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AN OVERVIEW ON CORRECTIVE AND PREVENTIVE ACTION, ROOT CAUSE ANALYSIS AND ITS EFFECTIVE IMPLEMENTATION

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ABSTRACT

The purpose of the corrective and preventive action (CAPA) in pharmaceutical industry is to identify the non-conformities, deviations or failures in the pharmaceutical industry. CAPA is the system which offers a mechanism for obtaining critical quality data to enable out of specifications (OOS). CAPA is also the method in which preventive measures are taken before deviations occur so that the occurrence of any non-conformity can be prevented. This study presents an overview on Root cause analysis and implementation the CAPA system in case of OOS results. CAPA helps primarily to determine and investigate the root cause of the problem or issue, which are identified, documented and the planned deviations will also be identified and will be recorded. By implementing an effective CAPA it ensures that the product quality can be improved and regulatory requirements are met. CAPA is a part of overall Quality management system (QMS) in the pharmaceutical industry. To reduce the losses incurred from non-compliance, the only way out is to investigate and prevent a recurrence of their cause. Analysis of root cause is used to address non-compliance issues and causes of the particular issue.

INTRODUCTION

Corrective and preventive actions (CAPA) are basic quality management system which must be used in the management of the quality in the product and service. CAPA are the important tools which are manufacturing pharmaceutical products. This management tools provide the step by step process for avoiding or minimizing the non-conformities in the system. The results will be completely and properly documented according to the regulatory requirements and compliance (1). It is a process which ensures that products which are produced in the pharmaceutical industry are safe and effective. CAPA which continuously improves the quality of the system or products and which is the essential part of quality management system and it should meet the regulatory requirements which are specified by the regulatory agencies, ISO and other quality system.

Correction: It is an immediate action taken by team to eliminate the detected non-conformities or undesirable situation.

Corrective action: Corrective action is a reaction or remedial action to the undesirable action or non-conformities which were exist. It assumes that the

undesirable situation or non-conformities which were exist and which has been reported by the concerned department either by internal or external source to the particular department (2). Following steps which are included in the corrective action:

- Documentation of the problem
- Analysing the problem
- Correction of the situation or non-conformities
- Recognition of the situation
- Installing of proper control system
- correction of the situation

Prevention action: It is an action or proactive approach for avoiding something from happening, which may affect the process or the system. It is the action which will be taken before occurring or existing the non-conformities (2). The preventive action process includes as follows,

- Identification of the non-conformance
- Analysing the cause of the non-conformance
- Development of the method or plan to prevent the non-conformities
- Implement the process or plan
- Review the action

Importance of CAPA:

- To assess the CAPA processes that address the criteria identified and recorded in the quality system regulations which have been defined and documented
- To recognize current product and quality issues requiring corrective action
- To identify potential product and quality problems which requires preventive action
- To determine whether CAPA are effective
- To confirm the corrective and preventive action do not cause adverse effects to the finished product or medical device
- Helps to detect recurring quality problems and analytical findings are contrasted with other information sources

Quality management system in CAPA:

Quality Management System (QMS) is the management process compilation that describes the process, management duties, organisational structure, processes and specifications required to fulfill the service or product development, customer satisfaction. It is a business process which is used to control and direct an organization for the product quality. Under the 21CFR-820 regulatory requirements the CAPA are established by the FDA to maintain the uniformity in the product development and the service, which are dispensing to the customer. The QMS is referred as quality system regulation under 21CR-820 part (3). This guideline provides, how to evaluate the non-conformance and issues which are occurred or occurring during the process. Quality system inspection technique (QSIT) are the published guidelines or procedures by the FDA which are used by the inspectors to evaluate the safety and quality of the product. QSIT mainly focuses on the four key subsystems which are design control, organization control, CAPA and production control and process control. Most of the pharmaceutical industries are recognized how to nurture the quality system to its effectiveness.

CAPA Procedures: By implementing an effective or essential corrective action (CA) or preventive action (PA) which ensure that improvement of the product quality and satisfies the QA and RA documentation requirements (2). The basic steps involved in the CAPA procedures are as follows:

Identification of cause: It is the first step in the process to clearly define the cause or

issue, it must include the cause source and accurate cause explanation, it must provide the cause or problem evidence. It is important to completely and accurately describe the situation or condition as it exists.

Examination of cause: Examination of the cause is the important step, in this step detailed study of the cause and the source of the cause will be identified and examined and the reason for the cause will be inspected. The written procedures must be followed to carry out an investigation to detect problems. Written procedure to ensure that the enquiry is complete and that the procedure should include the action's goal.

Evaluation of cause: The evaluation step which includes the situation that has been described and documented in the identification of the cause and should evaluated to determine the problem which exists. The impact of the cause and the risks to the organization and/or customer must be determined. The reason must be documented which involves in the concerned problem.

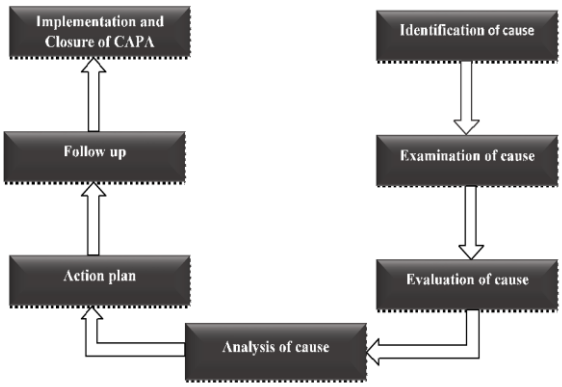
Analysis of cause: The primary objective of the study is to identify and investigate the root cause of the problem or issue that is recognized and recorded. The planned deviations will also be identified and will be recorded. It is important to differentiate between the observed symptoms of a cause and the root cause of the problem. The investigation procedure which are created and which will be used to investigate the cause of the problem (4).

Action plan or Implementation of CAPA

By using the results from the analysis of the root cause the suitable method for correcting the problem or situation is determined and action plan will be developed. The action plan should conclude in the products to be finished, process changes, procedural or system modifications, document needed modifications and personnel training and any necessary measures or controls to avoid the cause or condition of the issue. The action plan should also recognize the process participant and the individual responsible for completing the assignment.

Follow up: It is one of the most fundamental step involved in the process of CAPA evaluation of the action that were taken. some of the key questions must be answered in this section which are,

- Have all the objectives met the CAPA process, did the action corrects or prevents the problem or situation
- Have all the changes been verified and completed and implemented
- Has appropriate training has been given to the employees or implemented to assure the understanding the situation and the CAPA Procedure as follows in Fig1
- **Fig 1: CAPA Procedures**



Program of CAPA and Out of specification: The term out of specification (OOS) test results includes all suspect results that fall outside the predetermined specification which are established by the cGMP guidelines. United-state Food and drug administration provides the guidelines for investigating the OOS test results in the production of

pharmaceutical products. OOS results includes all the test results which do not meet the specification or acceptance criteria (5). In case of USFDA regulated pharmaceutical, medical device and biotechnology product industries, must meet the certain regulatory requirements to implement the CAPA system. Under quality system regulation i.e. 21 CFR part 820, manufacturer of medical devices are required to establish the CAPA procedures which helps to investigate the non-conformities (10). The common way of handling of OOS is by deciding the material or product issues. However, manufacturers must not only decide on the OOS outcomes after the product has been placed on the market, but also avoid the recurrence of similar non-conformities in the future. In this regard, the non-conformance process closely linked with the CAPA.

Out of specification investigation:

According to the FDA regulations an investigation must be conducted when the test results are OOS. The purpose of the investigation of OOS is to determine the cause or source for existing non-conformities in the process or system. The investigation of the OOS includes the Phase 1 (primary and laboratory investigation) and Phase 2 (manufacturing investigation and resampling and reanalysis of the sample) (5). The investigation of OOS plan must include the following:

- Description of non-conformance
- Scope of investigation
- Qualified investigation team
- Responsibilities of the personnel involved in the investigation
- Resources of OOS
- Tools and method of investigation

CAPA Management system: Upon rising the complaint, OOS and deviation reports about the process/system, review of the issue occurred will be verified by the concerned department. concerned department will gather the data or source of non-conformities which have happened in the process. once the source is identified correction will be made for the non-conformities which have occurred during the process and if, CAPA required to avoid the non-conformities, SOP of CAPA must be followed and then investigates the root cause analysis. Issues must be notified to the respective person and CAPA form will be issued by the QA head upon rising the issues by the concerned department head. The concerned department will implement the CAPA under the supervision of QA head. After the implementation of CAPA, conduct review process of the implemented CAPA. Once the implemented CAPA, meets the specification authorization will be done by the QA head and all the management of CAPA documents will be kept with the respective department head (6) and process as mentioned in Fig 2.

CAPA relationship with quality subsystem: The quality subsystem is the establishment for the other five assembling subsystems which helps to meet the consistent level, each of the quality subsystem work together to efficiently create quality product. CAPA system is an important component of QMS and it must be maintained in good and effective relationship with all the quality subsystems as in the Fig 3. The goal of the organization or industry to have effective, compliant and efficient CAPA system. These quality subsystems and CAPA which helps to identify the existing potential problems of products in which the internal data source includes: Test data, Process control data, Calibration and validation of equipment, Equipment maintenance, Change control and OOS. Externa data source includes: Customer complaints, Audits, Product service report and regulatory reports (7).

Fig 2: CAPA Management System

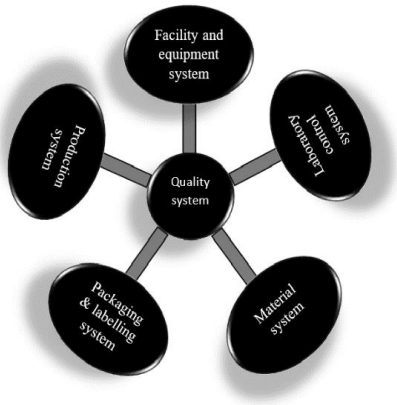
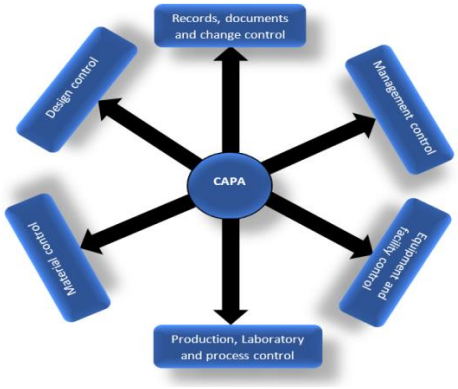


Fig 3: Quality Subsystems

The procedures and methods must be received and changed to incorporate the effective CAPA, personnel or employee responsible in QA must be provided with the information regarding the problems and change control systems as in the Fig 4 (8).

Fig 4: CAPA relationship with quality subsystem



Benefits of CAPA:

1. **Management control:**
   - Identifies the risk and facilitates the prevention
   - Improvement in teamwork
   - Improves the communication
   - Minimizes the issues
2. **Consistency:**
   - Uniform processing
   - Minimizes the human error
   - Usage of common language (9)
3. **Financial:**
   - Lowers the cost for identification of issues
   - Develops the opportunities for prevention
   - Implements the new technologies
   - Simplifies the issues
4. **Compliance:**
   - Faster the effective analysis
   - Readily identifies the information (10)

Documentation of CAPA: The initiation of CAPA needs that the department concern to submit the source of documents to the head of the department of QA (11).

- QA head will review the document submitted by the concerned department.
- QA head will decide the need for CAPA.
- The department head will receive the CAPA form which is issued by the QA head and shall fill all the required information, which should include source of issue, date of issue happened and other related information.
- Department head shall send the CAPA form to the QA head and QA head will review the CAPA form and assigns the CAPA number and then the CAPA form will be forwarded to the concerned department (12).
- Authorization are must be done by the QA head for proposed CAPA implementation actions.
- With the review of the supporting document, the QA head verifies the implementation and completion of CAPA.
- The change control procedure, SOP and records of each CAPA must be retained if any modifications are made.
- QA shall receive copies of the CAPA introduced, and QA shall compile all the records (13).

Root cause analysis: Analysis of the root cause (RCA) is carried out to direct the non-conformities or problem to the actual cause of the problem. The RCA technique is used to eliminate the cause or to avoid repeated problems. Analysis of the root cause means avoiding the particular cause or non-conformance from happening again. The underlying causes and non-conformances are identified by using a structured problem solving approach. It

avoids repetition of non-conformities; prevention of reoccurrences and it provides permanent solution for occurrence of the problem. In some organizations it is a part of the policy which minimizes the error and the goal for facilitating improvement of the system for a longer period. The root cause analysis depends on the set of minds and requires a long time at the beginning, but is a high return investment to prevent completely non-conformities. Analysis of root cause is a approach comprising a sequence of events of well-known new applications, tools and methods that can really generate and provide a productive, systematic, documented and quantified technique for finding and understanding underlying causes. The basic concept of assessing the root cause is to use symptoms as a way to find the origin of a cause. Treating the symptoms can minimize or even aggravate the problem identified. RCA's primary objective is to determine the real or actual root cause of an observed deficiency, failure, or problem, cause and use that information to rectify it. Since the root cause must be supported by proof, it is systematic and coherent to determine the root cause. Probable root cause(s) can be identified for a specified scenario. Root cause analysis is a technique created to identify the issues, not only how an incident happened or what that event is, but also why it led to the event occurring. Once the root cause is identified, the investigators will be able to specify appropriate corrective measures to prevent similar events from occurring in the future. The advantage of an efficient RCA is that the root causes recognized over time can be used to detect major possibilities for improvement and process steps as given in Fig 5 (14).

RCA Process and its Implementation:

1. **Collection of Data**

   The initial step of RCA is to collection of the data related to problem or event related information occurred. Without proper understanding and complete information about the problem or event, the root causes and casual factors related to the event or problem cannot be identified, since the collection of data plays important role in the collection of data.

2. **Causal factor charting**

   The causal factor test is a logic test that explains the occurrence, events and the conditions that surround these events. Casual factor charting facilitates the investigator framework for examining, arranging and analysing data gathered during the investigation. It helps understand knowledge deficiencies and gaps as the research progresses Once the entire event has been mapped, the researchers identify the main contributors to the event, called causal factors. Causal variables, such as human errors and component failures, would have either decreased their seriousness or avoided the event, if the casual variables would either have reduced the occurrence or prevented the event (15).

3. **Identification of Root cause**

   Identification of the Root cause involves the identification of the sources for the non-conformities after all the casual factors were recognized. In this step, by using the decision diagram, the reasons for each causal factor or variables are recognized. With the help of decision diagram the reasoning method of researchers are understood with the assistance of the decision diagram and it also helps answer the questions as to

why the specific causal factors occur or exist.

4. Decision to create and implement RCA

The last step is the generation of decision. Realizable suggestions or decisions that prevent recurrence and are produced for a specific casual factor after root causes have been identified. Organizations must ensure that suggestions are followed up to completion. Once the decisions are made by the organization the implement the RCA.

CONCLUSION:

From the above study, the corrective action and preventive actions are important tools for improving the quality management system and its efficiency. In Quality Risk Management System, it plays a significant role for producing the quality product. By applying CAPA, the root cause assessment of any issue or deviation can be accomplished readily and easily. The root cause analysis and CAPA which increases the safety and quality of the product.The pharmaceutical, healthcare and medical devices sectors should adhere strictly to the application of CAPA in their organization upon the identification of non-conformance.

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REFERENCES:

1. Kumar KB, Kumar TM. Corrective and preventive action a route cause analysis in manufacturing quality system: review. Innovare Journal of Sciences. 2016; 4(2): 1-4
2. Tashi T, Mbuya VB, Gangadharappa HV. Corrective action and preventive actions and its importance in quality management system: a review. International Journal of Pharmaceutical Quality Assurance. 2016 Jan 1; 7(1): 1-6
3. CFR - Code of Federal Regulations Title 21 [Internet]. Accessdata.fda.gov. 2019 [cited 11 March 2019]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm
4. R.M Baldwin, Inc. Preventive / Corrective Actions (CAPA) Guidelines
5. Chopra V, Shukla AK, Aiyyer R, Trivedi P, Nagar M. Investigating Out-of-Specification Results and Development CAPA Program for Pharmaceutical Industries: An Overview. Scholars Research Library. 2011, 3(2): 368-382
6. Raj A. A review on corrective action and preventive action (CAPA). African Journal of Pharmacy and Pharmacology. 2016 Jan 8;10(1):1-6.
7. Motschman TL, Moore SB. Corrective and preventive action. Transfusion science. 1999 Oct 1;21(2):163-78.
8. Alto P B. Corrective and Preventive Actions: The Cornerstone of Effective Quality and Compliance Management in Healthcare. 2010. 1-9
9. Sharonina TN. Corrective and preventive actions in quality management system. Issues of Modern science and practice 2010, 9(30): 7-30
10. Code of Federal Regulations CFR (2015). Title 21, Part 820, www.accessdata.fda.gov
11. Corrective Action Preventive Action (2015). Defining alternatives to training as a root cause, www.mnasq.org
12. Akelewicz F, Dickenson B. Points to Consider when Preparing for an

FDA Inspection Under the QSIT, Corrective and Preventive Actions Subsystem. Suite, Washington, DC: 2001. PP 4-24.
13. Rodriguez PJ. CAPA for the FDA Regulated Industry. Milwaukee, Wisconsin: ASQ Quality Press. 2005. 1-25.
14. Peerally MF, Carr S, Waring J. The problem with root cause analysis. BMJ Quality and Safety first. 2016 June; 1-6.
15. Menon N, Kamath KK, Shabaraya A.R. Conducting root cause analysis and its implementation: a review. MJPS 2016; 2(2): 21-25.