# ICHQ12 Opportunities & limits.

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The ICH finally published in December 2017 the draft version of its guideline ICH Q12 "Technical and regulatory considerations for pharmaceutical product lifecycle management"[(1)]. Highly discussed and awaited since the concept paper issued end 2014, this draft guideline provides a framework to facilitate the management of post-approval changes which impact the CMC part of the regulatory dossier. Its application is expected to promote innovation and continual improvement in the biopharmaceutical sector and ultimately, will benefit patients, industry, and regulatory authorities.

First ICH guideline specifically dedicated to commercial phase of the product lifecycle, the purpose of Q12 guideline is to extend the application of pre-existing guidelines (Q8 to Q11) concepts, to the commercial manufacturing steps. In the previous guidelines, the ICH was mainly focused on the early stages of the lifecycle (development / registration / launch) promoting the Science- and Risk-based approach, i.e. product knowledge and process understanding based on a scientific approach integrating quality risk management (ICH Q9). Admitted by the ICH itself in the introduction section of the text, "*experience with implementation of recent ICH guidelines has revealed technical and regulatory gaps that limit the full realisation of more flexible regulatory approaches to post-approval CMC changes as described in ICH Q8 (R2) and Q10 Annex I*". The biopharmaceutical industry is now expecting ICH Q12 application to facilitate this long-waited operational and regulatory flexibility, meaning a return of investment for these approaches.

To answer to industrial and regulatory needs, ICH Q12 will allow the management of post-approval CMC changes in a more predictable and efficient manner, using increased product and process knowledge to reduce the number of regulatory submissions. Thanks to the effective implementation of the tools and enablers described in this guideline, the industry should be able to limit CMC changes effort thanks to the firm's Pharmaceutical Quality System (PQS), avoiding an exhausting regulatory approval prior to implementation.

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**To achieve these goals, Q12 introduces four new tools**:

- Categorisation of Post-Approval CMC Changes, consisting in a risk-based categorisation, guiding the choice of regulatory process type to be used,
- Established Conditions that characterise the CMC "binding information" defined in CTD, as approved elements necessary to assure product quality,
- Post-Approval Change Management Protocol (PACMP) proposing to the authorities the specific conditions, methods, acceptance criteria that need to be met to support a CMC change and the type of regulatory submission,
- Product Lifecycle Management (PLCM) document built as a central repository for the Established Conditions and the post approval changes management.

An effective PQS and Change Management process are necessary to enable the application of these tools. In the published Q12 draft, two appendices are provided to consolidate the concepts. The first appendix indicates the CTD sections that may contain the Established Conditions and the second one defines the principles guiding the Change Management process, precising how to use the *Knowledge Management* (KM) linked to the *Risk Management* (QRM). The main document is supported by three annexes, presented in an independent document, to illustrate the concepts through examples using the main tools described in the core document.

More specifically, Established Conditions (ECs), defined by Q12, are globally aligned with the concepts introduced by the FDA in 2015[3]. In both guidelines, ECs are defined as necessary elements (Product/ Process/ Materials/ Analytics elements) that must be fulfilled to assure product quality. The ECs are part of the Control Strategy, and finally represent the knowledge space established during Pharmaceutical Development. In the same manner as the Critical Process Parameters (CPP) need to be justified, the appropriate justification should be provided to support the identification of ECs and those aspects that are not ECs. A helpful decision tree is available in the guideline for identification of ECs and associated reporting categories for manufacturing Process Parameters. This decision tree may raise some comments before endorsement in the final guideline.

ICH Q12 is the first ICH document integrating the KPP concept (Key Process Parameters) that were up-to-date neither required nor clearly defined by EMA and FDA, even though some industries like biotechnological industry had already adopted the concept in accordance with the authorities. The precise definition of "Key", the decision tree to identify the ECs, as well as the terms "Explicit ECs" and "Implicit ECs" introduced in this guideline, will require some clarification to allow its appropriation by the firms and the operational teams involved in the Change Management process. No doubt that ICH Implementation Working Groups (IWG) or Q&A publications will be awaited soon by the industry after the consultation phase to support the implementation of these concepts.

The Post Approval Change Management Protocol, designated by WHO as "*Comparability Protocol*"[2], is an essential tool described in Q12. It defines the requirements and the studies needed for post-approval change implementation. This protocol should be submitted to the Health Authorities for approval. Thus, it establishes an agreement between the Marketing Authorisation Holder (MAH) and the Regulatory Authorities.

The Product Lifecycle Management Document appears as a new tool for Quality, comprising five main parts: a summary of Control Strategy, the list of Established Conditions, a reporting category for changes to approved ECs, a prospective overview of the PACMP as submitted and CMC post approval commitments (e.g. monitoring, ECs modifications). This document will become the central reference providing the lifecycle dimension to the control strategy.

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**Finally, highly valuable for the harmonisation of the three regions practices in the management of post-approval changes, the Q12 extends the quality vision of ICH to the commercial manufacturing. Implementation and consistency considerations will surely require experience sharing for the concrete translation of the concepts. The approach laid down by Q12 enables opportunities to translate the concept of "regulatory flexibility" to promote innovation and continual improvement. However, industry must complete and adapt their PQS to allow the effective implementation of lifecycle management, as the targeted flexibility is subordinated to a robust management of the product knowledge and the process understanding.**

## References


**[1]** ICH Q12 – Technical and regulatory considerations for pharmaceutical product lifecycle management – Step 2 – November 2017.

**[2]** WHO/OMS – Guidelines on procedures and data requirements for changes to approved biotherapeutic products – WHO/PAC for BTPs_DRAFT/2016.

**[3]** FDA – GFI – Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products – Draft 2015.