Presentation Outline

• History of ICH Q12 including next step
• Content of ICH Q12
• Themes of comments given to ICH Q12 during public consultation
History of ICH Q12 development

- 2014-2017: First phase of drafting
- June 2017: Q12 Step 1 document signed by technical experts
- October 2017: Q12 Sep 2a and 2b*
- Public consultation launched in EU: 18 Dec 2017
- Deadline for comments: 18 Dec 2018
- Interim EWG meeting in Tokyo Feb 2019

- ICH meeting in Amsterdam 2-6 June 2019 – FINALISATION (?)
Guideline Objectives

Using the opportunities offered in ICH Q12 is optional

Guideline Objectives* include:

• To provide a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner across the product lifecycle… and across ICH regions

• … Facilitate risk-based regulatory oversight…

• Support continual improvement and facilitate introduction of innovation

• Enhance use of regulatory tools for prospective change management… enabling strategic management of post-approval changes…

• ICH Q12 is intended to complement the existing ICH Q8, Q9, Q10 and Q11 Guidelines

• This guideline is not intended to introduce new requirements necessitating changes to the regulations in the regions

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Endorsed by the ICH Steering Committee on 9 September 2014
How to archive that?

EWG Team representing European Commission:

Jean-Louis Robert (former QWP chair), Topic Lead
Nanna Aaby Kruse (Vice-chair BWP), Regulatory Chair for step 2
Brian Dooley (EMA Quality Office)
ICH Q12 is a GLOBAL guideline
ICH Q12 EWG Team

Moheb Nasr, Former GSK, Rapporteur of Q12 EWG for step 1 document
Ashley Boam, FDA, Rapporteur of Q12 EWG after step 1
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 2 – some confusion

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 (tell and do):
  – Notification (do and tell): moderate to low risk
  – No reporting (do and record)

  – **Essentially the “EU Variation Classification Guideline”**

<table>
<thead>
<tr>
<th>E.1.a.2 Changes in the manufacturing process of the active substance</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
<th>Procedure type</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>(a) Minor change in the manufacturing process of the active substance)</em></td>
<td>1, 2, 3, 4, 5, 6</td>
<td>1, 2, 3</td>
<td>IA</td>
</tr>
<tr>
<td><em>(b) Substantial change in the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product)</em></td>
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<td>II</td>
</tr>
<tr>
<td><em>(c) The change refers to a biological/immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol)</em></td>
<td></td>
<td></td>
<td>II</td>
</tr>
<tr>
<td><em>(d) The change relates to a herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production)</em></td>
<td></td>
<td></td>
<td>II</td>
</tr>
<tr>
<td><em>(e) Minor change to the restricted part of an Active Substance Master File)</em></td>
<td>1, 2, 3, 4</td>
<td></td>
<td>IB</td>
</tr>
</tbody>
</table>
Globally more than 900 comments were received to the GL

Guideline chapters primarily calling for comments:

– Chapter 3 Established Conditions
Chapter 3 (1)
Definition Established Conditions (ECs)

ECs are legally binding information (or approved matters) considered necessary to assure product quality

• As a consequence, any change to ECs necessitates a submission to the regulatory authority

• All regulatory submissions contain a combination of ECs and supportive information

• Supportive information is not considered to be an EC, but is provided to share with regulators the development and manufacturing information at an appropriate level of detail, and to justify the initial selection of ECs and their reporting category
Chapter 3 (2)
Established Conditions

ECs for manufacturing processes:

• Generally include unit operations and the sequence of steps
• Considering the overall control strategy
  • Critical process parameters (CPPs, as defined in ICH Q8(R2)) and key process parameters (KPPs) new

ECs for analytical method

• Potential conflict with ICH Q2 revision/Q14?

All types of ECs

• After identifying ECs, MAH proposes reporting category for post-approval changes
ECs for manufacturing processes fall on a continuum based on extent of development:

• A parameter-based approach, in which product development prior to regulatory submission provides a limited understanding of the relationship between inputs and resulting quality attributes, will include a large number of inputs (e.g., process parameters and material attributes) along with outputs (including in-process controls).

• An enhanced approach with increased understanding of interaction between inputs and product quality attributes together with a corresponding control strategy can lead to identification of ECs that are focused on the most important input parameters along with outputs, as appropriate.

• In certain cases, applying knowledge from a data-rich environment enables a performance-based approach in which ECs could be primarily focused on control of unit operation outputs rather than process inputs (e.g., process parameters and material attributes).
Chapter 3 (5)
Established Conditions

“This guideline is not intended to introduce new requirements necessitating changes to the regulations in the regions”

Comments:

- Implicit / explicit ECs
- KPP
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– Chapter 5 Product lifecycle management (PLCM)
Chapter 5
Product LifeCycle Management (PLCM) document

Product Lifecycle Management (PLCM) document
• Serves as a central repository for ECs, reporting category for making changes to approved ECs, PACMPs (when proposed), and any post-approval CMC commitments
• Intended to enable transparency and facilitate continuous improvement

Comments:
• Purpose?
• Mandatory?
• Addend value?
• Location in the dossier?
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Guideline chapters primarily calling for comments:

*Chapter 6 Pharmaceutical quality system (PQS) and change management*
ICH Q10 describes principles for the effective management of CMC changes under the PQS
Appendix 2 elaborates on Q10 principles and describes how the PQS can be utilized effectively in the application of Q12 concepts

Comments:
- Demonstration of an “effective” PQS
- Proposed: This section articulates the importance of timely communication across multiple sites (outsourced or not), and between the MAH and the regulators on manufacturing changes
- Regulatory action when a company meet minimum standards but not sufficient for Q12?
- Change during life-cycle – what action to take
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Guideline chapters primarily calling for comments:

– *Chapter 8 Post-approval changes for marketed products*
This chapter describes a strategy for a structured approach for frequent CMC changes (e.g., analytical methods) and data requirements for CMC changes (e.g., stability):

- 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”)

- Data Requirements to Support CMC Changes (8.2) - Stability
Chapter 8 (2)
Post-Approval Changes for Marketed Products

Comments:
• New title
• More examples
• The overall intent and concept described in chapter 8 is supported but the technical detail of the structured approach described in chapter 8.1.2 needs to be significantly improved and the relationship of ICH Q12 to ICH Q2/14 should be made clear.
ICH Q12 – further comments

- **Nov 2017:** Q12 Step 2 document signed, with a legal disclaimer inserted

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.

Comment:

- Delete!
This is a **GLOBAL** guideline
Thank you for your attention

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