



# **TECHNICAL AND REGULATORY ASPECTS OF PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT: ICH Q12**

**MOHEB NASR**

**PHRMA ICH Q12 TOPIC LEAD**

***WCBP 2018***

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***WASHINGTON, D.C.***

# DISCLAIMERS

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- The speaker is solely responsible for the content of this presentation
- The views presented here do not necessarily represent the views of PhRMA or ICH

# OUTLINE

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- Background
- ICH Q12
  - Scope and Objectives
  - Step 1 / 2a Montreal document
  - Key Sections and Enabling Tools
- Progress and Challenges after Montreal
  - Next steps
- Conclusions
- Acknowledgements



# ICH QUALITY VISION: A NEW PHARMACEUTICAL QUALITY PARADIGM (2003)

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*“Develop a harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science”*

- Science and risk-based approaches to product development, dossier submission, review, and post-approval change management
- Continuous improvement and innovation throughout the product lifecycle
- Effective and consistent global regulatory oversight
- Significant progress made between 2003 and 2014
  - ICH Q8, 9, 10 & 11
  - ICH Q IWG
  - QbD a preferred development platform
- Expected regulatory/operational flexibility, particularly as it relates to lifecycle management, was not realized

# ICH QUALITY STRATEGY WORKSHOP (1)

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- June 2014 in Minneapolis, Minnesota, USA
- Co-chaired by EU and PhRMA
- Purpose: To assess progress made since 2003 and develop a future strategy
- Conclusions made from the assessment:
  - Implementation of ICH Q8, Q9, Q10 and Q11 provides opportunities for more science and risk based approaches
  - Q8-11 emphasized the development stage of lifecycle
  - Opportunities and benefits have not been fully enabled, and the envisioned “operational flexibility” has not been achieved
  - Need to focus more on the Commercial Manufacturing phase of the lifecycle

# ICH QUALITY STRATEGY WORKSHOP (2)

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- Renewed alignment with 2003 quality vision and agreement on priorities and future needs
- Developed 5-year workplan
- Priorities Identified:
  - **ICH Q12: “Technical and Regulatory Considerations of Pharmaceutical Product Lifecycle Management”**
  - API Starting Materials (ICH Q11 IWG)
  - Quality Overall Summary
  - Enhanced Approaches for Development and Utilization of Analytical Procedures (AQbD)
  - Continuous Manufacturing of Pharmaceuticals



# ICH Q12: SCOPE AND OBJECTIVES (1)

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- Scope
  - Pharmaceutical drug substances (i.e., active pharmaceutical ingredients)
  - Pharmaceutical drug products (chemical, and biotechnological/biological products)
  - Marketed products
  - drug-device combination products that meet the definition of a pharmaceutical or biotechnological/biological product
- Q12 excludes changes needed to comply with revisions to Pharmacopeial monographs

# ICH Q12: SCOPE AND OBJECTIVES (2)

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- Objectives
  - Q12 provides a framework to streamline and enhance efficiency and predictability of regulatory aspects of post-approval CMC changes
  - Encourages innovation and continual improvement
  - Bring envisioned operational/regulatory flexibility to fruition, e.g., by demonstrating how enhanced product and process knowledge contribute to a reduction in the number of post-approval regulatory submissions
  - In summary, to realize regulatory and operational benefits of QbD (Q8-11)





## Q12 EXPERT WORKING GROUP (EWG)- MONTREAL MEETING

- Large team representing regulators (FDA, EC, MHLW/PMDA, HC, Swissmedic, ANVISA, MFDS, HSA, WHO, TFDA) and industry (PhRMA, EfPIA, JPMA, IGBA, BIO, APIC, WSMI)
- Diverse technical, quality and regulatory expertise
- Passionate leadership, dedication and collaboration
- Commitment to develop a transformational guideline
- Willingness to discuss and resolve difficult technical and regulatory issues

PRESENTATION TITLE

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Date

# PROGRESS IN MONTREAL (MAY 28 – JUNE 1, 2017)

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- Reached Step 1/2a
  - Document 1: Core guideline and appendices
  - Document 2: Q12 annex (illustrative examples)
- Step 1/2a document
  - Resolved issues described in the concept paper
  - **No deviation from concept paper**



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## - ICH Q12 CORE DOCUMENT AND APPENDICES

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1. Introduction
  2. Categorization 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 Regulatory Assessment and Inspection
  8. **Post-Approval Changes for Marketed Products**
  9. Glossary
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- Appendix 1: CTD Sections That Contain ECs
- Appendix 2: Principles of Change Management



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## - ICH Q12 ANNEX (ILLUSTRATIVE EXAMPLES)

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- Annex I: ECs – Illustrative Examples
  - Annex I A: Chemical Product
  - Annex I B: Biological Product
- Annex II: PACMP – Illustrative Examples
  - Annex II A: PACMP Example 1
  - Annex II B: PACMP Example 2
- Annex III: Product Lifecycle Management Document
  - Illustrative Example

# KEY SECTIONS OF Q12 STEP 1/2A DOCUMENT (1)

- **Categorization of Post-Approval CMC Changes**
  - Considers a risk based system for categorization of changes and regulatory communications
  - System exists in some markets
  - Global implementation will allow timely and efficient introduction of CMC changes and enable effective use of industry and regulatory resources
- **Established Conditions**
  - Describes a harmonized approach to defining “Regulatory Commitments” i.e. those elements in the regulatory submission which are subject to regulatory change control
  - Identifies “clearly” what are supportive information in a regulatory submission, which is not considered to be ECs.
  - Concept exists and/or is evolving in some regions
    - Japan: MHLW ‘Approved Matters’
    - USA: Draft FDA Guidance on ‘Established Conditions’

# KEY SECTIONS OF Q12 STEP 1/2A DOCUMENT (2)

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- ECs in a submission are either implicit or explicit:
  - **Implicit** ECs are elements that are not specifically proposed by the MAH but are derived from and revised according to regional regulation or guidance related to post-approval changes
  - **Explicit** ECs are specifically identified and proposed by the MAH together with their proposed reporting category as part of a regulatory submission.
    - **An MAH may use one or both approaches as described above to define ECs and their associated reporting categories**

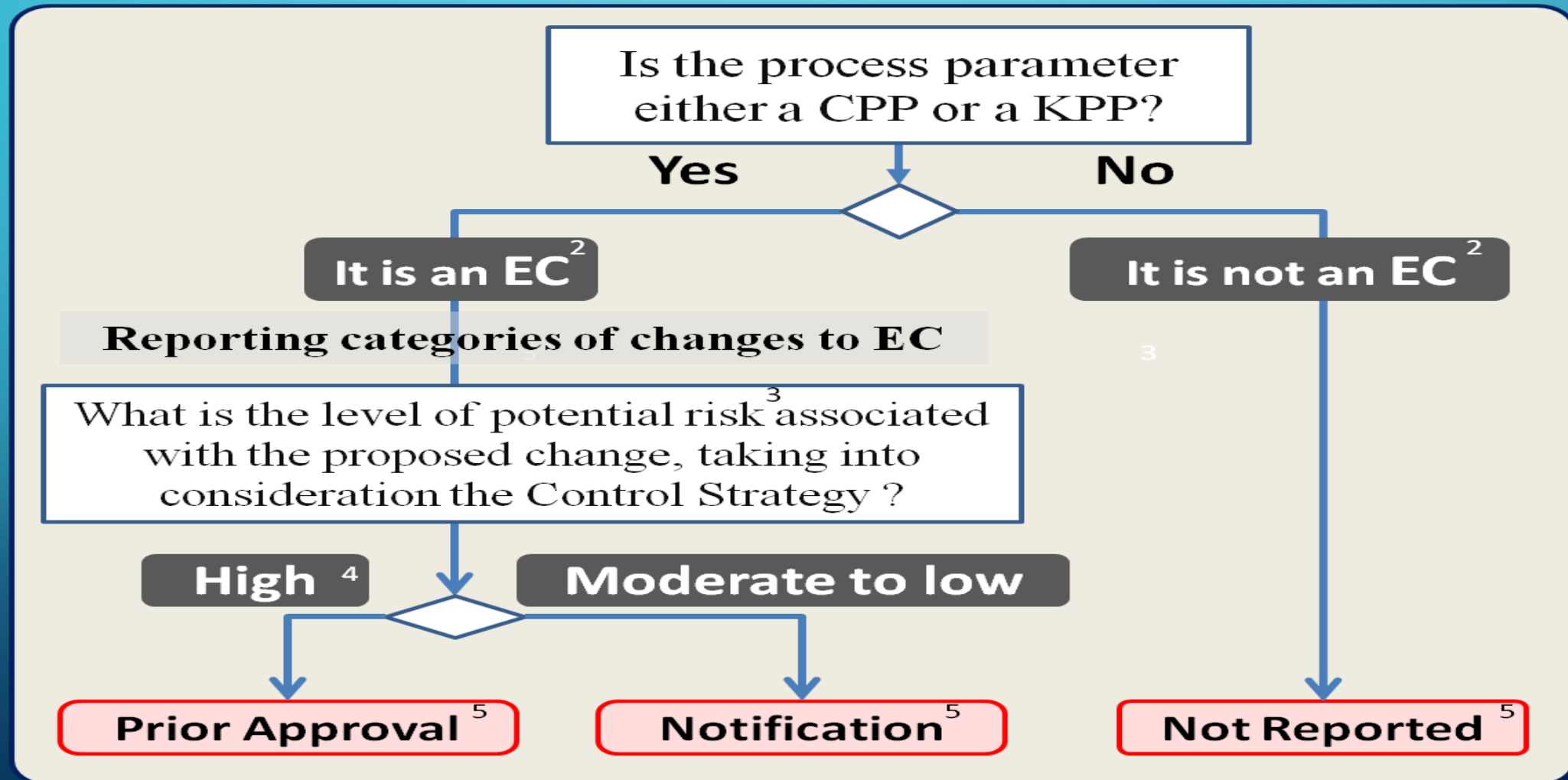


# KEY SECTIONS OF Q12 STEP 1/2A DOCUMENT (3)

**Identification of ECs for the Manufacturing Processes** (approaches described below can be used alone, or in combination, to identify ECs)

- **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).

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



# KEY SECTIONS OF Q12 STEP 1/2A DOCUMENT (4)

- **Post-Approval Change Management Protocol (PACMP)**
  - Describes the change(s) a firm would like to implement during the lifecycle of a product and proposed reporting categories
  - Provides predictability and transparency
  - PACMP exists in EU and US with limited utilization
- **Product Lifecycle Management (PLCM)**
  - Serves as a central repository of the ECs, reporting category for making changes to approved ECs, PACMPs, and post-approval CMC commitments
  - Provides a high level summary of product control strategy to clarify and highlight which elements of the control strategy should be considered ECs.
  - Facilitates and encourages a more strategic approach to lifecycle management
  - Enables transparency and facilitates continual improvement



# KEY SECTIONS OF Q12 STEP 1/2A DOCUMENT (5)

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- **Pharmaceutical Quality System (PQS) and Change Management**
  - ICH Q10 describes principles for the effective management of CMC changes under the PQS
  - This section articulates the importance of timely communication across multiple sites (outsourced or not), and between the MAH and the regulators on manufacturing changes
  - Appendix 2 elaborates on Q10 principles and describes how the PQS can be utilized effectively in the application of Q12 concepts
- **Relationship Between Regulatory Assessment and Inspection**
  - Encourages communication between assessors and inspectors to facilitate implementation of Q12

# KEY SECTIONS OF Q12 STEP 1/2A DOCUMENT (6)

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- **Post-Approval Changes for Marketed Products**

- Q12 regulatory tools/enablers are applicable to marketed products
- Describes a strategy for a structured approach for frequent CMC changes (e.g., analytical methods) and data requirements for CMC changes (e.g., stability)
- Without this section, Q12 will have very limited benefits to the majority of marketed products
- A case study to illustrate current challenges to continual improvement in next slide

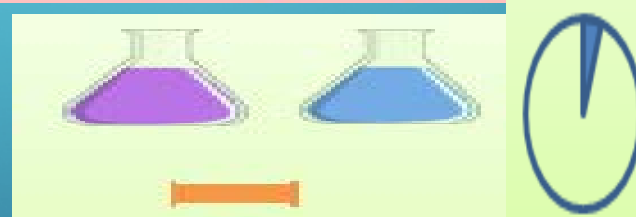
# MAGNITUDE OF CHALLENGE – ANALYTICAL EXAMPLE (COURTESY OF DAVID TAINSH, GSK)

- GSK central stability testing laboratory tests a wide range of different products which contain 20 different active and would benefit tremendously from being able to run these using a single “always on” method

**From: 22 mobile phases / 9 columns / Average Run Time : 45 minutes**



**To: 2 mobile phases / 1 column / Average Run Time : 3 minutes**



- These products are sold in 174 different countries
- And implementation require changing 6364 licenses!



# PROGRESS AND CHALLENGES AFTER MONTREAL MEETING

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- EU sponsored revisions to step 1 / 2a document
  - “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”
- EU proposed revision was adopted by ICH MC and Assembly in Geneva
- Q12 reached Step 2b in November 16, 2017

# NEXT STEPS - TENTATIVE

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- **Public Consultation extended for one year**
  - Regional review of comments Q1-4, 2018
  - Potential Q12 EWG F2F Meeting, Q4 2018
  - Step 4 Targeted for Q2 2019
- **Training**
  - Development of a comprehensive training program and supporting documentation sponsored by ICH is highly recommended to ensure the proper interpretation and effective utilization and implementation by industry and regulators
  - This is important for ICH and non-ICH regions

# CONCLUSIONS (1)

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- ICH Q12 reached step2b in Geneva, November 16, 2017
- Q12 can be a transformational guideline
  - Introduces a harmonized risk-based categorisation system for managing post-approval CMC changes under ICH framework
  - Provides clarity that distinguish EC and supporting information in a regulatory submission
  - Enables planning and implementation of future changes to ECs in an efficient and predictable manner by using PACMP
  - PLCM document serves as a central repository of the ECs, reporting category for making changes to approved ECs, PACMPs, and post-approval CMC commitments
  - Provides a strategy for a structured approach for frequent CMC changes (e.g., analytical methods) of marketed products



## CONCLUSIONS (2)

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- EU sponsored revisions and ICH step 2(b) process, may impact the utility of Q12 and speed of implementation within and outside ICH regions
  - Could also impact ALL future ICH guidelines
- Regional public consultation and discussions in public meetings will shape the final version of Q12
- Q12 EWG envisioned a transformational guideline combined with harmonized implementation beyond ICH regions
  - More work is needed between now and step 4 to realize our vision
- It is always difficult to make significant paradigm changes
  - We can learn from the QbD Journey

# ACKNOWLEDGEMENTS

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