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Quality Management System (QMS) Quality Planning, Quality Control And Quality Improvement

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ABSTRACT

The Quality Management System (QMS) is structured around interlinked processes that provide the necessary implementation controls to ensure customer and regulatory requirements are met and continual process improvement. It provides the basis for policies and procedures that implement a comprehensive quality management system. These processes are those that define activities that are directly necessary to create the product or service, and those that provide the supporting infrastructure to enable the direct processes to operate under the required controls, and continually improve. Quality management is a philosophy. It takes management understanding, commitment and responsibility before introducing and implementing the concept. Once practiced a good quality management system slowly develops or reshapes a sustainable organization culture that pays off rapidly. Quality system plans should be aligned with a manufacturer's strategic plans to ensure that the system is part of the manufacturer's mission and quality strategies. According to QMS a quality product comes from a quality process. This means that quality should be built into the process. Quality at the source is the belief that it is far better to uncover the source of quality problems and correct it than to discard defective items after production. If the source of the problem is not corrected, the problem will continue. It will be far more effective to see where the problem is and correct it for quality.

Keywords: Quality management system, quality planning, quality control and quality improvement

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INTRODUCTION:

Quality Management System (QMS) includes three parts. They are [1-2]

1. Quality planning
2. Quality control, and
3. Quality improvement.

The First part of the QMS, Quality Planning, is necessary so that companies identify their customers, product requirements, and overriding business goals. Processes should be set up to ensure that the quality standards can be met.

The Second part of the QMS, Quality Control, stresses the regular use of statistical control methods to ensure that quality standards are met and to identify variations from the standards.

The Third part of the QMS is Quality Improvement. According to Juran, quality improvements should be continuous as well as breakthroughs. Together with Deming, Juran stressed that to implement continuous improvement workers need to have training in proper methods on a regular basis.

Structure of QMS [3-5]**:**

The Structure of Quality Management System (QMS) includes:

Quality policy, Quality objectives: The quality manual, Mandatory documented procedures,

Regulations of processes and procedures, Work instructions and Quality records.

The quality manual is a general guidance document, which describes the interactionof all elements of the quality system. Policy and quality objectives define the direction of movement, the development company. Regulations of processes and procedures and work instructions - regulations that employees of the company guide in their activities. Quality records are carriers of information produced in the course of the organization; they recorded all the historical facts. Quality records provide information on the functioning of the quality management system and identify new and better ways of developing of the enterprise in terms of quality.

A good QMS will:

- Set direction and meet customers' expectations, Improve process control, Reduce wastage, Lower costs, Increase market share, Facilitate training, Involve staff, Raise morale

DISCUSSION:

Every pharmaceutical product has established identity, strength, purity, and other quality characteristics designed to ensure the required levels of safety andeffectiveness. The phrase achieving quality means achieving these characteristics fora product. It is important to recognize that quality cannot be tested into products i.e., quality should be built in by design. So the design, organization and documentation ofthe pharmaceutical quality system should be well structured and clear to facilitate common understanding and consistent application to reliably produce a product of theintended quality.

A QMS[6-10] can be defined as **"**Management system to direct and control a pharmaceutical company with regard to quality**"**.

A **Quality Management System** (QMS) can be expressed as the organizational structure, procedures, processes and resources needed to implement quality management. Early systems emphasized predictable outcomes of an industrial product production line, using simple statistics and random sampling. Bythe 20th century, labor inputs were typically the most costly inputs in most industrialized societies, so focus shifted to team cooperation and dynamics, especially the early signaling of problems via a continuous improvement cycle. In the 21st century, QMS has tended to converge with sustainability and transparency initiatives, as both investor and customer satisfaction and perceived quality is increasingly tied tothese factors. Of all QMS regimes, the ISO 9000 and ISO 14000 series are probablythe most widely implemented worldwide -the ISO 19011 audit regime applies to both,and deals with quality and sustainability and their integration.

Principles of QMS:

Quality management principles are the fundamental truth or laws that form the basisof quality management. QMS is guided by the below principles

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8 QMS Principles		
1	Customer focused organization	Organizations depend on their customers and therefore should understand current and future customer needs, should meet customer requirements and strive to exceed customer expectations
2	Leader ship	Leaders establish unity of purpose and direction.They should create and maintain the internal environment in which people can become fully involved in achieving the organization's objectives
3	Involvement of people	People at all levels are the essence of an organization and their full involvement enable theirabilities to be used for the organization's benefit.
4	Process approach	A desired result is achieved more efficiently whenactivities and related resources are managed as a process.
5	System approach to management	Identifying, understanding and managing a system of interrelated processes as a system contributes tothe organization's effectiveness and efficiency in achieving its objectives.
6	Continual improvement	Continual improvement of the organization's overall performance should be a permanent objective of theorganization.
7	Factual approach to decision making	Effective decisions are based on the analysis of data and information.
8	Mutually beneficial supplier relationships	An organization and its suppliers are interdependent and a mutually beneficial relationship enhances theability of both to create value.

QMS TOOLS[11-12]:

A Quality management tool that is automated and connects all departments is essential for a regulated or ISO-compliant Pharmaceutical industry. Any company with business operations that require communication between several departments is aware of the criticality of an effective quality management program in the system. FDA regulations clearly emphasize that companies should implement GxP quality management solutions to improve quality of processes. Successful culmination of any process requires automation and collaboration between operations of various departments.

Quality management tools such as CAPA, Deviations, Change control, APQR and Non-conformance, Customer Complaints, Employee Training, etc., that integrate with the rest of a company's system for quality management are critical. They ensure not only quality products, but they can also make processes more efficient and accelerate the time it takes for a product to get to market. With appropriate QMS tools, a company's quality management program can almost manage itself. As a result of implementing QMS tools, companies are able to produce more, faster, and at a much lower cost drug products.

The various benefits of implementing QMS tools are given below:

QMS Tools Guard Against Human Oversight and Error:

Process automation or a TQM (total quality management) system--can connecteach phase in a product's development with every department in a company. This is requisite because building quality into products requires a collaborative effort and thiscan be achieved through the quality management tools

QMS Tools Enhance Production Efficiency and Effectiveness of QA Departments:

QMS tools that consist of CAPA, Deviations, Non-Conformances, Training, etc., and the types of quality management tools discussed above literally build quality into products. This reduces the burden on the Quality Department while simultaneously speeding up a company's production and time-to-market.

QMS Tools Lead to Easy Quality Control:

Companies that are severely dependent on QA departments to report issues, non-conformances, or deviations in the product are aware of how difficult the recursive rounds of testing can be. Any carelessness or inability to test products thoroughly can lead to serious consequences. By employing QMS tools to quality control department it is easy to test and verify product batches without any chances of slippage and building quality into products via quality management tools.

QMS Tools Lead to Automated Processes and Quality Products:

Automated processes for assuring quality products and accelerating time-to-market can be tailored to meet the needs of any Pharmaceutical company, regardlessof size. Without quality management tools, companies will find it difficult to automate processes in the system. Any process is a series of events that requires collaboration between different departments. In order to execute a process to itsentirety, the

chain of events should be automated. If QMS tools are not used, this becomes a difficult task for companies to execute processes on a timely basis. Lack ofautomation causes a chain reaction in the system. The first hit comes in the form ofthe delay it takes in producing quality products. The second hit is the delay in the timeit takes for the company to market products. The final blow comes when the competition takes the lead in the market and the company faces heavy losses. Allthese factors prove the necessity of incorporating QMS tools for automating processesand developing quality products.

Some basic but essential elements of QMS as depicted in GMP guidelines and ISO 9001 guidelines for pharmaceutical industry can be listed as:

Preparation of standard operating procedures of a complete system maintaining cGMP principles, Preparation and maintenance of effective change control, Recording and reporting procedure of Deviations, Quality concern investigation process; Customer complaint investigation procedure;

Quality audit procedures; Vendor assessment, Quality control laboratory procedure,

Procedures on training for manufacturing staff and Recall procedure.

THE CONCEPTS/TOOLS OF MODERN QUALITY SYSTEMS:

The following concepts are used as they relate to the manufacture of pharmaceutical products.

A. Quality by Design and Product Development

Quality by design means designing and developing a product and associated manufacturing processes that will be used during product development to ensure that the product consistently attains a predefined quality at the end of the manufacturing process. Quality by design, in conjunction with a quality system, provides a sound framework for the transfer of product knowledge and process understanding from drug development to the commercial manufacturing processes and for post-development changes and optimization.

B. Quality Risk Management

Quality risk management is a valuable component of an effective quality systems framework. Quality risk management can, for example, help guide the setting of specifications and process parameters for drug manufacturing, assess and mitigate the risk of changing a process or specification, and determine the extent of discrepancy investigations and corrective actions.

Effective decision-making in a quality systems environment is based on an informed understanding of quality issues. Elements of risk should be considered relative to intended use of a product, and in the case of pharmaceuticals, patient safety and ensuring the availability of medically necessary drug products. Management should assign priorities to activities or actions based on an assessment of the risk including both the probability of occurrence of harm and of the severity of that harm. It is important to engage appropriate parties in assessing the risk. Such parties include customers, appropriate manufacturing personnel, and other stakeholders. Implementation of quality risk management includes assessing the risks, selecting and implementing risk management controls commensurate with the level of risk, and evaluating the results of the risk management efforts. Since risk management is an iterative process, it should be repeated if new information is developed that changes the need for, or nature of, risk management.

In a manufacturing quality systems environment, risk management is used as a tool in the development of product specifications and critical process parameters. Used in

conjunction with process understanding, quality risk management helps manage and control change.

C. CAPA (Corrective and Preventive Action)

CAPA is a well-known cGMP regulatory concept that focuses on investigating, understanding, and correcting discrepancies while attempting to prevent their recurrence. Quality system models discuss CAPA as three separate concepts:

- Remedial corrections of an identified problem
- Root cause analysis with corrective action to help understand the cause of thedeviation and potentially prevent the recurrence of a similar problem
- Preventive action to avert the recurrence of a similar potential problem

D. Change Control

Change control is another well-known cGMP concept that focuses on managing change to prevent unintended consequences. The cGMP regulations provide for change control primarily through the assigned responsibilities of the quality control unit. Certain major manufacturing changes (e.g., changes that alter specifications, a critical product attribute or bioavailability) require regulatory filings and prior regulatory approval (21 CFR 314.70, 514.8, and 601.12).

Effective change control activities (e.g., quality planning and control of revisions to specifications, process parameters, procedures) are key components of any quality system. In this study, change is discussed in terms of creating a regulatory environment that encourages change towards continual improvement. This means a manufacturer is empowered to make changes subject to the regulations based on the variability of materials used in manufacturing and process improvements resulting from knowledge gained during a

product's lifecycle.

E. Deviation

The deviation is another well-known cGMP concept that focuses on managing departure from an approved operating procedure, methods, specifications, protocols, instructions, processes, batch record or other official documentation. Effective deviation management is key components of quality management system.

F. Training

Training is the key by which the organization creates a TQM (Total Quality Management) environment.

Training is very important for employees to be highly productive. Supervisors are solely responsible for implementing QMS within their departments, and teaching their employees the philosophies of QMS. Training that employees require is interpersonal skills, the ability to function within teams, problem-solving, decision making, job management performance analysis and improvement, business economicsand technical skills, GMP and Quality training. During the creation and formation of QMS, employees are trained so that they can become effective employees for the company.

CHANGE CONTROL:

Change is inevitable, and because continuous improvement is impossible without change, progress is built on change. The key to making successful change in the pharmaceutical world is to manage it, both from internal and external perspectives.

Change control is the most critical element in a pharmaceutical company's quality management system - inadequate change control procedures end up creating a

huge risk of non-compliance. The FDA's guidance for Industry clearly reinforces the importance of implementing effective change control procedures as a criticalcomponent in an overall quality system.

The FDA has published regulations [21 CFR 314.70] describing how changes to drug manufacturing processes must be reported to the agency. Many pharmaceutical companies require formal change notification agreements with suppliers as a condition of doing business. This requirement includes the notification of intended changes before their implementation by the supplier, and the acceptance of any changes by the customer before they receive product that incorporates the change. Any changes made permanently to the existing document/ process/method/system shall be documented and controlled and can be referred as change control. Change control within Quality management systems (QMS) is a formal process used to ensure that changes to a product or system are introduced in acontrolled and coordinated manner.

Need For Changes:

To improve quality, To increase the yield, To reduce costs, For cutting waste

For streamlining processes etc.

Regulatory Perspective of Change Control:

Considering the regulatory perspective of change control procedures, it is important to note that there are many guidelines that describe the control of changes in manufacturing. Few references include:

21 CFR Parts 211: Sec. 211.100 – Suggests that

There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality and purity they purport or are represented to possess. These written procedures including any changesshall be drafted, reviewed and approved by the appropriate organizational units and approved by the quality control unit.

21 CFR Parts 211.194 Laboratory records – Suggests that

Complete records shall be maintained of any modification of an established method employed in testing. Such records shall include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

ICH Q7A – Suggests that

A formal change control system should be established to evaluate all changes that could affect the production and control of the intermediate or API. Written proceduresshould provide for the identification, documentation, appropriate review and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment, processing steps, labeling and packaging materials and computer software.

Objectives of Change Control Management:

- To prevent unauthorized modifications to a validated system.
- To identify changes and to evaluate proposed changes to assess their potential effects on the manufacturing process.
- To determine the impact of changes on the critical chemical and physical attributes of the drug product (such as impurity profile, stability and particle size)
- To ensure that all documents affected by changes are promptly revised, and
- To determine if, and to what extent, revalidation is needed.

➢ To have a track on all the changes made to validated existing system.

Classification of Change Control:

Changes are mainly classified as Major, Moderate and Minor.

Major Change: It is applicable

- When change is likely to have a detectable impact on the critical attributes ofthe product significantly.
- When change could shift the process in a discernible manner (such as quality, yield, stability, impurity profile, crystal form, particle size, bulk density).
- When change warrants definite additional/ major testing and suitablerevalidation studies. When change is reviewed by QA at the facility level and approved bycorporate groups.
- When change requires prior FDA approval.Examples of Major Changes

1. Change in type of solvent used for final crystallization (affects impurityprofile, physical attributes and other critical quality attributes of API)
2. Change in equipment type (dryer configuration, blender type, crystallizer type,tablet compression machine, coating equipment)
3. Change in critical process parameter
4. Revision of critical quality attributes (specification) such as assay limit,dissolution profile, related substances test
5. Revision of standard test procedure for assay (potentiometric to HPLC), forrelated substances (TLC to HPLC), for residual solvents (GC to Head space)
6. Change in the facility (site of manufacturing)
7. Change in batch size by more than 10%
8. Change in route of synthesis
9. Change of API source
10. Change in validated sterilization process
11. Change in the sequence of operations

Moderate Change: It is applicable

- When change is usually for improvements to process, materials, product orprocedure
- It does not require prior approval by the Regulatory/FDA before implementation. It can go in Annual reports to FDA.
- Can be evaluated by QA at the facility and then approved by corporate groups.Examples of Moderate Changes

1. Improvements in yield
2. Improvements in Critical Quality Attributes
3. Improvement in Process capability/efficiency
4. Cost-effectiveness

Minor Change:

- It is unlikely to have a detectable impact on the critical attributes of theproduct
- It does not shift the process in any discernible manner
- It can be implemented with minimal testing and revalidation
- Can be reviewed and approved by QA at the facility level
- It is reported in Annual Reports to FDA and does not require FDA approvalExamples of Minor Changes

1. Like-for-like equipment replacements
2. Noncritical process parameters
3. Revision of specifications (such as non-critical parameters) as per processcapability
4. Revised quantity of components & reagents marginally in case of APIintermediates
5. Revised operating procedure to add safety
6. Revised cleaning procedure to enhance GMP
7. Editorial changes

It is important to understand not only the types of changes that will be a part of change control process, but also the priority of those changes. Changes should never be expedited, but should be either planned or unplanned. Almost all changes can be planned only those that are emergencies occurring after hours or safety-related should be considered as unplanned. In all cases they should be submitted through change control and any required validation/re-validation must be completed before the changeis fully implemented.

Steps in Change Control:

Certain experts describe change control as a set of six steps: Record / Classify, Assess,

Plan, Build /Test, Implement and Close / Gain Acceptance

Record/Classify:

The client initiates change by making a formal request for something to be changed. The change control team then

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records and categorizes that request. This categorization would include estimates of importance, impact, and complexity.

Assess:

The impact assessor or assessors then make their risk analysis typically by answeringa set of questions concerning risk, both to the business and to the process, and follow this by making a judgment on who should carry out the change.

Plan:

Management will assign the change to a specific delivery team, usually one with the specific role of carrying out this particular type of change. The team's first job is to plan the change in detail as well as construct a regression plan in case the change needs to be backed out.

Build/Test:

If all stakeholders agree with the plan, the delivery team will build the solution, whichwill then be tested. They will then seek approval and request a time and date to carry out the implementation phase.

Implement: All stakeholders must agree to a time, date and cost of implementation. Following implementation, it is usual to carry out a post-implementation reviewwhich would take place at another stakeholder meeting.

Close/gain acceptance: When the client agrees that the change was implemented correctly, the change can be closed**.**

Contents of Change Control:

Details of Change:

- Change of facility {building, equipment, utility, instrument, system} should beclear in terms of modification, replacement, reinstallation or new installation.

- Location of the equipment/utility, instrument should bear the floor level and name of the room, the specific purpose of the equipment/utility/instrument should be described.

- If an appropriate change should be described through drawing of existing and proposed, Process change, except the change in standard batch size, clear distinction between existing process and proposed process should be given.

Reason for change:

Reason should be specific. The cost and /or quality benefits should be fulfilled.

Give the list of documents:

Which will get affected due to the proposed change?

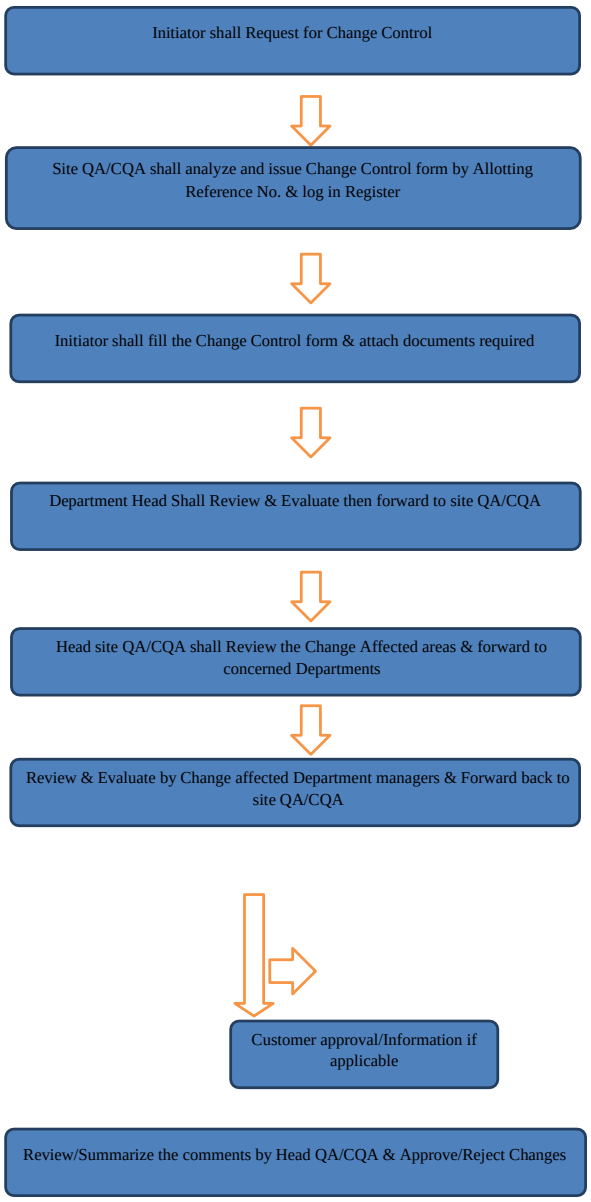
Write the name and sign

In the 'Prepared By' Department Head will check and then write his name along withsignature in the change request form.

Evaluation by QA:

Receive the change control format check the format for its completeness.

Flow Chart for Change Control



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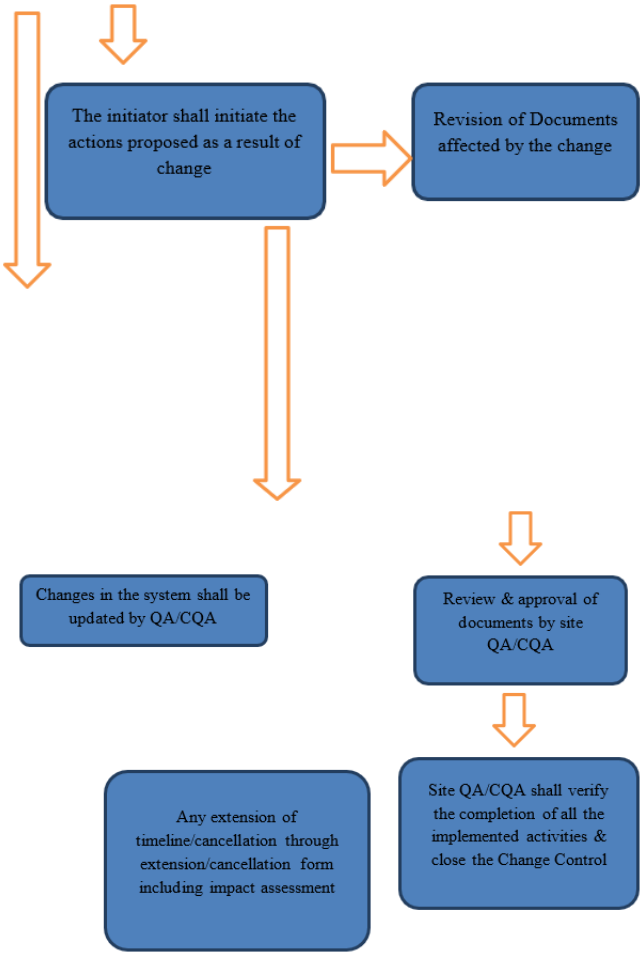

The initiator shall initiate the actions proposed as a result of change

Revision of Documentsaffected by the change

It is recommended that the following change request should be handled through aformal change control system:

New facility validation, Equipment qualification changes, Changes in existing processes, Changes in laboratory test methods and procedures, Changes associated with the product rework, Changes in labeling, Introduction of new procedures, Introduction of new processes, Changes to approved applications, Changes related to new drug approvals, Document changes, Changes associated with product specifications, Changes related to the CAPA system (from corrective action), New process validation, Changes related with the quality management system and Introduction of new products

Key Benefits of Change Control System:

Structured and consistent approach towards managing change, Documenting the details of the change, Routing of change requests to appropriate individuals/team for approvals, Documentation of change approvals and implementation, Maintenance of change history and easy retrieval of information, Tracking changes effectively and providing an audit trail, Demonstrate compliance to FDA regulations

DEVIATION:

Deviation is an aberration from the given procedure which is done intentionally or unintentionally. A deviation can be divided into critical & noncritical. Effects of critical deviations should be assessed through investigation & Corrective &Preventive Actions.

Classification of Deviations:

Deviations are two types

1. Planned deviation and
2. Unplanned deviation

Planned Deviations:

Planned deviations are classified as Major and Minor planned deviations.

Major planned deviations are those which have an impact on quality with respect to process parameters, testing parameters and GMP implications. These deviations should be evaluated before approving the same.

Examples for major planned deviations (but not limited to)

- Temporary change in processing area/facility/utility/equipment
- Batch size modification (Increase/decrease) for few batches
- Temporary deviation in the processing method.
- All process modification of existing process as a trail
- Analytical method related planned deviations
- Change in packing code/packing of product in different packing mode
- Shifting of equipment from one location to another location temporarily
- Postponed validation schedule due to various reason with proper justification
- Postponed calibration schedule with properly justified reasons

Minor planned deviations are those which have no impact on quality with respect to process parameters, testing parameters and GMP implications.

Examples for major planned deviations (but not limited to)

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- Material related planned deviations (e.g. Material stored temporarily in otherstorage area)

All temporary changes in the process are considered as planned deviations wherein if the changes are acceptable, the same changes should be implemented permanently through change control procedure.

Unplanned Deviations:

Unplanned deviations are classified as major and minor unplanned deviations

Major unplanned deviations are process and a testing-related deviation, which has impact on product quality and to be investigated in detail, identify the root cause and closed after necessary corrective and preventive actions. This major unplanned deviation also includes any incidents/events which has impact on product quality.

Examples for major unplanned deviations (but not limited to).

- All process-related deviations
- Process yield is not within the acceptance range
- Batch discontinued for any reasons
- Analysis of stability samples, outside the window/schedule period
- cGMP deviations like manufacturing instructions (BMRs/BPRs) not followed
- SOP's or method of testing not followed. Quality system and cGMPprocedures are not followed.

Minor unplanned deviations: Minor unplanned deviations are quality non- impacting incidents/occurrences/errors/lapses during execution of any activity which may have no direct impact on the quality, purity, strength and efficacy of a drug product. These have to be routed through necessary corrective and preventive actions. The minor unplanned deviation also includes any incidents/events which does nothave impact on product quality.

Examples for Minor unplanned deviations (but not limited to)

- Missed/errors in entries during documentation which do not affect the endresults
- Any minor documentation lapses
- Chromatographic sequence abandoned

Deviation Procedure:

The procedure for planned and unplanned deviation is given below as follows

1. Initiation of deviation

All the planned and unplanned deviations should be immediately reported to QA by the concerned user department. Only one deviation should be raised for any concerned issue, including those that may impact multiple departments. When any planned

deviation is initiated, a planned deviation report with details of deviation should befilled in by the user department.

When any unplanned deviation is initiated, an unplanned deviation report with detailsof deviation should be filled in by the user department. Standard against whichdeviation has occurred should be indicated. The details of deviation should alsoinclude when and who identified the deviation along with date, time and department. Immediate actions taken after the deviations should be explained like: Whether operations were stopped, Whether QA personnel was informed, Any additional steps taken to immediately mitigate the discrepancy, Whether the affected material was identified and segregated. The reason/justification for deviation should be mentioned by the user department. Userdepartment head should review and provide comments on deviation.

2. Deviation numbering

Planned and unplanned deviation reports should be forwarded to QA and a deviationnumber should be issued by QA.

3. Review/Comments by QA and other relevant departments

QA in-coordination with user department should make comments to define the scope of deviation for impact analysis. QA should classify the deviation as Minor or Major depending on the impact on the product. QA should indicate the departments which need to comment on deviation. RND/ Other departments should be consulted for impact on product quality for review and comments. The planned and unplanned deviation should be sent for RA review by user department and to QA under the following conditions like manufacturing process-related deviations, testing-related deviations, usage of material from new vendor prior to qualification of material.

Product quality risk assessment should be carried out by QA including review of RND data and decision should be taken. User department should take the comment by relevant departments who in turn should comment by evaluating impact of deviation on the product. User department should submit unplanned deviation report to QA. After review and comments, the user department should conduct investigation. For planned deviations after verification of justification/comments, conclusion should be drawn.

In case of unplanned deviation investigation should be done and the conclusion for the same should be documented. After review and comments the unplanned deviation report form

should be forwarded to user department for review/investigation and comments. The user department should conduct a detailed investigation of the general sequence of events that led to the deviation taking into account all possible following parameters (environment, personnel, process, measurement, and system or materials etc. Checking of concerned SOP's. Checking of batch records (BMR/BPR). Checking of QC testing reports. Impact of deviation on previously passed batches or other batches. A list of the impacted batches should be mentioned in the scope. Root cause analysis. RND should be consulted for impact on product quality review and comments where ever applicable. After investigation, user department should submit investigation report along with review/comment by relevant departments to QA.

4. Corrective and Preventive action and Deviation approval:

Corrective and preventive actions should be identified wherever applicable for planned and unplanned deviations. Corrective and preventive actions should be implemented within the set timelines.

Based on the evaluation QA should approve each planned and unplanned deviation and confirm that action plans have been identified. QA should classify the action plan as pre-batch release and post-batch release depending upon the impact on the product. Deviation should be approved by QA and signed off by all other departments.

5. Disposition of deviation (closeout):

After the deviation approval is completed and action plan is drawn and CAPA is initiated deviation monthly tracking should be initiated for the respective deviation and all the action mentioned as per the deviation. Review of the implementation of action plan should be carried out every 30±5 days by QA and the status of the same should be documented.

The batches impacted by the deviation should be released only after completion of pre-batch release action items and the deviation should be closed and signed off by QA. Post-batch release action items should be completed without affecting batch release and the follow up for completion should be done through CAPA and the effectivenessof the CAPA implementation should also be assessed.

If a deviation has been done, company must submit documented evidence to the FDA that their manufacturing process and controls will maintain the drugs identity, strength, quality, and purity at all times.

CORRECTIVE ACTION & PREVENTIVE ACTION:

The pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring.

A structured approach to the investigation process should be used with the objectiveof determining root cause. The level of effort and formality of the investigation should be commensurate with the level of risk. CAPA methodology should result in product and process improvements and enhanced product and process understanding. CAPAis a concept within good manufacturing practice (GMP). It focuses on the systematic investigation of the root causes of non-conformities in an attempt to prevent their recurrence (for corrective action) or to prevent their occurrence (for preventive action).

Implementation of Corrective & preventive actions is the path towards improvement & effectiveness of Quality Management system.

Corrective Action:

A corrective action is a term that encompasses the process of reacting to product problems, customer complaints or other nonconformities and fixing them. The processincludes:

- Reviewing and defining the problem or nonconformity, Finding the cause of the problem, Developing an action plan to correct the problem and prevent a recurrence

- Implementing the plan, Evaluating the effectiveness of the correction

Corrective actions are nothing but action/s based on the problem identification. The problem or a non-conformance can be identified internally through staff suggestions, management reviews, document reviews or internal audits. Customercomplaints / suggestions, customer rejections, non-conformities raised in customer / third party audits & recommendations by the auditors are the external sources which lead to find the root cause of the problem.

Corrective action is a reaction to any of the cause/non-conformance mentioned above & can be divided in two phases of action:

- **Identification of root cause:** For this purpose TQM tools such as fish-bone or cause & effects analysis can be practiced. Your CAPA would be appropriate& effective if & only if you have identified the root cause of problem.

- **Taking necessary actions:** In order to address the root cause takes necessary immediate action/s. The effectiveness of the corrective action taken has to be verified periodically through a systematic approach of the PDCA (Plan - Do - Check - Act) cycle.

Corrective action is a reactive tool for system improvement to ensure that significant problems do not recur. Both quality systems and the CGMP regulations emphasize corrective actions. Quality systems approaches call for procedures to

be developedand documented to ensure that the need for action is evaluated relevant to the possibleconsequences, the root cause of the problem is investigated, possible actions are determined, a selected action is taken within a defined timeframe, and the effectiveness of the action taken is evaluated. It is essential to document corrective actions taken (CGMP also requires this; see § 211.192).

It is essential to determine what actions will reduce the likelihood of a problem recurring. Examples of sources that can be used to gather such information include thefollowing: Non-conformance reports and rejections, Returns, Complaints, Internal and external audits: Data and risk assessment related to operations

and quality system processes. Management review decisions

Preventive Action:

A preventive action is a process for detecting potential problems non-conformance and eliminating them. The process includes:

Identify the potential problem or non-conformance, Find the cause of the potential problem, Develope a plan to prevent the occurrence, Implement the plan, Review the actions taken and the effectiveness in preventing the problem Preventive action is prediction of problem & trying to avoid the occurrence (fail safe)through self-initiated action/s & analysis related with your processes/products. Thiscan be initiated with the help of active participation of staff members/workers through improvement teams, improvement meetings, management review, customer feedback & deciding own goals quantized in terms of business growth, reducing rejections, utilizing the equipment's effectively etc.

Being proactive is an essential tool in quality systems management. Succession planning, training, capturing institutional knowledge, and planning for personnel,policy, and process changes are preventive actions that will help ensure that potential problems and root causes are identified, possible consequences assessed, and appropriate actions considered.

The selected preventive action should be evaluated and recorded, and the system should be monitored for the effectiveness of the action. Problems can be anticipated and their occurrence prevented by reviewing data and analyzing risks associated with operational and quality system processes, and by keeping abreast of changes in scientific developments and regulatory requirements.

CAPA Procedures:

Implementing an effective corrective or preventive action capable of satisfying quality assurance and regulatory documentation requirements is accomplished in seven basic steps:

1. The **Identification** of the problem, nonconformity, or incident or the potentialproblem, nonconformity, or incident.

2. An **Evaluation** of the magnitude of the problem and potential impact on thecompany.

3. The development of an **Investigation** procedure with assignments ofresponsibility.

4. Performinga thorough **Analysis** of the problem with appropriatedocumentation

5. Creating an **Action Plan** listing all the tasks that must be completed to correctand/or prevent the problem.

6. The **Implementation** the plan.

7. A thorough **Follow up** with verification of the completion of all tasks, and an assessment of the appropriateness and effectiveness of the actions taken.

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.

Report Source:

The specific origin of the information that initiated this action is recorded. Documenting the source of the information can be very useful when conducting an investigation into the problem and implementing the action plan that is created. It will also provide data for evaluating the effectiveness of the quality system and facilitate communicating the completion of the action to the appropriate individuals or departments. This information may come from many possible sources. For example, situations that require corrective actions may come from external sources such as customer concerns or service requests. Internal quality audits, staff observations, quality assurance inspections, trending data, and management reviews are all examples of possible internal sources of information.

Examples of sources that lead to preventive actions may include:

✓ Service Request, Internal Quality Audit, Customer Complaint / Concern, Quality Assurance Inspection Staff Observation, Trending Data, Risk Assessment, Process Performance Monitoring, Management Review, Failure Mode Analysis

Explanation of the Problem:

A complete description of the problem is written. The description should be concise but must contain sufficient information to assure that the problem can be easily understood from reading the explanation.

Evidence:

List the specific information available that demonstrates that the problem does exist. For example, the evidence for a

product defect may be a high percentage of service requests or product returns. The evidence for a potential equipment problem may be steadily increasing downtime.

Corrective/Preventive Action Request form:

A sample form is provided "Corrective/Preventive Action Request that can be used to initiate a CAPA action and collect the initial information.

2. Evaluation: The situation must 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.

Potential Impact:

Part of the evaluation is a specific explanation of specifically why the problem is a concern. This may include the possible impact that the problem may have in terms of costs, function, product quality, safety, reliability, and customer satisfaction.

Assessment of Risk:

Using the result of the impact evaluation, the seriousness of the problem is assessed. The level of risk that is associated with the problem may affect the actions that are taken. For example, a problem that presents a serious risk to the function or safety of aproduct may be assigned a high priority and require immediate remedial action. Onthe other hand, an observation that a particular machine is experiencing an increasing level of downtime each month may have a lower priority.

Remedial Action:

Based on the outcome of the impact and risk evaluations above, it may be determined that immediate remedial action is required to remedy the situation until a thorough investigation and a permanent solution is implemented. If remedial actions are necessary, the actions and the resources required are listed. The steps that must be taken immediately to avoid any further adverse effects are explained.

The actions that are taken are documented. This documentation will become part of the 'Action Implementation' and 'Follow Up' sections of the CAPA action.

In some instances it may be determined that the remedial action is all that is needed.In that case, a rationale is written for that decision, appropriate follow-up is done, and the CAPA is closed out.

Remedial Action form:

A sample "Remedial Action" form is included. This form should be used to explain the steps that must be taken to avoid any further adverse effects.

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 iscomplete 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.

Objective:

The first step in the investigation is to state an objective for the action. In the"Identification" section the problem was defined and the current situation was stated. Theobjective is a statement of the desired outcome of the corrective or preventive action.State what the situation will be when the action is complete. This may be a statementin the form of: "The problem will be corrected, all effects of the problem identified andrectified, and controls will be in place to prevent the situation from happening again.'

Investigation Procedure:

A set of specific instructions are created that outline what must be done to determine the contributing and root cause of the problem. The investigation procedure will vary depending on the circumstances, but must incorporate a comprehensive review and analysis of all of the circumstances related to the problem. Consider equipment, materials, personnel, procedures, design, training, software, and external factors.

Responsibilities / Resources:

An important part of the investigation procedure is to assign responsibility for conducting each aspect of the investigation. Any additional resources that may be

required are also identified and documented. For example, specific testing equipment or external analysis may be required.

Investigation Procedure form:

A sample "Investigation Procedure" form is included. This is a written plan of action for the investigation into the problem. It should include the overall objective and the instructions for conducting the investigation. The person or persons responsible for the investigation and an expected completion date should also be entered.

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 possiblecauses, 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.

Possible Causes / Data Collection:

A list of all possible causes is created. This will form the basis for collecting relevant information, test data, etc. For example, consider the situation where a large batch of parts from a CNC Mill was discovered to be out of tolerance. There are many possiblecauses for this condition including operator error, incorrect software, a dull or brokentool, an incorrect or obsolete print, a material problem, a design problem, etc. By considering all possible causes, appropriate information and data can be collected that will be ultimately be used to determine the root cause of the problem.

Results and Data:

The results of the data collection are documented and organized. This may include a combination of testing results and/or a review of records, processes, service information, design controls, operations, and any other data that may lead to a determination of the fundamental cause of the problem. The resulting documentation should be complete and address all of the possible causes that were previously determined. This information is used to determine the root cause of the problem.

Root Cause Analysis:

Determining the root cause often requires answering a series of 'why?' questions and digging deep into the situation until the fundamental reason for the problem is found. For example, in the out-of-tolerance parts situation described earlier, the investigation revealed that the operator had not been properly trained and had forgotten an essentialstep in the machining process. The improperly trained operator is the immediate causeof the problem, but may not be the root cause. Why was the operator not trained properly? Are the existing training programs adequate and are they being implemented properly? Further investigation revealed that the operator was on vacation when the training was given and, therefore, did not receive the training whenother operators did. The root cause of the problem was a lack of follow-up in the training program. No mechanism existed to cross-check training records to assure that a missed training session was rescheduled. The root cause of the problem is documented. This will be essential for determining the appropriate corrective and/or preventive actions that must be taken.

Problem Analysis form:

A sample "Problem Analysis" form is included. This form is optional but is intended to be used for recording information related to the analysis of the problem. The form can be used as a collection point for the information discovered during the analysis and any supporting data or documentation can be attached.

5. Action Plan: By using the results from the Analysis, the optimum method for correcting the situation (or preventing a future occurrence) is determined and an action plan is 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 theproblem or a recurrence of the problem. The action plan should also identify the person or persons responsible for completing each task.

Actions to be completed:

List all of the activities and tasks that must be accomplished to either correct the existing problem or eliminate a potential problem. For a CAPA program to be effective, it is very important to take a very global approach. Make sure to identify all actions that will be required to address everything related to the situation. For example, in the training situation described earlier, the root cause was a flaw in the training program. One of the actions that must be taken is to review all previous

training records to determine if this problem resulted in any other employee not receiving the necessary training.

Document or Specification changes:

List any documents that will be modified and describe in general terms what the modifications will be.

Process, Procedure, or System Change:

If any changes to processes, procedures, or systems must be made they are described. Enough detail should be included so that it is clearly understood what must be done. The expected outcome of these changes should also be explained.

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