ICH Q12 Lifecycle Management

Overview of draft guideline

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Acknowledgement and thanks to:

Dr. Jean-Louis Robert

Q12 EWG, EC, Europe

Agenda

- ICH Q12 current status
- Content of ICH Q12 and its connection to EU enviroment
- Conclusion

ICH Q12 current status

May 2017

- ICH Q12 step 1 signed by EWG
- European Commission (EC) announced a legal check

November 2017

The following text (introduction) has been agreed on **at ICH Assembly:**

> *"In certain ICH regions, the current ICH Q12 guideline is not fully compatible with the established legal framework with regard to the use of explicit Established Conditions ('EC') referred to in Chapter 3 and with the Product Lifecycle Management ('PLCM') referred to in Chapter 5 as outlined in this guideline. These concepts will, however, be considered when the legal frameworks will be reviewed and, in the interim, to the extent possible under the existing regulation in these ICH regions."*

ICH Q12 has been signed (step 2b) by **Regulators only** not by Industry

18th December 2017

ICH Q12 is published for **1 year** consultation

ICH Q12 current status

Steps in the ICH Process for Guidelines

Content of ICH Q12

Two Documents

A. Q12 Core guideline

1. Introduction/Scope
2. Categorisation of post-approval CMC changes
3. Established conditions (ECs)
4. Post-approval change management protocol (PACMP)
5. Product lifecycle management (PLCM)
6. Pharmaceutical Quality System (PQS) and Change Management
7. Relationship between assessment and inspection
8. Post-approval changes for marketed products
9. Glossary
10. References

Appendix 1: CTD sections that contain ECs

Appendix 2: Principles of change management

B. Annex

Examples on Established Conditions, PACMPs, PLCM

Chapter 1: Scope

- Pharmaceutical drug substances (i.e., active pharmaceutical ingredients)
- Pharmaceutical drug products, including marketed chemical, and biotechnological/biological products
  - *Note: While it is understood that **ATMPs** are biological products, how the tools described in Q12 could be used (or not) for ATMPs can be elaborated during regional implementation of the guideline (e.g. via question and answers or specific guidance document)*
- Drug-device combination products that meet the definition of a pharmaceutical or biotechnological/ biological product
- Changes needed to comply with revisions to Pharmacopoeial monographs are not in the scope of this guideline
- ICH Q12 is not mandatory

  If not applied regional regulation has to be followed

Chapter 2:
CATEGORISATION OF POST-APPROVAL CMC CHANGES

- Regulatory communication between a MAH and the Regulatory Authority for potential changes which need regulatory action (category, information requirements and associated time frames)
- Drug regulatory authorities are encouraged to utilize a system that incorporates risk-based mechanisms for (a) requesting approval from the regulatory authority, (b) notifying the regulatory authority, or (c) simply recording CMC changes, with associated information requirements and, where applicable, timeframes for decision.
- Describes high level the different categories of changes
    - Prior-approval
    - Notification moderate to low risk
    - No reporting
- Chapter is essentially needed for those regions where such a categorization/classification does not exist
- *Essentially the "EU Variation Classification Guideline"*

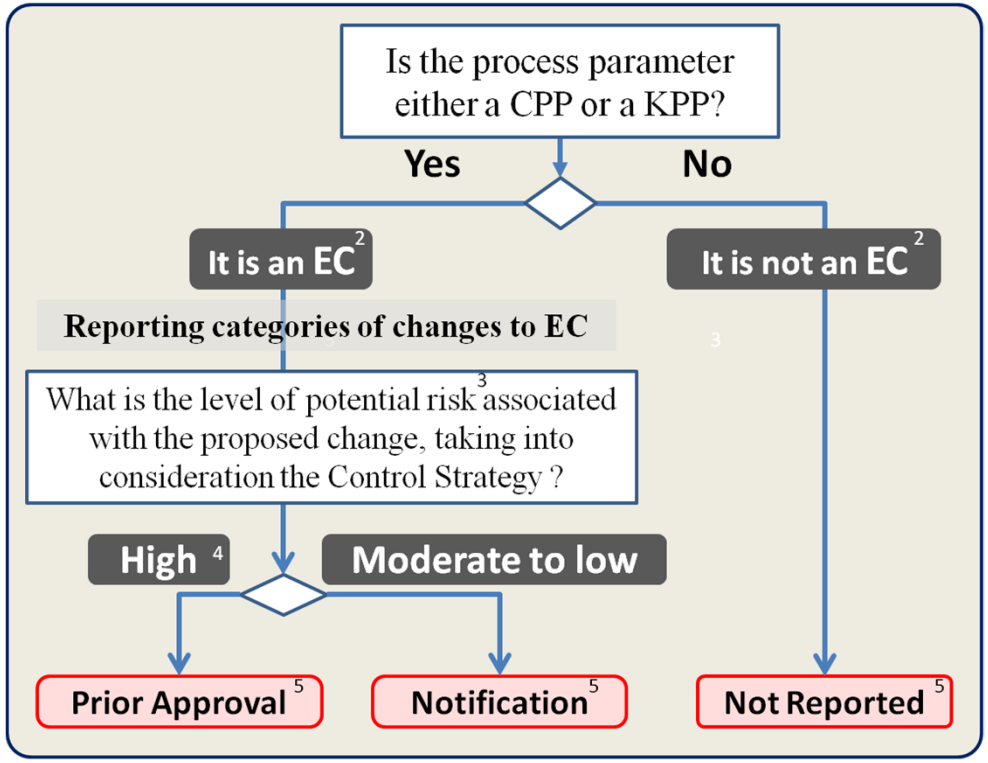
Chapter 3:
Definition Established Conditions (ECs)

- ECs are legally binding information/elements considered necessary to assure product quality.
  - Elements: e.g. process parameters, specifications, quality attributes, ……
- As a consequence, any change to ECs necessitates a submission (regulatory action!) to the regulatory authority.
- Implicit ECs (standard): derived from regional legislation or guidance
- Explicit ECs (product specific): specifically proposed by the applicant and authorized by the Regulators
  - Compared to implicit ECs, explicit ECs may lead to a lower reporting category
  - Subject to NCAs agreement
- Mainly focusing on manufacturing process and analytical methods

Chapter 3:
Definition Established Conditions (ECs)

- Critical Process Parameter (CPP):
  - Process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to assure the process produces the desired product quality. (Q8R2)
- Key Process Parameters (KKP):
  - Parameter of the manufacturing process that may not be directly linked to critical product quality attributes, but need to be tightly controlled to assure process consistency as it relates to product quality.
- Different approaches:
  - Parameter based approach
  - Enhanced approach
  - Performance based approach

Decision Tree for Identification of Established Conditions and Associated Reporting Categories for Manufacturing Process Parameters



Chapter 4:
Post Approval Change Management Protocols (PACMPs)

- Regulatory tool that provides predictability and transparency in terms of the requirements and studies needed to implement a change
  - Lower reporting category
  - Shortened review period

- Product specific protocols
- Broad protocols via work-sharing procedure

Well introduced in EU

Chapter 5:
Product lifecycle management (PLCM)

- The PLCM document outlines the specific plan for product lifecycle management that is proposed by the MAH, includes key elements of the control strategy, the ECs, proposed reporting categories for changes to ECs, PACMPs (if used) and any post-approval CMC commitments.
- The PLCM document serves as a central repository in the MAA for ECs and reporting categories for making changes to ECs. It includes the key elements and references to the related information located elsewhere in the MAA.

Submission of the PLCM document is encouraged; however, the document is expected when the MAH proposes explicit ECs.

Chapter 6: Pharmaceutical Quality System and Change Management

- An effective PQS as established in ICH Q10 and in compliance with regional GMPs is the responsibility of a firm (manufacturing sites and MAH where relevant)
- Chapter split into 2 parts:

1. General part with emphasis on supply chain knowledge (emphasis on communication)
2. Principles of change management (in Appendix)

It is not the intent of this guideline to require a specific inspection assessing the state of the PQS before the firm can use the principles in this guideline.

Chapter 7:
Relationship between assessment and inspection

- Regulatory assessment and inspection are complementary activities and their fundamental roles remain unchanged by this guideline.
- Communication between assessors and inspectors can facilitate regulatory review of a specific product submission. When required, information relating to GMP and marketing authorisation compliance may be communicated from inspectors to assessors, and vice-versa, via established mechanisms.

Common practice in EU.

Chapter 8: Post-Approval Changes for Marketed Products

- Two main chapters:
  1. Structured Approach to Analytical Procedure Changes (8.1)

     Basically to provide a recommendation how to make changes to an analytical procedure in a structured manner to allow a notification process (“Do and Tell”)

  2. Data Requirements to Support CMC Changes (8.2)

Appendices

1. **Table: CTD sections that contain ECs**

   The intention is to provide general guidance about:

   – those elements of manufacture and control that constitute ECs
   – those elements that are supportive information and
   – their location within the CTD structure

   Does not contain a complete list of ECs for a product

2. **Description of principles of change management (PQS)**
   – Management review
   – Use of knowledge in change management

Annex

- Annex I: illustrative examples ECs manufacturing process
  - IA: chemical product
  - IB: biological product

- Annex II: PACMPs
  - Alternative manufacturing site for a small molecule drug substance
  - Manufacturing site transfer of biotech drug substance

- Annex III: Product lifecycle management document

  - Example for a Solid Dosage Form Tablet X (small molecule) -dry blending

Conclusion

ICH Q12

- a natural follow-up of ICH Q8, 9, 10 and 11
- should allow a more transparent and predictable change management for both Industry and Regulators

Discussion are on-going, possibility to comment GL during this year is open (until 18th of December 2018)

THANK YOU FOR YOUR ATTENTION!

Any questions, comments?