A review on change control: A critical process of the pharmaceutical industry
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ABSTRACT
Change control is the most basic component in a drug organization's quality administration framework, deficient switch control techniques wind up making a tremendous danger of rebelliousness. The administrative direction for Industry plainly fortifies the significance of executing a successful change control technique as a basic part in a general quality framework. The idea of progress control is intently intertwined with administrative compliance. Vendors change cycles, sources, and details for crude materials, gear requires fix, administration, or substitution, producing areas are changed, clump sizes are expanded or diminished and headways in innovation are made that direct changes to the activities. In the wake of giving of Marketing Authorization as well as assembling, numerous progressions happen across the Product lifecycle, for example Scaling up of pilot clump into business bunch and variety in assembling measures, excipients and fabricating locales. Every one of these progressions are considered as post endorsement changes or varieties. These varieties should be endorsed by the particular administrative specialists of a country. If not, it puts the promoting approval holder or potentially permit holder in danger. Legitimate administration of changes is basic and appropriate change the board lessens the danger of suspension of licenses and the admonition letter from the administrative specialists. The current audit gives an industry insight on Change Control framework and significance of the Quality Management System.

Keywords: Change Control, Quality Management System, Change Management System, Risk Assessment

INTRODUCTION
Change is unavoidable in a drug fabricating activity. In change control proposition meeting item determination doesn't imply that the item has not changed and has not been affected. The effect of the change should be adjusted against the expense of rolling out the improvement (quality, safety, time and efficacy). Effect of progress may expect revisions to enlisted subtleties. Unapproved changes to material/part may in clearly cause end result disappointment in the field.

Change: According to the oxford dictionary the word “change” is defined as ‘decide on a new plan, have a new opinion, likely to alter, able to altered, different countries, used in place of another, alteration.

Change Management as a request began to create during the 1980s convinced by top directing affiliations working with Fortune 50 affiliations. During the 1990s, organizations experiencing huge and brisk change in areas, for instance, information advancement and HR began including the benefits of Change Management programs on a broader scale. The 2000's stepped wide affirmation of Change Management as a business competency for driving change. This change improved the constancy of Change Management in the business world and with adventure gatherings. The benchmarking data on 'use of a system' shows a recognizable augmentation from 34% in 2003 to 72% in 2011.

In pharmaceutical industry,[1] any sort of changes whether in assembling measure, quality control measures, quality confirmation measures, warehousing measures, measures with respect to designing or R& D divisions should be accounted for through change control framework. It means that a change control is having a significant part in drug businesses. All progressions ought to be officially mentioned, recorded and acknowledged by delegates of Production, QA/QC. Research and development, Engineering and Regulatory Affairs. The likely sway threat appraisal of the alternate at the object has to be assessed and the requirement for, and the diploma of Re-approval talked about. The probably sway hazard appraisal of the change on the item ought to be assessed and the requirement for, and the degree of Re-approval talked about. The change control framework ought to guarantee that all advised or mentioned changes are agreeably explored, recorded and approved. Holder of
showcasing approval should ensure that fundamental administrative pre-imperatives are met. On account of agreement fabricating, the assembling ought to educate the agreement supplier about the interior changes that could impact the application documentation.

PRINCIPLES OF CHANGE CONTROL

- The suitability of equipment, facilities and procedures must be proven with qualification and validation before implementation of the required change.
- This principle is not only valid the first time a medicinal product is manufactured or the first time a facility is used or a procedure comes into effect.
- To allow changes in any previously approved requirements, a review and authorization is required to keep the system in its original state of “proven suitability”.
- Formal change control guarantees that all changes are evaluated for their effect on product quality or validation status.
- Change control minimizes the risk that changes can have on the quality or process characteristics.
- Change control programs have become recognized as essential element of the pharmaceutical quality assurance.

CHANGE CONTROL PROCEDURE: FLOW CHART

The change control technique must require a controlled methodology. The change ought to be acted in an organized way including raising a change demand, exploring, playing out its danger appraisal by distinguishing the frameworks and reports getting influenced by the change.[4] In the wake of examining the effect of progress on existing cycle and records and getting endorsement, commencement of progress control technique should be done, for which appropriate schooling and preparing ought to be conferred to the faculty. As the cycle of progress control is extremely basic, composed report is needed for each single step just as coordination between the concerned office ought to be there to achieve vigorous and effective change the board framework. Such a framework can give proof of consistence to Regulatory Authorities (RA).[5]

Categories & Examples of Changes [6]

Various types of changes can take place throughout the process of pharmaceutical drug manufacturing. Categories with examples are given in (Table 1).[7]

In accordance to different guidelines

While examining about different administrative bodies separate rules are accommodated the cycle of progress control. For example, WHO-GMP give a rundown of changes that may require re-approval; The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-activity Scheme that gives the drug GMP rules to ventures essentially for sterile drugs likewise characterize the rundown of changes that need to experience change control. In PIC/S record PI 006 (section 6.7.4) there is a rundown of changes that may require re-approval. Remembering change for crude materials (actual properties that may influence the cycle or item), change in pressing material, change simultaneously (blending time, drying time and so forth), creation zone emotionally supportive network changes (eg. new water treatment strategy), move of cycles to another site, sudden changes (those saw during self-examination or during routine investigation of cycle pattern information).

As indicated by WHO-GMP rule things manufactured by measures that have been presented to changes should not be conveyed accessible to be bought without the full care and considered of the change and its impact on the cycle endorsement. Changes that liable to require revalidation may include: changes in the assembling cycle (blending time, drying time), Changes in the hardware (expansion of programmed location systems).[8]

Revalidation should be performed following a change that could influence the cycle, strategy, nature of the thing and moreover the thing ascribes.

The potential for essential changes to impact set up retest or expiry dates should be evaluated. If significant, thing conveyed by the adjusted cycle can be determined to a quickened dependability program also as can be added to the security noticing project.

Responsibilities

Quality Management system of the site is responsible for ensuring robust and easy handle of change procedure, by creating a simple procedure with the help of flow charts.[9] Training and education sessions must be imparted to all the employees. QA Responsibility: It is the responsibility of QA department to maintain a proper document of change control retrieving the wholesome information and proper description. (Table 2)

Risk Assessment [10]

On the basis of risk analysis performed prior initiating change control assessment should be done confirming that whether the change is having if having any impact on product quality, safety and efficacy. On the basis of which the change can be categorized in the category of critical, major or minor. Further the change is reviewed and approved by the quality management system.

Types of change control

Critical: Any change which may or can influence the quality, adequacy or personality of the item, bringing about antagonistic wellbeing outcomes or may cause genuine ailment or even demise of patient. This is may be because of the modification in actual substance properties of a medication item brought about by the change performed.

Major: Less basic results when contrasted and the progressions of the basic classification, implies this kind of changes can or can't influence the appearance or style of a medication item. Be that as it may, could conceivably have any modification in actual compound
properties of the medication item however without a doubt no affect the wellbeing and viability too it doesn't make any damage the patient.

**Minor:** This class of progress control manages the progressions that are not affecting physical or substance properties of medication item. It very well may be said that minor change control doesn't influences the safety, efficacy and identity of completed item by any means.

**CHANGE CONTROL IMPLEMENTATION**

To begin the change control interest inside the site the change control request structure should be filled and the proposed changes should be legitimized by acceptable and sufficient supporting data. The particular evaluation of the change is under the obligation of the concerned divisions. By talking with the affected division, methodology should be arranged and an authentic report portraying the movement plan and for following the stepwise headway of progress control practices should be set up to complete the change control in a suitable manner. Further the decision was made to one or the other help or article the change should be stayed aware of fitting support. A few changes may influence managerial fillings/premarket notice/premarket underwriting/upon the change and ought to be sufficiently dealt with through the RA division.

**Documentation**

All progressions that may influence item quality or reproducibility of the cycle ought to be officially mentioned, archived and acknowledged.

The probably effect of the difference in offices, frameworks and gear on the item ought to be assessed, including hazard examination. The requirement for and the degree of, re-capability and re-approval ought to be resolved.

**Change requests**

Changes requiring control are by and large recorded as a change demand, in which the candidate for the change propose the sort of evaluation/assessment of the change, determines the time spans and apportions for conveying the change, and demands that and the change is approved or declined by the change control advisory group.

The documentation for the change technique ought to demonstrate that the change was assessed (hazard investigation) and the hence characterized measures were actualized as foreordained.

**Post approval change management protocol**

A post-endorsement changes the board convention portrays explicit changes that an organization might want to execute during the lifecycle of the item and how these futures arranged and checked.

It is a stage shrewd methodology in the appraisal of changes, which permits an early assessment of the system for the change and a later isolated assessment of the information delivered dependent on the concurred strategy. A particularly stepwise methodology is relied upon to prompt quicker and more unsurprising execution of changes post-endorsement, since the MAH will have gotten understanding from the Regulatory Authorities about the proposed technique and tests to confirm the impact of the change on item quality [11].

**CONTENT OF THE CHANGE MANAGEMENT PROTOCOL**

As a rule, to help the proposed change, the organization ought to present all important data that can exhibit that it has procured sufficient information to plan and deal with the effect of the change.

The substance of the convention could incorporate the accompanying, contingent upon the idea of the change.

1. Justification that there is a perceived future requirement for the particular change inside a sensible time period and that sufficient information has been gained to characterize rules to fittingly assess and deal with the change for the particular item concerned; An itemized portrayal of the proposed change. The distinctions with what are now affirmed ought to be unmistakably featured (ideally in a plain arrangement). Contingent on the idea of the change, it ought to be illustrated, ideally with information from advancement or pilot scale examines, that the proposed approach is attainable. In the event that lone lab scale information are given the expected scale up impact ought to be talked about;

2. Risk evaluation of the effect of the change on item quality. This ought to incorporate recognizable proof of the expected dangers and itemized methodology of how these dangers will be moderated or overseen.

3. Discussion on the fittingness of the endorsed control technique to recognize and deal with these dangers and, whenever required, portrayal of the extra controls that may be should have been set up. This should think about the degree of the change and along these lines the likely effect on the nature of the dynamic substance or potentially completed item, as suitable;

4. Description of the investigations to be performed, and the test techniques and acknowledgment measures that will be utilized to completely survey the impact of the proposed change on item quality. The candidate ought to legitimize the fittingness of the techniques proposed to survey the effect of the proposed change. Information from advancement or pilot scale studies can give confirmation about the significance and sufficiency of the proposed tests;

5. For biologics, the way to deal with be utilized to show the equivalence of the pre-and post-change item;

6. A arrangement for strength studies ought to be incorporated, if fitting;

7. Commitment to refresh the affirmed convention, if this gets invalid, because of critical changes to the proposed test strategies/acknowledgment standards or a huge assortment of
new information or new administrative prerequisites.

8. In case that the convention depicts a few changes, a legitimization indicating how the progressions are connected, and that a synchronous survey under a solitary convention is significant;

9. For substance therapeutic items, a proposition of how the usage of the change will be accounted for to the applicable capable specialists utilizing the current variety strategies;

10. For organic therapeutic items, as per the Variations Classification Guideline.

**Table-1: Categories with examples of change control**

<table>
<thead>
<tr>
<th>Specification Changes</th>
<th>Changes in any specification Bill of Material (BOM) or data sets. This may include:</th>
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<tbody>
<tr>
<td></td>
<td>• Raw materials, packaging component. In process testing, packaged product &amp; equipment specifications</td>
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<tr>
<td></td>
<td>• BOM for bulk &amp; finished products</td>
</tr>
<tr>
<td></td>
<td>• Data sets for starting materials or finished products</td>
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<tr>
<td>Analytical Method Change</td>
<td>Any change to or deletion of a testing procedure or inclusion of a reduced testing schedule. This include but not limited to:</td>
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<tr>
<td></td>
<td>• Raw materials, packaging components in process products &amp; calibration tests</td>
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<tr>
<td>Raw Materials Change</td>
<td>Any change to raw material supplier manufacturing site, manufacturing process, mode of transport or storage of containers</td>
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<tr>
<td>Packaging Components</td>
<td>Any change other than artwork to a packaging component. This includes but is not limited to:</td>
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<tr>
<td></td>
<td>• Bottles, caps, tubes, foils etc. (thickness, material dimensions)</td>
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<tr>
<td>Manufacturing Process Change</td>
<td>Any change to the processing procedure. This includes but is not limited to:</td>
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<td></td>
<td>• Manufacturing process (e.g. stirring time, blending, order of addition drying time or temperature where variation is not specifically covered in the manufacturing instructions)</td>
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<td>• Packaging process (e.g. cap torque, filling temperature, line set up &amp; shut down procedure, fill volume, blister seal temperature etc.)</td>
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<td></td>
<td>• Cleaning process (e.g. time, temperature method, cleaning agents, HVAC Systems, etc.)</td>
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<td></td>
<td>• Transfer of an in-house manufactured product to an alternate manufacturing site</td>
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<td></td>
<td>• Introduction of a new product to the manufacturing facility</td>
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<tr>
<td>Equipment/computer change</td>
<td>Any modification or alternation to equipment or the environment where the equipment operates, or the relocation of the equipment from one place to another or the introduction of a new equipment or consumables to existing equipment. This is not limited to:</td>
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<td></td>
<td>• Manufacturing equipment (e.g. manufacturing &amp; storage tanks, blender, stirrer, compressing machine, drying ovens, granulators, fluid bed dryers, storage hoppers, transfer lines etc.)</td>
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<tr>
<td></td>
<td>• Purified water system (e.g. pumps, valves, dosing mechanism etc.)</td>
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<td>• Packaging equipment (vision system, capper, labelling machine, bottle blower, shrink wrapper, cartonner, case packer etc.)</td>
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<tr>
<td></td>
<td>• Testing equipment (e.g. pH meter, viscometer, scales, thermometer, HPLC, balance, spectrophotometer etc.)</td>
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<td></td>
<td>• Environment (e.g. air conditioning, humidity, pest control, lighting etc.)</td>
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**CHANGE CONTROL MEASURE AT REGULATORY SUBMISSION LEVEL**

The report should contain data about the plan, including defences for any. Changes made in the techniques during the advancement cycle. Moreover, the report will incorporate data about the accompanying:

1. Justification for all ingredients utilized.
2. Justification for all analytical methods used.
3. Justification for the entirety of the last assembling and insightful cycles expressed in the application (IND, ANDA or NDA).
4. Types of equipment’s utilized.
5. Manufacturing cycle (portrayal of development of the cycle)
6. Scale-up to creation
7. In-measure results
8. Final measurement structure test results
9. Critical boundaries of mass medication substance
10. Acceptance rules for basic advances
11. Conclusions with key factors distinguished
12. Stability
13. Description of pilot batches

The whole reason for this change control report is to direct the position to an archive that depicts the science and innovation that
went into making the item and that incorporates all fundamental investigations straight up to the regulatory submission stage.

**BENEFITS OF CHANGE MANAGEMENT FOR THE ORGANIZATION**

The potential gains of the change are alluded to before use and fill in as inspirations and assessment of progress.

- Change the chiefs allows the relationship to study the overall impact of a change, through which generally speaking effect of progress can be evaluated in a superior manner.
- The affiliation can satisfy the client request all the more productively.
- Authoritative amleness and viability is kept up or even improved by perceiving the concerns of staff bringing about expanded profitability.
- Helps to change the current assets inside the association.
- By change the executives the specific Change can be executed without conflictingly influencing the regular running of business.
- Change the board can prompt time and cash saving action and decreasing the odds of disappointment having not so much speculation but rather more benefit.

**CONCLUSION**

In the current examination, it is verified that occupied with drugs change control doesn't mean the completion of any change; it proposes the specific control of changes to guarantee the developments made don't inimically affect the wellbeing, quality, adequacy, or strength of the medicine thing. Changes made in a medicine making plant that can impact the safety, quality, viability, intensity, or nature of a prescription planning should be made in a manner that guarantees these attributes are not antagonistically affected. Thinking about the altogether globalized level of the genuine prescription industry, finishing the change in the design or possibly activity isn't as essential as no vulnerability. With the advances in science and advancement that we have seen all through the long stretch, it is opined that a change should be struck to fittingly use the entire of the gadgets accessible to improve ordinary conditions and address clinical issues over the globe. Doubtlessly the main gathering of post endorsing changes is a multidimensional errand and calls for various activities and strategies which should be concurred with public laws and generally settlements and practices. Post Approval Changes in GMP level are really impacted by the market needs, market reaction, etc. All things considered, exchange and business contemplations are critical in the association of post help changes. Various types of changes request specific treatment, managing, engineering, and methodology and obligation of people with various district information, for example, life science, arranging, arrangements, drug administrative expert and showing. Every industry should develop its own change control protocol, the frameworks, for smooth functioning of the processes.

**ACKNOWLEDGEMENTS**

The authors thankful to Head of department, College of Pharmacy, Graphic Era Hill University, for providing the necessary facilities and support to carry out the research work.

**CONFLICT OF INTERESTS**

The authors declared that there are no conflicts of interest.

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**How to cite this article**