PDA Points to Consider:

Technical Product Lifecycle Management

Communication and Knowledge Exchange

between Marketing Authorization Holders and Health Authorities

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Introduction

Changes occur throughout a product's commercial life—changes in raw materials, manufacturing equipment, processes, sites, analytical methods, and suppliers. A product Marketing Authorization Holder (MAH) can introduce manufacturing changes as part of continual improvement to enable implementation of innovative technologies, exchange obsolete equipment, or improve the availability of drug products for patients. Changes are also made to comply with evolving regulatory requirements. Changes are a common and unavoidable part of a product's lifecycle.

This Points to Consider paper is intended to focus on a company's technical product lifecycle management strategy. It includes elements and benefits of such a strategy, its use in post-approval change (PAC) management, and considerations to enable effective communication and knowledge sharing between MAHs and health authorities.

Background

Initial product and process understanding is achieved during the development phase of the product lifecycle, which is summarized in the Common Technical Document (CTD) at the time of dossier submission. However, substantial further process and product knowledge is achieved in the post-approval phase of the lifecycle as well. It is important that new knowledge is managed in a structured and institutionalized manner that includes updates to relevant internal Standard Operating Procedures, other pertinent documents, and applicable regulatory filings.

Since approved in 2009, International Conference on Harmonization (ICH) Guideline Q10–Annex 1 has described "Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches," stating that when a company "demonstrate[s] an effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles," it provides a potential opportunity to "optimize science and risk based post-approval change processes to maximize benefits from innovation and continual improvement" (1). In other words, many more PACs should be covered only in the company's Pharmaceutical Quality System (PQS) so they can be implemented faster, and then can simply be reported to regulatory agencies as a "change being effected." Yet, since the approval of ICH Q10, this option has not been effectively utilized. In the past seven years, almost no PACs have been expedited and/or managed only in the PQS utilizing a science- and risk-based approach, even when a given change improves the overall risk profile for the product, reduces risk to patients, reduces process variability, enhances product availability, or improves technical innovation and continual improvement.

In late 2014, ICH began to work on ICH Q12, an additional guideline to establish harmonized approaches on technical and regulatory considerations for lifecycle management (2). ICH Q12 is intended to streamline regulatory processes for post-approval changes by providing clarity on binding regulatory elements in a dossier ("Established Conditions" or EC) and general principles for lifecycle management,

discussing what makes a PQS effective, and proposing tools, such as post-approval change management protocols (PACMPs).

PDA is supporting work on ICH Q12 through a task force, formed in 2015, which focuses on the practical aspects of technical lifecycle management and aims to provide practical recommendations and examples that will facilitate the implementation of ICH Q12. Additionally, the PDA task force is also actively engaged in supporting WHO and IFPMA activities to enable effective management of post-approval changes and technical lifecycle management in non-ICH regions.

Why is Product Lifecycle Management Important?

It is important for the MAH to establish a lifecycle management strategy to holistically and prospectively manage a product globally during its commercial life. A product's technical lifecycle management strategy describes how the overall product lifecycle will be managed within the company's PQS, to ensure that the relevant quality requirements and processes are implemented and maintained according to any global or regional regulatory commitments and the company's PQS. As it grows during the commercial life, product and process knowledge enables a deeper understanding and opportunities for more effective management of product and process risks. Based on this, the lifecycle management strategy can provide a foundation for risk-based quality and regulatory decisions, which take into consideration the science (product and process understanding) and the risk management approach adopted by the MAH to manage the product during its commercial life. Relying on appropriate scientific knowledge and application of risk management, a lifecycle management strategy will ensure availability of quality product throughout its commercial phase, while establishing and maintaining a state of control, facilitating continual updates and improvement, and spurring innovation. These objectives have been put forward in and are supported by ICH Guidelines Q8(R2), Q9, Q10, and Q11 (1,3,4,5). Product lifecycle management is essential to realize these objectives. It is also a way for companies to clearly describe how knowledge is managed throughout the commercial phase of the product lifecycle, and how new knowledge about the product and processes will be systematically captured, shared, and incorporated into updates to dossiers.

Documenting a product's lifecycle management strategy can bring transparency, internally and externally, to plans for significant changes (and their interdependencies) in a product during the commercial phase. The document can be used to provide visibility to health authorities and to improve predictability and planning of anticipated regional or global post-approval chemistry, manufacturing, and control (CMC) changes to product or processes. An example of how a company may document their lifecycle management strategy was recently published by Roche (6). In some cases, the lifecycle management strategy may be leveraged to hold proactive discussions with health authorities to potentially reduce reporting categories for changes to Established Conditions and/or to articulate which planned changes are required for continued supply.

Elements of a Lifecycle Management Strategy

The MAH should describe within its own PQS how the overall product lifecycle will be managed effectively to ensure that the relevant quality requirements and processes are implemented and maintained according to any global or regional regulatory commitments and to its internal PQS. A product's technical lifecycle management strategy should cover quality, manufacturing, supply chain and regulatory CMC aspects.

Figure 1 outlines what PDA considers as key elements of a product lifecycle management strategy.

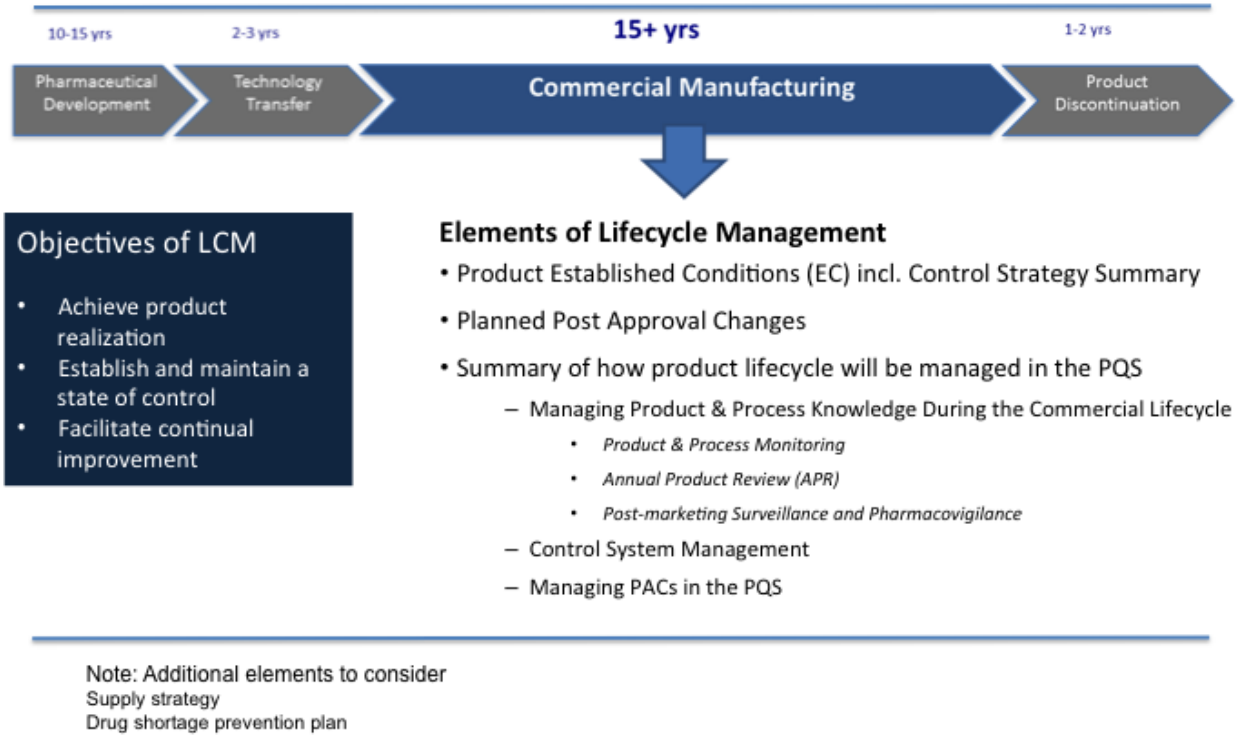

Figure 1. Product Lifecycle Management Elements

The elements described below are important components of a product's lifecycle strategy, and summarize the globally agreed upon Established Conditions including a summary of the Control Strategy (1) for the product, planned major post-approval changes and how the product lifecycle will be managed in the PQS, including the management of post-approval changes. Much of this information is product-specific and is not typically described in a comprehensive manner in a MAH's PQS.

1. Product **Established Conditions** (ECs) including Control Strategy Summary – Provides the list of parameters that the MAH identified in the CTD as ECs for the product; the appropriate sections of the dossier may be referenced for the description and justification of ECs. The desired state should be to have a global set of ECs. The lifecycle management strategy may facilitate harmonization of ECs across different countries/regions, thus enabling a clear segregation of ECs and non-ECs at a global level. Where there are country-specific differences in ECs, these should be listed within the MAH's PQS. This section also includes a summary of the product specific Control Strategy; appropriate sections of the dossier may be referenced for the description of the Control Strategy.

2. **Planned Post-Approval Changes** - This section may include the following for one or several planned changes.

    - A high level plan for ECs that are expected to be changed (e.g. product version changes, change/addition/expansion of a manufacturing site, site transfers, analytical control system updates, new manufacturing technology, new analytical technology etc.). The changes may be categorized as global or regional as applicable.

    - A rationale for each change.

    - **An assessment of potential risks to product quality and/or patient safety resulting from the change(s)**. If multiple changes are to be implemented, the assessment should address any potential linkages and cumulative effect of multiple changes. In general, changes should not result in unacceptable risk to patient safety, product quality and/or efficacy.

    - **The category proposed by the manufacturer for potential changes to ECs or a subset of ECs.** It is important to acknowledge that there is an increasing application by many health authorities of risk-based approaches for categorization of PAC submissions, based on potential impact of the PAC to safety, quality and/or efficacy of the product. However these risk-based categorizations and resulting submission requirements by different health authorities are yet to be harmonized globally. The category proposed by the manufacturer, as appropriate to each relevant region, would be used to report a change to that condition ("Submit a variation"; "Use of a Post Approval Change Management Protocol (PACMP)"; "Manage within the PQS only"). In doing so, the company should apply the guidance given in ICH Q10–Annex 1 to develop an effective PQS, as appropriate. The reporting category proposed for each EC should be appropriate to the risk posed by the change and the available knowledge about that EC for the product. The applicant may also propose how it would manage changes to non-ECs under the PQS.

    - **A listing of proposed PACMPs that the MAH anticipates submitting.** The MAH may provide a list of proposed PACMPs that briefly describe any specific risk assessment requirements, comparability criteria, stability requirements, and reporting requirements. PACMPs may be

developed and submitted to describe proposed changes in Established Conditions, associated rationale, risk assessment, proposed studies, and associated acceptance criteria. As PACMPs require approval by relevant health authorities prior to implementation of the proposed changes, developing standard PACMPs that can be filed without modifications in multiple countries would expedite global implementation of a PAC. PDA is encouraging and leading the development of such standard PACMPs to be used for specific post-approval changes including post-approval changes across multiple products.

3. **Summary of How Product Lifecycle will be Managed in the PQS**

- **Managing Product Knowledge During the Commercial Lifecycle.** Provides a brief overview on how the MAH will manage the product knowledge acquired during the commercial life of the product. This includes leveraging the scientific basis for knowledge gained through product and process monitoring /continuous and continued process verification including knowledge gained from deviations, complaints, CAPAs, annual product reviews (product quality reviews), pharmacovigilance, and post-marketing surveillance programs.

- **Control System Management.** Provides a high level description of how the product control system will be assessed on a regular basis and managed as part of the PQS to incorporate new product/process knowledge (e.g. results from the monitoring plan, continuous and continued process verification, annual product reviews, clinical and non-clinical studies, changes in attribute criticality, improvements in test method performance, changes to specifications, etc.) or changes in regulatory expectations, in order to maintain a modern and robust testing strategy.

- **Managing Post-Approval Changes.** Describes how the company's change management process will be used to assess post-approval changes within the internal and external network for all relevant regions, and determines whether the changes need to be submitted for prior approval (i.e., changes to certain ECs), or if they will be managed through the company's PQS and change control process only. For those post-approval changes that will be solely managed in the PQS and not communicated to regulators, describe how the MAH will ensure that such changes are managed effectively in the PQS, and how access will be provided to regulators upon request.

Figure 2 depicts the current and anticipated future state where a science and risk-based approach for post-approval change management can enable the realization of ICH Q10 objectives and the ICH Q12 vision.

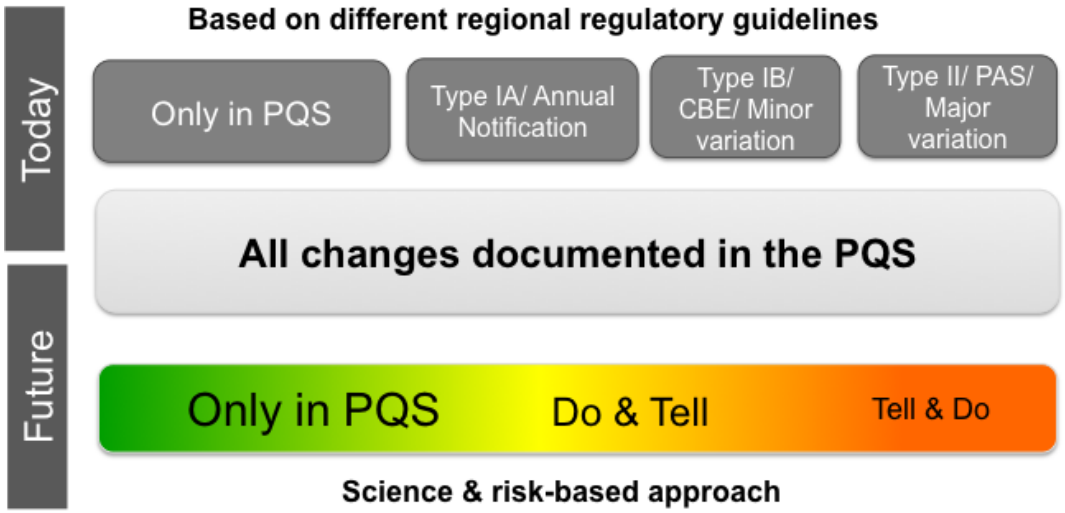

Figure 2. Science- and Risk-based Approach for PAC Management

Lifecycle Management for Legacy Products

Legacy products may face the greatest challenges for lifecycle management including post-approval change management. In many cases, the applicant would not have submitted an original application with a clear delineation of established and non-established conditions, or processes, methods and equipment may have been validated before modern paradigms for design, qualification, validation, monitoring, and continual improvement were introduced. Each of these factors further complicates lifecycle management and post-approval change management, and each must be addressed to ensure legacy products maintain compliance with evolving regulatory expectations. The advantage legacy products have relative to new products is the extensive body of historical product and manufacturing process knowledge. This knowledge can and should be leveraged effectively for lifecycle management and post-approval change management. Lifecycle management and regulatory strategies for legacy products therefore need to be adapted for the body of knowledge and lifecycle stage of a given product. Companies should describe the differences in lifecycle management strategy for new and legacy products. It is important that lifecycle management not only addresses new products, but also supports the transition of existing products to a paradigm that will allow the use of ICH Q12 principles.

Benefits of Proactively Sharing Lifecycle Management Strategy with Health Authorities

The description of a product's lifecycle management strategy is currently not a required section in the dossier. As a best practice, PDA proposes that the dossier may contain an optional section describing the product's lifecycle management strategy, either in the initial submission or filed as a post-approval variation. Such a section provides an opportunity for the MAH to prospectively provide information to the regulator(s) regarding their plans for managing the post-approval phase of the product during its

commercial life including the management of knowledge. It can serve either as a mutual understanding between the MAH and the Health Authority (Assessor and Inspector), or as a valuable mechanism for early communication, knowledge exchange, and prospective planning for post-approval changes during the commercial life of a product (6).

While it should define the lifecycle management strategy in its PQS, the MAH would also benefit from proactively sharing its lifecycle management approach with health authorities. By sharing its approach to managing the product during its commercial stage, including significant changes planned and their interdependencies, the MAH builds a mutual understanding with health authorities (assessors and inspectors) across multiple geographic regions. This enhanced transparency allows regulators and MAH to plan well in advance of implementing (multiple) post-approval changes. Additional benefits of sharing the lifecycle management strategy with health authorities include:

- Providing an opportunity to reduce the reporting category for changes to Established Conditions.
- Enhancing the ability of both company and health authorities to better plan resources and timing for anticipated post-approval changes.
- Expediting reviews and implementation of planned post-approval changes.
- Facilitating harmonization of ECs across several countries thus creating a clear segregation of ECs and non-ECs globally.
- Enhancing predictability, certainty and transparency of studies to implement a change, thus helping MAHs to effectively plan and communicate implementation of changes.
- Facilitating development of a single global PACMP for filing a specific change for one or more products across countries and regions that expedites global implementation of a post-approval change.
- Allowing the MAH to communicate to assessors how product knowledge is captured and managed during the commercial stage of the product lifecycle, how post-approval changes are managed in the PQS, and how they assure an effective PQS.
- Summarizing, where considered appropriate, the lifecycle management strategy the MAH plans for ensuring drug product availability, including associated risks and mitigations, and providing an opportunity to explain the post-approval changes needed to ensure continued product availability.

Conclusion

Because a product can reside in the commercial phase for more than 15 years post-launch, the product must be actively managed and product knowledge captured in a structured manner during this

commercial life. Effective lifecycle management is not an option, but a necessity due to the inevitable changes a product undergoes once it is launched. Such changes reflect the growth in process knowledge, improvements in process equipment, or required updates due to obsolescence or age. Managing knowledge throughout the commercial phase of the product is essential. Even maintaining the product in a state of control and beyond that, driving continual improvement to assure product quality and availability, is essential. The PQS should clearly describe how it can be effectively used to manage post-approval changes, even those that will no longer need to be submitted to health authorities for prior approval.

A defined lifecycle strategy not only facilitates the objectives of ICH Q8(R2), Q9, Q10 and Q11, but also provides a proactive, clear and transparent approach on how the product will be managed by the MAH during its commercial life. The lifecycle management strategy can be leveraged as an excellent communication mechanism to proactively engage health authorities, build trust, enable a risk-based approach to regulatory review of changes, and accelerate implementation of changes for the ultimate benefit of patients.

Glossary

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

Continual Improvement: Recurring activity to increase the ability to fulfil requirements. (ISO 9000:2005)

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)

Established Conditions (EC): The description of the product, manufacturing process, facilities, 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: Legally binding information defined in an approved Marketing Authorization Application (MAA) (Draft ICH Q12 version 5, July 2016)

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)

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

Product Lifecycle: All phases in the life of a product from the initial development through marketing until the product's discontinuation. (ICH Q8)

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. (Draft ICH Q12 version 5, July 2016)

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

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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