PDA Points to Consider: Technical Product Lifecycle Management Pharmaceutical Quality System Effectiveness For Managing Post-Approval Changes

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Pharmaceutical Quality System Effectiveness
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Conflict of Interest Declaration

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Introduction

The International Council for Harmonisation Quality Guideline 10 (ICH Q10) describes the Pharmaceutical Quality System (PQS), indicating it is intended to apply throughout a product's lifecycle, in conjunction with good manufacturing practice (GMP) requirements, in order to achieve quality in a consistent and reproducible manner. Implementation of an effective PQS is essential for a company to achieve product realization, establish and maintain a state of control, and facilitate continual improvement (1). When changes are made during the commercial life of a product, an effective PQS, product and process understanding, and use of quality risk management should ensure that product quality, patient safety, and adequate supply to patients are maintained; this, according to ICH Q10 – Annex 1, should provide companies the opportunity to manage post-approval changes (PAC) with reduced regulatory oversight (1).

But what exactly constitutes an effective PQS? And how does it support change management for PACs?

This paper intends to answer these questions and guide companies to seize the opportunities outlined in ICH Q10 – Annex 1, to manage product and process changes within the PQS, and downgrade the level of regulatory submission required. This is the second of a series of PDA "Points to Consider" papers on technical product lifecycle management; the first paper focused on the technical product lifecycle management strategy including communication and knowledge exchange between Marketing Authorization Holders and Health Authorities (2).

Background

During the commercial manufacturing phase of the product lifecycle, specific elements of the PQS are used to identify and manage PACs. Per ICH Q10, these include management responsibilities, the four quality system elements (process performance and product quality monitoring (PPPQM), corrective and preventive action (CAPA), change management, management review), and the PQS enablers (knowledge

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management and quality risk management (QRM)). When successfully implemented, together these elements will support an effective change management system.

ICH Q10 – Annex 1, *Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches,* states that when companies can demonstrate an effective PQS and product and process understanding, including the use of QRM principles, they "gain the opportunity to optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement." (1) In other words, companies can manage more changes without the need for prior regulatory approval, provided they operate under a framework comprising an effective PQS, along with sound product and process knowledge and risk management practices. This framework should extend to and include PACs in outsourced operations and supplier management to ensure that these are also planned, managed, and communicated appropriately.

Because commercial scale batches are manufactured following license or application approval, initially, manufacturing process knowledge is limited. As commercial production experience and knowledge is gained, adjustments are generally needed to improve manufacturing processes and control. Changes are thus a natural part of a product's commercial lifecycle. When a change clearly generates an improvement in terms of (a) reduced risk to patients, (b) improved process capability, (c) enhanced product availability, and/or (d) technical innovation and continual improvement, these changes should be allowed to be implemented without prior approval or with downgraded notification, provided the risk assessment concludes that the changes introduce no additional risk to patient safety, product quality, and/or product efficacy. The PQS must ensure such changes are robust by demonstrating change effectiveness. This is consistent with continued process verification concepts and provides more data to establish confidence in risk management decisions.

As a result, regulators should accept that the PQS is capable of an appropriate degree of self-governance in ensuring product quality and safety. This would allow most PACs to be managed under the PQS, without requiring prior review and approval by the regulator. In the event the PQS is subsequently found

to be ineffective, restrictions on the ability to make changes with downgraded notification to regulatory authorities may be put in place.

Building an effective PQS is the responsibility of the company, one that extends beyond having a license or a GMP certificate to manufacture medicines.

PQS Effectiveness for Post-Approval Changes

Management responsibilities and the four specific elements of PQS outlined in ICH Q10, enabled by QRM and knowledge management, when applied to PACs will support an effective change management system. The key elements that characterize an effective PQS are described in more detail below.

Management Responsibilities

Company management is ultimately responsible for ensuring that an effective PQS is in place for managing PACs. This includes defining and communicating roles, responsibilities, and authorities for PACs (for internal and outsourced operations) and providing adequate resources and budget for effective PAC implementation.

Management develops the overall strategy of PACs for a product. Consequently, it needs to ensure that appropriate internal audit and self-audit mechanisms enable proactive assessment and mitigation of compliance risks in the PQS, including any issues that might be introduced by the PACs. Management is accountable for driving timely improvements when significant variation or major failure modes are detected.

Management needs to promote and support the application of QRM and knowledge management activities as key enablers of an effective PQS for PAC management. And finally, management is responsible for developing the desired quality culture at all levels throughout the company to ensure the sustainability of PQS effectiveness.

Process Performance and Product Quality Monitoring (PPPQM)

An effective PPPQM program provides for proactive monitoring of processes and product quality to confirm that the control systems are performing as intended, that the desired state of control is maintained, and that new knowledge is captured in a structured way. Systems should be in place for the early detection of process drifts and unexpected variability and trends, as well as for the effective handling of adverse events, complaints, and defects. Systems should identify PACs needed to ensure an ongoing state of control and product availability, and to drive continual improvement. An effective PPPQM program further includes formal continual improvement programs, as needed, for products, processes, and the control strategy.

Corrective and Preventative Actions (CAPA)

An effective CAPA program monitors and manages unintended risks and consequences of PACs, and should enable identification of root cause(s) so that appropriate actions can be taken to correct problems and prevent their recurrence. The program also monitors and verifies the effectiveness of any CAPAs associated with PAC initiatives. Designed to deliver low rates of deviation and emphasize the need to learn from deviations, deviation trends, and complaint/recall incidents, an effective CAPA program focuses on preventative measures rather than corrective actions.

Change Management

An effective change management system is characterized by change implementation per the product lifecycle management strategy (including plans and protocols), achievement of change objectives, and high success rates for PAC approvals by regulatory authorities. It ensures maintaining conformity of products and manufacturing processes with regulatory filings and established conditions. It also includes the development and maintenance of a comprehensive system for reliable control of PACs in outsourced operations and the effective management of suppliers. Effective change management relies on a data-driven, science- and risk-based assessment of changes that takes into account the potential impact on all

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relevant aspects of the product and process, established conditions, and any unintended consequences. Such an assessment will ensure that changes are implemented in a timely manner and objectives of the change will be achieved. Through the application of good science in PAC-related risk assessments, effective change management provides assurance that any potential risks associated with PACs are identified and managed adequately.

Effective change management further relies on the quality of a company's post-change monitoring activities. These monitoring activities may be short- or long-term, as appropriate, and based on pre-defined criteria.

Effective change management improves product quality, process performance, state of control, and/or product availability, and lowers residual risks. It delivers compelling and documented examples of continual improvement and results in adequate control and management of risks to product quality and availability as well as to patient safety.

Knowledge Management (PQS Enabler)

An effective knowledge management system leverages existing and newly achieved/newly identified product and process knowledge for change management. This comprises innovation and technology advancements, as well as knowledge gained from PPPQM, deviations, trends, complaints, recalls, annual product review/product quality review (APR/PQR), and management reviews. Through the use of robust testing and monitoring plans, it captures new product and process knowledge gained over time and during change implementation, and fosters knowledge-sharing between internal and outsourced operations.

Effective knowledge management ensures that the right knowledge is used by the right people at the right time, to allow for effective decision-making. Such a system better provides for the tacit knowledge held by individuals to be converted into explicit, documented knowledge that can be made accessible and understandable to others involved at each stage of the product lifecycle. The existence of active expert networks, sharing of best practices/lessons learned at defined stages (e.g., after a PAC), ongoing risk

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management, and a company culture that allows for open communication, collaboration, and learning from near misses and mistakes, are all signs of effective knowledge management.

Quality Risk Management (PQS Enabler)

An effective QRM system provides for a risk-based decision-making framework and ensures that systematic and proactive risk-based and data-driven decision-making is used for all PACs. Such a system will enable identification of changes that reduce the risk of quality failures and manufacturing problems and improve process capability. It distinguishes changes that require regulatory reporting or notification from changes that can be managed solely in the PQS. In certain cases, the risk assessment can be shared and discussed with regulators in a post-approval change management protocol (PACMP) (3).

Furthermore, an effective QRM system assesses the risk level before and after implementation of the PAC to ensure that the PAC presents no increase in risk to product quality and/or patient safety.

Management Review

Effective management review of process performance, product quality, and the PQS should include a review of PAC initiatives, their timely implementation, intended objectives, and outcomes. Where 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.

Effective management review assesses strategies for PAC implementation to identify opportunities for continual improvement, ensures appropriate internal categorization of PACs, and increases the probability of approval by regulatory authorities.

Effective management review also monitors regulatory inspection and internal audit observations related to PACs, and includes a regular review of the performance of the PQS elements that support effective change management. It ensures products and processes are continually improved, new knowledge is adequately managed within the PQS, and regulatory filings are maintained.

Measuring PQS Effectiveness

The extent to which the different PQS elements are implemented and maintained reflects the maturity and robustness of a company's PQS, and can indicate that the company sustainably operates in a state of control with respect to PAC management. Measurement of PQS effectiveness therefore represents another important aspect of providing assurance that the PQS is adequate and effective in providing oversight of PACs to ensure product quality and adequate supply. In addition, ongoing measurement and associated actions ensure continuous improvement of the PQS.

Effectiveness of a PQS can be monitored using appropriate key performance indicators (KPIs) based on absolute data and trends. These should be meaningful, simple, and not subject to interpretation. **Figure 1** illustrates some KPIs that can be useful in assuring the effectiveness of the PQS for PACs. Alternative KPIs may be used as deemed appropriate by quality and senior management.
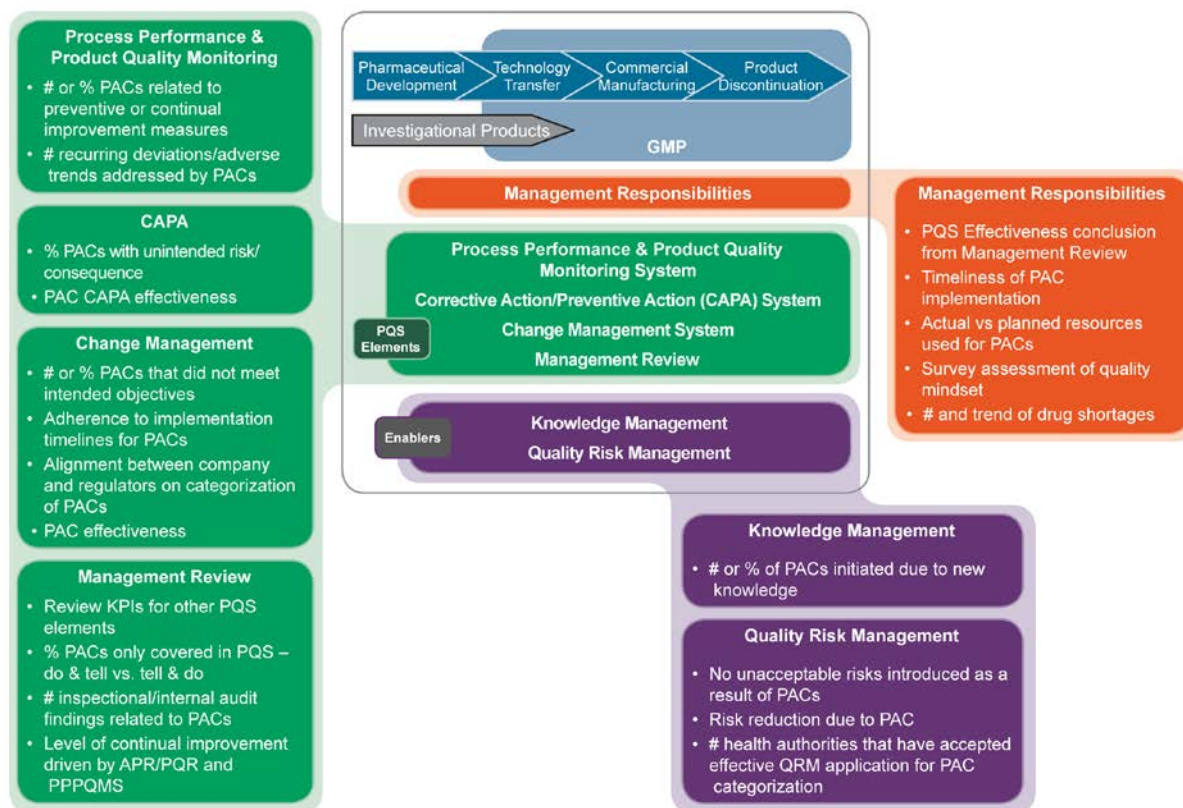

Figure 1. PQS elements relevant for PAC and examples of related KPIs

The Role of Quality Culture in Enabling PQS Effectiveness

For sustained effectiveness, the PQS needs to be embedded in the company's quality culture—a set of shared values, beliefs, and behaviors that support product quality- and patient-centric decision-making.

A company can achieve the desired quality culture when its management clearly demonstrates leadership, commitment, and engagement of the entire organization. In this environment, management shares a common vision, fosters transparent, open and "no-blame" communication throughout the company based on trust, and invests in employee education and training to ensure a proficient and knowledgeable workforce. Employees engage in activities that emphasize quality performance and continual improvement across all functional areas, and a rewards and recognition program drives the desired quality culture with a strong focus on the patient.

Organizational changes can impact company culture and thus affect PQS effectiveness. Changes in senior leadership, major organizational changes such as mergers, acquisitions, or joint ventures, or changes in business or governance models, can generally result in cultural changes. When companies undergo these changes, the potential impact on PQS effectiveness will need to be considered, assessed, and appropriately addressed.

Conclusion

The U.S. FDA Office of Pharmaceutical Quality's *White Paper: FDA Pharmaceutical Quality Oversight, One Quality Voice* identified one of the challenges for regulators:

> The number of post-approval supplements received for review has increased over the past decade, in part owing to our current practice of "locking in" an applicant's manufacturing process before it is fully optimized. A burdensome regulatory framework requires manufacturers to submit supplements as they strive for process optimization (4).

ICH Q10 – Annex 1 offers a solution to this challenge, recognizing that potential opportunities for risk-based regulatory approaches exist and can be leveraged to reduce regulatory burden. An effective PQS

provides an appropriate framework — one grounded in science- and risk-based decisions and knowledge management — to determine which PACs do not require prior approval and could be handled solely within the company's PQS, potentially without prior notification. ICH Q12, *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*, proposes that several PACs can be managed in the PQS, or via "do and tell" notification, without the need for regulatory approval prior to implementation (3). Based on the PQS framework described in ICH Q10, this paper describes elements specifically related to effectiveness of the PQS, in managing such PACs.

The regulatory framework for PACs needs to be simplified globally allowing companies to innovate, continually improve their processes, methods, and facilities, and ensure product quality and availability. PDA believes that industry is responsible for effectively managing products through their entire lifecycle. Essential to that undertaking is ensuring that the PQS effectively covers many PACs that currently require regulatory approval prior to implementation or notification. This change of focus will enable industry to achieve the desired state described in FDA's "Pharmaceutical Quality for the 21st Century Initiative" and further articulated by Dr. Janet Woodcock, Director of FDA CDER, of a "maximally efficient, agile, flexible manufacturing sector that reliably produces high-quality products without extensive regulatory oversight" (5).

Glossary

Change Management: A systematic approach to proposing, evaluating, approving, implementing and reviewing changes. (ICH Q10)

Continual Improvement: Recurring activity to enhance performance. (ISO 9001:2015)

Control Strategy: A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility, and equipment operating

conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Enabler: A tool or process which provides the means to achieve an objective. (ICH Q10)

Established Conditions (EC): The description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy, as defined in an application, that assure process performance and quality of an approved product. (Draft FDA Guidance on Established Conditions, May 2015)

Established Conditions for Chemistry, Manufacturing, and Controls are legally binding information defined in an approved Marketing Authorization Application (MAA).

Innovation: The introduction of new technologies or methodologies. (ICH Q10)

Knowledge Management: Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components. (ICH Q10)

Management: Coordinated activities to direct and control an organization. Management can include establishing policies and objectives, and processes to achieve these objectives. The word "management" sometimes refers to people, i.e., a person or group of people with authority and responsibility for the conduct and control of an organization. (ISO 9001:2015)

Organization: Person or group of people that has its own functions with responsibilities, authorities and relationships to achieve its objectives. (ISO 9001:2015)

Performance: Measurable result. Performance can relate either to quantitative or qualitative findings. Performance can relate to the management of activities, processes, products, services, systems or organizations (ISO 9001:2015)

Performance Indicators: Measurable values used to quantify quality objectives to reflect the performance of an organization, process or system, also known as "performance metrics" in some regions. (ICH Q10)

Pharmaceutical Quality System (PQS): Management system to direct and control a pharmaceutical company with regard to quality. (ICH Q10 based on ISO 9000:2005)

Product Lifecycle: All phases in the life of a product from the initial development through marketing until its discontinuation.

Product Realization: Achievement of a product with the quality attributes appropriate to meet the needs of patients, health care professionals, and regulatory authorities (including compliance with marketing authorization) and internal customers' requirements. (ICH Q10)

Post-Approval Change Management Protocol (PACMP): A regulatory tool that enables planning of future change(s). It describes the change(s) an applicant/MAH would like to implement during the lifecycle of a product, how these would be prepared and verified, including assessment of the impact of the proposed CMC change(s), and the proposed (usually lower) reporting category in line with regional requirements. The PACMP also identifies specific conditions and acceptance criteria to be met.

Process Capability: Ability of a process to realize a product that will fulfill the requirements of that product. (ISO 9001:2015)

Quality: The degree to which a set of inherent properties of a product, system, or process fulfills requirements. (ICH Q9)

Quality Risk Management: A systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle. (ICH Q9)

Risk: The combination of the probability of occurrence of harm and the severity of that harm. (ICH Q9, ISO/IEC Guide 51)

Senior Management: Person(s) who directs and controls a company or site at the highest levels with the authority and responsibility to mobilize resources within the company or site. (ICH Q10 based in part on ISO 9001:2015)

State of Control: A condition in which the set of controls consistently provides assurance of continued process performance and product quality. (ICH Q10)

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