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# The Challenges of Regulatory Change Management: Does ICH Quality Trio Provide the Solution?

by Mary Oates, Michael Marini, and Barry McCloy

## Introduction

**R**obust change management is a critical element of a strong pharmaceutical quality system. Accordingly, ICH Q10, “Pharmaceutical Quality System,” describes it as a vital part of the lifecycle approach to product quality. However, in an environment of increasing globalization for both pharmaceutical firms and health authorities, regulatory change management presents significant challenges to all parties involved. This same globalization has resulted in ICH documents that may provide the solution to this complex issue. Individually, the ICH Quality trio of Q8, Q9, and Q10 provide significant benefits, including guidance on approaches to demonstrating process and product understanding throughout the product lifecycle, tools that can be used to assess and mitigate risk and a comprehensive description of a robust quality system. When applied collectively as part of a purposeful and cohesive approach, the benefits can be exponentially greater, including in the area of change management.

A regulatory change management system that is enabled by ICH Q8, Q9, and Q10 also will encourage and accelerate continuous improvement. Such a system would foster the identification of the critical few changes that must be approved by health authorities in advance of implementation and those that can be managed internally by the firm. Currently, many changes must be submitted to regulatory agencies for prior approval. This can discourage and undermine significant improvements, many of which simplify the manufacturing process and reduce uncertainty, from being rapidly implemented and result in nonconformance situations in some markets. Implementation

of a regulatory change in multiple countries can be a conformance challenge given the differences in regulatory expectations governing the content of the change justification and the variety of review and approval times. If global approval is not received for a given change in a timely manner, a great deal of supply chain complexity can be introduced. Of even more importance, a firm could be placed in a position of nonconformance in those countries that have approved the change due to the fact that some regulatory authorities expect implementation within a defined period of time post-approval (e.g., within six months). Firms are faced with the following options:

1. Implement change(s) only after approval has been received from all affected markets.
2. Maintain two separate processes at the manufacturing site; one for markets where the authorization to implement the change(s) has been received and a different process for markets where authorization to implement the change(s) has not been received. This may only be possible if both processes can be utilized concurrently and the resulting products can be adequately segregated and controlled to ensure that only the product produced for a specific market (or markets) is distributed into those markets.
3. Build sufficient inventory with the material manufactured via the current process in order to supply the countries where the change has not yet been approved, and implement the change to accommodate those markets that have already approved the change(s). In order to implement this approach, an accurate forecast of inventory is required to assure constant supply to those markets

that have not yet approved the change.

4. Implement change(s) to accommodate those markets that have approved the change(s) and accept that the site cannot supply “changed” material to those countries where prior approval is required, potentially resulting in the unavailability of medicine needed by patients for an undetermined period of time.
5. Not to pursue the change. A site could find it practically impossible to comply with all markets simultaneously; therefore, the most prudent option may be to maintain the current process for all markets.

Of the options discussed above, option 1 represents the ideal situation as this assures full compliance with all existing registrations and the site only has to manage one process/product. However, depending on the complexity of the change and the differing review periods by various health authorities, a site may find the change has been approved expeditiously (e.g., within a three month period) in some markets, while others are on an entirely different time schedule (e.g., up to two years). In these cases the site may find itself out of compliance with its registration in the early-approving markets.

Over time, the impact of the options available and the challenge to simultaneously comply with all markets in a practical manner results in sites, and on a larger scale, industry failing to take advantage of innovations in production and testing technology. Therefore, it is important that solutions to these challenges be identified and implemented.

An ideal solution to these challenges is a more agile and consistent global regulatory change management system that would be of benefit to industry, regulators and patients. One way to accomplish this is to provide firms the ability to internally manage the vast majority of changes that currently require regulatory approval prior to implementation provided a firm can demonstrate appropriate control over these changes and their impacts. The application of robust change management within the framework of ICH Q8, Q9, and Q10, specifically a strong pharmaceutical quality system combined with appropriate process knowledge and understanding and mitigation of risks, should enhance the confidence of global health authorities that firms have the ability to appropriately assess and implement changes internally with minimal regulatory involvement. In other words, is it possible for the firm to move into a “low risk” category for change management?

The key elements that firms should include in their change management process in order to demonstrate a high level of control and understanding are depicted in Figure 1. These include:

- A strong overarching quality system of which change management is one aspect (Q10).
- Active knowledge management (Q10).
- Tools and culture that support science-based risk assessments followed by appropriate decision-making (Q8, Q9).
- Organizational Agility (inherent in the ICH Quality trio).

- Timely and accurate internal and external communication (Q10).
- Management oversight of the performance of the change management system (Q10).

This article will provide insight into these critical components of a robust change management system and propose a solution to the current challenge of global regulatory change.

## The Importance of an Overarching Quality System

Robust change management cannot exist in the absence of a strong, overall quality system. As defined in ICH Q10, other elements of the quality system include process performance and product quality monitoring, corrective and preventive actions, and management review of process performance and product quality. It is actually the outputs from these systems as well as scientific and technological advances that serve as stimuli for change. This relationship is illustrated in Figure 1. As the body of knowledge about a process and product grows from development to commercial manufacturing, monitoring and trending will likely result in increased opportunities for improvement. A strong mechanism must be in place to capture these stimuli for change. There also must be a process for identification and mitigation of any risks associated with proposed changes. Following approval and implementation, the impact of the modification (e.g., to parameters, specifications, procedures, etc.) will be assessed as part of routine monitoring and trending, adding again to the overall body of knowledge. Equally essential to change management is organizational agility, ensuring that changes can be made quickly and efficiently, having appropriate systems in place to control change and effective communication of changes, both within the firm, and where necessary, to external bodies such as regulatory agencies and customers. Management review of the overall process is key to maintaining the system’s robustness.

## Active Knowledge Management

No change management system can be successful without

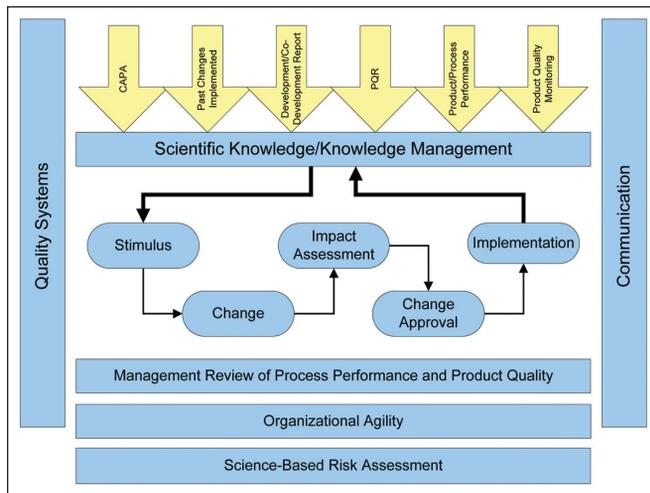


Figure 1. Elements and inputs of a robust change management system.

active knowledge management, described in ICH Q10 as an enabler of the quality system. Stimuli for change can be found in the inputs and outputs of many other systems and processes and must be captured, trended, understood, and used for continuous improvement. In addition to this proactive approach, the need for change also may be identified on an ad hoc basis as events occur. A well-designed change management system will allow for the identification and implementation of changes from both proactive and reactive sources. Management alone is not responsible for determining changes that may be needed; rather, every member of an organization must be vigilant in identifying opportunities for continuous improvement and sponsor their implementation via the change management process.

A listing of potential sources for change stimuli is given below. This listing is not intended to be comprehensive and it should be recognized that other opportunities exist to identify opportunities for improvement:

- trend reports
  - release and stability testing
  - manufacturing deviations
  - laboratory investigations
  - product complaints
  - environmental monitoring, including facility, utilities, and personnel
  - calibration
  - production trending (yields, waste, reconciliation)
- monitoring (internal and external)
  - supplier performance
  - statistical process control
  - new or revised regulatory requirements
  - changing needs of internal and external customers
  - external benchmarking
- others
  - process improvement to achieve greater efficiency and/or capability
  - implementation of innovative processes and/or equipment
  - response to isolated process or product non-conformances that could impact quality

In addition to these individualized mechanisms, the Product Quality Review (PQR) provides a holistic view of quality performance relative to a specific product or product family on a regular (e.g., annual) basis. This allows management to identify further need for change not apparent when system data is viewed in isolation.

Appropriate, necessary change serves as an indicator of the effectiveness of the other elements of the quality system. Change provides evidence that quality systems are functioning per expectation and attests to an organization's agility and commitment to continuous improvement.

## Science-Based Risk Assessment

When assessing a proposed change, the impact of any associated risk should be evaluated using available data. It should

be noted that changes are typically made to reduce known risk, rather than increasing known or unknown risk. However, this assessment must be considered as part of the process. It is also important to ensure that a change made in one system will not adversely affect another area of operation. The impact of the change must be evaluated in a holistic manner.

Risk can be assessed using classical tools to identify the hazard(s) associated with each type of risk, the criticality or severity of the potential risk, and the probability of its occurrence to obtain a resulting "risk score." Definition of severity and probability must be predetermined and included in the overall risk assessment. Criteria for acceptance of each potential issue, or the threshold for the "risk score," should be established in advance to determine the overall risk profile for the proposed change.

Changes may be categorized and classified using a risk-based approach. The level of risk includes an assessment of the level of understanding and knowledge of the process and associated inputs and outputs, impact to safety and efficacy, and experience with the execution of similar changes. The process is designed to ensure that the effort associated with making a change is commensurate with the risk associated with the change and the level of product and process understanding. This includes the amount of justification required for the change as well as the approvals required to make it.

This concept of using risk to determine the rigor necessary for individual changes also can be applied to the risk presented by a firm's regulatory change management process. Ideally, firms or sites with low risk due to their application of Q8, Q9, and Q10 should be able to self-manage more changes than those who have not adopted the ICH Quality trio.

## Organizational Agility

Organizational agility represents an organization's ability to respond to the need for change. Changes are driven by regulators, business needs, and product and process improvements. The ability of an organization to both quickly and effectively respond to these stimuli will be an important factor toward its success in meeting the needs of all customers, internal and external, including patients and regulators.

In the context of a change management system, organizational agility refers to the ability of the organization to quickly, yet effectively, implement changes. The system design allows for flexibility by specifying the scope of included changes as well as empowering individuals throughout the organization to make changes that have proven to have no impact on the quality of the product or process. An example of this is found in the application of Quality by Design. In a design space environment, stimuli for change may present themselves from one batch to the next or within a batch, perhaps resulting from differences in the attributes of raw materials or data from in-process testing (on, at or off-line). The change management system must be designed to allow rapid responsiveness to these multivariate inputs.

Design space defines relationships and boundaries that have been demonstrated experimentally. Therefore, the need for additional assessment within the design space as would

typically occur in a change management process prior to implementation is absent. The only requirement should be second party verification that the appropriate response was selected; much the same as manufacturing equipment settings are verified for products with traditional boundaries and regulatory applications. Therefore, it is essential that batch records reflect the matrix of interrelationships and the related acceptable ranges for process parameters. Only when a firm proposes to exceed the boundaries of the established design space should the formal change management process need to be invoked, which may include review and approval by health authorities.

An aspect of organizational agility not yet addressed is the ability to manage changes not only within the firm, but at external contractors. As supply chains become increasingly dependent on contractors to meet demand needs, it is essential that change management accommodate this extension of the operation. Since the product owner bears the ultimate responsibility for integrity of the product, regardless of where manufactured, it is vital they maintain visibility to proposed changes with potential impact on the product. This is most readily accomplished through the requirement for a product owner's approval of any changes that may impact product quality or regulatory registrations. The quality agreement with the contractor should include a provision to require review and approval of these changes prior to implementation. The product owner shall bear final responsibility for assessing the impact of the proposed change on the filed process and product quality. A mechanism should be established to provide the product owner with periodic status updates on open changes affecting their products. On an annual basis, the contractor should provide a summary of all changes made to the product, which may be accomplished through an annual document (e.g., the PQR) or as established in the quality agreement.

People agility is an important element that impacts a firm's effectiveness in implementing change. Employees themselves must be managed within the change management system, ensuring that effective, relevant, and recordable training is provided.

Organizational agility is a contributing factor that will allow a firm to self-manage changes in a timely and controlled manner, promoting rapid continuous improvement and reducing risk.

## Communication

Ongoing success of change management is dependent on clear and timely communication to all stakeholders. As changes are proposed, feedback from parties that will be impacted by the change must be evaluated to ensure that the change will have the desired effect. Key to these discussions is an agreement on the timeline and steps needed to achieve approval and implementation. In the future, the few changes that must be approved by health authorities, particularly complex ones, may benefit from an early discussion with regulators regarding expectations and timing. The more relevant information that is shared about a change in advance

with impacted parties, the more smoothly the approval and implementation should prove.

## Management Oversight of Change Management Performance

It is the role of senior management to ensure the existence of a sustainable and effective change management system. Management sponsors the initial design of a robust program and once implemented, uses a variety of tools and techniques to measure the effectiveness of the various stages of the process. There are three indicators which can effectively summarize the health of a change management system, specifically: timeliness, quality (degree of "right first time" performance), and post-implementation verification.

In an effective change management process, changes are implemented in a timely way that meets the needs of the specific situation. Certain changes will require greater urgency than others, but all should be progressed through the process so due dates are consistently met. Management has two responsibilities in this area. The first is to monitor the timeliness of the change management system using appropriate metrics and take corrective action, as needed. The second is to ensure adequate oversight of changes that have been delayed exists in order to understand and mitigate any risk introduced by these delays. In such cases, the potential impact on product quality, patient safety, and customer satisfaction should be assessed, documented, and addressed.

The second key indicator of the change management process is the "right first time" metric. At each critical stage of the process, there is a review and approval gate. A measure of the number and frequency of submissions that are denied approval or require rework is a key indicator of effectiveness. Rejection or rework not only results in costly waste of resources and time, but also may point to deficiencies in other processes, such as training, clarity of requirements, or an inability to appropriately assess and mitigate risk. Management has the responsibility to monitor the right first time metrics of the change process and take necessary corrective action.

The third key indicator is post-implementation verification that changes have been effective in achieving the desired outcome (including no unintended consequences). If the appropriate end state has not been successfully reached in the expected timeframe, an assessment should be completed to understand why this has occurred. Additional work may be necessary, either in the form of revision to the change control or in resolving roadblocks that may be impeding progress. Management should ensure the results of the verification step are trended and that any necessary improvements are made to the overall change management process.

Each of the three indicators described above and their associated metrics are staples of a firm's management review process. Targets should be established for these key indicators and action taken if the desired performance is not achieved. This may include redesigning the overall system if it is not functioning efficiently, providing training to users, addressing specific issues that arise or assessing if the resources allocated to change management are appropriate. The management

review also provides a forum for developing continuous improvement initiatives for a change management process that is already performing within expectations.

Fundamentally, management oversight of the design and execution of change management results in a self-sustaining process which will control change, mitigate any associated risks and allow for rapid improvement to processes and products.

## Synergistic Benefits of the ICH Quality Trio

By applying ICH Q8, Q9, and Q10 in the context of change management, the firm or site is able to:

- Control the change process.
- Identify the need for change.
- Accurately assess the risk of the change and correlate it with the effort required.
- Rapidly implement needed change.
- Continuously improve systems, processes, and change management itself.

This purposeful and cohesive approach may allow a firm to be viewed by health authorities as “low risk” and enable greater self-management of changes that today must receive prior regulatory approval.

The use of risk-based change management is a well-accepted concept. In fact, “Pharmaceutical GMPs for the 21st Century – A Risk-Based Approach” (September 2004)<sup>1</sup> states, “Decisions on postmarket changes need to be made based on an understanding of the process and risks associated with the changes on the quality of the manufactured product.” The application of risk for changes affecting US-marketed products was further clarified in the FDA Guidance for Industry, “CMC Postapproval Manufacturing Changes Reportable in Annual Reports” (June 2010)<sup>2</sup>, which provided a list of changes considered to be “very low risk” and that do not need to be submitted in supplements. Certainly the firm’s ability to understand its processes, mitigate risks, and control the change process are factors in assessing the overall risk of a change.

Recently, FDA sponsored a research assessment<sup>3</sup> to determine if a comparability protocol can satisfy FDA’s expectations for a specific type of change while enhancing the efficiency of the change process. It was found that the use of an approved comparability protocol is feasible for making a change from one sterile manufacturing site to another under current FDA regulations. Given the potential significance and impact to patient of a change in sterile manufacturing site, the self-management of other, lower risk changes by firms deemed to be capable seems to be a concept worth considering.

The FDA is not alone in their application of risk in assessing changes. Commission Regulation (EC) 1234/2008<sup>4</sup>, which became effective in January 2010, describes a system in which certain minor variations can be reported and implemented without prior approval for centralized marketing authorizations in the EU. This change was made “to enable competent

authorities to focus on those variations that have a genuine impact on quality, safety, or efficacy.”

It is clear that health authorities accept that risk can be differentiated based on the type of change and the controls in place to manage it. The adoption of ICH Q8, Q9, and Q10 as a comprehensive approach reduces the risk of the firm or site’s change management process. The proposal described in this article adds an assessment of the firm to the assessment of the change when defining the total risk of the change.

## Industry and Health Authority Responsibilities

In this scenario, industry would be required to demonstrate that their application of Q8, Q9, and Q10 reduces the risk of change. This could be accomplished during routine inspections or via inspections for this specific purpose. All documentation pertinent to changes would be available for review by health authorities during inspections, providing regulators the opportunity to verify that the firm has appropriate and effective systems in place for self-management of these changes.

Health authorities would need to agree upon a globally accepted criteria for “low risk” change management systems. In addition, an evaluation would need to be made if the concept herein proposed is feasible under existing global regulations. Firms and/or sites would need to be assessed for risk categorization and routinely evaluated to update the original classification. Again, this could be achieved during routine inspections.

In addition, changes that under no circumstances could be included in such a program, i.e., always require prior approval, should be delineated.

## Conclusion

Numerous benefits would result from the adoption of a regulatory change management system that permits self-management of certain changes by firms or sites deemed to be “low risk” based on their implementation of ICH Q8, Q9 and Q10. These include the acceleration of innovation and continuous improvement of product quality; increased adoption of the principles in the ICH Quality trio; more efficient use of health authority and industry resources, focused on higher risk areas; reduced complexity and cost in the supply chain; ensured conformance in all markets and the enhanced ability to supply needed medicines to patients. It is hoped that this article will stimulate the necessary dialogue amongst industry and regulators to establish the baseline criteria to achieve a system in which the majority of changes can be self-managed globally within the framework of ICH Q8, Q9, and Q10 with total visibility to the health authorities upon request.

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## About the Authors

**Michael Marini** received a BS in biology and chemistry from Wagner College in Staten Island, NY. He began his career as an analytical chemist supporting stability and method validation activities at Marsam Pharmaceuticals in Cherry Hill, NJ. He held similar positions with Dupont Merck in Wilmington, DE and the Robert Wood Johnson Pharmaceutical Research Institute in Raritan, NJ. In 1994, Marini joined Warner-Lambert in Morris Plains, NJ as a member of its Analytical Technology Group supporting method validation, transfer, and troubleshooting activities. During his tenure with the Group, he held positions of increasing responsibility, the last of which as a Senior Supervising Scientist tasked with oversight of a group of method development chemists. After the acquisition of Warner Lambert by Pfizer, Marini moved into a series of quality compliance/assurance roles supporting Pfizer's network of manufacturing sites. In April of 2010, he moved to his current position as Senior Manager of Quality Systems for the Capsugel Division of Pfizer in Greenwood, SC. In his current role, Marini provides Quality guidance and oversight to the Capsugel affiliates involved in the manufacture of dietary supplements and pharmaceuticals for clinical and commercial use. He can be contacted by email: michael.marini@pfizer.com.

Capsugel – A Division of Pfizer, 535 N. Emerald Rd., Greenwood, South Carolina 29646, USA.



**Barry McCloy** received his PhD in applied chemistry from Strathclyde University in Scotland. His thesis was modeled around synthesis of novel small molecule anti-cancer agents and their controlled release from hydrogel polymer systems. He began his career in the United Kingdom with Exxon Corporation in 1983, first as a QC analyst,

then via a number of other roles including Manager of the Quality Systems Group where he led a successful campaign to gain ISO9001 accreditation in the manufacturing operations business unit. After relocating to California in 1997, McCloy held a number of positions with Chevron Corporation and was instrumental in the development of their EHS Quality System – *protecting people and the environment* – which was successfully rolled out at Chevron sites worldwide. McCloy joined Amgen Inc. at the Fremont manufacturing facility (formerly Abgenix) in 2002 and developed and implemented the Non-Conformance, CAPA, and Change Control processes for all GMP governed systems. He is currently engaged in designing and advancing a new generation of systems, including Quality by Design, and maintains responsibility for the Environment,

Health, and Safety function at the Amgen Fremont site. He can be contacted by email: bmcclay@amgen.com.

Amgen Inc., 6701 Kaiser Dr., Fremont, California 94555, USA.



**Mary Oates** received a PhD in analytical chemistry from the University of North Carolina at Chapel Hill and holds an undergraduate degree in biochemistry from Queens College. She began her career at Glaxo in North Carolina as an analytical chemist supporting R&D activities. In 1994, she joined Pfizer as a methods validation scientist.

She subsequently held positions of increasing responsibility, including oversight for all post-approval regulatory changes and responsibility for Quality at all manufacturing facilities in North America. Oates is currently Vice President of Global Quality Operations at Pfizer. In this role, she is responsible for Quality oversight of all products made by and for Pfizer for both clinical and commercial use. Oates is actively involved in industry initiatives that are aimed at enhancing product quality. For example, she is the immediate past Chair of the Steering Committee of the Product Quality Research Institute. She can be contacted by email: mary.oates@pfizer.com.

Pfizer, 100 Route 206 N., Peapack, New Jersey 07977, USA. 