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Review Article

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Change Control Management: An Overview

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Abstract: Change control is a basic element of the quality management system of a pharmaceutical company, that focuses on controlling change to provide a quality product by preventing non - compliance. Changes may occur at any time during the product life cycle, leading to changes in the manufacturing process, the number of materials, and the manufacturing location. All of these changes are post-approved changes. These changes can be controlled and not eliminated, through proper assessment and action plans. The change control committee consisting of the head of quality assurance, manufacturing, sales and other members of relevant disciplines, inspect the proposed changes that may alter the validated and qualified state of facilities, equipment or process. The proposed change will likely have an impact on the quality of production or Good Manufacturing Practice as there are done to be in line with the International Standard Organization requirements. These approved changes should not impact the quality, safety and potency of medicinal product. If ignored, it makes the patient life - critical which may even lead to death. This present review provides an overview of the industry's Change Control change management protocol in Quality Management System in a company. The major objective is to identify, evaluate, measure, provide action and final authorization to ensure that the changes should not affect the product strength, integrity, purity, quality, or safety. There are many aspects of view on the change control management that take place in the pharmaceutical industry, where we can gain knowledge on concepts of change control. This article also delivers a flow of change management process starting from the request on change by an initiator to the closure of change with appropriate remedial action and follow up assigned by Quality Unit and other responsible authorities.

Keywords: Quality management system, change control, post approval change, Quality assurance.

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1. INTRODUCTION

Change control management is the crucial aspect of a quality management system, that focuses on controlling change to provide a quality product by preventing non-compliance. It is a formal system to ensure that changes do not affect the validated state of facilities, equipment, processes or, systems and through which qualified representatives document that the system remains in an approved state. Any key changes in the manufacturing process, including equipment or material changes, require verification, that may affect product quality, safety and reproducibility of a quality product.[1-3] There should be a written procedure to identify, analyze and control changes. It should cover all plans, protocols and requirements involved in change control management. If there is any deviation from the approved state, it should be formulated, reviewed and approved by the corresponding organizational unit, and reviewed and approved by the quality control department. Any deviations from written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms must be recorded and justified.[4,5] There should be a written procedure describing the measures that should be taken when raw materials, product components, processing equipment, and processes change. The environment (or location), manufacturing or testing process, or any other changes that may affect product quality or process reproducibility must be taken into account. Change control procedures should ensure that there is sufficient evidence that the modified process meets the required quality of the product with approved specifications.[6-8]

2. SOURCES OF CHANGES

- **Formulation** - composition and percentage of active and inactive ingredient.
- **API** - change in grade, new manufacturer, process and physical characteristics.
- **Equipment** - change in scale (pilot batch, commercial batch, bio batch) change in principle and process optimization.
- **Cleaning procedure** - change in manual to automated, change in configuration, schedule of equipment[9].

4. CHANGE CONTROL CHANGE MANAGEMENT

Change control change management is the protocol that mainly concentrates on the following steps (Figure 1) to implement the complete change control process in pharmaceutical industry:

- **Identification**: This involves identifying a deviation, OOS &OOT in any procedure, testing method (or) test limits.
- **Manufacturing process**- change in critical parameter, operating condition, scale up, technology transfer.
- **Analytical method**: change in qualification, validation state, modification of compendial method.
- **Stability study:** change in storage condition, container closure system, expiry period and shelf life.
- **Facility and utility:** change in cross contamination maintenance, validated classified area, HVAC system, compressed air and dust collection system.
- **Packaging components**: change in container, closure, change in labeling, inserts, change in packaging material. [10]

3. RESPONSIBILITY

Production managers, QC managers, sales managers and communications officers in their respective fields are responsible for the appropriate planning, implementation and approval of changes.[11] They should ensure that the ranking status of rooms and places affected by the change or re-certification is maintained when the change occurs; the verification status of the process/procedure affected by the change or re-verification is retained.[12] The changes in drug production, testing and labeling are based on valid approval documents required to update the changes. The Change Control Committee (CCC) is responsible for the organization and processing of the change control procedures and the preparation of documents. The members of the CCC are the regulatory affairs supervisor and the quality assurance officer. The committee is responsible for evaluating the risk of modification, approval or rejection of the request. The application implements the necessary measures through installation and programming. The QA officer the chairman of the CCC, is responsible for convening CCC meetings and minuting the meeting, filling in change requests, submitting change requests control, record distribution procedures, and maintaining the change database. Control procedures, control compliance deadlines. The QA representative is responsible for reviewing periodically and to ensure whether documents are revised and updated whenever necessary; and release a new version at least every two years.[13]

- **Investigation:** This involves different phases of investigation to find the probable root cause for deviation, OOS & OOT by using appropriate investigation tool[14].
- **CAPA:** once the probable root cause is identified, the investigation is closed, by assigning a CAPA. This is followed by login, implementation & closure of CAPA.
- **Change control:** as part, of implementing CAPA change control is logged in. Followed by review, approval, classification, implementation of action plan & closure of change control. [15]

Fig 1. Change Control Management Process

5. IDENTIFICATION

Facility

It includes changes in design, the layout of building, addition or deletion of materials, shifting or replacement of equipment, change in the utility system such as generation unit, distribution system, storage facility. Air Handling Unit /HVAC and any other utility system which may directly or indirectly have an impact on the manufacturing process/quality of the product. [16]

Manufacturing Process

It includes the change in the level of Batch Size, change in Master Formula, i.e,. raw materials quantity, change in batch manufacturing process and packing material and method, critical process parameters and in-process control.[17]

Specifications

Change in specifications of Raw Material/Packaging Material {including the active ingredient, excipients, solvent, reagent, etc. In-process materials, intermediate products, finished products and any other material that directly or indirectly have an impact on the product quality.[18]

Test Procedure

Change in the validated procedure for an actual manufacturing process, analytical or microbiological test procedure and related standard procedure, stability study program (frequency and storage condition).[19]

Documentation

Batch Manufacturing Record, Master Formula Record, Validation Protocol, Validation Master Plan, Site Master File, Standard Operating Procedure and other formats.[20]

6. CHANGE REQUEST

Observation of the initiator of the change that needs to be controlled is usually recorded in the change request form, in which the applicant must propose the qualification/evaluation type of the change, stating the date and deadline of the change and the basic steps to insert it. Changes and requests for action plan changes can be approved or rejected by the change control committee. The change request document for a change process must show that the change has passed risk assessment and then certain actions have been implemented by default.[21]

6.1. Initiation of change control

The initiating unit negotiates with the head of the department and initiates the change based on the change control record. The initiating department will provide detailed information on the current process/use, proposed changes, reasons and results of the preliminary impact assessment and acceptance criteria. The initiating department classifies the changes based on their impact on product quality or safety, health and environment as major, minor and no impact (Table 1)[22]

Table 1: Grading of changes

	Changes to be controlled		No need to control
	Major	Minor	
SIGNIFICANCE	Impact on product quality or process reliability.	Affect an entity that requires control	Not relevant for GMP compliance or approval
MEASURES	Post approval verification; Revalidation; Renovate license.	Modification; Qualification; Documentation.	No relevance to GMP or authorization.
EXAMPLE	Change of manufacturing: synthetic route. Change in processes step from one site to another. Change in composition of product. Change in critical process parameter.	Change in parts of equipment of same design. Change in composition of cleaning agents. Change in the order of addition of ingredients. Change in sterilization site for packaging components when process is same.	Change in work schedule. change in administrative work and renovation in administration area. Change in utility requirements. Installation of air conditioner in non manufacturing area. Introduction and change in security level .

The QA personnel assigns the change control number on the signed form with the respective date and then QA issues the change control record to the corresponding department; QA will complete change control logbook with an excepted completion date as a reference to change records[23].

6.2. Change control number

QA assigns a unique alphanumeric character to each change control record. Change control number can be represented as CM/YY/XXX; CM stands for change management; YY represents the last two digits of the current year; XXX stands for serial number. Product details and their designated change category (such as site, batch size, equipment, composition change) are also included in the change control record.[24]

6.3. Date of issuance

QA must specify the release date in a logbook on which control number is assigned and justified. The timeline for closure of the change control form provided by QA will be reviewed by the relevant department, if the date is applicable, then they will accept the updated date and complete the change control within 90 days from the date of approval.[25]

6.4. Title of change

A suitable, appropriate and relevant title name for the proposed change is provided with the acceptance of the initiator. Then note the same in the logbook too. The representative should ensure that there are no records for the repetition of titles for similar changes. The title must be self - explanatory without any complex words, which are clear, concise and understandable. [26]

6.5. Change details

The change control records should consist of the following details such as product name, material name, document name, standard operating procedure name detailed to the deviations and changes related. The batch number/Analytical Record number/document number assigned to the representatives Process/method/procedure of the change involved in the existing equipment or new equipment, specifications and requirements to be met for the changes implemented should also be specified in the change control report and records.[27]

6.6. Reasons / justification for the change

A clear and accurate reasons must be provided for initiating the change. The changes as well as reasons of change based on applicable data, such as history, trends, stability data or analysis/formula department documents, scientific reasons, audit events/observations and experience, or other should be in place to ensure regulatory compliance and to provide evidence. There should be no negative impact on product quality on the proposed changes [28].

7. INVESTIGATION

After filling in the details of the change, the proper flow should be followed for the completion and closure of change management (Figure 2). The initiator signs and indicates the date of the change, and sends the complete change control record to the person in charge of his department for review and comment. Detailed information of changes shall be reviewed and provide comments as needed. Head initiator may approve and request additional information or reject with justification in change management records.[29] After the initiator department has reviewed and approved; the change control record shall be forwarded to the quality assurance officer. The quality assurance officer shall evaluate the change management record and the relief plan provided by the initiator based on the risk/impact assessment to decide whether to proceed with the change control review process and provide the initiator with an appropriate feedback. Alternatively, they can request more information or provide a justification to reject the proposed changes. The person in charge/representative of the relevant department will also make suggestions on the relevant points and conduct an impact analysis on the subsequent signature/date to confirm the root cause.[30]

7.1. Risk assessment

When relevant departments make recommendations and it is approved by the quality assurance manager, the risk assessment should be carried out by following the SOP for risk assessment.[31]

7.2. CAPA

In the risk assessment report and after consultation with relevant departments, the quality assurance department issues the CAPA of long-term corrective and preventive measures to the person in charge of the relevant department to follow up any suggestions.[32]

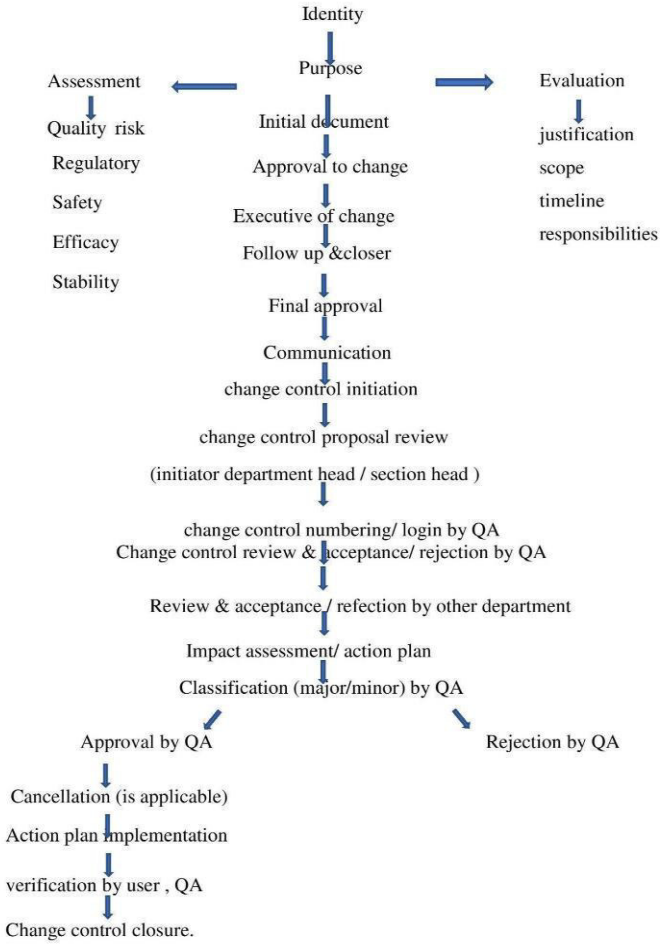

Fig 2: Flow Chart of Change Control Management

8. ACTION PLAN

The initiator/evaluator/Quality Assurance manager creates an action record based on the analysis of the change management record investigation report. Each action item record is assigned a unique ID and is referenced in the change control record. The action item number shall be assigned with reference to change control record and irrespective of types /category of change, the number will be provided in sequence continually.[33] After opening the action point data record, the initiator can cancel the data record and must attach a file to the data record that supports cancellation. The initiator must complete a document-based action item and must be reviewed by another person in the initiator's department before the QA review, and then the QA must complete the review action based on the change control record. If the verification fails, QA will notify the initiator of the verification failure with a supporting document. If the inspection result is satisfactory, the designated QA can take the following measures- The action item entry shall be closed and send the action element data record along with the justification to the initiator [34-36]

9. IMPACT EVALUATION OF CHANGE CONTROL RECORD

If the proposed changes require further processing, QA officials shall classify the changes into different levels based on the risk of changes affecting quality and safety of products reaching end users. Then, the QA officer determines the appropriate department to send the change management record for evaluation and submit to the head of each designated department for approval before submitting to QA Head/Designee. Based on the type and level of changes, a list of departments responsible for evaluation shall be selected and forwarded. After the impact analysis and suggestions from the concerned department, all change control records must be approved by the production department manager/quality department head. The change review level is determined by the quality manager or representative based on the following norms.[37]

LEVEL 1: Changes that have no impact on product quality, safety, integrity, strength and purity.

✔ change in clean and dirty hold time

✔ change in specification limit for an in-process and finished product.

✔ change in frequency of in-process control checks.

LEVEL 2: Changes that have an impact on validation, qualification of control, which does not affect product's quality and safety.

✔ Change in duration (increase) of hold time.

✔ Change in existing system/addition of new count.

✔ Change in In-process checklist.

LEVEL 3: According to relevant guidelines, changes that have a significant impact on product's quality and safety and impact on product compliance to regulatory bodies standards.

✔ Change in calibrated control state of critical process instrument and system.

✔ Change in quality control limit for a finished

product.

✔ Change in grade, quality, strength, purity of raw materials.

Once all relevant data are recorded in the change management data set, the QA manager or representative update the same in the Change Control Record and forward the change control data set to the initiator for subsequent impact assessment [38].

10. COMPLETION AND EVALUATION OF THE ACTION PLAN

Evaluation of the impact of the action plan based on departmental standards: Impact evaluation on regulatory requirements: indicate whether action plan of change control has impact on regulatory approval.[39] if applicable, provide the relevant details, required type of submission, submission authorization, and expected submission date. Impact evaluation on stability studies: determine whether further stability study is needed, and if necessary, provide detailed information about storage conditions, batch size, test frequency, stability commitment, and periodic report. Impact evaluation on Validation studies: determine whether or not a validation study needed, based on type of change and provides information about scope, objective, authorization and period of revalidation.[40] Assess the regulatory impact of the change control agreement, and explain to the organization the need to change the plan. Organize the change proposal according to the evaluation category initiated by QA or notify the initiator of the change management record to initiate the change proposal.[41] Quality assurance personnel record comments wherever required and attach documents if required. Regulatory affair department will also create a register of measures as per their requirement. Evaluation of impact of the change in process validation studies will be held by Head/designated person of interdisciplinary functional team and provide information and comments/suggestion provided. Evaluation of impact of change in market approval, requires trend analysis on quality, efficacy, purity and stability of product; provide complete study document on the basis of existing requirement for marketing authorization. [42]

11. IMPLEMENTATION AND COMPLETION DETAILS

After the completion of the action plan, the quality assurance department shall finally approve the change management records based on the opinions/suggestions of the responsible department. The final approval of the change control record will be communicated to the applicant and the applicant's line manager and other related departments involved in the initial change control approval and finalized approval process. Only after the QA change management data set is finally approved, the responsible department closes all action points for implementation.[43] The applicant shall complete all activities determined during the multi-stakeholder change audit trail evaluation period and send a copy of the report to the quality assurance department. The person in charge of the initiator's department suggests to the quality assurance officer to suspend the change proposal and prove the rationality of the documents during or after the implementation of the change implementation measures.[44] At the request of the sponsor, the QA manager reviews the suspension request for approval and evaluates the implementation status of the action elements. If the quality assurance manager approves the initiated change request, the change control record and all related action items and change proposals remain closed. If QA rejects the request to suspend the change control record, the request is initiated with appropriate documentation, and the change control record and action items will remain valid until completion. If there is an interruption in the change control record, QA assesses whether the action points implemented by the product are acceptable and justified in record. If the implementation of the action points are unacceptable, QA will record the situation in the change control record and include instructions for taking corrective actions before requesting the final approval.[45] Once the quality assurance manager's response is approved, the applicant must ensure that all identified action points are completed satisfactorily. The designated quality assurance personnel should also check whether all measures taken by the sponsor have been completed and whether the documents are complete and correct. The QA manager will draw a conclusion based on the review of the assessment report/assessment results/action plan results[46]. If the implemented changes are satisfactory/unsatisfactory, they will forward the final statement to the quality assurance and responsible person. When the record is closed, the QA manager also decides whether it should be reviewed after the change. If there is a need for follow up action on changes or to conduct impact assessments, the QA manager will make suggestions after consulting with the initiating manager and attached comments from representatives. [47] After the change is evaluated and implemented, the QA manager can complete the inspection with the consent of all relevant personnel from the initiator department. QA shall update the change control register with the closure details of the initiated change and QA Head shall sign on all documents as "obsolete copy" and archive it in QA's safe custody for future reference. If necessary, QA reviews the change management log monthly to determine the status of the change management request activities that need to be completed or whether the expected completion date has been reached [48].

12. CLOSURE OF CHANGE CONTROL

Inspection/analysis of impact changes shall be done periodically or at predetermined frequencies or at least annually by QA, either as a part of Batch product review, Annual product review, product quality review, site and process management review or a separate activity. They shall carry out the analysis of trend on more than one critical parameter on various aspects of the manufacturing process, scaling of batch etc and its impact.[49] Analysis of change classification (Major/Moderate/Minor), after the closure of change in parent molecule of the product, manufacturing site, Market impact shall be determined and the Status of change shall be verified (open/closed). If any adverse trends are identified and if any additional action is needed, the proposed action plan shall be addressed to the same. Documentation of the same shall be done by QA and Communicate the results of trends analyses to the site/ Global Quality Review Board.[50] QA head and RA head shall report all documents related to assessment of action plan, closure and update of change management should be done at least monthly to site quality Head/Designee. If this closure has been overdue for progress, then appropriate actions to be taken should be included and directed to QA personnel through an

appropriate reporting system [51].

13. CONCLUSION

The current study, provides an overview of the pharmaceutical company's change control change management process in the Quality management system. This review provides the need for a change control process, different types of changes in a pharmaceutical company and the protocol needed to implement change control. The proposed change will likely have an impact on the quality of production (or)GMP as there are done to be in line with ISO requirements. Change management minimizes the risks that may have an impact on the quality or critical attributes of the process. This well-established Change control change management protocol helps to find out deviations at the earliest and make it comply with appropriate FDA regulation.

Future Recommendations

It is noted that post approval change control management is a critical and brainstorming task and change control committee must have advanced technology knowledge, troubleshooting skill, and unique style, strategy for this implementation. Post Approval Changes seriously influence the market authorization and regulatory approval, so there should be appropriate planning, scheduling and implementation in compliance with GMP.

14. AUTHOR CONTRIBUTION STATEMENT

Both the authors have contributed equally in conceptualizing the design and compiling the review and preparing the manuscript.

15. CONFLICT OF INTEREST

Conflict of interest declared none.

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