Points to Consider for Implementation of ICH Q12 for Post Approval Change Management

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Disclaimer:

"The views expressed here are my personal opinions and may not necessarily express the views of the organization that I am part of"

Builds on other ICH guidelines to **enable flexible regulatory approach**

QbD Quality by Design

ICH Q8
Pharmaceutical Development
Step 4: Nov 2005

ICH Q9
Quality Risk Management
Step 4: Jan 2023

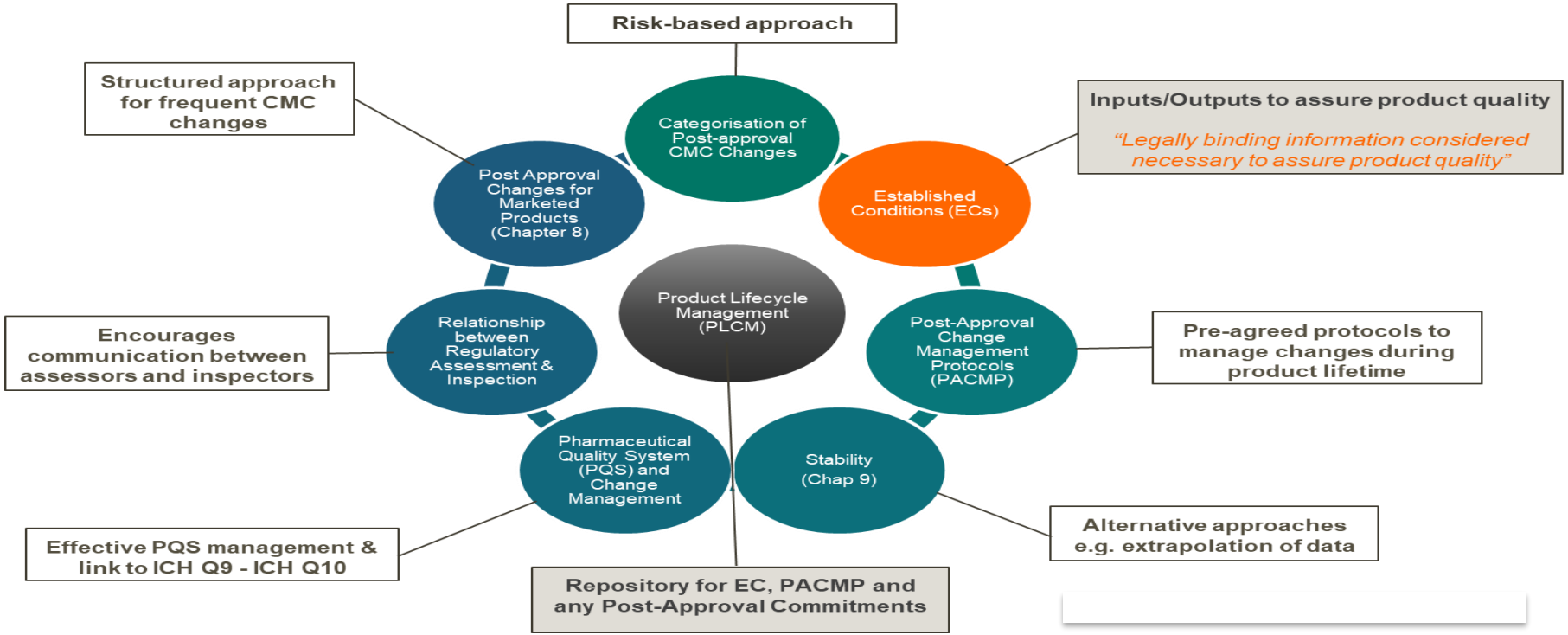
ICH Q10
Pharmaceutical Quality System (PQS)
Step 4: June *2008*

ICH Q11
Development and Manufacture of Drug Substance
Step 4: May 2012

ICH Q12
Technical & Regulatory Considerations for Pharmaceutical Product Lifecycle Management
Step 4: Nov 2019

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**

ICH Q12 Guideline Main Sections



ICH Q12 Opportunities

- ✓ Provides a framework to facilitate the management of post-approval CMC changes in a more predictable & efficient manner.
- ✓ "A harmonized approach regarding technical and regulatory considerations for lifecycle management will benefit patients, industry, and regulatory authorities by promoting innovation and continual improvement in the pharmaceutical sector, strengthening quality assurance and improving supply of medicinal products"
- ✓ It is also intended to demonstrate how increased product and process knowledge can contribute to a reduction in the number of regulatory submissions.

Comparison of change categories

The same change may fall into different categories depending on the region

China	Taiwan	Japanese	United States	EU	Note
PAS (major)	Post-approval changes	Partial Change Application	PAS (major)	Type II (major)	Prior review is required, and the change becomes effective after approval.
Notification * (moderate)	Not applicable	Not applicable	CBE-30 (moderate)	Type IB (minor)	Prior review is required. If no inquiry for verification, etc. is made, the change will become effective 30 days after receipt.
	Not applicable	Not applicable	CBE-0 (moderate)	Not applicable	Prior review is required, but the change becomes effective after receipt.
Not applicable	Not applicable	Minor Change Notification	Not applicable	Type IA_{IN} (minor)	This is a report after implementation. In Japan, it should be submited within 30 days after the change, and in Europe, it should be submitted immediately after the change.
Annual Report (minor)	Not applicable	Not applicable	Annual Report (minor)	Type IA (minor)	This is a report after implementation. In the United States, all the changes are reported together annually. In Europe, the report may be submitted no later than 12 months after the change and the Type IA can be bundled as an annual report.
Non-reportable	Non-reportable	Non-reportable			Changes under PQS

Established conditions (ECs) introduction

- ECs (following ICHQ12) are **legally binding information** considered necessary to **assure product quality** and process consistency
  - **Changes to an ECs** requires reporting to regulators using pre-agreed regulatory reporting categories (RRCs)
  - All other information is **supportive information** (as described in ICH Q12)
  - **Non-Established Conditions (Non-ECs):** Non-ECs (*non ICHQ12 terminology*) are supportive information that is shared with regulators as development and manufacturing information.
  - **Changes to Non-ECs** do not require submission to a regulatory authority but are maintained in the Active Dossier (AD) for visibility / lifecycle maintenance (more details in Post-Approval Change management section).
- ICH Q12 formalizes the concept of identifying *specific* ECs in certain sections whereas previously all the information in that section would have been considered an EC (*as is still the case in non-EC accepting regions*)
  - A major benefit of ECs is that changes to the non-EC content of such sections will *not trigger regulatory reporting*
- **Justification of ECs is based on QbD (ICHQ8-11) principles – no additional experimentation or data is required (depending on your current Process Understanding)**
  - Justification is linked to criticality and risk, defined through ICH Q8-Q11 QRM processes (e.g., TRA)

Identifying ECs in Regulatory Dossier – An approach

- ICH Q12 identifies many different types of information that are ECs in the Common Technical Dossier (CTDs)
  - "Appendix 1: CTD Sections That Contain ECs"
    - indicates many sections that contain ECs, and others containing Supportive Information
- A suggested approach is focusing EC implementation to certain types of information:
  - **DS & DP manufacturing process**: definition, parameters & in-process controls.
- Items for future EC implementation. (Suggest to implement later):
  - DS name & structure; manufacturers;
  - DP description & composition; batch formula;
  - Storage conditions & shelf-life; in-use storage conditions;
  - Reference Standards/Materials
  - Material attributes
  - Specifications & analytical procedures (pending ICH Q14 implementation update)
  - Container closure
  - Facilities & equipment

Identification of ECs

Driven by QbD understanding of control strategy

Process parameters that need to be controlled should be considered ECs.

These should include CPPs and other process parameters "where an impact on product quality cannot be reasonably excluded".

In addition to the unit operation and the sequence of steps, ECs should be those inputs (e.g., process parameters, material attributes) and outputs (including in-process controls) that are necessary to assure product quality.

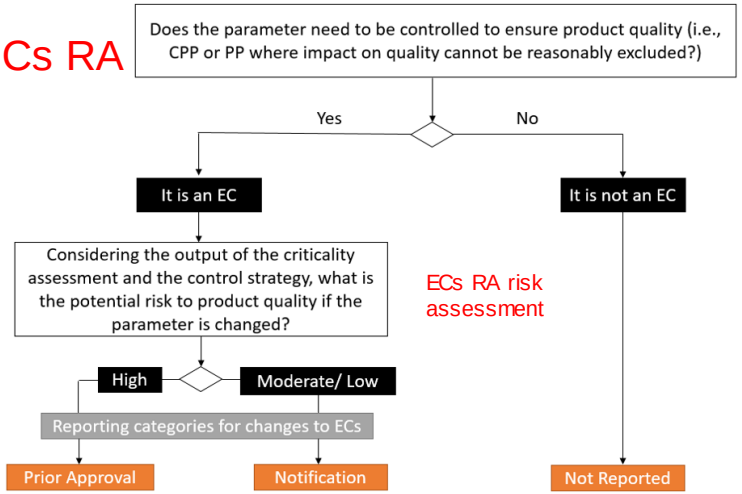
We need to perform a criticality assessment to differentiate the level of impact for each EC.

The criticality assessment should account for severity of harm and whether the ranges studied sufficiently account for the expected variability in the EC.

TRA

ECs RA

Decision Tree for Parameter ECs*



* Figure 1 from ICH Q12

Identification of ECs builds on TRA process

Leverage product and process understanding and prior knowledge

Step 1

- Can the impact of a parameter on quality be reasonably excluded?

Step 2

- Assess risk of change to parameter taking into account overall control strategy

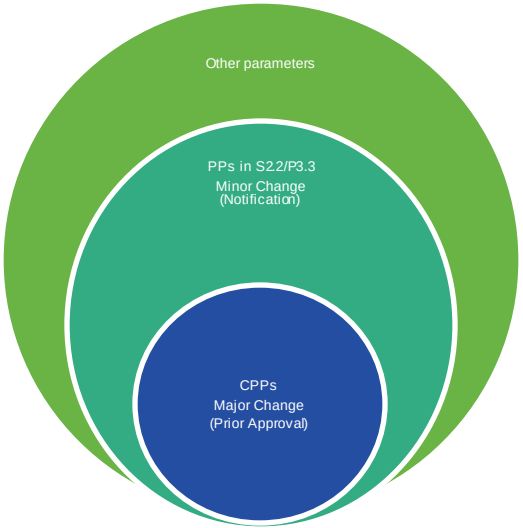
- All CPPs are considered ECs
- non-CPPs ranked Slightly Severe (Sev=4) require further assessment; some may be ECs (Scutiny from Regulators!)
- Need to integrate this analysis into the overall QbD workflow

Severity Scoring – beware of Regulatory Focus – ICHQ9 updated Jan 2023

Severity level	Severity criteria	Designation
Extremely severe	A small to moderate change in this process parameter has a significant impact on a drug substance CQA	Critical Process Parameter
Moderately severe	A large change in this process parameter, or a small change in this parameter in combination with other factors, has a significant impact on a drug substance CQA	
Slightly severe	A large change in this process parameter, in combination with other factors, has a significant impact on a drug substance CQA	Process Parameter
Not severe	The process parameter has no impact on drug substance CQAs	

Impact on Manufacturing Process Description

Non- Q12 Approach



Enhanced Q12 Approach

Benefit:
Implementation of changes to non ECs managed internally

Established Conditions (ECs) – Take-Home Messages

Apply ECs in new marketing applications or post-approval supplements

Modified QbD development workflow enables identification of specific ECs and justification of RRCs (Regulatory Reporting Categories)

- Evolution of existing tools
- Potential to reduce registered detail

A **lifecycle plan** of potential post approval changes is an essential tool to understand where ECs can be exploited. Examples:

- Process or equipment changes
- Scale up
- Site changes
- Control strategy

- Risk assessment tools are available to aid with EC identification
- Suggestion; only justification for ECs is presented in the file
  - i.e., no need to justify non-ECs
- PLCM doc. required for EC files-central repository for all EC information

- ICH Q12 has been fully implemented by FDA (even if their Implementation Guidance is still in draft)
- Adoption of the guideline is evolving in other markets
- ICH Q14 is expected to cover lifecycle changes for specifications and analytical methods.

Post-Approval Change Management Protocols (PACMPs)

An option for management of planned changes

- **A PACMP describes:**
  - Specific changes that the Marketing Authorization Holder (MAH) plans to implement during the lifecycle of the product
  - How the specific changes would be implemented and how they would be evaluated for success
- **Provides an opportunity to downgrade the RRC:**
  - Evaluate risks to quality based on the nature of the change and the data
  - Propose reduced Regulatory Change Reporting Category (RRC) if risks are well managed
- **Procedure (tool) for faster and more predictable implementation of a change.**
- **Not to be confused with GMP change management!**

Benefits of Using a PACMP

Documents any CMC change(s) the Manufacturing Authorization Holder MAH intends to implement during the product's lifecycle, including how they would be implemented and how they would be evaluated/verified. A PACMP would provide:

- **Predictability** and **transparency** of requirements to implement a change
- **Certainty** regarding acceptability of the proposed change
- **Agreement** on data & analysis required to support the change
- **Possible downgrade** of regulatory change reporting category (vs. without a PACMP)
- **Potential reduction** in time to implement

PACMP will be reviewed and approved by Regulatory Authorities **prior to execution**

Categorization of Post-Approval CMC Changes within the PACMP

Risk Based Approach

- Following a risk assessment of the change with suggested reporting category (in line with regional requirements)
  - i.e., a propose a lower reporting category and/or shortened review period as compared to similar change procedure that would be without an approved PACMP

High risk	Moderate to low risk	Lowest risk
• Sufficient risk to require regulatory authority review and approval prior to implementation • **Prior Approval**	• Does NOT require prior approval and generally requires less information to support change • **Notification**	• Internally managed and documented and not reported to regulators, but may be verified during routine inspection • **PQS**

Potential to accelerate approval of change vs standard post approval change

Example Outline of **Contents** for PACMP templates

PACMPs are intended to be applicable to a broad variety of changes:

Biopharmaceuticals/Vaccines

- Introduction
- Detail of Planned Changes
- Impact of Planned Changes
  - Background
  - Risk Assessment
  - Risk Mitigation Plan
- Process Validation / Analytical Validation / Material & Equipment Qualification
- Comparability Study Plans
  - Process Comparability
  - Analytical Comparability
  - Stability Comparability
- Data to Be Reported
- Regulatory Strategy
  - Proposed Reporting Category
  - Facility Inspection History (if relevant)
  - Protocol Amendments
  - Deviation from the Approved PACMP
  - Confirmation & Commitment

Small molecules

- Introduction (with phased regulatory submission plan)
- Detail of Planned Changes
- Impact of Planned Changes
  - Background
  - Risk Assessment
  - Risk Mitigation Plan
- Comparability Study Plans
  - Analytical Procedures
  - Acceptance Criteria
- Data to Be Reported
- Regulatory Strategy
  - Proposed Reporting Category
  - Equivalence Not Demonstrated Using the Approved Comparability Protocol
  - Protocol Amendments
  - Deviation from the Approved PACMP
  - Confirmation & Commitment (Stability)

PACMP take home messages

A **PACMP**:

- is a prospective agreement between the MAH and an agency on a planned change
  - description of change & criteria for successful implementation
- is a flexible tool - can be used for many different types of change
- provides a mechanism for proposing a downgrade to the reg change reporting category
- Anecdotally, is already accepted by the US FDA, EMA, and PMDA
  - pilot programs initiated in other regions
- usually filed with a marketing application in CTD section m3.2.R (US market)

ICHQ12 Implementation – Conclusions (1)

- ICH Q12 provides the framework to facilitate the management of Post Approval Changes (PACs) in a more predictable and efficient manner across the product life cycle within ICH regions. It aligns with the stated intention of increasing acceptance of science and risk-based approaches manifested in ICH Q8-11, and the understanding of the Pharmaceutical Quality System (PQS), as pre-requisites to enable post approval flexibility.

- This presentation has looked at definition of what ICHQ12 calls “Established Conditions” (ECs) and how they can be incorporated to advantage in Submissions. What can then follow at PAC proposal, is that a PACMP (a PAC Management Protocol) can be written, which when implemented significantly streamlines and accelerates changes to enable faster access of medicines to patients. (This assumes that the ECs are still met when defining the PAC.)

ICHQ12 Implementation – Conclusions (2)

- Harmonization of PAC requirements worldwide, particularly through the implementation ICH Q12 will ensure consistent global regulatory expectations for PACMPs. Change categorization of PACs should be based on science and risk-based approaches, and product/process knowledge and understanding, including full knowledge of what the ECs are.
- Agencies can adopt some or all of the tools in ICH Q12 sequentially (e.g. early adoption of PACMPs) but full adoption per the guideline, without additional requirements will be required to achieve the full intended benefits.
- Fundamental to full implementation is the acceptance of the ICH M4Q CTD dossier and the principles for science and risk-based development in ICH Q8-11.
- Challenges to implementation can be addressed with robust training and awareness programs; cross-business unit strategy; external cross-industry and Health Authority knowledge sharing

ICHQ12 FDA feedback – Quality Symposium 31Oct2023

Dr Ramanadham - ICH Q12: What Industry Needs to Know

Applicant's use of ICH Q12 is voluntary & Implementation is flexible:

– Established Conditions can be proposed at any point in the lifecycle (e.g., original application, post approval supplement)

– Established Conditions can be proposed for as little as a unit operation or method, or as large as the CMC section for the application

ICHQ12 is official FDA Policy since 2021, and draft guidance published in 2021

Pending: CDER Manual of Policies and Procedures on ICHQ12 implementation

Established Conditions (ECs) are legally binding information [within an application] considered necessary to assure product quality & any change to an EC necessitates a submission to the regulator

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Impact to Inspections

- No expectation for investigators to review ECs on site
- Inspection activities gather critical information on the effectiveness and health of the PQS
- Inspections should assess change management effectiveness at the facility and product specific level

Scientific justification for proposed ECs and reporting categories

– Justifications for ECs should focus on explaining the approach to criticality assessment, etc. (not necessarily changing the approach)

– Justifications and risk assessments should clearly describe scientific rationale for why an element is considered an EC (or not) accounting for the overall control strategy

Thank you

Session IV: Mature Pharmaceutical Quality Systems Enabling Ease of Post Approval Change Management

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