Will ICH Q12 truly goes beyond Q8/11??

*Opportunities and Challenges*

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Presentation Outline

• ICH Quality Vision
• Life Cycle Management Challenges
• Current State of Q8/11 implementation
• Opportunities for Q12: Established Conditions
  • Case Study for selection of EC’s
• Next Steps…
ICH Quality Vision 2003

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

*Intended to ensure quality products and reliable supply to patients*
Reflection on the 2003 ICH Quality Vision

• 2003 Quality Vision expectations achieved
  o Guidelines developed to meet ICH 2003 expectation to enable realisation of the vision
  o Additional needs identified based on implementation experiences and expectations, advances in science and current needs by both industry and regulators

• Do we need to update 2003 ICH Quality vision? - No
  o However, more efforts needed to fully address challenges and strengthen product life cycle management
Realisation of ICH 2003 Quality Vision

• Q8, Q9, Q10, Q11 Guidelines
• Q-IWG Q&As
• Points to consider
• Training in the three regions
• Training outside ICH regions
• Extensive implementation activities in ICH Regions and beyond
  o Include Discussion groups, Workshops, Parallel Assessments, Q&As
LifeCycle* Management

- **Problem statement**
  - Implementation of ICH Q8/Q11, Q9 and Q10 provides opportunities for a more science and risk based approach to assessing changes across the life cycle
    - Main emphasis is during the Development stage
  - Opportunities and benefits have not been fully realized/enabled, and the envisioned ‘operational flexibility’ has not been achieved
  - We now need to focus on the Commercial Manufacturing phase of the lifecycle

- **Desired state**
  - A system that facilitates managing quality and continual improvement throughout the product lifecycle i.e. emphasis on post-approval

*Product and Process LifeCycle:*
Pharmaceutical Development → Technology Transfer → Commercial Manufacturing → Product Discontinuation
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Regulatory environment requires convergence

*Fragmented landscape delays innovation*

- Represents one dossier (for one product)
  - One global submission can lead to **several** separate registration dossiers with different content
  - **Complexity for post-approval changes leads to long/unpredictable timelines**
Bringing a post–approval change through the global systems can take years*

*example: manufacturing site-transfer for a biologic drug substance
Roche supporting efforts for harmonization at regional and global levels

- Improvements in supply, quality and safety
- Better outcomes for patients
- Global access for innovative pharmaceuticals
Post approval changes/Variations guidelines

- WHO guidelines on procedures and data requirements for changes to approved vaccines *(WHO Technical Report Series 943, Annex 6)*
  

  

- WHO general guidance on variations to multisource pharmaceutical products *(Annex 10, WHO Technical Report Series 996, 2016)*
  
3. Post-approval changes for biotherapeutics - Guidelines under development

- **Updates during life-cycle of products:**
  - Changes after licensure, often improvements, e.g. manufacturing process, state-of-the-art controls
  - Request demonstration of comparability of pre-change and post-change product (comparability exercise)

- **Development of the document has been initiated:**
  - in response to requests from regulators and manufacturers, and in line with WHA 67.21, ICDRA, APEC Harmonization Center initiative
  - 1<sup>st</sup> round public consultation – planned for Dec 2016 – Jan 2017
  - Consultation with regulators, manufacturers and other experts – April 2017
  - 2<sup>nd</sup> round of public consultation: July – Sep 2017
  - Submission to the ECBS for review in Oct 2017
WHO Governing Bodies ...
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Current State of Q8/11…my perspective

• Expanded use of risk-based tools…often too many

• Exponential expansion of content of module 3

• Limited utilization of Design Space claims

• Approved Design Space inclusive of too many parameters, with restrictions on movement within it…..and unclear overall value

• Concepts in principle understood, however transition to implementation quite challenging…. 
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• Next Steps…
Established Conditions Selection (I)

**Must have for Biologics—for discussion…..**

- Name/structure/composition
- Manufacturing site (DS, DP, packaging) and testing sites
- Source material including specifications and storage conditions (e.g., master cell line…)
- Generation of a working cell bank from a master (working seeds for viruses…)
- Storage conditions, Shelf-life and container closure system
- Manufacturing Process Description
  - Unit operations and their sequence (process flow)
  - Other process parameters linked to process knowledge and options outlined in case study
Established Conditions Selection (II)

*Must have for Biologics—for discussion…..*

- Specifications (DS, DP, excipients, reference material) including tests and acceptance criteria and elements of the procedure (output/principle of method vs details of operation)

- Raw material of biologic origin including specifications; other raw material depends on whether they are used in process parameter deemed EC

- In-process testing linked to a rejection limit; other in-process controls can be EC’s based on impact to process performance and product quality

- Critical Hold times (sterility/microbial assurance)—Other hold times based on impact??

- Manufacturing Process Description
  - Unit operations and their sequence (process flow)
  - Other process parameters linked to process knowledge and options outlined in case study
Established Conditions- Working Principles (I)

- Established Conditions:
  - **Legally binding information** defined in MAA
  - Any change to EC: requires a regulatory post-approval change process.
  - Any change to a non-EC: does not require regulatory interaction.

- Extent of EC in submission:
  - Depends on the level of knowledge and understanding of the product and process
  - **Continuum** spanning from traditional (i.e. detailed inclusion of process parameters and controls) to a performance based/enhanced approach (i.e. expected output) for given unit-operation or analytical method

- Process/ Method **description and validation are submitted in all cases**
Relationship between knowledge and established conditions

A company may choose a combination of these approaches based on the product and process knowledge, the complexity of the steps, and associated risks to patients.
Established Conditions- Working Principles (II)

Draft Q12 Text.......For Discussion

• In a traditional development approach, the EC’s typically include a significant number of input parameters (process parameters and materials) along with control of output elements, as the relationship between input elements and resulting quality attributes may not be very well understood (i.e., resulting in a higher number CPP’s).

• In an enhanced development approach, the greater product and process knowledge (including interaction between inputs and outputs) can better inform the CQA’s and resulting CPP’s, generally leading to the justification of fewer EC’s linked to CPP’s.

• In certain cases (performance based), the EC’s can be solely focused on the intended outputs rather than process inputs. This can include less complex steps with readily defined outputs as well as steps with in-line continuous monitoring (e.g., NIR for a blending step).
Example of manufacturing process:
Combination of approaches across the manufacturing process

Cell Bank Vial → Seed Train → Inoculum Train → Production Culture → Centrifuge Harvest

Protein A Chromatography

Anion-exchange Chromatography

Mixed mode Chromatography

Virus Retentive Filtration

UF/DF
Extent of EC: Continuum taking into account knowledge for a given step

TRADITIONAL APPROACH

Performance based

Parameter based

Cell expansion

Anion exchange

Anion exchange

Cell expansion

ENHANCED APPROACH
Established Conditions for a Biotechnology Product Unit Operation—Defining Unit Purpose—Ion-Exchange Step

- Product Flow through Column designed to deliver the following output
  - Viral Clearance by $x \log$
  - Host-cell Impurities removal by $X$…
  - DNA removal by $X$…
  - Endotoxin removal by $X$…

- At Operational level, need to ensure:
  - No microbial contamination
  - No product degradation
  - Product concentration/amount
  - Product solution pH

- 20 operating parameters, resin, resin housing, input raw materials…
Example: Risk Ranking of Ion Chromatography Process Parameters— *From ICH Q11 Example 2 (10.2)*
What We Need for Continued Success…

- Implementation of a pragmatic approach for Established Conditions selection with emphasis on patient risk/benefit, and link to product/process understanding

- Strive towards harmonized international regulatory policy with reduced regional or local requirements
  
  • Implement spirit of ICH, and expansion of ICH adoption to all countries—(e.g.; Comparability Protocols, classification…)
Thanks to...

ICH Q12 EWG

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Doing now what patients need next