ICH Q12 TOOLBOX AND CHANGE MANAGEMENT

With present day circumstances including the pandemic affecting almost all sectors of society, the pharmaceutical industry is gravitating towards a complete revision of the traditional manufacturing environment. Today's innovative therapies has increased complexity of manufacturing, supply chains, and the regulatory burden associated with maintaining compliance amid diverse regulatory expectations.

In the words of U.S. FDA CDER Director Janet Woodcock, 21st century pharma should be a "maximally agile, flexible manufacturing sector that reliably produces high quality medicines without extensive regulatory oversight."

We have seen significant progress with the application of science and risk-based approaches outlined in prior ICH guidelines Q8, Q9, Q10 and Q11, however lack of harmonized requirements for lifecycle management are a disincentive to manufacturers to make improvements to increase process robustness on Established Conditions (ECs) and one post-approval change can take up to 5 years to implement across all regions, resulting in significant costs and potential supply disruption to the patient.

ICH Q12 focuses on post-approval changes to chemistry, manufacturing, and controls (CMC) in a more predictable and efficient manner supported by a company's pharmaceutical quality system (PQS) that follows regional GMP requirements. One of the guideline's underlying aims is to globally harmonize CMC change management, and industry has high expectations that it will significantly reduce regulatory burden, related costs, and approval timelines.

However, it is up to each regulatory region to choose how to implement Q12, and in Europe this has come with disappointment. Due to the current EU legal framework the guideline cannot be implemented, reducing the impact that it can have on ECs. Other tools and concepts in the Q12 guideline that are not in the EU legal framework will be considered when this framework is reviewed.

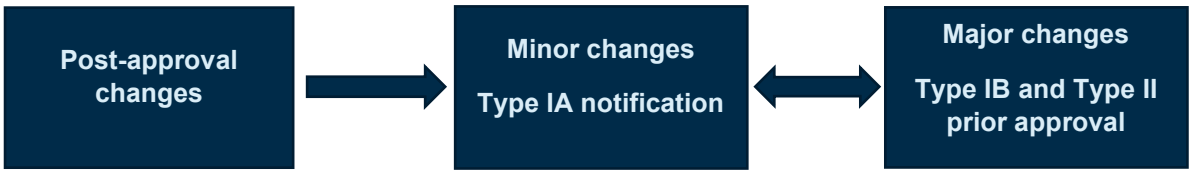
Note on EU implementation of ICH Q12 (guideline on technical and regulatory considerations for pharmaceutical product lifecycle management)

Outlined below is a detailed look at the primary points of ICH Q12.

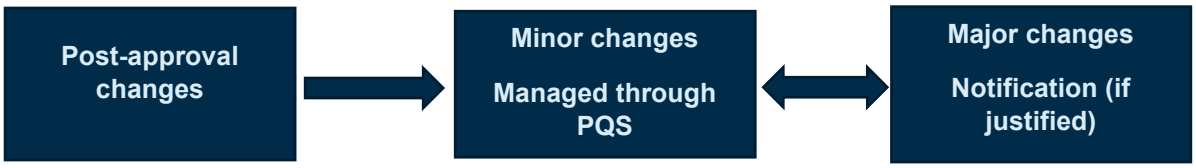
From initial concept, the aim of ICH Q12 was to 'promote innovation and continual improvement, and strengthen quality assurance and reliable supply of product, including proactive planning of supply chain adjustments.'. ICH Q12 intends to achieve this through the use of increased product and process knowledge to benefit patients, industry, and regulatory authorities.

The drivers for improving the product life cycle include innovation, patient access, compliance, process robustness and improved supply chain.

The traditional model for post approval changes involves prior approval by Regulatory Authorities or post change notification:



Using the ICH Q12 toolbox, the approach could be seen as follows:



Implementing this new approach under ICH Q12 will require using the tools and enablers throughout the product life cycle.

Below, the guiding principle of each tool is discussed.

PACMP

At present, the most globally useful tool is the 'Post-approval Change Management Protocol (PACMP).' The PACMP has been in place for several years in the EU and US and the introduction of ICH Q12 is expected to increase the frequency of use. PACMP or Comparability Protocol (US terminology) is a comprehensive plan for assessing the effect of a proposed change or multiple (related and consequential) CMC (chemistry, manufacturing, and controls) only post-approval changes on the quality of a product (identity, strength, purity, potency, performance, and stability). These protocols provide predictability regarding the information required to support a change and the type of regulatory submission based on prior agreement.

PACMP is a two-step process – first, a review of change and alignment of requirements by the Regulatory Authority prior to execution, second, a shorter review of protocol execution by the Regulatory Authority. The benefits of a PACMP include a clear agreement between Regulatory Authority and Marketing Authorization Holder on information required to support the change and potential to reduce timeline for approval. A PACMP can also support continuous process improvements, access to expanding markets with accelerated addition of manufacturing sites, and improved supply chain efficiency.

Established Conditions

Established Conditions (ECs) are legally binding information (registered details) considered necessary to assure process performance and desired quality of a medicinal product. ECs for a drug product include manufacturers, batch formula, storage conditions, and specifications. Changes to ECs require reporting to the relevant Regulatory Authority. In contrast, information provided in narrative form is considered supporting information and is required to accompany ECs. It is intended to provide background and auxiliary information on the development and manufacture of a product. It also aids in justifying the initial selection of ECs and their reporting category. Changes to 'supporting information' will not require regulatory action but will be managed by the PQS. Process validation would be considered supporting information.

The MAH must clearly identify the conditions considered to be ECs and supporting information in the various CMC sections of the CTD module. The rationale for the ECs must also be provided. Post-approval changes to ECs require different reporting categories dependant on the level of risk associated with them. Changes to High-Risk ECs must be reported for prior approval.

In the current variation guidelines EU, there is no framework to recognise Established Conditions or the PLCM. In contrast, the FDA fully recognises ECs.

Product Lifecycle Management (PLCM)

The PLCM document intends to facilitate regulatory assessment and inspection by acting as the central repository for key elements of the product lifecycle strategy e.g., ECs, PACMP, post-approval CMC commitments. Simply put, it is a summary that conveys to the regulatory authority how the MAH plans to manage post-approval CMC changes. The document should be maintained throughout the product lifecycle as needed.

A detailed example is provided as an annex to ICH Q12. This example is a clear and well-structured tool for creation of a product lifecycle management document. It is intended that the PLCM is submitted with a new product application or alongside variation defining ECs.

Summary

As global implementation of the tools presented in ICH Q12 is still some way off, it remains to be seen if there will be a reduction in administrative and regulatory burden for the MAH. An effective PQS as described in ICH Q10 and compliance with regional GMPs are necessary and will be vital for the success of the ICH Q12 toolbox.

References

Final Concept Paper Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management dated 28 July 2014 Endorsed by the ICH Steering Committee on 9 September 2014

Note on EU implementation of ICH Q12 (guideline on technical and regulatory considerations for pharmaceutical product lifecycle management)