

Change Management in Development White Paper

Introduction/Background

In 2008, the International Conference on Harmonization published the ICH tripartite guideline titled, *Pharmaceutical Quality System: Q10* which describes a model for an effective pharmaceutical quality system. The document stresses that a pharmaceutical quality system actually starts in pharmaceutical development and carries over for the entire lifecycle of the product. During the first quarter of 2013, the ICH Q10 Working Group conducted a survey in order to establish a foundation on how member companies are currently implementing the ICH Q10 system elements.

The survey results indicated that, while most companies seem to have the majority of the individual quality systems well under control, there may be room for additional guidance on the proper implementation of certain systems. One of the quality system elements highlighted as needing additional guidance was the change management system.

Throughout this white paper, we have used the term “change management”. The terms “change control” and “change management” are frequently used interchangeably and somewhat confusingly. When used as a noun, change is defined by Merriam-Webster as “the regulation of an activity especially by directive (regulate)” while management is defined as “the act or process of deciding how to use something (administration)”.

Change control is a systematic approach to regulating all changes made to a product or system. The purpose is to ensure that no unnecessary changes are made, that all changes are documented, that processes are not unnecessarily disrupted, and that resources are used efficiently. Change control is typically associated with commercial manufacturing where product understanding is mature and clearly defined processes have been validated and submitted to regulatory authorities.

Change management, on the other hand, is the mechanism used to initiate, record, assess, approve, and resolve changes. The purpose of a Change Management System is to manage change requests so that approved changes will be controlled. The primary objectives of change management are to:

- administer each change request from initiation through to closure;

- communicate the impact of changes to appropriate personnel; and
- allow small changes to be managed with a minimum of overhead.

Change management in the clinical development phase is fundamentally different from change control in commercial manufacturing. During development, product and process understanding is still evolving and changes occur frequently. The ICH Q10 guideline recognizes that “There is generally a difference in formality of change management processes prior to the initial regulatory submission and after submission”. The ICH Q10 guideline also states that “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 goal of this white paper is to create a better understanding of how to implement a change management system in the clinical development phase of a product’s lifecycle including the appropriate level of oversight for change management activities at CMOs. This white paper will:

- describes the regulatory requirements for a change management system
- provide a summary of a brief survey to establish a baseline for current change management practices within the IQ member companies
- describe the key elements of a change management system
- effective oversight of change management at CROs/CMOs
- provide final conclusions

Regulatory Requirements for a Pharmaceutical Development Change Management System

Change is intrinsic to the development and commercialization of a pharmaceutical product; as such, establishment of a robust change management system is an essential part a company’s pharmaceutical quality system. Throughout the lifecycle of a product, changes must be planned, controlled, and well-documented.

ICHQ8, Section 2 states, “The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls. Information from pharmaceutical development studies can be a basis for quality risk management. It is important to recognize that quality cannot be tested into products; i.e., quality should be built in by design. Changes in

formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space.”

Additionally, ICH Q10, Section 3.2.3 states, “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....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.” ICH Q10, Section 3.2.3 also encourages a change management system to employ phase appropriate elements of quality risk management (QRM) to evaluate proposed changes, where the level of effort and formality of evaluation should be commensurate with the level of risk.

There are numerous external regulations that define several basic expectations for a change management system, including the identification, preparation, implementation, and evaluation of changes to pharmaceutical processes, analytical methods, and manufacturing facilities. However, there are only a few references in the external regulations regarding change management which are particularly relevant to a pharmaceutical development quality system.

- ICH Q10, Section 3.2.3 notes that formality of a change management process should be commensurate with the stage of development.
- FDA Guidance for Industry, Quality Systems Approach to Pharmaceutical cGMP Regulations, Sept 2006, Section III.B states the following regarding product knowledge and process understanding during development: “Quality by design means designing and developing a product and associated manufacturing processes that will be used during product development to ensure that the product consistently attains a predefined quality at the end of the manufacturing process. Quality by design, in conjunction with a quality system, provides a sound framework for the transfer of product knowledge and process understanding from drug development to the commercial manufacturing processes and for post-development changes and optimization.”
- ICH Q8 (R2), section 2.2.1 focuses on the importance of change management in formulation development, ensuring that changes to product or process design are clearly evaluated with sufficient rationale to establish the link between clinical formulations and the commercial formulation.
- ICH Q11, section 9 reiterates the integral role of change management in knowledge management, including process development activities: “There should be a systematic approach to managing knowledge related to both drug substance and its manufacturing

process throughout the lifecycle. This knowledge management should include but not be limited to process development activities, technology transfer activities to internal sites and contract manufacturers, process validation studies over the lifecycle of the drug substance, and change management activities.”

The attached spreadsheet in the Appendix provides an overview of the current regulations regarding a change management system.

Summary of Survey Results

During the first quarter of 2015, the IQ Change Management working group conducted a brief survey in order to establish a baseline on how member companies are currently implementing change management systems. The survey examined four general topics:

1. Do you have a system in place?
2. How does that system function?
3. Are the regulatory aspects, including QP/Responsible Person, included?
4. How are changes at third parties managed?

The survey was sent to all IQ member companies and 21 responses were returned. The overall response rate was 57%. This is considered a high response rate so the results should reflect the status of change management within the IQ community. In addition, since the companies within IQ represent a strong cross section of the pharma industry, these results most likely reflect the state of change management systems within the pharma industry in general.

The following is a summary of the survey results for each section. The complete survey results are also available in the Appendix.

a. Do you have a system in place?

- i. The majority of companies (~90%) have an overall process and tracking system in place for change management in clinical development. In addition, the majority of companies (~70%) use some type of electronic system to track the change requests, although some companies that using paper or a mix of paper and electronic systems.

b. How does that system function?



- i. There was general consensus with what types of changes should be captured in a formal change management system. Approximately 80% of the respondents or higher agreed that process changes, equipment changes, site changes (e.g., packaging, testing, etc.), analytical method changes, and specification changes should be captured within the formal change management system. There was more variability, however, when assessing when a formal change management system was applied. Half of the companies apply their formal change management system to all changes within clinical development whereas the other half apply some type of phased approach (only for changes after phase 2 [~11%] or phase 3 [~17%], for example, or only for those changes impacting regulatory documents [~22%]).
 - ii. There was also more variability when examining how other changes that may occur outside the formal change management system are captured. A majority of companies (~60%) use executed batch records and the document history section (e.g., analytical methods, specifications, SOPs, etc.) to capture changes but companies also used equipment use records, laboratory notebooks, and project meeting minutes as mechanisms for documenting changes.
 - iii. In the majority of respondent companies (~74%), the QA group has the responsibility to monitor the change management system using a standard distribution list to ensure all affected functions are notified of the change. At almost all companies (~95%), QA is also responsible for approving the change requests, although frequently regulatory or the functional departments (e.g., analytical, API, oral solid dosage, etc.) also approve the change requests.
- c. Are the regulatory aspects, including QP/Responsible Person, included?**
- i. One key aspect of a formal change management system is ensuring that regulatory filings are current with respect to the proposed changes prior to the release of clinical material. The majority of companies (~85%) have such a system in place and document this as part of the formal change management system.
 - ii. Another key aspect of a formal change management system is ensuring the Qualified Person (QP) or the Responsible Person for Release (RP) is aware that any change request has been closed prior to releasing affected clinical material. The majority of companies have some system in place (~90%), although how this is



done varies from company to company. Some use a formal system (electronic or paper), some use e-mail, and still others use some type of informal communication.

d. How are changes at third parties managed?

- i. One of the most challenging aspects of a formal change management system is the oversight of changes at third party vendors. The majority of companies (~90%) use the Quality Agreement as a mechanism for defining how third party vendors notify sponsor companies of changes that occur at their site.
- ii. More variable was the level of quality oversight companies employ for changes at third party vendors. Half of the companies rely on non-approval notification of changes as the oversight mechanism. However, many companies (~30%) approve all changes while some companies rely on post-execution review (e.g., batch record review, ~12%). One company relied on person-in-the-plant to ensure oversight of changes. No companies relied solely on audits.

In summary, the majority of IQ member companies have an overall process and tracking system in place for change management in clinical development. However, when a formal change management system is applied is inconsistent among the IQ member companies. The survey results indicate that some companies apply a more holistic approach to change management utilizing a phased-approach and supplementing the formal system with other mechanisms for capturing changes with the appropriate QA oversight. In addition, the practical application of quality oversight to changes at third party vendors remains challenging. In developing this white paper, these results were taken into consideration.

Elements of a Development Change Management System

As indicated in the survey results, when a formal change management system is applied is inconsistent among the IQ member companies. Half of the companies apply their formal change management system to all changes within clinical development whereas the other half apply some type of phased or staged approach (e.g., only for changes after phase 2 or phase 3 or only for those changes impacting regulatory documents). In those instances when change is handled outside a formal change management system, separate procedures need to be established describing these alternative processes and the appropriate QA oversight. For example, like-for-like equipment changes may not need to be captured within a formal change

management system, but suitable procedures need to be in place describing how these changes are handled.

The remainder of this section will describe the elements of a formal change management system.

A formal change management system provides a structured approach for the identification, preparation, evaluation, review, implementation, and verification of changes in a GMP environment covering facilities, utilities, equipment, instruments, processes, and controlled documents (e.g., specifications, submission documents, stability protocols, etc.).

The fundamental principles of a formal change management system generally transcend the lifecycle of a product, and are independent of the phase of development or commercialization. Core elements of a formal change management system, regardless of pharmaceutical development or commercial manufacturing purposes, should govern the following activities:

- a. Process documentation
- b. Initiation of a change proposal
- c. Classification of the change
- d. Evaluation of risk and impact of the change
- e. Notification of key stakeholders
- f. Approval of the implementation plan and timelines by key stakeholders
- g. Implementation of the change
- h. Effectiveness check
- i. Change closure

a. Process documentation:

There needs to be written procedures that define the change process, roles and responsibilities, key elements and documentation, and approval requirements. This procedure should define what is/is not a change and when changes need prior approval or may follow a do, then tell approach. If a phase-approach is used, the phase-appropriate elements of QRM to evaluate proposed changes commensurate with the level of risk needs to be described.

In addition, the process needs to allow for the awareness and oversight of the Change Management System by management and quality including the review of Key Performance Indicators (KPIs).

b. Initiation of a change proposal

The change documentation should contain a description of the change and a justification for the change. In addition, the initiation of a change should include the notification of all relevant functions to ensure that all follow-up activities are considered and implemented.

c. Classification of the change

There should be a classification of change (e.g., minor, major, critical) commensurate with the risk to the product, process, equipment, etc. The greater the risk, the stronger the reliance on QRM to ensure appropriate changes are implemented.

Quality Assurance is responsible for the final determination of the classification.

d. Evaluation of the risk and impact of the change

Procedures need to be in place for the evaluation of changes by cross functional teams contributing the appropriate expertise and knowledge from relevant areas, to ensure the change is technically justified, using quality risk management tools, as necessary. The evaluation of the change also needs to consider any additional activities resulting from the implementation of the change.

The following aspects should be taken into consideration:

- i. Quality
- ii. Safety, identity, strength, purity
- iii. Efficacy
- iv. Internal Regulatory notification and approval, if required

Changes are reviewed by appropriate organizational units and SMEs to ensure that all aspects of change have been fully considered.

A change review board may be established to review the appropriateness and timing of critical/major changes. In adherence to ICH Q10, senior management must be involved in the overall governance of the development change management system, periodic review, and KPIs. This may be through a change review board or other mechanisms as defined in written procedures.

e. Notification key stakeholders

A key aspect of a Change Management system is the notification of all relevant functions so that they may evaluate the change for any additional required activities. For instance, a change to the final crystallization solvent to improve the impurity profile will require that the analytical group modify the residual solvents method to be able to monitor the new final crystallization solvent.

f. Approval of the implementation plan and timelines by key stakeholders

There must be documented agreement by all relevant functions to the change and any additional required activities. The approval of the change by all relevant functions is necessary before the implementation of the change occurs.

The Quality Unit is responsible for the overall management of the Change Management system, including the decision to accept, reject or request further clarification of the change.

Quality Assurance is responsible for the final review and approval/rejection of a proposed change.

g. Implementation of the change

Once a change is agreed to by all relevant functions and approved by Quality Assurance, the change may be implemented.

h. Effectiveness check

The change needs to be evaluated for the effectiveness of the change. This effectiveness/verification check should be commensurate with the risk to the product, process, equipment, etc. including a review of any unintended consequences.

i. Change closure

Following the closure of a change, change reports are maintained in a controlled repository or system (paper or electronic) by the Quality Unit.

Oversight of Change Management at CROs/CMOs

While variability also exists in pharmaceutical companies' oversight of change management at CROs/CMOs, there are certain key elements required in managing changes at third parties.

- a. The roles and responsibilities should be described in MSA/QAA agreements between the contracting firm and the third party.
- b. A process for notification of proposed changes at third party manufactures must be established, including any potential impact on regulatory commitments and product quality.
- c. Prior-approval requirements by the contracting firm need to be defined.

- d. The Quality Unit at the contracting firm should acknowledge the more significant changes at the third party.
- e. Routine auditing should verify adherence to these requirements.

Defining these aspects in MSA/QAA agreements will help ensure proper quality oversight of change management at CROs/CMOs.

Conclusions

Change is intrinsic to the development and commercialization of a pharmaceutical product. As such, establishment of a robust change management system is an essential part a company's pharmaceutical quality system. Throughout the lifecycle of a product, changes must be planned, controlled, and well-documented.

There are numerous external regulations that define basic expectations for a change management system; however, there are only a few change management requirements that are specific to a development pharmaceutical quality system. ICH Q10, Section 3.2.3 specifically encourages a change management system to employ phase appropriate elements of quality risk management (QRM) to evaluate proposed changes, where the level of effort and formality of evaluation should be commensurate with the level of risk and the stage of development.

As indicated in the survey results, when a formal change management system is applied is inconsistent among the IQ member companies. Half of the companies apply their formal change management system to all changes within clinical development whereas the other half apply some type of phased or staged approach (e.g., only for changes after phase 2 or phase 3 or only for those changes impacting regulatory documents). In those instances when change is handled outside a formal change management system, separate procedures need to be established describing these alternative processes and the appropriate QA oversight.

While variability exists in change management procedures and practices in development from pharmaceutical company to pharmaceutical company, certain core elements of a formal change management system emerged from our analysis.

- a. Process documentation
- b. Initiation of a change proposal



- c. Classification of the change
- d. Evaluation of risk and impact of the change
- e. Notification of key stakeholders
- f. Approval of the implementation plan and timelines by key stakeholders
- g. Implementation of the change
- h. Effectiveness check
- i. Change closure

While variability also exists in pharmaceutical companies' oversight of change management at CROs/CMOs, there are certain key elements required in managing changes at third parties (well defined roles and responsibilities, an agreed notification process, defined prior-approval requirements, and routine auditing). Defining these aspects in MSA/QAA agreements will help ensure proper quality oversight of change management activities at CROs/CMOs.

During development, product and process understanding is still evolving and changes occur frequently. This white paper has tried to create a better understanding of how to implement a change management system in the clinical development phase of a product's lifecycle including the appropriate level of oversight for change management activities at CMOs.

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APPENDIX

Summary of current regulations regarding a change management system:



IQ Change
Management Regulatc

Summary of survey results for implementation of Change Management Systems at IQ member companies:



IQ Change
Management Survey (