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Change Management in Pharmaceuticals: The most critical element of Quality Management System

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ABSTRACT

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 regulatory guidance for Industry clearly reinforces the importance of implementing an effective change control procedures as a critical component in an overall quality system. The concept of change control is closely interwoven with regulatory compliance. Changes can happen at any time during a product's lifecycle. In change control proposal meeting product specification does not mean that the product has not changed and has not been impacted. The impact of the change needs to be balanced against the cost of making the change (quality, safety, time and investment). Impact of change may require amendments to registered details. Unapproved changes to material/component may inevidently cause final product failure in the field.

Key words: Change Control, Quality Management System, Change Management System, Risk Assessment

INTRODUCTION:

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. Making uncontrolled changes is a violation of several sections of the Quality System regulation. It bears repeating: all changes should be made according to the approved policy and procedure. The FDA's guidance for Industry clearly reinforces the importance of implementing an effective change control procedures as a critical component in an overall Quality System (QS). The concept of change control is closely interwoven with regulatory compliance. Pharmaceutical companies are required to control any change to established processes - meaning the change has to be recorded, reviewed, impact accessed and approved by the Quality Assurance unit. According to PS 9000: 2001,§,3.7 Change control is "A process that ensures that changes to material, methods, equipment and software are properly documented, validated, approved and traceable" . IPAC-RS guideline (§ 3.3) adds the additional requirement for change control "The process includes evaluation to determine whether validation is required and the level of validation required". Change control proposal is a documented procedure to report, record, categorize and assess / evaluate the impact of changes relevant to existing system & procedures. The change control proposal or format assesses impact of proposed change on purity & quality, identity, productivity of drug product, facility, documents, safety and personal. FDA-regulated pharmaceutical companies are expected to establish a Pharmaceutical change control systems as a way to improve product quality and safety and to ensure compliance. Under the Current Good Manufacturing Practice (cGMP) regulations outlined in 21 CFR Parts 210-211, anticipated changes should be evaluated to determine impact on component quality and validation status. In change control proposal Meeting product specification does not mean that the product has not changed and has not been impacted.

SCOPE:

The scope of the change control program must also cover a broad set of possibilities of risk and including changes to product formulation or design, upgrades to facilities, utilities, equipment and computer systems, manufacturing instructions, Operating Procedures, test methods and specifications, any new raw materials as well as any changes in policy and vendor (International Conference on Harmonization, Good Manufacturing Practice for Active Pharmaceutical Ingredients (CPMP/ICH/4106/00), 2000).

In addition, change control activities and procedures may also apply to: labeling and packaging, software and all associated documentation such as Quality System procedures, quality acceptance procedures and data forms, and product-specific documentation.

KEY BENEFITS OF CHANGE CONTROL SYSTEM AND MANAGEMENT:

The following are the key benefits in using a change control system:

- Structured and consistent approach towards managing change
- Documenting the details of change
- Risk assessment and management
- Routing of change requests through 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 Health Authorities (HA)

PROCEDURE:

The change control system requires a structured approach towards managing change in an environment focused on continuous improvement. The system must manage the end-to-end change control process including initiating, reviewing, approving, distributing, tracking and storing change history. Such a system can provide evidence of compliance to Regulatory Authorities (RA). In addition, the system should also help capture relevant information about the objective, nature & scope of change, and allow rapid change, approvals, and implementation. It is obvious that for a large manufacturer or for complex operations, the person responsible for the change would not or could not "pass the word" to everyone that has a need to know. Hence, the need for written procedures. Following critical steps allows for a robust change management system for the enterprise that can help manufacturers manage change and implement continuous improvement.

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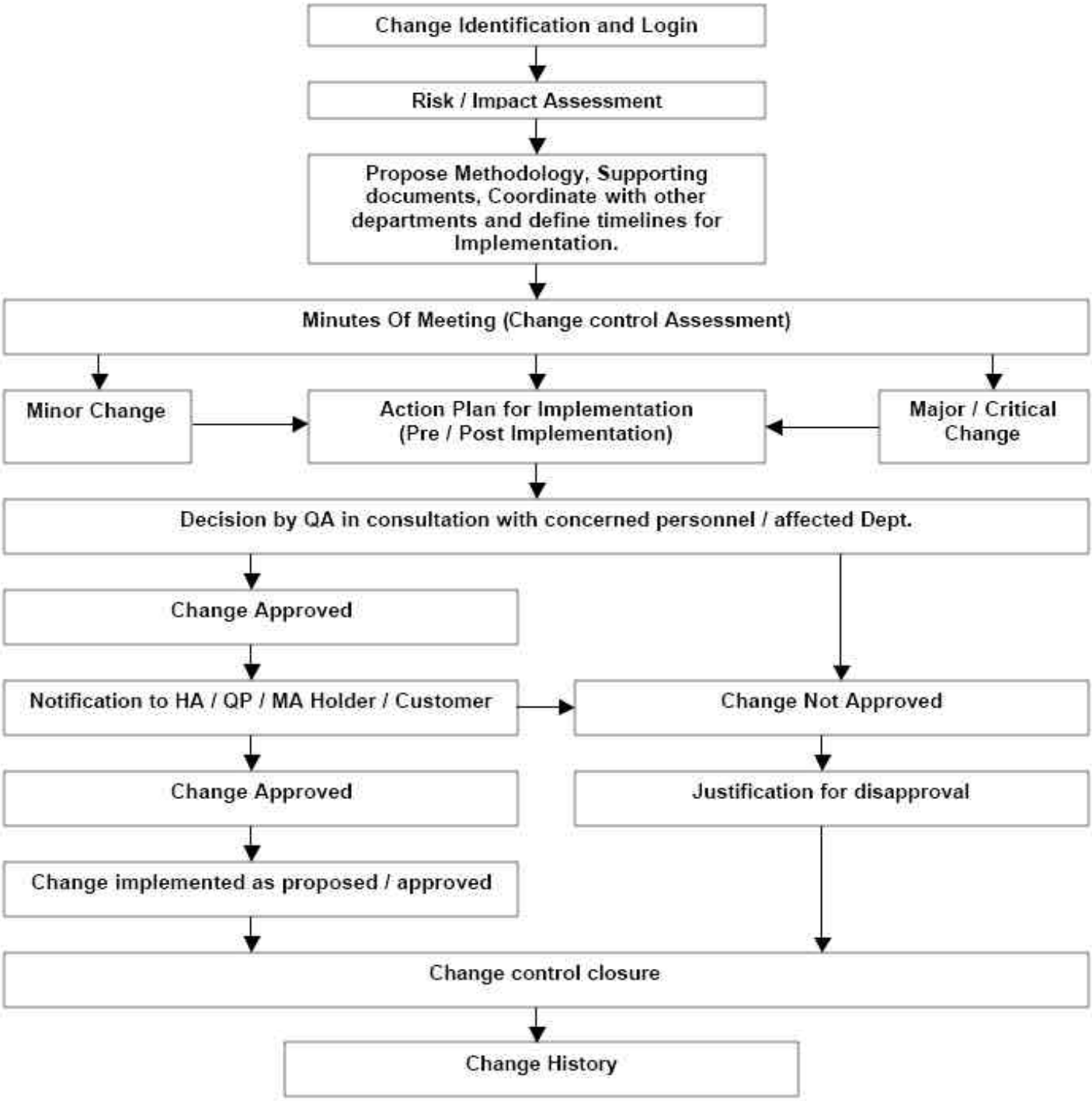

Initiators Responsibility:

Change identification, initiation and description:
Identify the change, which could be due to continuous improvement, risk identification etc. On identification of the change, initiate the change control by filling the change request. Provide suitable description, reason / justification for the proposed change(s).

Risk Assessment:
The change control procedure can have an appropriate degree of flexibility integrated into it, i.e all changes need not have the same degree of evaluation and approval. Based on the change initiated, carry out impact / risk assessment, identification of the affected system, procedure, document and propose mitigation plan.

Methodology / Supporting Documents / Coordinate:
Considering the proposed change and the impact / risk assessment, propose a methodology for initiating, reviewing and implementing the change. To substantiate the change provide supporting documents and coordinate with all concerned personnel / affected departments i.e RA dept., R&D, Operations / Production, Engineering and other ancillary departments.

Expected timelines:
A reasonable timeline should be fixed for implementation of the proposed change. Changes which needs to be implemented on priority needs to be suitably justified and highlighted. If for some reason the timeline can't be adhered, than suitable justification with prior approval should be provided by the initiating department.

QA Responsibility:

Change control Login:
In case, change control is manually managed than every change control initiated should be logged in. The log in details should be easy to maintain and retrieve with proper description.

Change Control Assessment:
Asses the change if having any impact on product quality, safety, Quality Management System, operating procedures, environment, personnel based on the Risk Analysis (Huma Ali & Rajesh Hajela, Journal of Pharmacy Research, Vol 4, No 6 ,2011), if change control impacts any one of the above, classify the change control as critical, major or minor. Change may reviewed and approved by an individual(s) in the same function or organization that performed the original review and approval unless there is a specific designation that states otherwise**.**

Critical:
Applicable to those proposed change controls which predictably or probably may affect the final product quality in such a manner, which may results in serious impact on chemical, physical attributes of Drug product and may results in adverse health consequences or causes a temporarily or medically reversible adverse health problem which may lead to critical health consequences even death of patient. And / OR pre assessed consequences that may / may not have impact on Product appeal/elegance but can also effect efficacy and identity.

Major:
Applicable to those proposed change controls which predictably or probably may affect the chemical and / or physical attributes of final product quality, but are unlikely to cause any adverse health reaction. And / OR pre assessed consequences that may / may not have impact on Product appeal/elegance but no impact on efficacy and identity.

Others:
Applicable to those proposed change controls which predictably shall not have any direct or indirect impact on quality attributes of final product. And / OR pre assessed consequences that may / may not have impact on Product appeal/elegance but no impact on efficacy and identity.

Change Control Action Plan for Implementation:
Based on the risk analysis a detailed implementation plan (pre implementation and post implementation) to be prepared. Details of action to be taken and their completion status with respect to activities to be tracked.

QA Approval:
Based on the risk analysis, methodology proposed and in consultation with concerned personnel / affected department i.e RA Dept, R&D, Production & Operation, Engineering and any other department identified, the change is approved / disapproved. These decisions to be communicated to the appropriate personnel / affected parties in a timely manner. Document suitable justification for non approval of change proposed.

Notification to QP / Customer / Client:
Notify QP / Customer / Client / License Holder / Marketing Authorization (as applicable) holder based on the category classification, risk identification and impact assessment for approval or information.

Notification to Health Authority (HA) / Regulatory Submissions:
Some change proposals may impact regulatory fillings / premarket notification / premarket approval / supplement depending on the change and needs to be adequately handled through the RA department.

Change Control Tracking & Closure:
An adequate tracking mechanism with defined time frame is required for evaluating / assessing the satisfactory completeness /effectiveness of the Change proposed. Assessment that incremental changes have not altered the overall process needs to be done.

Maintenance of change history:
Maintenance of change history for easy retrieval of information.

CONCLUSION:
The process of change is the end result of initiatives aimed at improving quality, increasing yield, reducing costs, cutting waste, streamlining processes etc. It would be very difficult to carefully manage change control in a large company or a fast growing organization without an enterprise-wide change control system. One of the most important aspects of change control is to maintain a history of changes for audit trail purposes - a capability better facilitated by such systems. The change control system requires a structured approach towards managing change in an environment focused on continuous improvement (EC Guide to Good Manufacturing Practice for Medical Products and Active Pharmaceutical Ingredients, compiled and edited by Gert Auterhoff, 4th. Ed., edition cantor Verlag Aulendorf, 2002). The system must manage the end-to-end change control process including initiating, reviewing, approving, distributing, tracking and storing change history. Such a system can provide evidence of compliance to regulatory authorities. In addition, the system should also help capture relevant information about the objective, nature and scope of change. The scope of the change control program must also cover a broad set of possibilities including changes to product formulation or design, upgrades to facilities, utilities, equipment and computer systems, manufacturing instructions, SOPs, test methods and specifications, any new raw materials as well as any changes in policy.

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