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Industry One-Voice-of-Quality (1VQ) Solutions: Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS) ––through Enhanced Science and Risk-Based Approaches

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COMMENTARY

Industry One-Voice-of-Quality (1VQ) Solutions: Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS)—through Enhanced Science and Risk-Based Approaches

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ABSTRACT: Post-approval changes are inevitable and necessary throughout the life of a drug product—to implement new knowledge, maintain a state of control, and drive continual improvement. Many post-approval changes require regulatory agency approval by individual countries before implementation. Because of the global regulatory complexity, individual post-approval changes usually take years for full worldwide approval even when they reduce patient risk, improve compliance, or enhance the manufacturing process or test methods. This global complexity slows down continual improvement and innovation and can cause drug shortages and current good manufacturing practices compliance issues. Manufacturers that market products globally experience the greatest challenge and risks in their daily operations because of this post-approval change complexity. A global problem needs a global solution. This paper has been sponsored and endorsed by senior quality leaders (Chief Quality Officers/Heads of Quality) from >20 global pharmaceutical companies who have collaborated to speak with "One-Voice-Of-Quality" (1VQ). The paper provides two specific solutions that lay the foundation for an aligned and standardized industry position on the topic of effective management of post-approval changes in the pharmaceutical quality system (PQS). This document represents the 1VQ standard approach for the steps necessary to establish and demonstrate an effective quality system to fully leverage a risk-based approach to post-approval changes as laid out by ICH Q10 Annex 1. Implementation of the solutions presented in this paper can help achieve a transformational shift with faster implementation of new knowledge, continual improvement, and innovation through post-approval changes. The Chief Quality Officers/Heads of Quality are inviting other companies to join the 1VQ (contact either Emma Ramnarine or Anders Vinther) and other stakeholders to join the dialog.

KEYWORDS: Pharmaceuticals, Post-approval change (PAC), ICH Q10, Pharmaceutical quality system (PQS), ICH Q12, Science and risk-based approach.

Context and Current State, May 2020

This paper lays the foundation for an aligned and standardized industry position on the topic of effective management of post-approval changes (PACs) in the pharmaceutical quality system (PQS). Senior quality leaders (Chief Quality Officers/Heads of Quality) from more than 20 global pharmaceutical companies have collaborated to speak with "One-Voice-Of-Quality" (1VQ). The first two solutions identified in the One-Voice-of Quality (1VQ) Concept Paper "*Solving the Global Continual Improvement and Innovation Challenge: How an Effective Pharmaceutical Quality System Can Transform Post-Approval Change Management*" (1), published in the *PDA Journal of Pharmaceutical Science and Technology*, are presented here. This document represents the 1VQ standard approach for the steps necessary to establish and demonstrate an effective quality system to fully leverage

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the risk-based approach to PACs as laid out by ICH Q10 Annex 1. Demonstrating a detailed understanding, effective implementation, and compliance with ICH Q10 will allow companies to overcome barriers to continual improvement and innovation. Additionally, it will help reduce drug shortages in the global environment by allowing faster implementation of PACs and reducing the PAC burden on both industry and regulators. This paper also provides the foundation for implementation of ICH Q12. It is intended to drive a paradigm shift from a country-specific and "one size fits all" approach to an enhanced[1] science and risk-based approach for approval expectations focused on patient safety and product availability.

PACs are inevitable and necessary throughout the life of a drug product—to implement new knowledge, maintain a state of control, and drive continual improvement. Many of these PACs require regulatory agency approval by individual countries before implementation. Owing to global regulatory complexity, individual PACs often take years for full worldwide approval, even when they reduce patient risk, improve compliance, and/or enhance the manufacturing process or test methods. The consequence of this can ultimately lead to potential drug shortages for patients and possible compliance risks for companies.[2]

The current COVID-19 pandemic, although an exceptional situation, is challenging pharmaceutical companies and regulators alike in making life-saving decisions for patients in unprecedented ways to ensure drug products are available with no shortages. The global impact of COVID-19 has demonstrated that diseases know no borders, and solutions to fight such diseases need be global in nature to be timely and effective. It has also underscored the necessity to transform our current national or regional-based systems and processes whereby changes to manufacturing and testing of drug products already marketed or for new indications, can be implemented quickly. The highly complex global regulatory framework for managing PACs is simply not capable of dealing with a crisis like the COVID-19 pandemic, and systems have to be bent to prevent drug shortages. Opportunities to learn from and adopt new ways of working that emerge from the COVID-19 crisis should be integrated into transforming how patient needs are met by making products available with the highest sense of urgency, by an industry that is capable of globally implementing improvements in a timely manner.

The 2005 ICH Q10 Concept Paper (2) recognized the challenge with global filing of PACs, including: "Delays may occur in the availability of medicines to patients around the world" and "Delays in the implementation of innovation and continual improvement for existing products may occur due to different expectations in the three regions". To address these issues caused by the PAC global complexity within the current regulatory framework, a solution to reduce the size of this challenge has already been described in ICH Q10 Pharmaceutical Quality System. The benefits of the ICH Q10 guideline upon completion and implementation, as stated in the Concept Paper, include "Encourage industry to improve manufacturing processes", "Facilitate innovation and continual improvement", and "Encourage a science and risk-based approach to quality decisions".

The ICH Q10 guideline was approved by the ICH parties in 2008 (3). Annex 1 of the document describes potential opportunities to enhance science and risk-based regulatory approaches to PACs as follows: When a company can "demonstrate effective PQS and product and process understanding" this is an opportunity to "optimize science and risk-based PAC processes to maximize benefits from innovation and continual improvement". Since the ICH Q10 approval in 2008, no regulatory guidance has been made available on what the measures for an effective PQS are and how to demonstrate effectiveness of a PQS. Current regulatory mechanisms and guidance for PACs also do not consider the company's latest product and process knowledge when determining the type of filing required to implement the change. Further, the effectiveness of the company's PQS to manage PACs is not considered during the assessment of individual PACs or during inspections. The 1VQ Concept Paper addresses these challenges. It details the perceived problem, strategic importance of the topic, actions proposed, deliverables, and issues to be resolved.

This document expands on the main deliverables from the 1VQ Concept Paper. It outlines how PACs can be effectively managed in the PQS utilizing enhanced

[1] **Enhanced risk-based approach:** For companies—risk assessments are updated with the latest product and process knowledge, regardless of filing geography (science knows no borders). For regulators—effectiveness of the PQS and current product/process knowledge (vs. general risk understanding) is used in risk-based decision-making for PACs.

[2] **FDA Drug Shortage Report to Congress** "Drug Shortages: Root Causes and Potential Solutions" October 2019. https://www.fda.gov/media/131130/download.

science and risk-based regulatory strategies that are aligned with ICH Q10; this could allow more changes to be managed in the PQS or via notification pathways, instead of by prior approvals. It identifies specific PQS elements to further develop and define for managing PACs in the PQS, provides points to consider for PACs for each of these elements, and how the effectiveness of PAC management in the PQS can be demonstrated. It includes a standard risk-based assessment of PACs that incorporates latest product and process knowledge at the individual change level.

Purpose

Although this document is intended foremost to define a standardized approach to demonstrate effective management of PACs in the PQS using product and process knowledge in industry, it is also an opportunity to encourage dialog with and among regulators on this topic, thus ultimately resulting in global regulatory harmonization for managing PACs. In order for these 1VQ solutions to deliver the value envisioned, it is essential for regulatory agencies to accept an enhanced science and risk-based approach to managing PACs. This can require changes to current practices, regulations, and/or guidelines. Upon implementation, this approach can further reduce the regulatory burden for PACs and allow regulatory agencies and companies to focus on the changes that are a higher risk to product quality as it relates to patient safety and efficacy. Health authorities relying on each other for assessments of the same PAC submitted by the company to multiple countries would further reduce the challenge both industry and regulators face.

Although this document is based on ICH Q10—and hence applicable to countries that are members of ICH—the full benefit for patients and companies in terms of reduced drug shortages and enhanced innovation will only be achieved when health authorities around the world engage in a dialog on PAC management complexity with industry and with each other. This document is written to encourage a convergence and harmonization dialog between the industry 1VQ and regulators. Upon adoption of the solutions presented in this paper, companies will be able to gain the benefits of implementing latest product and process knowledge to improve quality, ensure a sustainable supply, and ultimately reduce the potential for drug shortages.

Prior to reading this document, reading ICH Q9 (5), ICH Q10 (3), ICH Q12 (6), the "One-Voice-Of-Quality" Concept Paper (1), and the PIC/S paper "PIC/S Recommendation on How to Evaluate/Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management" (4) is recommended.

Background

Implementation of an effective PQS is essential for a company to achieve product realization, maintain a state of control, and facilitate continual improvement (3).

As commercial product experience and knowledge is gained, changes are generally needed to improve daily operations, manufacturing processes, and the control strategy. PACs are thus a natural and essential part of a product's commercial life cycle. PACs are needed for many different reasons, such as (but not limited to):

1. upgrading aging facilities and equipment;
2. maintaining current good manufacturing practice (cGMP) compliance and a state of control;
3. evolving regulatory requirements;
4. new technologies;
5. supplier changes; and
6. acquisition of new knowledge about products and processes (e.g., monitoring of product quality controls and trends, post market surveillance, adverse event reporting, annual product review, etc.).

To better serve patients, PACs should be implemented in a timely manner. However, today many PACs require regulatory prior approval that can take years before full implementation worldwide. Moreover, the accumulation of multiple PACs awaiting regulatory approvals with time lines that cannot always be predicted increases the potential for drug shortages.

Additionally, sometimes companies and quality leaders find themselves in a dilemma when a PAC is needed to maintain cGMP compliance in certain countries while the change requires approval in the same or other countries before implementation. This dilemma of cGMP

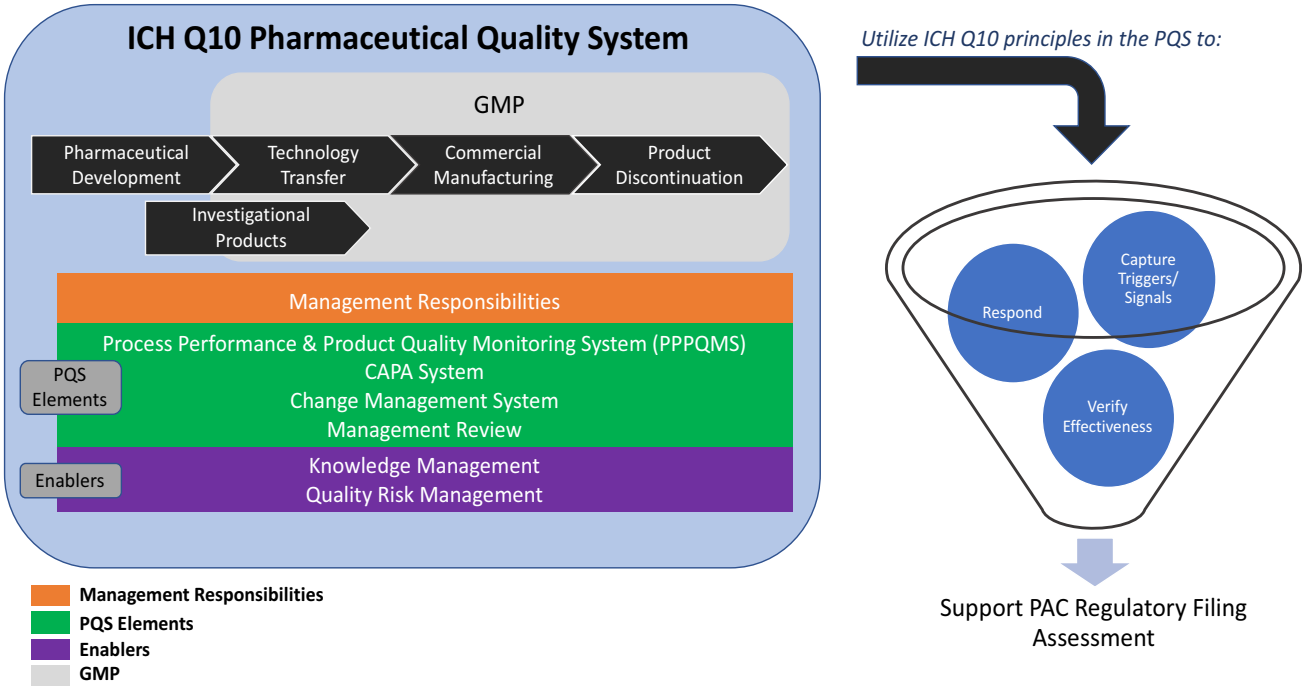

Figure 1

Utilizing ICH Q10 for effective management of post-approval changes.

compliance vs. regulatory *conformance* poses a complexity for timely and effective PAC management. The intended enhanced science and risk-based approach cannot be used to justify noncompliance with cGMP requirements. Companies should remain compliant with cGMP requirements while using the enhanced science and risk-based approach to determine regulatory strategy and manage conformance to global registrations. Regulatory filings should be kept current on a regular basis.

Utilizing ICH Q10 for Effective Management of PACs

When PACs are introduced, the combination of an effective PQS, product and process understanding, use of quality risk management (QRM), and a mature quality culture should ensure that product quality, patient safety, and adequate supply to patients are maintained. ICH Q10 (3) states that when a company can *"demonstrate effective pharmaceutical quality system and product and process understanding"*, this is an *"opportunity to optimize science and risk-based postapproval change processes to maximize benefits from innovation and continual improvement"* (ICH Q10 Annex 1). However, ICH Q10 does not provide specific details on how each of the quality system elements and key enablers can be further defined and detailed to effectively manage PACs in the PQS. This document provides enhanced science and risk-based guidance on how companies can effectively manage PACs within the PQS, building on the principles laid out in the ICH Q10 Guideline, by adding specific PAC-related details for each of the two enablers and the four quality system elements. Figure 1 depicts the PQS elements, enablers, and principles discussed in ICH Q10 that can support effective management of PACs through the PQS.

The PQS elements include: the process performance and product quality monitoring system (PPPQMS), the corrective action and preventive action (CAPA) system, the change management system, and management review. The enablers include: knowledge management (KM) and QRM.

Figure 2 depicts how a company can maintain a state of control and facilitate continual improvement through a PQS that (1) captures triggers/signals for changes or corrective and preventive actions, (2) manages these within the PQS, and (3) verifies them for effectiveness. All of this information should be utilized to determine the regulatory filing approach for a PAC.

Building an effective PQS is the responsibility of the company, one that extends beyond having a license or

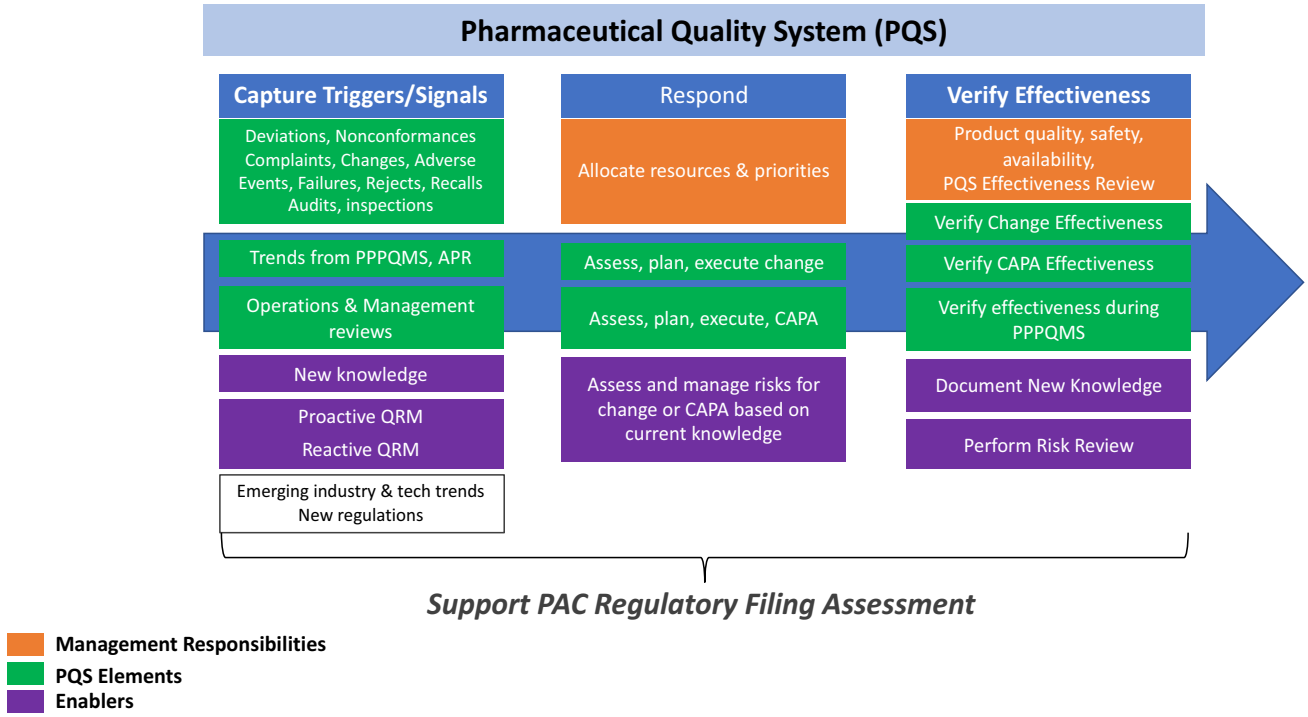

Figure 2

Maintaining state of control, facilitating continual improvement, and effectively managing post-approval changes in the pharmaceutical quality system.

a cGMP certificate to manufacture medicinal products. Being compliant with cGMP is a critical requirement and a prerequisite to gain the benefits of regulatory flexibility and timely PAC management. The framework should extend to also include PACs in outsourced operations and supplier management, to ensure that these are also planned, managed, and controlled by the company's PQS and communicated appropriately. In order to achieve the benefits of ICH Q10 Annex 1 through an enhanced science and risk-based approach, companies are encouraged to implement and demonstrate these 1VQ solutions within their PQS (e.g., the quality manual or quality plan).

The effectiveness of the company's PQS to manage PACs for each manufacturing site and across multiple sites should be considered during the assessment of individual PACs and can be evaluated during health authority inspections. Management should conduct reviews of the PQS to effectively manage PACs. This includes developing performance indicators and allocating adequate resources and budget for continual improvement and planning, implementing, and monitoring PACs. Additional management responsibilities include accountability for the overall PAC management strategy, including implementation of the 1VQ solutions, ensuring that internal audits, change mechanisms (or change management system), and QRM enable proactive assessment and mitigation of risks in the PQS, and for developing and maintaining the desired quality culture at all levels in the company.

PQS Enablers

ICH Q10 describes QRM and KM as enablers of the PQS because they:

1. facilitate product realization, state of control maintenance, and continual improvement and

2. enable a company to successfully and effectively implement ICH Q10.

Therefore, structured KM and QRM (as described in ICH Q9 (5)), should be implemented and integrated throughout the product life cycle and into the four PQS elements, and appropriate resources should be allocated by management accordingly.

Knowledge Management (KM)

ICH Q10 defines KM as *"a systemic approach to acquiring, analyzing, storing and disseminating information related to products, manufacturing processes and components."* In practice, KM aggregates existing and newly acquired information to inform risk management and guide PAC decisions. Examples include knowledge gained from PPPQM, deviations, trends, complaints, recalls, product quality reviews, and management reviews. Development studies, including designs of experiments, should also be considered for gaining new knowledge, as well as, but not limited to, the use of enhanced data analysis and analytics, statistical tools, and mathematical and predictive models. The expanded access to and use of technical and operational information, combined with increased competency of employees based on latest product and process knowledge, enables faster implementation of new knowledge to continually improve the quality and availability of a product during its commercial phase.

To enable effective PAC management, KM should be utilized as part of the PQS. KM should incorporate both explicit and tacit knowledge with an aim to further understand the risks and benefits of a given PAC. For example, product and process knowledge should serve as an input to the control strategy to better understand relationships between parameters and attributes. The same inputs may be used during risk management of PACs.

The elements of KM should be defined in the PQS and maintained through appropriate mechanisms to enable ready access to product and process knowledge. Methods for information capture and dissemination should be systematic and standardized. Management should take an active role in the promotion and utilization of KM, defining roles, expectations, and incentives to maintain the robustness of the system and timely implementation of new knowledge. Learning interventions, after-action reviews ("lessons learned"), job shadowing, and active expert networks are some examples of processes and tools that require active promotion to maintain their viability and benefit to PAC management. As ICH Q10 describes KM as an enabler of the PQS, review of new knowledge should occur in the context of identifying candidates for PACs as well as when reviewing change requests.

Quality Risk Management (QRM)

Effective QRM should provide a patient-centric decision-making framework to ensure that systematic and proactive risk-based and data-driven decision-making is used for all PACs. This includes decisions related to whether or not to proceed with a PAC based on an appropriate risk-benefit balance, how to control risks that might be introduced by a PAC, and regulatory conformance strategy for the PAC based on risk level.

The elements of the PQS and the enablers should collectively drive identification of risks to product realization, state of control, or the need for continual improvement. It is important to demonstrate product and process understanding to identify the level of risk and manage the control strategy accordingly. QRM should help identify changes that can reduce the risk of product and process failures and issues and/or improve process performance. Effective QRM should ensure that no unacceptable risks are introduced to product quality and/or patient safety as a result of the PAC. At a minimum, the PAC should not increase risks beyond current levels.

A risk assessment based on current product and process knowledge, the control strategy, and the product life cycle should be performed for identified PACs. The risk assessment of the PAC should assess potential risks and benefits to all relevant products, processes, and/or systems that might be impacted by that change. A specific PAC may be categorized differently depending on the level of knowledge, risk controls, and PQS effectiveness. The outcomes of the risk assessment should drive change planning, prioritization, implementation, and time lines. The rigor of the risk assessment associated with a PAC should be commensurate with the complexity and/or criticality of the change.

Residual risks or any unintended consequences of the change (during and after change implementation) should be assessed to ensure that they have been managed to acceptable levels for impacted products, processes, and systems. As appropriate, residual risks and the effectiveness of the change should be monitored post-implementation (via relevant ongoing review/monitoring systems), to ensure that a state of control is maintained.

A process/mechanism should be established to capture, manage, and track key risks to product quality, efficacy, and safety for implemented and pending PACs.

ICH Q10 Annex 1 provides the opportunity for risk-based regulatory oversight when an effective PQS can

be demonstrated. Therefore, QRM should also help determine the change category based on the risk level; it should distinguish changes that require regulatory approval reporting from changes that can be managed solely in the PQS. In certain cases, the risk assessment may be shared and discussed with regulators in a post-approval change management protocol or product life cycle management document, to proactively align on change categorization.

PQS Elements

The sections following describe how the four PQS elements shown in Figure 1—PPPQMS, CAPA system, change management system, and management review—should be utilized to support effective management of PACs.

Process Performance and Product Quality Monitoring System (PPPQMS)

An effective PQS should include an enhanced PPPQMS that proactively ensures the process and product remain in a state of control and are continually improved as appropriate, to provide increased assurance of product quality and process performance. Product quality reviews should include a summary evaluation of process performance and product quality.

Although ICH Q10 identifies high-level principles for the monitoring program, additional details can provide increased insights into determining the effectiveness of the program. An enhanced PPPQMS may include:

1. Tools for measurement of process and method performance including process capability, that is, statistical process controls.
    - Use statistical tools to establish and monitor process and analytical method capabilities and ensure a high degree of confidence that the process and methods are capable and continuously improved, as needed.
    - Establish control charts for evaluating trends that warrant additional investigations.
    - Provide tools to measure method performance including frequency of invalid results.
    - Establish limits beyond which additional evaluations are performed to identify sources of variation and appropriate corrective or preventive actions.
    - Perform process performance monitoring in near real-time to enable early detection of process drifts/unexpected variability/trends and react in a timely manner to prevent quality issues or failures.
2. Periodic evaluation with cross-disciplinary subject matter experts to monitor trends and/or deviations in process and method performance and integrate information from product complaints, audits/inspections, and the pharmacovigilance program.
3. Identification of PACs needed or desired to maintain a state of control, ensure product availability, and drive continual improvement of product, processes, and the control strategy.
4. A quality plan to identify, communicate, and implement key quality objectives to drive continual improvement within the PQS.
5. Escalation of significant issues or trends (e.g., product impact, cross-product, and cross-facility issues) for management review and potential changes to the quality plan.
6. Enhanced monitoring and sampling of product quality following major changes including notification to the pharmacovigilance program.

Corrective Action and Preventive Action System (CAPA)

The design and use of the CAPA element of the PQS should result in product and process improvements. An effective CAPA system monitors and manages unintended risks and consequences of PACs and should enable appropriate actions that can be taken to correct problems and prevent their recurrence. The CAPA system also provides insight into how the PQS can be improved.

Corrective actions (CAs) can be driven by an unanticipated event such as a complaint investigation, product rejection, nonconformance, recall, deviation, audit, regulatory inspection finding, QRM, and adverse trend from process performance and product quality monitoring. For each of these, it is expected that a thorough investigation and root cause analysis is conducted.

Preventive actions (PAs) can be driven by continual improvement initiatives as new product and process knowledge is gained. These PAs are designed to anticipate and prevent issues, deliver low rates of deviation, and emphasize the need to learn from deviations, deviation trends, and complaint/recall incidents.

CAs and PAs may identify the need for PACs to maintain or improve the assurance of product safety, efficacy, and supply. An effective CAPA program monitors and verifies the effectiveness of any CAPAs associated with PAC initiatives. Unintended risks or consequences should be addressed in a timely manner.

Change Management System

Prioritization of changes should be considered and regularly reviewed as part of management responsibilities to ensure that the company maintains a state of control and for resource planning. Additionally, in considering PACs to implement, management should ensure product availability to patients during and post completion of such changes. Where the supply chain contains multiple locations providing the same product, management should ensure that there is consistency in the change being implemented at different locations as relevant for national and regional regulatory filings.

Effective change management should result in improved product quality, process performance, state of control, and product availability. Change management should rely on a data-driven, enhanced science, and risk-based assessment of changes. Human factors should also be considered when proposing and implementing a change.

The QRM principles outlined in ICH Q9 (5) should be used during all steps of the change management process—change proposal, change evaluation, change implementation, change review, and closure. Based on the outcomes of the quality risk assessment, an appropriate regulatory reporting category (prior approval, notification, or not reportable) should be proposed. Figure 3 describes the overall flow for risk-based assessment of PACs and determination of regulatory reporting category.

Step 1: Change Proposal: When a PAC is proposed and entered into the change management system, the potential quality, safety, and efficacy (QSE) and legal/regulatory impact of the change needs to be considered during the initial high-level impact assessment. This can be assessed by using the following risk questions: what might go wrong when changing from the current situation to the proposed one? Why could this happen? This initial impact assessment should consider existing product and process knowledge (including process performance and variability) and current control strategies.

If the initial impact assessment indicates that

1. there is no additional potential QSE risk associated and there is no legal/regulatory impact per local/regional regulation, the change can be processed to the next step without the need to perform a detailed quality risk assessment. Additionally, the change can be categorized as a non-reportable and managed within the company's PQS. Rationale supporting this decision to manage the change internally with no regulatory submission/reporting should be clearly documented within the change management system.

2. there might be a potential QSE risk OR a potential legal/regulatory impact, a more detailed risk assessment needs to be performed to define the reporting category of the change.

Step 2: Change Evaluation:

A. Quality Risk Assessment**:** If the initial impact assessment concludes that there might be a potential impact associated with the change, or if the potential impact is unclear, a quality risk assessment should be performed. When assessing potential risks of the change, any potential impact (direct or indirect) on the identity, strength, quality, purity, or potency of the product should be considered, based on current product/process knowledge and the control strategy; some examples of risk questions include:

   - Can the change impact product safety?
   - Does the change impact a critical quality attribute, a critical process parameter and/or a critical material attribute?
   - Can the change potentially affect conformity of the product to current specifications?
   - Can the change potentially affect the purity of the product? Can the change introduce a new potential source of contamination or increase an existing potential source of contamination (e.g., including adventitious agents)?

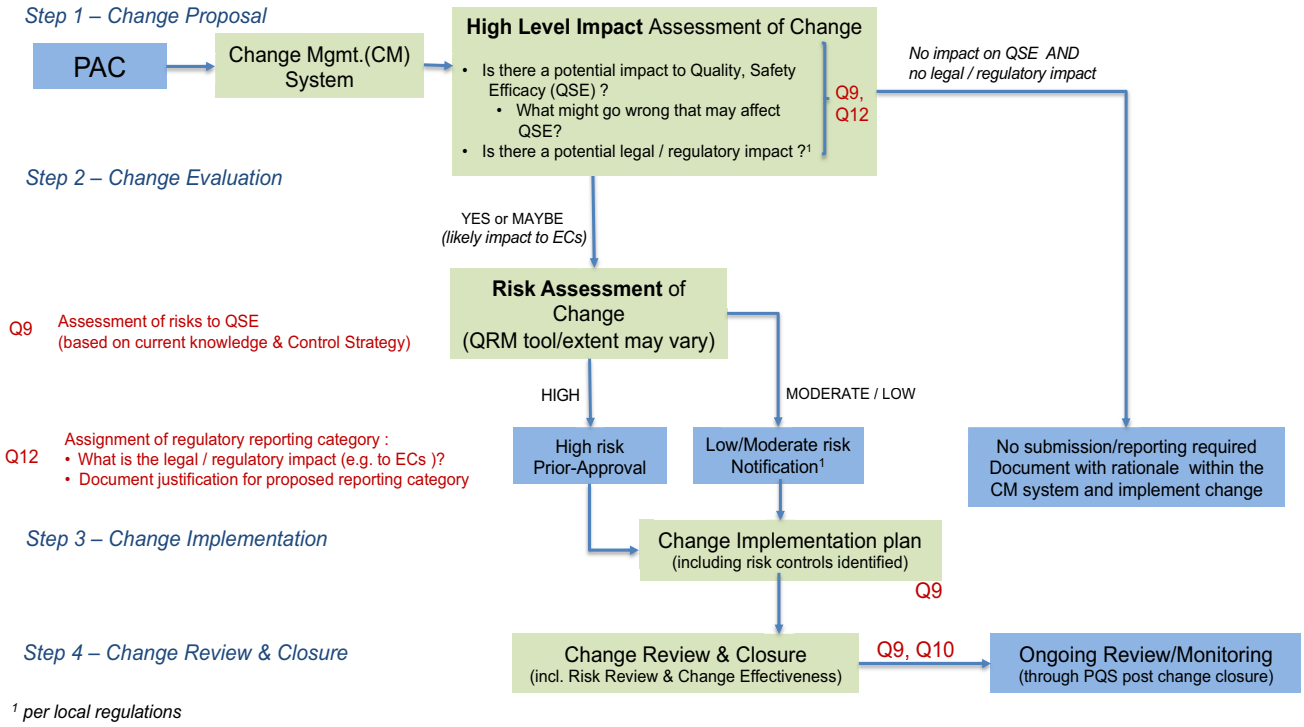

Figure 3

Risk-based assessment of post-approval changes and determination of regulatory reporting category.

- Can the change potentially affect the potency of the product (i.e., the ability of the product to yield a given result)?
- Can the change potentially affect the homogeneity of the product?
- Can the change potentially impact the sterility of the product?
- Can the change potentially impact the stability of the product?
- Can the change impact the performance of an analytical method?
- Can the change affect any of the above for another product or process?

The rigor of the risk assessment may vary and should be commensurate with the complexity and potential adverse impact of the change. Regardless of the tool used, the risk assessment should categorize the various risk levels based on the current product/process knowledge and risk controls. Changes should be evaluated by experts with relevant technical, scientific, and quality competencies and background. Peer or independent reviews can be done in teams like change review boards. A decision about acceptance or mitigation of the identified risks needs to be made before implementation of the change and documented in the change record, including appropriate rationale.

B. Assignment of Regulatory Reporting Category: Consistent with ICH Q12 (6), it is recommended that:

- High-risk changes are categorized as prior-approval and as such require regulatory authority review and approval prior to implementation.
- Moderate- to low-risk changes are communicated to the regulatory authority as a formal notification that takes place within a defined period of time before or after implementation, according to regional requirements.

The quality risk assessment (performed in step 2A) should be used to determine the level of risk associated with a change. Additional factors may also play a role as part of the evaluation. Possible documentation approaches include narrative evaluation, decision tree, checklists, and so forth. Rationale supporting the proposed regulatory

reporting category should be documented in the change management system. In certain circumstances in which the risk level and recommended change category is not commensurate with the local/regional regulations, companies should consider their strategy for regulatory conformance to implement the change.

Steps 3 and 4: Change Implementation, Review, and Closure: Change implementation, review, and closure should be performed per the change management process. Outcomes of impact and risk assessments should be integrated into the overall change implementation plan. After implementation of the change, residual risks should be assessed and managed to acceptable levels before change closure; any unintended consequences or risks introduced as a result of the change should be evaluated, documented, and handled adequately through effectiveness verification mechanisms. In case several changes are introduced at the same time or are related to each other, the company should assess the cumulative effectiveness of the changes.

After change closure, relevant risk assessment tools/documents are updated post effectiveness assessments. Other elements of the PQS, in particular the process performance and product quality monitoring system, should be used post closure for the ongoing review/monitoring of the risks associated with the change as well as for continuous process verification.

All PACs should be included and assessed as part of the periodic product quality review process, which should ensure that the regulatory filing information is consistent with all implemented PACs. ICH Q12 (6) provides additional details of PQS change management. The PIC/S paper "PIC/S Recommendation on How to Evaluate/Demonstrate the Effectiveness of a Pharmaceutical Quality System in Relation to Risk-Based Change Management" (4) provides a practical checklist tool that can be used by a company and inspectors to evaluate the effectiveness of a company's PQS in relation to risk-based change management.

Management Review

Management review is comprised of oversight activities including product and process performance monitoring and PQS effectiveness. Effective management review should include a review of PAC initiatives, their timely implementation, intended objectives, and outcomes. Management review should include an assessment of the effectiveness of PACs management in the PQS.

Management review can be organized in a tiered structure that links the PQS with specific product/process reviews as appropriate. Performance indicators should be defined that allow management to understand the capability of the internally managed PAC process and the successful implementation of PACs. Management should decide which specific PAC-related performance indicators will be implemented, tracked, and acted upon by the company. Examples include:

1. KM: PACs initiated because of new knowledge.

2. QRM: Unacceptable risks introduced as a result of PACs, risk reduction because of PACs, health authorities that have accepted the company's PQS for managing PACs.

3. PPPQMS: PACs related to preventive or continual improvement measures, recurring deviations, or adverse trends.

4. CAPA: PACs with unintended risk or consequence, CAPA effectiveness.

5. Change Management: PACs that did not meet intended objectives, adherence to PAC implementation timelines, or PAC effectiveness.

6. Management Review: review performance indicators for each PQS element, percentage of PACs covered in the PQS without requiring prior approval vs overall PACs, inspectional or internal audit findings related to PAC management.

7. Management Responsibilities: PQS effectiveness conclusion from management review, actual vs planned resources for PACs, timeliness of PAC implementation, survey assessment of quality culture/mindset, drug shortages.

The preceding are some examples. For several of these examples the company could report and discuss an actual number or percentages or both.

Management should be vigilant and aware of the cumulative impact of changes to a product over time.

Audit and internal inspection findings related to implemented PACs serve as an input to the review. Management should ensure that responses or actions related to any such findings are appropriate. If the objectives of

PAC initiatives are not achieved, effective management review ensures that formal CAPA action plans are developed and implemented, and that lessons learned are captured and incorporated into future PAC activities.

The management review should provide visibility of the status of in-progress PACs as well as any other PACs that are pending to evaluate any potential impact on product availability and ensure that a state of control is maintained.

Management review outputs and decisions should be documented. Continual improvement input should be driven by outputs of the management review process.

Conclusion

This 1VQ document describes how a company can leverage the PQS to effectively manage PACs through an enhanced science and risk-based approach. For each of the four quality system elements and the two enablers, it provides guidance to realize the opportunities outlined in ICH Q10 Annex 1, to manage more PACs within the PQS without increasing the risk to the patient and drug product QSE. Establishment of an effective PQS can achieve the objectives of realizing product, maintaining a state of control, and facilitating continual improvement.

The benefits of applying the principles described in this document are:

1. continual improvement with timely implementation of many PACs;
2. enhancing product availability and mitigating potential drug shortages;
3. focusing regulatory resources on PACs that may have a potential to impact product quality as it relates to safety and efficacy;
4. eliminating regulatory approvals for low-risk changes that can be handled by an effective PQS; and
5. faster implementation of innovative technologies.

Full implementation of this enhanced science and risk-based approach for managing PACs will require dialog and discussion with regulatory agencies and further changes to current national or regional regulations and guidance pertaining to managing PACs.

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Conflict of Interest Statement

The authors declare no conflict of interest related to the content of the article.

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