop a plan to prevent the occurrence
- Implement the plan
- Review the actions taken and the effectiveness in preventing the problem.

CAPA RELATIONSHIP WITH QUALITY SUBSYSTEMS

The CAPA system is a critical component of an effective QMS, and it must maintain a close relationship with other quality subsystems. The ultimate goal of any regulated company must be to have a CAPA system that is compliant, effective, and efficient. All relevant subsystems that may produce non-conformances must be part of the process. Internal processes encompass both non-conformance and in-conformance results, internal audits and assessments, management reviews, and so on. External sources of CAPA process inputs are supplier audits and assessments, customer feedback, and results from external audits and assessment such as regulatory agencies, ISO, and so on (Fig. 1).

Identifying existing and potential causes of quality problems: Internal data sources may include inspection and test data, process control data, equipment calibration and maintenance data, device history records, change control records, out-of-specification (OOS) and, non-conforming material reports. External data sources can include field service reports, legal claims, product warranties and complaints from customers, employees, and the FDA. Failure investigation: An investigation should be carried out to determine the root cause of a quality problem. The investigation should ask whether procedures were followed and whether there was appropriate control to prevent the distribution of the defective product. The magnitude of the investigation should correlate with the significance and risk of the problem. Determining appropriate CAPA: Actions should be identified to correct the quality problem and prevent its recurrence. Similarly, procedures should be in place to allow the recognition and solution of a potential problem to avoid its occurrence. Such actions should be verified to ensure that they are effective and do not have an adverse effect on the products [4,5].

Changing procedures: Methods and procedures should be changed to incorporate the CAPA. People directly responsible for quality assurance should be provided with information regarding quality problems and procedural changes [6].

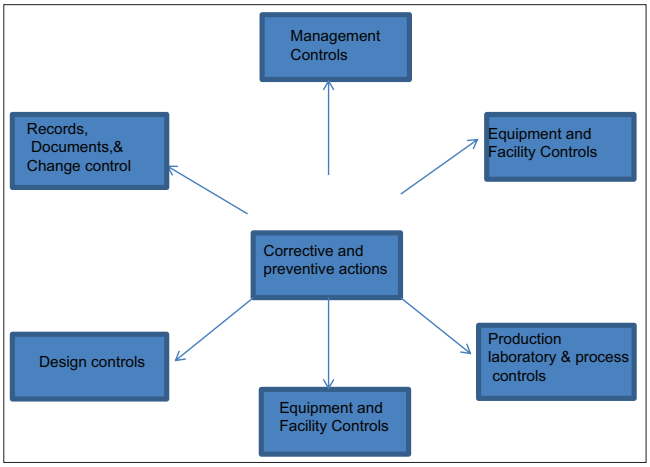

Fig. 1: Corrective and preventive action and manufacturing quality system

Management review: Relevant information on problems and the CAPA taken should be submitted to management for review.

Benefits of unified CAPA system [7]

1. Financial
   - Influence technologies
   - Opportunities for prevention
   - Simplification through elimination of manual steps
   - Lowers cost through centralized functions.

2. Consistency
   - Uniform processing
   - Common language.

3. Compliance
   - Readily retrievable information
   - Faster proactive analysis
   - Connects the dots to identify systemic issues
   - Visibility for cross-site issues (e.g. inspections and supplier problems).

4. Management control
   - Early alert system that facilitates prevention
   - Instantaneous, real-time view of company-wide issues
   - Improved communication and teamwork
   - Facilitates integrated trending for large volumes of data
   - Linkage among sites for products that are sold as a system.

Common CAPA violations

- No established procedures for implementing CAPA
- Complaint handling too specific, do not look at overall system
- Failure to document CAPA
- No validation
- Inadequate procedures for quality audits.

INDUSTRY'S COMMON FAILINGS

It seems that one of the biggest challenges for companies is to complete investigations and actions in a timely manner. In many cases, incorrect assumptions are made that everything is an isolated incident. In other instances, problems are not corrected, and everything is blamed on a single employee or a simple laboratory error, or the system fails to ensure that a problem does not extend to other lots, and the incident recurs. The ultimate criterion for adequate correction is to ensure that it does not happen again. CAPA was adopted as a new quality management tool following the introduction of the ICH Q10 guideline. According to the ICH Q10 document, which was adopted by the FDA in April 2009 as an industry guideline, a pharmaceutical QMS consists of four central elements:

- Process performance and product quality monitoring
- CAPA
- Change management
- Management review of process performance and product quality.

The guideline states that a pharmaceutical company should have a system in place to detect and evaluate non-conformances to take respective CAPA. Among other things, the information regarding non-conformances can result from complaints, deviations, recalls, observations at audits and inspections, or from monitoring findings. The examinations within the system must have the objective of determining the actual root cause. As a result, the process and product should be better understood so that improvements can be derived from it. The EU Commission has now published a suggestion for the revision of chapter 1 of the EU GMP Guide to incorporate the recommendations of ICH Q10. Now, specific requirements for the CAPA system shall be included. Accordingly, the extent of the actions, technical complexity, and documentation of the necessary CAPA has to be managed according to a risk assessment.

OOS AND CAPA PROGRAM

In 2006, FDA provides guidance "Investigating OOS test results for pharmaceutical production" which provides current thinking on how to evaluate out of specification test results. The term OOS results includes all test results that fall outside the specifications or acceptance criteria established in drug applications, drug master files or by the manufacturer [8].

A common way of handling OOS is by fixing the product or material. Increasingly, however, manufacturers realize that they must not only fix existing problems but also avoid future recurrence of a similar non-conformance. In this sense, the non-conformance disposition process is closely related to the CAPA process.

In the case of the FDA-regulated medical device, pharmaceutical, and biotech companies, certain regulations require them to implement CAPA as part of the resolution of material non-conformance issues. Under QSR (21 CFR Part 820.100), medical device manufacturers are required to establish a CAPA procedure that will investigate the cause of any product non-conformance and identify the action that would prevent the recurrence of such non-conformance. The CGMP regulations for finished pharmaceuticals similarly require that any failure of a batch, or any of its components, to meet specifications must be thoroughly investigated and documented, including the investigation's follow-up and conclusion (21 CFR Part 211.192).

INVESTIGATIONS OF OOS

FDA regulations require that an investigation to be conducted whenever an OOS test result is obtained. The purpose of investigation is to determine the root cause of existing or potential non-conformities and to provide recommendations of solutions. The scope of the investigation should be adequate with the determined risk of the non-conformity. Good practice shows that a documented plan should be in place before conducting the investigation. The plan should include:

- Description of the non-conformity expressed as a problem statement
- Scope of the investigation
- Investigation team and their responsibilities
- Description of activities to be performed
- Resources
- Methods and tools
- Timeframe.

CAPA PROCEDURES

Implementing an effective CA or PA capable of satisfying quality assurance and regulatory documentation requirements is accomplished in six basic steps:

1. Identification

The initial step in the process is to clearly define the problem. It is important to accurately and completely describe the situation as it exists now. This should include the source of the information, a detailed explanation of the problem, the available evidence that a problem exists.

2. Evaluation

The situation that has been described and documented in the "Identification" section should now be evaluated to determine first, the need for action and then the level of action required.

The potential impact of the problem and the actual risks to the company and/or customers must be determined. Essentially, the reasons that this problem is a concern must be documented.

3. Investigation

In this step of the process, a procedure is written for conducting an investigation into the problem. A written plan helps assure that the investigation is complete, and nothing is missed. The procedure should include an objective for the actions that will be taken, the procedure to be followed, the personnel that will be responsible, and any other anticipated resources needed.

4. Analysis

The investigation procedure that was created is now used to investigate the cause of the problem. The goal of this analysis is primarily to determine the root cause of the problem described, but any contributing causes are also identified. This process involves collecting relevant data, investigating all possible causes, and using the information available to determine the cause of the problem. It is very important to distinguish between the observed symptoms of a problem and the fundamental (root) cause of the problem.

5. Action plan

Using the results from the analysis, the optimum method for correcting the situation (or preventing a future occurrence) is determined and an action plan developed. The plan should include as appropriate: The items to be completed, document changes, any process, procedure, or system changes required, employee training, and any monitors or controls necessary to prevent the problem or a recurrence of the problem. The action plan should also identify the person or persons responsible for completing each task.

6. Follow-up

One of the most fundamental steps in the CAPA process is an evaluation of the actions that were taken. Several key questions must be answered:

- Have all of the objectives of this CAPA been met. Did the actions correct or prevent the problem and are there assurances that the same situation will not happen again.
- Have all recommended changes been completed and verified
- Has appropriate communications and training been implemented to assure that all relevant employees understand the situation and the changes that have been made (Fig. 2 and Table 1).

Fig. 2: Implement a corrective and preventive action system with a closed loop

Table 1: Risk assessment tool matrix

Frequency	Impact			
	Negligible	Minor	Important	Critical
Constantly	M	H	H	H
Frequently	L	M	H	H
Occasionaly	L	M	M	H
Rarely	L	L	M	M

M: Middle, L: Low, H: High

CHALLENGES OF IMPLEMENTING CAPA

Historically, most organizations have relied on the wisdom and experience of their internal experts to identify root causes. Experts attempt to solve all problems using their experience of tried and true past solutions. The main pitfall of this strategy, however, is that their solution is completely dependent on and limited by their expertise. If the root cause happens to lie outside the scope of their expertise levels, they are not likely to find it. Therefore, they must design a series of closely monitored experiments to test their hypotheses and to determine if they are on the right track in locating the root cause. The problem with designing and implementing these experiments is that they are invasive requiring personnel, equipment, laboratory resources, downtime, and funding. If the experiment is a failure, the internal experts must repeat the same costly process again: Brainstorming another probable cause and conducting yet another experiment. This process can be time-consuming and lower the morale of those involved.

The companies are discovering that deductive reasoning and comparative analysis are faster, easier, and more cost-effective ways to identify root cause and implement a CA. Several proprietary programs use deductive reasoning and comparative analysis. The primary focus of such processes is improving a diagnostic technique through better data collection. Data are collected using an observed and comparative questioning technique. A unique and simple tool is used to synthesize the collected data into information that tells the root cause story.

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