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A Review on Change Management System in Pharmaceutical Industry

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Abstract

Change control system provides a consistent and well-structured approach towards managing deviations and changes. Changes are unavoidable in a pharmaceutical manufacturing operation. Change management system is a systemic approach adopted by the pharmaceutical industries wherein qualified representatives of appropriate disciplines and personnel review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The change management system includes the implementation plan, installation, verification and the closure of the change control. Changes are classified as critical, major and minor. After the implementation of proposed change, an evaluation of the change should be undertaken to confirm the change objectives are fulfilled and achieved and to make sure that there are no detectable impact on final product quality.

Keywords: Change control, Implementation, Quality Management System, SUPAC, Quality assurance

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1. Introduction

Pharmaceutical industry is an important segment of the health care system, which deals with manufacturing and marketing of pharmaceuticals, biological products and medicinal devices, used for the diagnosis and treatment of diseases as well as conducts research for the development of new products for human welfare. So it is very important to maintain the quality of the final products to prevent health hazard as many pharmaceutical products are lifesaving. Thus if products are not of appropriate quality then they may result in severe adverse effects or even death of the consumer or patient. The need of implementing effective change control processes as a crucial component of an overall quality system is strongly emphasized in the regulatory guidance for industry. Regulatory compliance and the concept of change control are inextricably linked. Inadequate change control methods end up causing a substantial risk of non-compliance in a pharmaceutical company's quality management system. The need of implementing effective change control processes as a crucial component of an overall quality system is strongly emphasized in regulatory guidance for industry. (1) Changes can happen at any time during the product 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 change needs to be balanced against the cost of making the change. Impact of change may require amendments to registered details. Unapproved changes to material may cause final product failure in the field.

The change initiatives are aimed at improving quality, increasing yield, reducing costs, cutting waste, streamlining processes etc. It would be very difficult to carefully manage and expedite change control in a large company or a fast growing organization without a six sigma or Lean thinking concept. Lean thinking can best start by giving due consideration to value, which ultimately is the customer's requirement. The value of any product is defined by customer needs and not by any nonvalue added activity at the supplier's or producer's end. That is, the customer is prepared to pay for the operations by producers or their suppliers that transforms the product in a way that is meaningful to the customer. Customers do not want to pay for "waste at the producer's end". The starting point and focus of successful change planning is having a clear vision about what the scope and impacts of the future changed state will be. Stakeholders must be clear about their contribution to the desired improvement. If the change vision is not clear or shared, commitment is unlikely, and change efforts will be short-lived at best and will

likely fizzle out. Further, without a clear vision, change efforts can easily dissolve into a list of confusing tasks, directives and sometimes incompatible projects that can take the organisation in the wrong direction. The vision should provide the direction, which ties everything together, showing where individual projects and initiatives fit into the big picture. (2,3)

The change vision must also align with and be seen to align with the organisation's and the government's overall vision and mission, with the desired culture and values of the change reflecting the vision and mission statements. Articulating a direction and desired behaviours/values sets up a sense of the ideal culture the organisation is striving to achieve with the change. A vision that is misaligned will bring about early resistance and a lack of support for resources and for change. Change management research indicates that if a proposed change cannot be aligned with the core vision, mission or goals of an organisation then the collective commitment of organisation members to the change may be difficult to obtain. (4,5)

Change management system is a precise and formal system by which qualified representatives of appropriate disciplines reviews proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. Change control system provides a consistent and well-structured approach towards managing deviations and changes. It enables documenting the details of a deviations and changes. It helps in risk control and management. Change control system enables assessment of change requests through appropriate individuals for approvals and documentation of these change approvals and implementation by the Quality Assurance department. It also ensures maintenance of change history in easy retrieval manner and Effective change tracking. Changes in the manufacturing processes of drug substance or drug product even in a validated system are inevitable. Improvement in the plant, machinery and utilities are also a common occurrence in manufacturing units. Even though validated systems are in place, any change to the set parameters does affect the product quality and hence it may adversely impact the product safety and efficacy. Thus implementation of an effective change control system is an important GMP concept that focuses on managing change in a manufacturing set up. (6)

Change control system is the essential part of Quality Assurance which is aimed at ensuring that products are consistently manufactured to a quality appropriate to their intended use. It is a formal system, where qualified representatives of appropriate discipline review, evaluate, and approve the proposed or actual changes to already approved system. It provides a mechanism to ensure that changes are documented and implemented in a controlled manner. A good robust change control system is imperative for ensuring that the organization's facilities, equipment, procedures, processes and systems remain in a validated and a compliance state. Change control system is designed to prevent unintended consequences that may occur when making a change. (7)

With FDA citing inadequate change control constantly in its 483s and Warning Letters, the prerequisite to ensure that changes are accurately described, justified, assessed for risk, implemented, and documented has come to the fore. Changes must also be prospectively reviewed by appropriate subject matter experts. Furthermore, certain major changes (e.g. manufacturing, specifications) may require regulatory filings and/or prior regulatory approval. So this project involves structured, consistent, approach towards managing change as per cGMP guidelines.

2. Regulatory Guidelines

The GMP regulations are quite limited in their approach to change control, 21CFR 211.100a, the relevant portion of the US GMPs for Finished Pharmaceuticals, does not even mention the topic directly. They require: "Written procedures for production and process control to assure that the drug product has the strength, quality, identity, purity they are purported to have. Procedures including any changes reviewed and approved by appropriate functions and Quality Control unit.

In highly regulated countries such as USA, the concept of change control is closely interwoven with regulatory compliance. FDA regulated pharmaceutical companies are expected to establish a change control procedure as a way to improve product quality and safety and to ensure compliance Under the current good manufacturing practice regulations outlined in 21 CFR parts 210-211, pharmaceutical companies are required to control any change to established processes ,which means the change has to be recorded, reviewed, and approved. 21 CFR Part 211.194 states that Complete record shall be maintained of any modification or changes executed in an established method employed in testing. Such records shall include the reason for the modification and data to be verify that the modification produced results that are at least as accurate & reliable for the material being tested as established method. ICH Q7A states that a formal management system should be established to evaluate all changes that could affect the production and control of the intermediate or the Active Pharmaceutical Ingredient [API]. Written procedures should be provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment, processing steps, labelling, packaging materials and computer software. Also USFDA Guidance for Industry: Change to an approved NDA or ANDA provides recommendations to holders of a new drug application (NDAs) and abbreviated new drug application (ANDAs) who intend to make post approval changes in accordance with section 506A of federal, Food, Drug and cosmetic Act and 21 CFR 314.70.The guidance covers recommended reporting categories for post approval changes for drugs other than specified biotechnology and specified synthetic biological products.(8)

3. ICH Q10 Pharmaceutical Quality System

The perception of the Quality management system is based on the International Council for Harmonization

[ICH] of Technical Requirements for Registration known as ICH Q10 guidelines which is a risk-based approach and is applicable at different stages of the product life-cycle. Q10 guidelines ensures the final product quality and customer satisfaction. It provides guidance on the means to implement Quality management system in a pharmaceutical industry. Two basic elements of Quality Management System include: "Pharmaceutical Quality System," states that: "The change management system ensures continual improvement is undertaken in a timely and effective manner while providing a high degree of assurance there are no unintended consequences of the change It is clear that the purpose of change management is to prevent the unintended consequences that are sometimes encountered when making a change to a product or a system. However, Q10 is a voluntary guidance; therefore, we might think that we could ignore it or adopt those parts that suit us while conveniently ignoring the rest. From a formal regulatory perspective, as of now, no inspector can record an observation for a change management system solely based on lack of risk assessment. (9)

Table 1. Application of Change Management System throughout the Product Lifecycle (9)

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Change is an inherent part of the development process and should be documented; The formality of the change management process should be consistent with the stage of pharmaceutical development.	The change management system should provide management and documentation of adjustments made to the process during technology transfer activities.	A formal change management system should be in place for commercial manufacturing. Oversight by the quality unit should provide assurance of appropriate science and risk based assessments	Any changes after product discontinuation should go through an appropriate change management system.

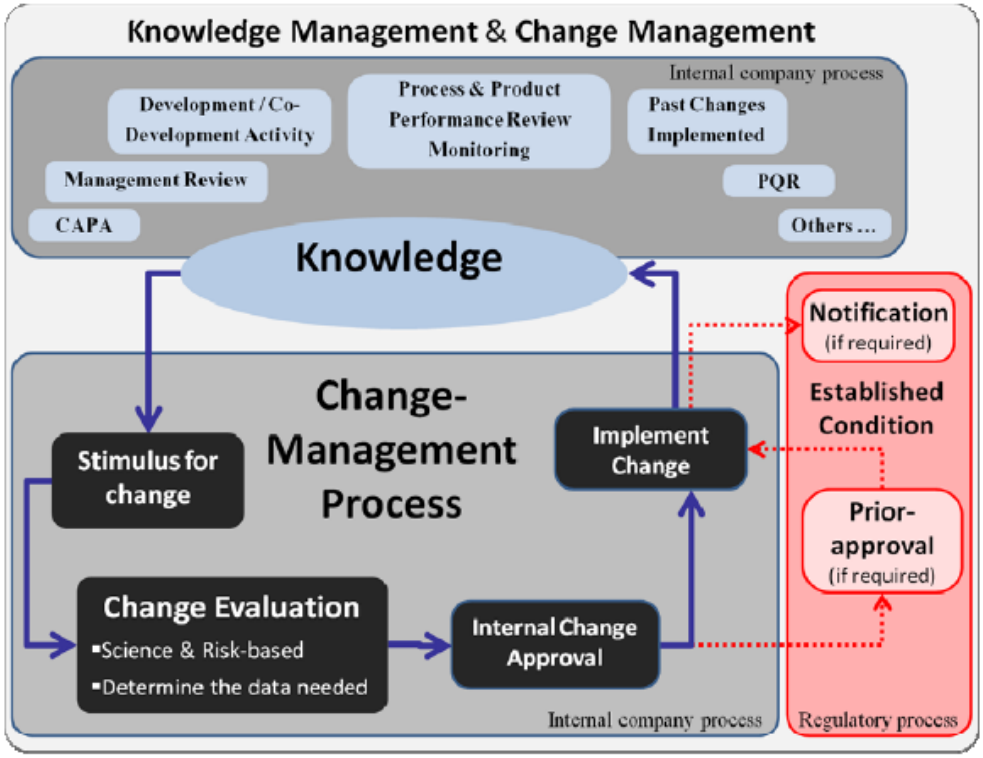

Figure 1. Connection between knowledge management and change management process (10)

4. Scale-Up and Post approval Changes or SUPAC guidelines

The scale-up process and the changes made after approval in the composition, manufacturing process, manufacturing equipment, and change of site have become known as Scale-Up and Post approval Changes, or SUPAC. Changes are being made in the manufacturing process and chemistry of a drug product following approval and continue throughout its life. Depending upon foreseen (or unforeseen) requirements, there can be changes in the raw materials, process, equipment or manufacturing site, and batch size which ultimately affect quality attributes of a drug or finished product. Therefore, there is a need to anticipate and fully evaluate the impact of any kind of change on the quality of a drug or finished product. The intensity of the adverse effect produced by a particular change depends

on the type of dosage form. This guidance provides recommendations to sponsors of new drug applications (NDA's), abbreviated new drug applications (ANDA's), and abbreviated antibiotic applications (AADA's) who intend, during the post approval period, to change.(11)

In order to evaluate, approve and implement the changes properly, the firm should have an effective change management system. There is generally a difference in formality of change management processes prior to the initial regulatory submission and after submission, where changes to the regulatory filing might be required under regional requirements. The change management system guarantees that a continual improvement is undertaken in a timely and effective manner. It should provide a high degree of assurance that there are no unintended consequences of the change. The change management system should include the following, as appropriate for the stage of the lifecycle: a) Quality risk management that should be utilized to evaluate proposed changes. The level of effort and formality of the evaluation should be commensurate with the level of risk; b) Proposed changes should be evaluated relative to the marketing authorization, including design space, where established, and/or current product and process understanding. There should be an assessment to determine whether a change to the regulatory filing is required under regional requirements. c) Working within the design space is not considered a change (from a regulatory filing perspective). However, from a pharmaceutical quality system point of view, all changes should be evaluated by a company's change management system; d) Proposed changes should be evaluated by expert teams contributing the appropriate expertise and knowledge from relevant areas (e. g., Pharmaceutical Development, Manufacturing, Quality, Regulatory Affairs and Medical), to ensure the change is technically justified and explained. Prospective evaluation criteria for a proposed change should be set; e) After implementation, an evaluation of the change should be undertaken to confirm the change objectives were achieved and that there was no deleterious impact on product quality. (11-14)

5. Change control system

A change control system manages the end to end changes through initiating, reviewing, approving, distributing and tracking change history. Following critical steps results in a robust and intact change management system that can help an organization to manage change and implement continuous improvement.

- The initiator individual/department identifies the change. On identification, initiator should initiate a change proposal. It consists of description, reason and justification for the proposed changes.
- There is a need for evaluation and approval for every proposed change based on change initiated, impact on existing procedure and documents and identification of the affected system. On consideration of type and evaluation of proposed change, a methodology is proposed for initiation and review process.
- The review process would coordinate with all concerned personnel /affected departments i.e., Quality assurance, Operation, Production, Analytical, Engineering and other ancillary departments. An expected timeline should be fixed for the initiated actions. If for some reasons the process out of the fixed timeline an extension memo will be issued by Quality assurance department upon request by the initiator department.
- Change Control Assessment is the process of determining the impact of the proposed change on Product quality, Safety, Quality Management System, Operating procedures, Environment and Personnel based on the Risk Analysis. If the change possesses any impact on any of the mentioned factors, the change is classified as critical, major or minor. Based on the risk assessment a detail implementation plan is prepared; it describes the details of action to be performed.
- Based on the risk assessment and in consultation with the respective department the proposed change will be approved/ disapprove by Quality Assurance Department with justification.
- A system should be present to assess the completeness/ effectiveness of the Change proposed. (15-19)

6. Conclusion

In the current review, it is justified that changes are unavoidable in a pharmaceutical industry and can impact the final product quality. The change management system includes the entire management of proposed or actual changes from the proposal of change request to approval of changes, implementation plan and final tracking of the changes. Thus a robust change management system is established in the pharmaceutical industry which can control and manage these changes in the most efficient manner.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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