Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 7, Issue 5, 2015

Review Article

QUALITY MANAGEMENT SYSTEM IN CHANGE CONTROL AT INDUSTRY LEVEL: AN OVERVIEW

LOKESH M. S., N. VISHAL GUPTA*

[1]Pharmaceutical Quality Assurance Group, Department of Pharmaceutics, [2]JSS College of Pharmacy, JSS University, Sri Shivarathreeshwara Nagara, Mysuru 570015, Karnataka, India
Email: vkguptajss@gmail.com

Received: 09 Jan 2015 Revised and Accepted: 08 Feb 2015

ABSTRACT

Change is inevitable in a pharmaceutical manufacturing operation. Vendors change processes, sources, and specifications for raw materials, equipment requires repair, service, or replacement, manufacturing locations are changed, batch sizes are increased or decreased and advancements in technology are made that dictate changes to the operations. After issuing of Marketing Authorization and/or manufacturing, many changes occurs across the Product lifecycle, i.e. Scaling up of pilot batch into commercial batch and variation in manufacturing processes, excipients and manufacturing sites. All these changes are considered as post approval changes or variations. These variations need to be approved by the respective regulatory authorities of a country. If not, it puts the marketing authorization holder and/or license holder at risk. Proper management of changes is critical and proper change management reduces the risk of suspension of licenses and the warning letter from the regulatory authorities. The present review provides an industry perception on Change Control system and importance of the Quality Management System.

Keywords: Marketing Authorization, Post Approval Changes, Marketing Authorization Holder.

INTRODUCTION

Changes to approved system

Change is an inevitable phenomenon especially in the pharmaceutical industry where, with an advent of technology and knowhow, machines and manufacturing processes tend to change over a period of time in efforts to improve manufacturing and operating efficiencies.

The question "How can we update or change the information in an approved application?" is often asked. The answer varies (the batch sizes needs to change, there are new methodologies and specifications developed, we want to manufacture and test at a different site, etc.). These changes are called "post approval changes" (PACs) because they effect applications that have already been approved [1].

Changes in the Pharmaceutical system are entirely different from the deviation.

Table 1: Comparison between change control and deviation

Change control	Deviation
Change control is a strategic activity to bring about changes in document/process/method. It can be for the smaller period of time or it can be long term usable. It must be informed to all the concerned departments for official approval of Change Control.	Deviation is an aberration from the given procedure which is done pre-plannedor accidently. A deviation can be divided into critical & non critical. Effects of critical deviations should be accessed through investigation CAPA

Deviation is defined as "Any non-compliance of an established GMP standard or of approved requirements, specifications and standard operating procedures. Deviations need to be documented, evaluated and when appropriate, investigated in order to determine the originating causes to prevent recurrence" [2].

There are many different circumstancestouse the term "deviation". No well-established definitions were found in the various regulatory documents in the USA or the EU. The terms used by these authorities are not always the same (for example, deviation, discrepancy, a typical situation, nonconformity). Therefore, it is authoritative for a company to define internally, what is deviation? in order to avoid ambiguity and possible mistakes concerning workflows and responsibilities [3].

Examples for potential deviations in different areas are listed in table 1 [3].

Table 2: Examples of potential deviations

Production process	Machines, plants, equipment, facilities, and media (including laboratory)	Quality control
➢ Manufacturing Formula ➢ Processing Parameters (e. g. Equipments, machines and instruments) ➢ In process parameters (IPQC limits and/or specification) ➢ Standard operating procedures to conduct IPQC tests ➢ Controls (e. g. Using obsolete versions) ➢ In-process specifications ➢ Anomalies in the process	➢ Machine defects ➢ System failures ➢ Temperature, humidity, number of particles or pressure differences outside ➢ of limits ➢ Deviations in microbiological monitoring ➢ Calibration results outside of limits ➢ Failure to keep calibration or maintenance intervals	➢ Statistical reports of IPQC test results which results in deviation (OOS) ➢ Statistical results of IPQC tests which results in out of trend (OOT) ➢ Results close to specification limit ➢ Using expired ➢ Reference standards

Sources of the changes in GMP

Change can come from many different directions, experience has proven that change(s) within a critical compliance and quality system will have the largest impact. The following are some area which is the sources for change: [4].

Potential changes during development and post commercialization [4].

Regulations	Vendors
Customer requests/complaints	Facility
Personnel	Validation
Technology	Research
Testing methodology	Development

Table 3: Changes during product development & post commercialization

Particular	Changes
Formulation	Composition: Percentage of active and inactive ingredients per unit dose
Active Pharmaceutical Ingredient (API)	Alternate manufacture
	Altered impurity profile
	Physical characteristic
	New manufacturing process
	New raw starting materials(s) excipients
	Official grade change
	New raw starting materials(s) excipients
	Official grade change
	Raw material change
Equipment	Bench scale
	Pilot plant
	Biobatch
	Scale batches
	Commercial size
	Continuous improvement
	Process optimization
	Repairs and maintenance
Cleaning Procedures	Manual to automated
	Equipment configuration changes
Manufacturing Process	Critical parameter changes
	Operating range changes
	Optimal condition changes
	Scale-up
	Technology transfer
	Rework/reprocessing procedure
Analytical Method Development	Qualified method
	Validated method
	Optimize and/or modernize method
	Customize a compendial method
Stability Profile	Container closure system(s)
	Storage conditions
	Expiry period
Facilities	Controlled environment requirements
	Preventative maintenance
	Emergency repairs
	Validated classified areas
	Structural changes
	Cross contamination prevention
	General housekeeping and sanitation
	Cleaning agents and pest control
	Critical utilities
Critical utilities	Clean steam
	Potable and purified water systems
	HVAC systems
	Compressed air system
	Dust collection system
	Emergency repairs to critical utilities
	Changes in PM maintenance schedule
Natural disasters	Facility changes
	Utility changes
	Validated system changes
	Personnel turnover and loss
Critical components	Containers
	Closures
	Labeling
	Packaging materials
	Inserts

	Desiccants Vials Tubes Changes to any critical parameters of these components must be monitored

Change management system

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state. Paragraph is the definition [6].

History of change management [7]

Change Management as a discipline initiated to emerge in the 1980s motivated by top consulting organizations working with Fortune 50 organizations. Initial adopters, like as GE, Ford, and AT&T, were very large companies that might derive important savings through more competently applying new packages and were accustomed to cutting edge thought management roles. This work resulted in early Change Management models such as GE's Change Acceleration Process (CAP) and John Kotter's Eight Step Process for Leading Change. At the moment, Change Management offerings were typically accessible through consulting services, with a limited number of books and textbooks available.

During the 1990s, industries undergoing important and fast change in areas such as information technology and human resources began highlighting the benefits of Change Management programs on a wider scale. The practices, consequences, and prices of applying change without anorganizedmethod has helped staff and companiesembrace Change Management tools. Though use of Change Management was still incomplete primarily to large corporations in the habit of regularly utilizing specialized consulting firms, Change Management was getting more and more perceptibility and reliability.

The 2000's marked extensive acceptance of Change Management as a business competency for leading change. This alteration improved the reliability of Change Management in the commercial world and with project teams. The benchmarking data on 'use of a methodology' shows a noticeable increase from 34% in 2003 to 72% in 2011. The value of Change Management was further validated through additional research on the impact of Change Management on business success by Prosci, IBM and McKinsey.

The market for Change Management tools and training grew fast through this period, with as many as 320 accessing firms recognized as offering Change Management facilities by 2011. Some were recognized with their own Change Management procedures while others, that previously only offered consulting services, also provided exercise and some level of product offerings as well.

Benefits of change management process [8]

- Change is a planned and managed process. The advantages of the change are well understood before execution and serve as motivators and assessment of progress
- The firm can respond quicker to client demands
- Helps an organization to line up current resources within the system
- Change control & management permits the firm to measure the total influence of a change
- Variation scan be applied without undesirably effecting the regular process in company
- Organizational effectiveness and efficiency is continued or even improved by allowing the concerns of employees
- Timeline to implement the change will be reduced
- Shortcomings in the process can be reduced
- Employee's will aware about the change associated with the company and performance of employee will also increased
- Customer service and effective service will increase to clients and customer
- Change management offers a way to anticipate challenges and respond to the prescribed changes efficiently
- Proper change management process lowers the risk associated with the process and change
- investment on capital will be reduced and helps to contain costs associated with change
- Increases revenue of the company
- Generates an chance for the growth of "best practices", leadership development, and team development

Opinion on change management system by various authorities

As per EU GMP: "A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state" [6].

EU GMP also provides notes regarding handling of the Changes: "Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process, should be validated" [9].

21 CFR 211.100 and 21 CFR 211.160 is also provides two brief notes on "Change Control"

211.100 Written Procedures; deviations: "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. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit" [10].

211.160 General Requirements: "The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit.

The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified" [11].

As per the Pharmaceutical Inspection Convection and Pharmaceutical Inspection Co-operation Scheme (PIC/S)

Change Management: Written procedures should be in place to describe the actions to be taken if a change is proposed to a starting material, product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or reproducibility of the process. Change control procedures should ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specifications [12].

Change Control: "Change control is an important element in any Quality Assurance system. Written procedures should be in place to describe the actions to be taken if a change is proposed to a product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or support system operation" [13].

Responsibilities

Process Owner/Principle Investigator [14]

- Responsible for technical changes and to follow the valid change control procedure
- Decides about the impact of the technical change on product quality (major/minor impact). The participation of the QU in this decision should be clearly established according to the company in this matter.
- It is recommended that the process owner prepares a list of changes with no impact expected on product quality (Standard changes).

Quality Unit [14]

- The involvement of the quality unit is required if the change is thought to have, or potentially have, impact on the product quality.
- The quality unit is responsible for the implementation and maintenance of the change control system.
- The quality unit has to approve the standard change list.

Process owner/Principle Investigator and quality unit [15]

Every technical change with major impact should be assessed at least by the process owner and/or principal investigator and the quality unit.

They should decide about the measures to be taken to document the change appropriately.

Functional Group Responsibilities [1].

Table 4: Functional group responsibilities

	Initiation of Change Control	Proofr eading	Conformance to regulation (cGMP) and applicability to other system	Review and Approval	Regulatory Impact and Worldwide Filling Strategy	Validation
Quality Assurance	✓	✓	✓	✓	-	✓
Quality Control	✓	-	-	✓	-	-
Manufacturing	✓	-	-	✓	-	-
Process Engineering	✓	-	-	✓	-	-
Technical Services	✓	-	-	✓	-	-
Regulatory Affairs	✓	-	-	✓		-
Owner of System or procedure being changed	✓	-	-	✓	-	-

Elements of an Integrated, Comprehensive, and Far-reaching change management system [4]

1. Empowers an organization's personnel by inviting anyone to propose a change: Everyone in your organization holds unique knowledge and perspective. Make it easy for anyone to suggest a change by having a simple form and an SOP on how to use it.

2. Affords a way to communicate both vertically and horizontally around issues of change: with many changes occurring simultaneously, it is very important to have a system that will keep track of them and keep people current as to the status of each pending change.

3. Provides a viable mechanism for continuous improvement to forward quality: Change can be a big contributing factor toward continuous improvement. A good system gives you a systematic, documented way to evaluate and incorporate product and process improvements.

4. Allows for full assessment of a particular change prior to implementation: What appears to be a good change for one area may in fact have a negative impact on another area. A good system allows for everyone to give input regarding the impact of change.

5. Provides a systematic and formalized approach to review proposed changes: A system helps ensure that change justification is documented and the right people are evaluating and approving each change, and identifies other systems impacted.

6. Allows for a coordinated implementation. With the potential for many areas to be impacted by a change, all these activities and documents must have a synchronized implementation.

7. Provides a documented trail and various levels of accountability. ''Not documented, not done.'' This old rule is still applicable when it comes to change management.

Pharmaceutical quality system (PQS) [16]

Management system to direct and control a pharmaceutical company with regard to quality; the elements described below might be, required in part under regional GMP regulations. These four elements are:

- Process performance and product quality monitoring system
- Corrective action and preventive action (CAPA) system
- Change management system
- Management review of process performance and product quality

Change management system [16]

Innovation, continual improvement, the outputs of process performance and product quality monitoring and CAPA drive change. In order to evaluate, approve and implement these changes properly, a company 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 ensures continual improvement is undertaken in a timely and effective manner. It should provide a high degree of assurance 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 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 standpoint, 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. 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.

Application of Change Management System throughout the Product Lifecycle:

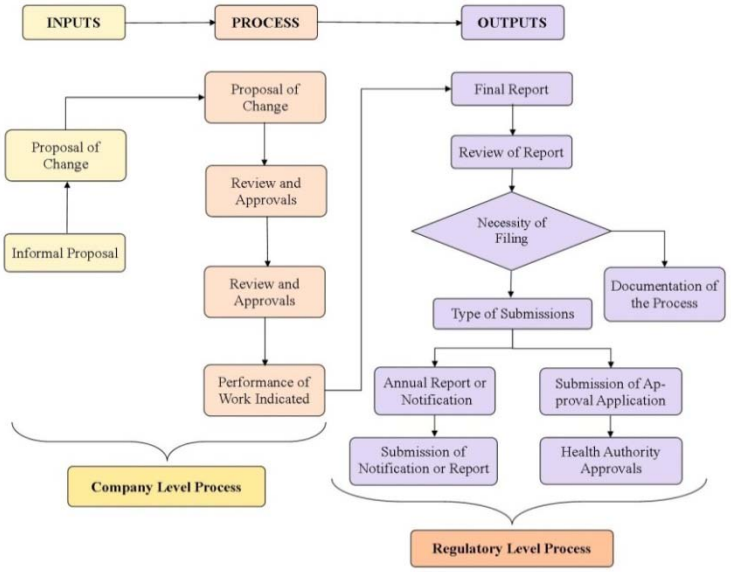
Table 5: Application of change management system

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.

Procedure of change control

Process of change control [13]

"Commitment of the company to control change to premises, supporting utilities, materials, equipment and processes used in the manufacture of medicinal products is essential to ensure a continued validation status of the systems concerned. This commitment should be stated in the relevant company documentation. For example, the Quality Manual, Quality Policy Documents or the Validation Master Plan; as part of its Quality Management System the company should have a defined and formalized Change Control Procedure."



Flowchart 1: Process of change management system [1]

Procedure for change control process at Company and/or Sponsor Level

Following procedure is applies for both GMP [14]

- The procedure should always begin with a request for a change. This request should be formalized in some way, for example as a form, and be signed.

- The request triggers the question of the impact of the change on the product quality/safety of the population. It can be necessary to define several levels of impact on product quality but there should be at least two categories; major and minor impact. The treatment of these two options should be clearly different.

- There should be clear rules for the decision, whether the impact of the change on the product quality and/or on study is major or minor: who decides and why the decision is taken.

- For the management of changes, an early decision is required of who should be involved. The decision should be taken by the process owner, who normally has the best knowledge of the impact of changes on the product or study (or at least can estimate it with a high degree of certainty). The principle of double checking should be implemented at this point of the procedure. A signature by the technical department is first required. Depending on the company's or sponsor's procedure, the quality unit can be involved as an approver to check periodically by self-inspection audits.

- If the owner has decided that the change is minor and there is no likely to impact on the quality of the product, it can be implemented. The change should be adequately documented.

- The implementation of the changes with minor impact can be achieved in a very rapid and efficient manner using checklists of standard changes. The list of these changes should have been approved by the quality unit.

- If the decision has been taken that the change can or will have an impact on the quality of the product and/or safety of the population, the quality unit has to be involved. An adequate rationale and an appropriate action plan should accompany such request. This builds the basis for the approval by the quality unit.

- After the Quality Unit approval, the change can be implemented. If other aspects are affected by the change, for

example safety aspects, additional release activities can be needed. Where such activities have been defines, these should be fulfilled before the refuse of the equipment. Release of the equipment itself can be one of these activities.

- The start of a change control system for technical equipment should be established after the completion of qualification. This will ensure that the qualified status is maintained.

- Change control before completing qualification need not possess the same degree of formality as it can be easier regulated and can proceed without the formal and immediate involvement of the quality unit. The required activities in this case are adequate documentation of the changes and a periodical adaption of the documentation.

- The change requests for emergency changes can be formalized after the replacement. Emergency cases should be defined by each company in an appropriate way.

Documentation

"All changes should be formally requested, documented and accepted by representatives of production, QC/QA, R&D, Engineering and Regulatory Affairs as appropriate. The likely impact (risk assessment) of the change on the product should be evaluated and the need for, and the extent of Re-validation discussed. The change control system should ensure that all notified or requested changes are satisfactorily investigated, documented and authorized"[13].

"All changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. The need for, and the extent of, re-qualification and re-validation should be determined."

Change control requires a written procedure (change control program) to regulate at least the following points: [5]

- What types of changes does change control take into account; for which areas does this operating instruction apply?

- Who can suggest/initiate changes?

- How changes are requested (forms, methods of communication)?

- How changes are graded, who is responsible for the grading?

- How are the measures necessary for carrying out the change determined; who compiles the directions required?

- Who is responsible for the execution and monitoring of all necessary measures?

- How is the change controls committee assembled; what are the duties of the committee?

- How the change is documented (format, content, storage)?

- Who is responsible for authorizing changes?

- What are the special regulations for urgent changes?

Change requests

Changes requiring control are generally documented in the form of a change request, in which the applicant for the change proposes the type of grade/evaluation of the change, specifies the time frames and measures for carrying out the change, and requests that and the change is authorized or declined by the change control committee. The documentation for the change procedure should prove that the change was evaluated (risk analysis) and the subsequently defined measures were implemented as predetermined [5].

Post approval change management protocol

A post-approval change management protocol describes specific changes that a company would like to implement during the lifecycle of the product and how these would be prepared and verified. It is a step-wise approach in the assessment of changes, which allows an early evaluation of the strategy for the change and a later separate evaluation of the data produced based on the agreed strategy. Such a stepwise approach is expected to lead to faster and more predictable implementation of changes post-approval, since the MAH will have obtained agreement from the Regulatory Authorities about the proposed strategy and tests to verify the effect of the change on product quality [15].

Content of the change management protocol [15]

In general, in order to support the proposed change, the company should submit all relevant information that can demonstrate that it has acquired adequate knowledge to prepare and manage the impact of the change.

The content of the protocol could include the following, depending on the nature of the change [15].

- Justification that there is a recognized future need for the specific change within a reasonable timeframe and that adequate knowledge has been acquired to define criteria to appropriately evaluate and manage the change for the specific product concerned;
A detailed description of the proposed change. The differences with what is already approved should be clearly highlighted (preferably in a tabular format). Depending upon the nature of the change, it should be demonstrated, preferably with data from development or pilot scale studies, that the proposed approach is feasible. If only lab-scale data are provided the potential scale up effect should be discussed;

- Risk assessment of the impact of the change on product quality. This should include identification of the potential risks and detailed strategy of how these risks will be mitigated or managed;

- Discussion on the appropriateness of the approved control strategy to identify and manage these risks and, if required, description of the additional controls that might be needed to be put in place. This should take into consideration the extent of the change and therefore the potential impact on the quality of the active substance and/or finished product, as appropriate;

- Description of the studies to be performed, and the test methods and acceptance criteria that will be used to fully assess the effect of the proposed change on product quality1. The applicant should justify the appropriateness of the methods proposed to assess the impact of the proposed change. Data from development or pilot scale studies can provide assurance about the relevance and adequacy of the proposed tests;

- For biologics, the approach to be used to demonstrate the comparability of the pre-and post-change product;

- A plan for stability studies should be included, if appropriate;

- Commitment to update the approved protocol, if this becomes invalid, due to significant changes to the proposed test methods/acceptance criteria or a significant body of new knowledge or new regulatory requirements;

- In case that the protocol describes several changes, a justification showing that how the changes are related, and that a simultaneous review under a single protocol is meaningful;

- For chemical medicinal products, a proposal of how the implementation of the change will be reported to the relevant competent authorities using the existing variation procedures;

- For biological medicinal products, in accordance with the Variations Classification Guideline.

Change control process at regulatory submission level

The report must contain information about the formulation, including justification for any and all Changes made in the methods during the development process. Additionally, the report will include information about the following [4].

- Justification for all ingredients used

- Justification for all analytical methods selected
- Justification for all of the final manufacturing and analytical processes stated in the application (IND, ANDA or NDA)
- Types of equipment used
- Manufacturing process (description of evolution of the process)
- Scale-up to production
- In-process results
- Final dosage form test results
- Critical parameters of bulk drug substance
- Acceptance criteria for critical steps
- Conclusions with key variables identified
- Stability
- Description of pivotal batches

The entire purpose of this change control report is to point the authority toward a document that delineates the science and technology that went into making the product and that includes all preliminary studies right up to the regulatory submission stage.

CONCLUSION

In the current study, it is affirmed that in the pharmaceutical industry, change control does not mean the elimination of any change; it means the systematic control of changes to ensure the changes made do not have any adverse impact on the safety, quality, purity, or potency of the pharmaceutical product. Changes made in a pharmaceutical manufacturing plant that has any potential to impact the safety, quality, purity, efficacy, or potency of a pharmaceutical preparation must be made in a way that assures these characteristics are not adversely impacted. Because of the highly globalized level of the modern pharmaceutical industry, implementing the change in the system and/or operation is not as simple as it would seem. With the advances in science and technology that we have witnessed over the decades, it is opinioned that a balance must be struck in order to properly utilize all of the tools available to improve living conditions and address health problems across the globe.

It is obvious that management of post approval changes is a multidimensional task and calls for many different actions and strategies which need to be aligned with national laws and international treaties and practices. Post Approval Changes in GMP level are seriously influenced by the market needs, market response and so on. In other words, trade and commerce considerations are important in the management of post approval changes.

Different forms of changes demand different treatment, handling, planning, and strategies and engagement of persons with different domain knowledge such as life science, engineering, medicines, pharmaceutical regulatory professional and marketing. Each industry should evolve its own change control policies, management style, strategies, etc. Depending on its area of specialty.

CONFLICT OF INTERESTS

Declared None

REFERENCES

1. Water land NH, Kowtna CC. Change control and SUPAC, in Nash RA, Wachter AH. Eds. Pharmaceutical Process Validation, Marcel Dekker, New York; 2003. p. 699, 748.
2. Quality V, Medicines E, Products H. Deviation Handling and Quality Risk Management. 2013: Available from: http://www.whoint/immunization_standards/vaccine_quality/risk_july_2013.pdf
3. Gausepohl C. Deviations–Definition and Requirements Requirements for deviation management. 2013;(10):1–3. 2014; Available from: http://www.gmp-publishing.com/media/files/leitartikel_2013/lOGFILE-10-2013-Deviations-Definition-Requirements.pdf
4. Freeman S. Change management: a far-reaching, comprehensive, and integrated system compliance. Handbook for Pharmaceuticals, Medical Devices, and Biologics. Ed. Carmen Medina. 1st edition. Marcel Dekker, New York; 2004. p. 315-46.
5. Implementation of pharma change control. Available from: http://www.fdanews.com/ext/resources/files/The_Food_And_Drug_Letter/2013/Pharma-Change-Control-Peither-ExecSeries.pdf. [Last Accessed 15 Dec 2014].
6. Directorate-general C. European commission. 2014. Available from: http://ec.europa.eu/health/files/gmp/2014-02_pc_draft_gmp_annex.pdf. [Last Accessed 15 Dec 2014].
7. History of Change management. 2014. Available from: http://www.prosci.com/change-management/change-management-history. [Last Accessed 15 Dec 2014].
8. Change Management. 2014. Available from: http:// www.change-management-coach.com/benefits-of-change-management.html. [Last Accessed on 20 Dec 2014].
9. GMP in production. 2014. Available from: http://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/cap5en.pdf. [Last Accessed on 20 Dec 2014].
10. Medical devices. CFR-Code of Federal Regulations Title 21. 2014. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.100. [Last Accessed on 20th Dec 2014].
11. Medical devices. CFR-Code of Federal Regulations Title 21. 2014;5–7. 2014. Available from: http:// www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.160. [Accessed on 20 Dec 2014].
12. Committee P. Working party on control of medicines and inspections final version of annex 15 to the EU Guide to Good Manufacturing Practice Title: 2001. 2014. Available from: http://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/v4an15_en. pdf. [Accessed on 20 Dec 2014].
13. Recommendations on validation master plan for non-sterile process. 2014. Available from: http://www.picscheme.org/pdf/25_pi-006-3-recommendation-on-validation-master-plan.pdf. [Last Accessed on 20 Dec 2014].
14. Guideline for the establishment of a control procedure for technical equipment, including related utilities, computerised systems and facilities used in the manufacture of API's. 2014. Available from: http://apic.cefic.org/pub/Guideline Technical Change Control.doc.pdf. [Last Accessed on 20 Dec 2014].
15. International Conference on Harmonization of technical requirements for registration of pharmaceutical for human use guidelines, Q 10, 2008. 2014. Available from: http:// www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf. [Last Accessed on 20 Dec 2014].
16. Questions and answers on post approval change management protocols use of post approval change management protocols. 2014. Available from: http://www.ema.europa.eu/ docs/en_GB/document_library/Scientific_guideline/2012/04/WC500125400.pdf. [Last Accessed on 20 Dec 2014].