ICH Q12
Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Step 4 document – to be implemented

6 February 2020

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Legal Notice

Background

- **This document has been signed off as *Step 4* document on 20 November 2019 to be implemented by the ICH Regulatory Members**
- **This document was developed based on a Concept Paper (9 September 2014) and Business Plan (9 September 2014)**

Key Principles

This guideline:

- Provides a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner
- Presents a number of harmonised regulatory tools and enablers with associated guiding principles
- Demonstrates how increased product and process knowledge can contribute to a more precise and accurate understanding of which post-approval changes require regulatory submission
- Emphasizes the importance of an effective pharmaceutical quality systems in the management of changes during the product lifecycle

Guideline Objectives

- …Harmonize management of post-approval CMC changes…in a more transparent and efficient manner…across ICH regions
- …Facilitate risk-based regulatory oversight…
- Emphasize…control strategy as a key component of the…dossier
- Support continual improvement and facilitate introduction of innovation
- Enhance use of regulatory tools for prospective change management…enabling strategic management of post-approval changes…

Potential Benefits

- Reduce unnecessary cost and time burdens on industry and regulators, while assuring that patients have reliable access to high quality medicinal products
- Support continual improvement, which can result in decreased product variability and increased manufacturing efficiency
- Help to mitigate drug shortages related to manufacturing and quality issues
- Facilitate the introduction of innovations in manufacturing

Guideline Scope

- Pharmaceutical drug substances and products (both chemical and biological) that require a marketing authorisation
- Drug-device combination products that meet the definition of a pharmaceutical or biological product
- Does not include changes needed to comply with Pharmacopeial monographs

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  - Identification of Established Conditions for the Manufacturing Process - Biological Medicinal Product
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  - PACMP Example 1
  - PACMP Example 2
  - Product Lifecycle Management Document - Illustrative Example
- **Annex II - Structured Approach to Analytical Procedure Changes**

Selected Acronyms and Definitions*

- Critical Process Parameter (CPP) – process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to assure the process produces the desired product quality. (ICH Q8(R2))
- Critical Quality Attribute (CQA) – a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to assure the desired product quality. (ICH Q8(R2))
- Post-approval CMC commitment – commitment by the MAH to undertake specific CMC activities to be implemented during the commercial phase
- EC – Established Condition
- MAA – Marketing Authorisation Application
- MAH – Marketing Authorisation Holder
- PACMP – Post-approval Change Management Protocol
- PLCM – Product Lifecycle Management
- PQS – Pharmaceutical Quality System

* From the Glossary

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Categorisation of Post-Approval CMC Changes – Chapter 2

Convergence toward risk-based categorisation of post-approval changes is encouraged as an important step toward achieving the objectives of Q12

- CMC changes vary from low to high potential risk with respect to product quality, safety, and efficacy
- Guideline describes a framework that encompasses a risk-based categorisation for the type of communication expected of the MAH with the regulatory authority regarding CMC changes
  - Prior-approval: Changes with sufficient risk to require regulatory authority review and approval prior to implementation
  - Notification: Moderate- to low-risk changes that do not require prior approval and generally require less information to support the change
    - These changes are communicated to the regulatory authority as a formal notification that takes place within a defined period of time before or after implementation, according to regional requirements
- In addition, the changes that are not required to be reported to regulators are only managed and documented within the PQS, but may be verified on routine inspection by regulators

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Established Conditions – Chapter 3

- The concept of ECs provides a clear understanding between the MAH and regulatory authorities regarding the elements to assure product quality and that involve a regulatory communication, if changed
- This guideline describes how ECs are identified as well as what information can be designated as supportive information that would not involve a regulatory communication, if changed. In addition, guidance is included for managing revisions of the ECs
- ECs should not be confused with CMC regulatory commitments (e.g., stability, postapproval CMC commitment, and other commitments) made by an MAH to provide data or information to the regulatory agency in an MAA.
  - Such information, in the context of this guideline, is considered supportive information
  - Changes to CMC regulatory commitments are managed according to existing regional regulations and guidance

Established Conditions – Chapter 3 (2)

- ECs are legally binding information 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
- Appendix 1 provides an overview of CTD sections that generally contain ECs

Established Conditions – Chapter 3 (3)

Identifying ECs and the role of risk:

- The number of ECs and how they are defined will vary based on a number of factors, including:
  - product and process understanding
  - characterization
  - the company's development approach, and
  - 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 ECs

Established Conditions – Chapter 3 (4)

ECs for manufacturing processes:

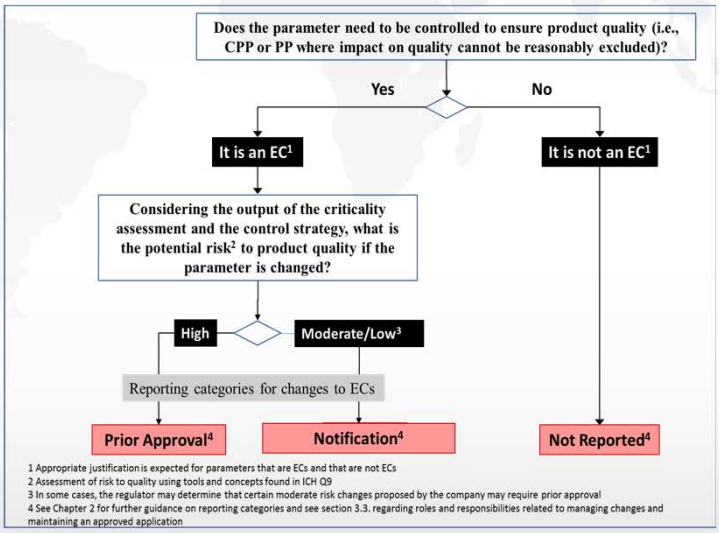
- Include individual unit operations and their sequence in the manufacturing process
- Comprise those inputs (e.g., process parameters, material attributes) and outputs (may include in-process controls) necessary to assure product quality
- Should consider the overall control strategy

Established Conditions – Chapter 3 (5)

ECs for manufacturing processes (cont.):

- Process parameters that need to be controlled to ensure that a product of required quality will be produced should be considered ECs
- CPPs and other process parameters where an impact on product quality cannot be reasonably excluded should be identified as ECs
- Identification of ECs draws upon:
  - An initial risk assessment
  - Prior knowledge
  - Application of knowledge gained from executed studies
  - A criticality assessment that determines the level of impact that a process parameter could have on product quality
    - Should account for severity of harm and whether the ranges studied sufficiently account for the expected variability in the EC

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



Established Conditions – Chapter 3 (6)

ECs for manufacturing processes can vary based on extent of knowledge:

- Parameter-based approaches
  - Minimal approach, with 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 tests)
  - 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 a performance-based approach, ECs could be primarily focused on control of process outputs (e.g., attributes, measurements, responses) rather than process inputs (e.g., process parameters and material attributes)
  - Enabled by knowledge gained from an enhanced approach, a data-rich environment, and an enhanced control strategy (e.g., models, Process Analytical Technology (PAT))
- Different approaches can be used alone or in combination

Established Conditions – Chapter 3 (7)

ECs for analytical procedures

- Include elements which assure performance of the procedure
- Extent of ECs and reporting categories can vary based on the degree of understanding of the relationship between method parameters and method performance, method complexity, and control strategy
- Different approaches can be used to identify ECs:
  - When more limited development studies have been conducted this may result in a narrow operating window to ensure method performance. In such cases ECs may be more extensive with fixed and/or tight conditions
  - Enhanced understanding can lead to a wider operating window that ensures method performance, where ECs can be reduced and focused on method performance (e.g., method parameters acceptable ranges rather than set points, performance criteria)

Established Conditions – Chapter 3 (8)

Reporting categories for post-approval changes:

- Reporting category should consider:
  - an assessment of the potential risk to product quality associated with changing the EC
  - the overall control strategy
- Risk assessment activities
  - Should follow approaches described in ICH Q9 (Risk Management)
  - Output can include changes that range from high to low risk to product quality
- Reporting category should be defined based on level of potential risk; justification for the risk and proposed reporting category should be provided in the MAA

Established Conditions – Chapter 3 (9)

Revision of ECs

- It may be necessary to change approved ECs as a result of knowledge gained during the product lifecycle (e.g., manufacturing experience, introduction of new technologies, or changes in the control strategy)
- ECs may be revised through:
  - Appropriate post-approval regulatory submission describing and justifying the change
  - Submission of a PACMP, in the original MAA or as part of a post-approval submission, describing and justifying a revision to ECs
  - Use of an approved post-approval regulatory commitment, as appropriate

Post-Approval Change Management Protocol – Chapter 4

- Regulatory tool that provides predictability regarding the information required to support a CMC change and the type of regulatory submission based on prior agreement between the MAH and regulatory authority
- Enables planning and implementation of future changes to ECs in an efficient and predictable manner
- May address one or more changes for a single product, or may address one or more changes to be applied to multiple products
- May be submitted with the original MAA or subsequently as a stand-alone submission (supplement/variation)
- Located in Module 3.2R; may be located in Module 1 in some regions

Post-Approval Change Management Protocol – Chapter 4 (2)

Step 1

- Submission of a written protocol
  - proposed change(s) with rationale(s)
  - risk management activities
  - proposed studies and acceptance criteria to assess the impact of the change(s)
  - other conditions to be met, if any
  - the proposed reporting category
  - any other supportive information
- Approved by regulator in advance of execution

Step 2

- Carry out tests and studies outlined in the protocol
- If results/data generated meet the acceptance criteria in the protocol and any other conditions are met, submit to the regulatory authority according to the category in the approved protocol
- Depending on the reporting category, approval by the regulatory authority may or may not be required prior to implementation of the change

Product Lifecycle Management Document – Chapter 5

- Serves as a central repository for:
  - ECs
  - Reporting category for making changes to approved ECs
  - PACMPs (when proposed), and
  - Any post-approval CMC commitments
- Encourages prospective lifecycle management planning by MAH
- Facilitates regulatory assessment and inspection
- Intended to enable transparency and facilitate continuous improvement

Product Lifecycle Management (PLCM) Document – Chapter 5 (2)

Submitting the PLCM document

- Initial PLCM document is submitted with the original MAA, or
- With a supplement/variation for marketed products when defining ECs

Maintenance of the PLCM Document

- Updated PLCM document should be included in post-approval submissions for CMC changes
- MAH should follow regional expectations for maintaining a revision history for the PLCM document

Format and Location of PLCM Document

- Tabular format recommended, but not mandatory
- Located in Module 3.2R; may be Module 1 in some regions

Pharmaceutical Quality System and Change Management – Chapter 6

An effective PQS as described in ICH Q10 (Pharmaceutical Quality System) and compliance with regional GMP requirements are necessary to gain full benefit from this guideline

- ICH Q10 describes principles for the effective management of CMC changes under the PQS
- This guideline provides recommendations for robust change management across single or multiple entities involved in the manufacture of a pharmaceutical product
- Appendix 2 elaborates on ICH Q10 principles and describes how the PQS can be utilized effectively in the application of Q12 concepts
- If a manufacturing site has deficiencies that do not require regulatory action, but have an impact on the effectiveness of change management, it may result in restrictions on the ability to utilise flexibility in this guideline

Pharmaceutical Quality System and Change Management – Chapter 6 (2)

- Maintaining an effective PQS is the responsibility of a company (manufacturing sites and MAH where relevant)
  - Not the intent to require a specific inspection assessing the state of the PQS before the company can use the principles in ICH Q12.
- Implementation of robust change management across multiple sites (outsourced or not) is necessary
- Changes to ECs should be communicated in a timely fashion between the MAH and the regulators, and between the MAH and the manufacturing chain (and vice versa)

Relationship Between Regulatory Assessment and Inspection – Chapter 7

- This guideline outlines the complementary roles of regulatory assessment and inspection in the oversight of post-approval changes; and how communication between assessors and inspectors facilitates the use of the tools included herein
- Roles of regulatory assessment and inspection are unchanged
- Effective assessor-inspector communication can facilitate regulatory oversight of product lifecycle management
- Communication is encouraged between regulators across regions, in accordance with appropriate bilateral/multilateral arrangements

Structured Approaches for Frequent CMC Post-Approval Changes – Chapter 8

- This guideline describes a strategy for a structured approach applicable to frequent CMC changes, and a discussion of data expectations, to enable the use of immediate or other post-implementation notification.
- Simplified approach to accomplish certain CMC changes for products whose marketing authorization did not involve identification of ECs and reporting categories
- Structured approach may be applied when a company's PQS change management process is effective, in compliance with regional GMPs, and incorporates an appropriate risk management system
- The structured approach describes scope and steps to be followed including, where appropriate, data to be generated and criteria to be met
  - An example of this approach for certain analytical procedure changes is described in Annex II
- If the approach is followed and all criteria met, change can be made with immediate or other post-implementation notification, as appropriate

Stability Data Approaches to Support the Evaluation of CMC Changes – Chapter 9

- Stability data needed for submission to the regulatory authority in support of a post-approval change is established by regional regulations and guidance
- This guideline provides additional science- and risk-based approaches that are relevant to strategies for confirmatory stability studies to enable more timely implementation of CMC changes
- Scope and design of stability studies are informed by the knowledge of and experience with the drug product and drug substance acquired since authorisation

Annex I

- This Annex contains illustrative examples of:
  - Identification of established conditions and proposed reporting categories for the manufacturing process
  - Identification of established conditions and proposed reporting categories for analytical procedures
  - PACMPs
  - Product Lifecycle Management Document
- Considerations:
  - Are mock examples that are provided for illustrative purposes; only suggest how the tools described in chapters 3, 4, and 5 could be applied
  - Should not be used as a template or the sole basis for a regulatory submission.
  - Reporting categories may differ across regions depending on regional legislation, the nature of the product, and the MAH's demonstrated understanding of the product, process, and analytical procedure

Annex II

- This Annex describes an approach wherein specific criteria are defined for changes to analytical procedures used to test marketed products
- If this approach is followed and all criteria are met, the analytical procedure change can be made with immediate or other post-implementation notification, as appropriate, to the relevant regulatory authorities
- Intent of this approach is to incentivise structured implementation of at least equivalent analytical procedures that are fit for purpose

Results of Public Consultation

- **Significant revisions as a result of public consultation included:**
  - Removal of the terms “implicit” and “explicit” as they referred to ECs
  - Removal of the term “key process parameter (KPP)” and revision of text to better explain the concept of critical process parameter and identification of ECs for manufacturing processes
  - Revision of the description for identification of ECs for analytical methods and development of an illustrative example
  - Revisions to the recommended content of the PLCM document and agreement regarding the recommended location within the CTD
  - Revisions to clarify the use of tools described in the guideline for master files

Considerations

- The ICH Q12 guideline should be applied in conjunction with other ICH “Q” guidelines, including Q8(R2), Q9, Q10, and Q11
- See Chapters 3, 4, and 5 of the Core Guideline for recommendations regarding the appropriate location for information to be submitted within a dossier

Guidelines for Implementation

- MAHs wishing to use the tools and enablers described in ICH Q12 should consult publicly available information provided by regulatory authorities (e.g., see regulators' websites) about the implementation of ICH Q12 in their region, especially with regard to regulatory considerations

Conclusions

Use of the harmonised regulatory tools and enablers with associated guiding principles described in this guideline will enhance the management of post-approval CMC changes, and transparency between industry and regulatory authorities, supporting innovation and continual improvement

Contact

- **For any questions please contact the ICH Secretariat:**

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