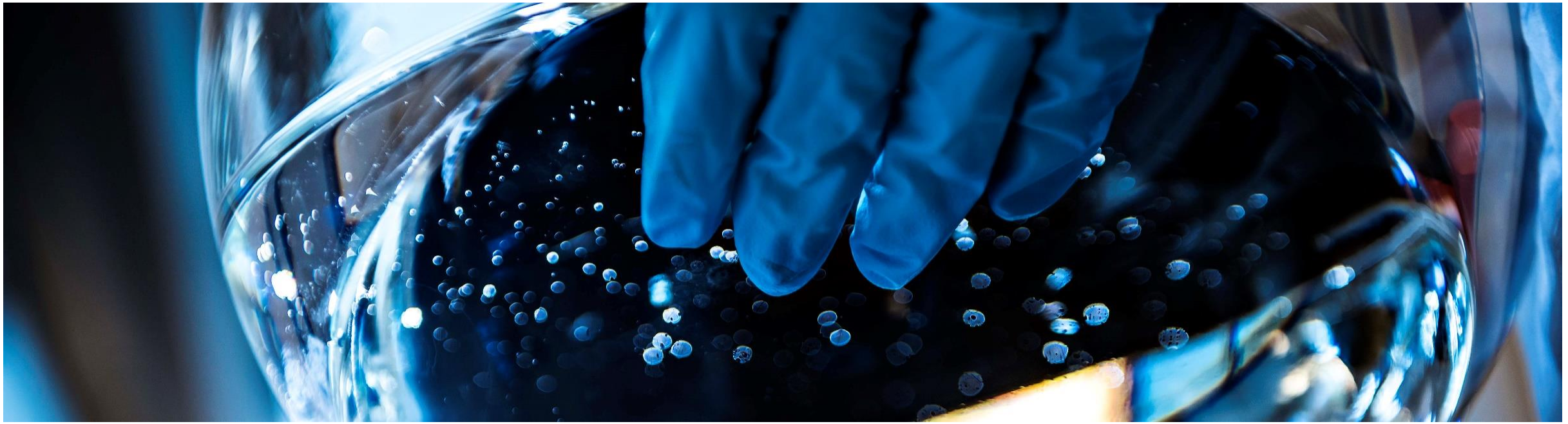
CASSS Europe 2020
ICH Q12 EU implementation
(+ Q5A / Quality Discussion Group status update)

Nanna Aaby Kruse, Senior Biological Expert, Team manager, BWP Vice-Chair



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ICH Q12 Lifecycle management

- **Goal:** To agree a harmonised approach to technical and regulatory considerations for CMC lifecycle management, across regions.
- **How:** By providing a framework to facilitate the management of post-approval CMC changes in a predictable and efficient manner.

  (i.e. EU: ‘variations’, US: ‘supplements’, JP: ‘approved matters’)
- Builds on the existing concepts in ICH Q8, Q9, Q10, Q11 for a more science and risk-based approach to assessing CMC changes across the lifecycle, and the existing tools available in the various regions. - Not mandatory to follow Q12
- New term ‘Established Conditions’
- **Whom:** EU Expert team: Jean-Louis Robert (QWP), Brian Dooley (EMA) and Nanna Aaby Kruse (BWP)

ICH Q12 Lifecycle Management

ICH meeting summary

- **2014-2017:** First phase of drafting.
- **Dec 2017 – Dec 2018:** 12 month public consultation
- **Nov 2019:** Full EWG meeting (ICH Singapore) – guideline was finalised

Overview of content

- ICH Q12 Core Guideline text
- Annexes: Illustrative Examples
- Planned Training Material

Next steps

- Finalise training material
- EU implementation in practices

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ICH Q12 EWG (Singapore, 16-20 November 2019)

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ICH Q12 Core Guideline text

- Chapter 1 Introduction
- Chapter 2 Categorisation of Post-Approval CMC Changes
- Chapter 3 Established Conditions
- Chapter 4 Post-approval Change Management Protocol
- Chapter 5 Product Lifecycle Management Document
- Chapter 6 PQS and Change Management
- Chapter 7 Relationship between Regulatory Assessment and Inspection
- Chapter 8 Structured Approaches for Frequent Post-Approval CMC Changes
- Chapter 9 Stability Data to Support Frequent CMC Changes
- Appendix 1 CTD Sections That Contain ECs
- Appendix 2 Principles of Change Management

Annex I: Illustrative Examples

- Annex IA Established Conditions for the Manufacturing Process (Chemical product)
- Annex IB Established Conditions for the Manufacturing Process (Biological product)
- Annex IC Established Conditions for Analytical Methods (Minimal development)
- Annex ID PACMP for site transfer (Chemical product)
- Annex IE PACMP for site transfer (Biological product)
- Annex IF Product Lifecycle Management Document
- Annex II: Structured approach to analytical procedures changes

Note on EU implementation of ICH Q12

EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

04 March 2020
EMA/CHMP/ICH/78332/2020

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

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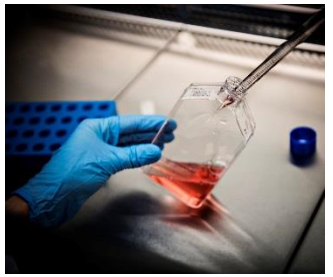
Note on EU implementation of ICH Q12

- *Several of the tools and concepts foreseen in the ICH Q12 guideline are considered compatible with the EU legal framework on variations and some even stem directly from this framework. These tools and concepts can already be applied, as such, by industry by following the current EU variations framework. In other words, no particular actions are required in the EU in order to implement these parts.*
- i**.e. risk-based categorisation of changes (type IA-IB-II), PACMPs, PQS change management, structured approach to frequent CMC changes (analytical methods) can be implemented already**.

B.I.a.2 Changes in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor change in the manufacturing process of the active substance	1, 2, 3, 4, 5, 6, 7	1, 2, 3	IA
b) Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product.			II
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.			II
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.			II
e) Minor change to the restricted part of an Active Substance Master File.		1, 2, 3, 4	IB

Note on EU implementation of ICH Q12



- *While this term does not exist in the EU variation legal framework, generally speaking, Established Conditions mirror information and quality characteristics that are subject to a variation, as described in the EU Variation Regulation (EC) No 1234/2008 (as amended) and associated EU Variation Guidelines.*

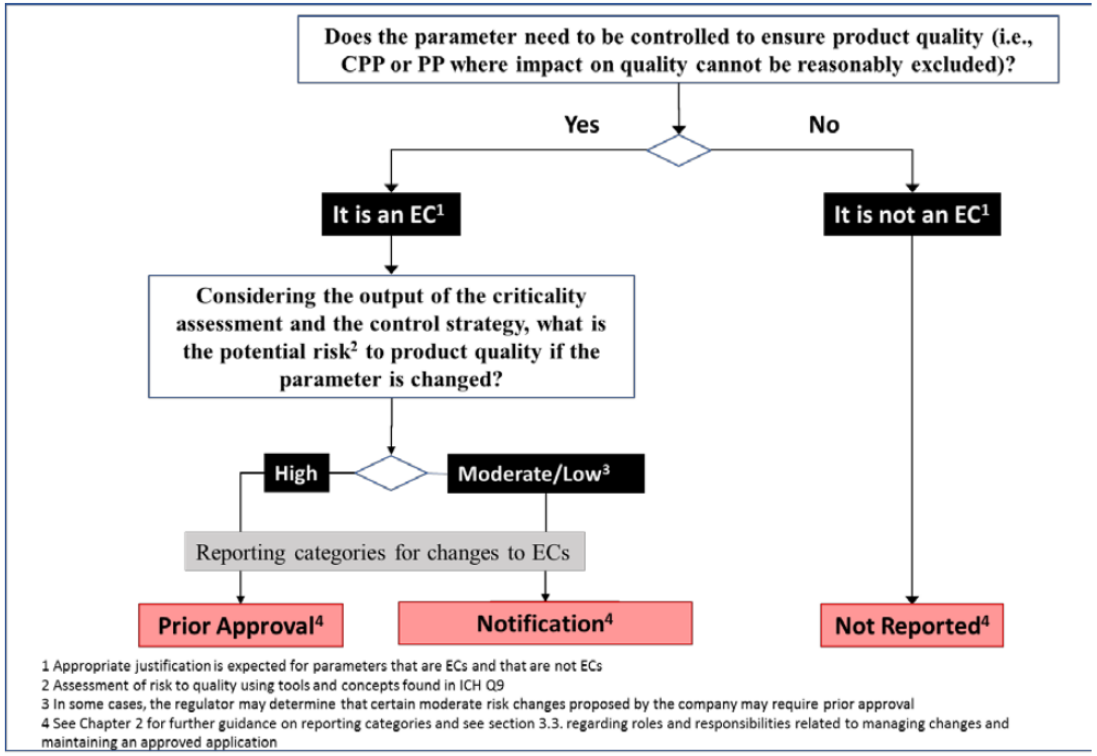
- *However, additional scientific risk-based approaches to defining Established Conditions and associated reporting categories, as described in Chapter 3.2.3, and the Product Lifecycle Management (PLCM) Document, as described in Chapter 5, are* ***not considered compatible with the existing EU legal framework on variations****.*

Note on EU implementation of ICH Q12

Chapter 3.2.3 - Identification of ECs

- *This chapter outlines approaches to define ECs for manufacturing processes and analytical procedures. …… should be justified by the applicant and approved by the regulatory agency.*
- *The extent of ECs may vary based on the company's development approach, product and process understanding, and the potential risk to product quality.* ***Appropriate justification should be provided in support of the identification of ECs, the proposed reporting categories for ECs, and those aspects that are not EC***

Figure 1: Decision Tree for Identification of ECs and Associated Reporting Categories for Manufacturing Process Parameters



Note on EU implementation of ICH Q12

- *It is important to note that the legal framework always takes precedence over technical and scientific guidelines.*

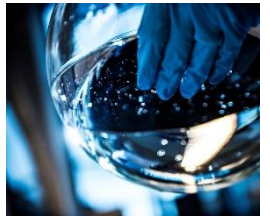
- *More specifically this means that* ***the definition of Established Conditions and their reporting categories must follow the requirements laid down in the current EU Variations Regulation and associated EU Variations Guidelines****.*

- *With respect to the Product Lifecycle Management (PLCM) document, in case such a document is submitted, it cannot be currently recognised in the EU due to the fact that it is not referred to in the EU legal framework.*

EU implementation – in practice ?

- Many aspects of the practical implementation in EU – and globally – still need to be solved/clarified
- Company's are encouraged to identify ECs in their EU dossiers.
  - Although the full realisation of Q12 in EU has not happened yet.
  - It will help Assessors and EU Implementation Working Group to get experience and can inform us where further guidance is needed
  - An EU Q&A may be developed
  - ?????

Useful References



ICH Q12 Step 4 Guideline, Annexes and summary presentation are available on ICH website: https://www.ich.org/page/quality-guidelines#12

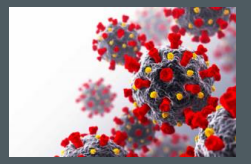
Q12 Step 4 Presentation

https://database.ich.org/sites/default/files/Q12EWG_Step_4_IntroTrainingPresentation_2020_0206.pdf

EU implementation note for ICH Q12:

– https://www.ema.europa.eu/en/documents/other/note-eu-implementation-ich-q12-guideline-technical-regulatory-considerations-pharmaceutical-product_en.pdf

– Training material is under development and will be published at a later stage



Revision of ICH Q5A

Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

ICH Q5A(R1) was finalized in **1999**

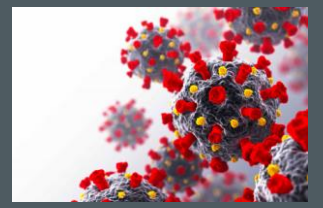
Recognized that a revision was necessary to reflect current scientific knowledge and biotechnology advances (Initial proposal from US FDA)

Main issues to be addressed in the revision

- **New classes of biotechnology products**
- **Additional validation approaches for virus clearance**
- **New virus assays and alternative analytical methods**
- **Virus clearance validation and risk mitigation strategies for advanced manufacturing**
- **Aspects of virus clearance validation that have emerged or evolved**

Joel Welch, US FDA, act as Rapporteur and Johannes Blümel, EC Europe, act as Regulatory Chair

Revision of ICH Q5A - Main issues to be addressed



- ICH Q5A(R2) Concept Paper and Business Plan endorsed in Singapore in November 2019

- Completion of first technical document draft: November 2020

- Completion of Step 1, Step 2a and 2b: **June 2021**

- Completion of Step 3 and 4: **November 2022**

Genesis of the Quality Discussion Group (QDG)

2003 ICH Quality Vision

"Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science"

2005-14 ICH Quality Guidelines

- ICH Q8 Pharmaceutical Development (Parent guideline Nov 2005; Annex Nov 2009)[2]
- ICH Q9 Quality Risk Management (Nov 2005)[3]
- ICH Q10 Pharmaceutical Quality Systems (June 2008)[4]
- ICH Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Products) (May 2012)[5]

ICH Informal Quality Discussion Group (IQDG)

5 Year Plan for Quality Topics
Proposed to the Steering Committee
Minneapolis
June 3rd, 2014

November 2018, QDG formed

ICH harmonisation for better health

Remit of the Informal Quality Discussion Group

22 October 2018

Endorsed by the ICH Management Committee on 13 November 2018

June 2018

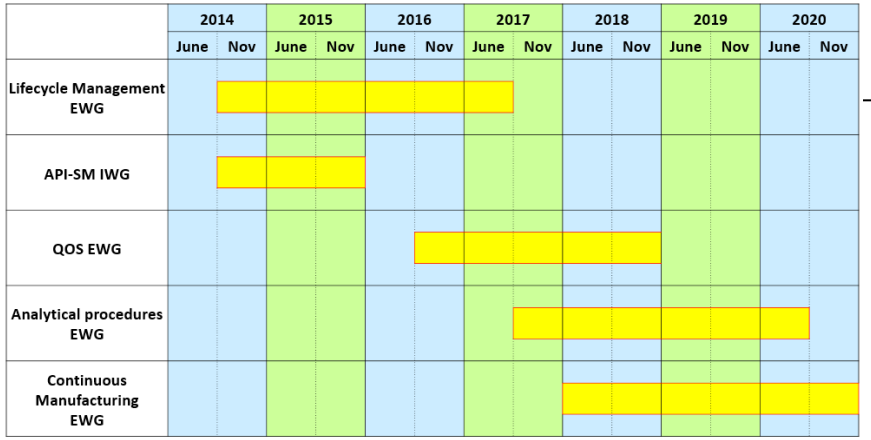
ICH harmonisation for better health

ICH Reflection Paper
Endorsed by the ICH Assembly on 6 June 2018

ICH Reflection Paper

Advancing Biopharmaceutical Quality Standards to Support Continual Improvement and Innovation in Manufacturing Technologies and Approaches

2014 IQDG 5 year Plan



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SLIDE: MATT POPKIN, GSK/EFPIA

ICH QDG Remit and membership

- The QDG will support the ICH Quality vision and the ICH MC through:
  - Review and recommendations for new ICH Quality-related harmonization work (including new guidelines, updates, Q&As etc)
  - Review and recommendations for training related to the content and/or implementation of ICH Quality guidelines (working to support the ICH training subcommittee)
  - Review and recommend any necessary updates to the ICH Quality Reflection Paper and ICH Quality Vision - Long term strategy framework
  - Current term is 2019 – 2020, - may need extension
  - 33 members
  - Determine & prioritize recommendations to the ICH Management Committee

QDG particular tasks in year 1

In support of the IQDG Scope of Activities, the IQDG should specifically endeavour upon completing the following actions in its first calendar year:

- Assess the **impact of ongoing ICH Quality Topics on future ICH Quality harmonization work** envisioned under the ICH Quality Vision (i.e., the impact of ICH Q12 on other ongoing or newly proposed ICH Quality topics)

- Consider ICH Quality topic proposals envisioned under the ICH Quality Vision that have not been endorsed by the ICH with the goal of assessing how the proposal could be strengthened for reconsideration

- **Design and recommend to the ICH Management Committee for execution a survey of existing ICH Quality Guidelines in need of revision**

Type of Action – How to Choose **What** to Do

Type of Action	Choose When…
New Guideline	Harmonization on this topic would have a high impact/provide substantial benefit; Harmonization focus can be either **pro**spective (e.g., digital health, cell and gene therapies) or **retro**spective
Revision of an Existing Guideline	Scientific issues with current version; Full revision would have a high impact/provide substantial benefit
Annex or Addendum	New information needs to be added to an existing guideline **without** amending the existing text
Maintenance of an Existing Guideline	Only specific chapters require an update, but a full revision is not needed
Q&A	Additional guidance is needed to help the interpretation of the guideline to ensure consistent implementation
Implementation Assessment	Existing guideline is adequate, but industry feels interpretation/adoption varies across regulators **and** guideline implementation has **not** yet been assessed via ICH survey
Training	Existing guideline is adequate, but interpretation/adoption varies across regulators

SLIDE: MATT POPKIN, GSK/EFPIA

EU Regulators – need for action - outcome of survey

VERY HIGH (1)

1. **ICH Q1A, Q1D, Q1E Stability**
2. **ICH Q5C Stability (Biologicals)**

HIGH (2)

3. **ICH Q6A Specifications**
4. **ICH Q6B Specifications (Biologicals)**

5. **ICH Q7 Q&A GMP for APIs**

EFPIA priorities (EFPIA have kindly accepted to share their priorities)

efpia
European Federation of Pharmaceutical Industries and Associations

- **Priority #1: Stability (ICHQ1 and Q5c)**
- Revision of guidelines or addition of new annexes and training materials
- **Priority #2: Specifications (ICHQ6a and Q6b)**
- Addition of new annexes and training materials
- **Joint priority 3**
  - **ICHQ8, 9, 10 Points to Consider:**
    - Issues encountered with global implementation of QbD, particularly control strategy (e.g. CPPs, design space/PARs)
    - Seen as fundamental to ICHQ12 Established Conditions
  - **ICHQ5b and 5d:**
    - need to modernise and address current knowledge (e.g. for established monoclonal antibody platforms)
  - **ICHM4(Q)**
    - Focus on “telling the story” and “enhanced QOS”
    - Need to address regional “registered detail” forms and data standard proposals

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