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The Role of Change Management in Supporting Innovation in the Pharmaceutical Industry

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INNOVATION AND THE PHARMACEUTICAL INDUSTRY

Innovation is the life blood of the pharmaceutical industry. Innovation occurs at every stage of the product lifecycle that is described in "The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)" ICH Q10: Pharmaceutical Quality System (PQS): Pharmaceutical Development>Technology Transfer>Commercial Manufacturing> Product Discontinuation. This guideline, which has been adopted by major regulators across the globe, including the EU, USA, and Japan, describes the significance of the change management system:

"Innovation, continual improvement, the outputs of process performance and product quality monitoring and CAPA drive change. In order to evaluate, approve and implement these changes properly, a company should have an effective change management system."

The guideline goes on to recognize the difference in the formality of application of the change management system during the product lifecycle and the requirement to assess changes against the regulatory submissions where appropriate.

Pharmaceutical companies must balance the requirement to comply with the Good Manufacturing Practice (GMP) standards specified by regulatory authorities, and the requirement to drive continual improvement in products, processes, and systems. This is typified by the introduction to Eudralex Volume 4 (The Rules Governing Medicinal Products in the European Union), which states: "The Guide is not intended to place any restraint upon the development of any new concepts or new technologies which have been validated and which provide a level of Quality Management at least equivalent to those set out in this Guide." Regulations in other jurisdictions include similar principles.

The implementation of a series of ICH guidelines over the last decade or so has accelerated innovation throughout the lifecycle and the transfer of ownership of many aspects of change management to pharmaceutical companies. These include:

1. ICH Q2: Validation of Analytical Procedures Q2 (Revision 2 Draft Endorsed March 2022)
2. ICH Q8: Pharmaceutical Development (adopted August 2009)
3. ICH Q9(R2): Quality Risk Management (under public consultation from November 2021, first version adopted November 2005)
4. ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (adopted November 2019)
5. ICH Q13: Continuous Manufacturing of Drug substances and Drug Products (signed off November 2022)
6. ICH Q14: Analytical Procedure Development (Draft Endorsed March 2022)

To implement these guidelines, pharmaceutical companies must establish and maintain an effective PQS as described in ICH Q10.

This progressive regulation, and the advent of new manufacturing and analytical equipment and technology, has increased the emphasis on innovation and continual improvement of products, processes, and systems in pharmaceutical companies. For example, the adoption of continuous manufacturing and in-line or online analysis has allowed some testing to be moved to the manufacturing plant from the QC laboratory to enable monitoring and adjustment of manufacturing processes in real time as part of the control strategy, as defined in ICH Q8. Rapid and reliable data feedback is crucial in being able to diagnose and adjust process performance, and ultimately the supply of a more consistent quality product to the patient.

INNOVATION AND THE CHANGE MANAGEMENT SYSTEM

The pharmaceutical industry is a highly regulated industry, which must deploy an effective PQS to meet the needs of key stakeholders, including patients and regulators. The change management system is a core part of an effective PQS, since it networks with so many other elements of the PQS and is utilized to drive the continual improvement and innovation in products, processes, and systems as described in ICH Q10.

ICH Q10 defines change management as "A systematic approach to proposing, evaluating, approving, implementing and reviewing changes". Consequently, the change management systems deployed consist of a series of stage gates from assessment of whether to proceed with a change proposal through confirming that the change has been effective on implementation. The use of ICH Q9: Quality Risk Management is a vital consideration in an effective change management system.

Documentation for all the stages in this change management lifecycle must be available for internal and external review, *e.g.*, during corporate audits and regulatory inspections. This may include documentation from software and hardware providers when utilized in change management.

Barriers to continual improvement and innovation include the availability of data, resource availability and capability, and the alignment of organizational objectives. The use of ICH Q9 is key in the assessment of changes and the allocation of limited resources throughout the change management process.

The rapid generation, availability, and assessment of process performance data and knowledge, *e.g.*, analytical trend data from in-process or finished product testing, is crucial in allowing management to review performance of products, processes, and systems and implement corrections, improvements, and innovation swiftly. This extends to knowledge of the performance of the analytical procedures and their impact on manufacturing cycle times.

Regulators consistently communicate the need to evaluate the error-provoking conditions that allow "human error" to occur. This requires companies to evaluate whether process, procedural or system-based errors, or problems have been overlooked, if present. Innovation to preferably remove or refine steps in the underlying processes, procedures, and systems should subsequently be implemented to address these error provoking conditions. This innovation may encompass the planning and execution of tasks, including the modification, improvement, and replacement of analytical test methodology, and/or the application of artificial intelligence and intelligent workflow automation.

ASSESSING THE IMPACT OF CHANGE

Assessment of change proposals principally requires evaluation of the impact of the change against the marketing authorization (MA), Good Manufacturing Practice (GMP; notably the validation status of processes, analytical procedures, and systems), and patient safety.

The MA, which is derived from knowledge acquired during development and describes manufacturing and testing aspects in some detail, is the contract between the regulatory authorities and the company that is applying to sell the product. The MA may include specific details of hardware that is utilized by a company for testing and manufacturing processes.

Depending on the type of variations proposed, there are a series of more onerous graduated regulatory authority responses, from simple notification to the regulatory authority to prior approval by the regulatory authority before the change may be implemented. Changes that require prior approval typically consume significant multi-department resources and may not be enacted until the change is approved by the respective regulator(s). Changes in the EU, for example, that require prior approval, include changes outside the approved specification range, alterations to test procedures for active substances, or variations to the introduction of approved real-time release schemes. Minor changes that require notification only, include minor changes to an approved test

procedure or deletion of a test procedure if an alternative test is already authorized. The FDA has established similar guidelines under its SUPAC (scale-up and post approval changes) guidance for industry. These long-standing guidelines describe the agency's view of the impact of different levels
of change and the associated regulatory filing standards.

Thus, the construction of the MA and agreement of the contents requires a specific skill set and is extremely important in enabling post approval changes. In general, the greater the level of the detail, beyond the essential requirements described in ICH M4: Common Technical Document, the greater the effort needed to effect change.

Regardless of the classification of the change, companies must determine what validation activities must be enacted to maintain the validated state. This includes demonstrating and documenting changes to hardware and software from validation planning to execution. This is an area where organizations can work closely with vendors by delineating responsibilities for each stage of the validation cycle, notably during definition of the user requirements specification, functional specification, design qualification, and factory acceptance testing. It may also be feasible for vendors to conduct some traditional on-site validation testing, *e.g.*, installation and operational qualification.

Finally, but most importantly, consideration must be given to the impact of the change on the well-being of the patient. This is the primary concern when managing change.

STRATEGIC MANAGEMENT OF CHANGE

In short, organizations want to continually improve and innovate manufacturing and analytical procedures but must carefully consider the impact described earlier, the change plan, and associated resources to deliver a proposed change. This is compounded by the sheer number of changes that a typical organization would like to implement, and hence requires a risk-based method of prioritization in resource-constrained environments.

Considering individual changes as part of an overall improvement and innovation strategy is an important mechanism to ensure only relevant, beneficial changes are supported and driven to completion. Without effective strategic management, individual changes tend to languish in the change management system and are often not realized. Organizations that consider change as part of a continuous improvement and innovation strategy tend to make the optimum use of resources to implement changes and to achieve the desired benefits. This is consistent with the "Leadership and Vision" and "Management Oversight and Review "dimensions of quality culture described below.

Once a change is approved, it proceeds to planning and execution while continuing to consider the impact described above. Companies are required to demonstrate that changes are effective on implementation.

CHANGE MANAGEMENT AND REGULATORY INSPECTIONS

Given its significance, regulators usually assess the change management system and its effectiveness during inspections. It is noteworthy that deficiencies regarding change management systems consistently appear in the top 5 of critical and major observations made by the UK Medicines and Healthcare Products Regulatory Agency (MHRA). Equally, the US Food and Drug Administration (FDA) frequently cites the inadequate management of changes on Warning Letters. The consequences of non-compliance may have significant financial and reputational consequences for organizations that require remediation to achieve the regulatory requirements, regardless of the agency concerned.

THE ROLE OF QUALITY CULTURE

Regulators and world class pharmaceutical companies recognize that quality is not just about having an effective PQS, it is also about having a quality culture in the organization that enacts the requirements of the system, while recognizing and identifying innovation and improvements, and enabling decisions to maintain or improve patient safety.

In this regard, the QC laboratory, which is at the end of the manufacturing process, has a prominent and unique significance when one considers it is required to provide timely and compliant data to support the certification of batches for release. As a unit with finite resources and extensive responsibilities, it is in a key position to identify, promote, and adopt new technology and innovations that result in reductions in cycle time and improved customer service.

The International Society of Pharmaceutical Engineering (ISPE) Cultural Report, issued in April 2017, describes a roadmap to achieving a quality culture by considering six dimensions:

1. Leadership and Vision
2. Mindset and Attitudes
3. Gemba Walks
4. Leading Quality Indicators
5. Management Oversight and Review
6. Structural Enablers

This pan-industry report, which is supported by major regulators, provides a set of tools and techniques to assess and improve the quality culture. It is now being widely adopted across the pharmaceutical industry.

PROGRESSIVE REGULATION AND CHANGE MANAGEMENT

The pharmaceutical industry has long lobbied for greater autonomy in the management of change. Recent developments in the global domain under the auspices of ICH are allowing the industry to take increased responsibility for change, including improvement and innovation of analytical procedures. These include:

1. ICH Q2 Validation of Analytical Procedures (Revision 2 Draft Endorsed March 2022) states that "Changes may be required during the lifecycle of an analytical procedure. In such cases, partial or full revalidation may be required. Science and risk-based principles can be used to justify whether or not a given performance characteristic needs revalidation. The extent of revalidation depends on the analytical performance characteristics impacted by the change".
2. ICH Q14: Analytical Procedure Development (Draft Endorsed March 2022) expands on this point: "Changes to analytical procedures can occur throughout the product lifecycle and could involve modification of existing procedures or a complete replacement including introduction of a new technology". The tools and enablers discussed in ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management are applicable to analytical procedures and methodology irrespective of the development approach.
3. ICH Q12 (adopted 2019) introduces the Post-Approval Change Management Protocol, which can be used to describe the change a Marketing Authorization Holder (MAH) intends to implement during the commercial phase. The protocol may be submitted with the original Marketing Authorization Application or subsequently as a standalone submission. Such protocols may include innovation or changes to analytical procedures.

These are examples of guidelines that are allowing pharmaceutical companies to take greater ownership of change management under the company PQS, while meeting registration and GMP requirements. They also allow companies to collaborate with software and hardware vendors and service providers on improvements and innovation during the product lifecycle across multiple specialisms, including analytical procedures.

CONCLUSIONS

Change management in the pharmaceutical industry is an integrated system element that is required to be interfaced with multiple other system elements within the PQS to ensure that innovations and improvements are managed effectively. Interaction with regulators as a key stakeholder is essential in the management of changes that impact on marketing authorizations.

The culture of an organization is an important factor in identifying improvements and innovations and ensuring that change is implemented effectively.

The number and complexity of the changes requires excellent strategic management and risk management to prioritize which changes should be progressed to improve products, processes, and systems.

The analytical procedures used during in-process and finished product testing provide potentially significant opportunities for improvement and innovation, in line with the adopted and emerging ICH guidelines. This includes the opportunity for collaboration with external providers.

There has been a gradual shift to enable the management of specific aspects of changes to support improvement and innovation from regulatory authorities to pharmaceutical companies. The implementation of more progressive regulations has underpinned this transition and reinforced the potential benefits.

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