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ICH Q12 – Challenges, Opportunities …. and more Challenges

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YOUR HEALTH AND SAFETY... OUR PRIORITY.

Presentation Outline

N.B. Some views presented are personal and do not necessarily represent those of Health Canada or the ICH …… yet. ☺

- An non-controversial overview of the ICH Q12 guideline using a consensus presentation developed by the EWG
  - Objectives from the Concept Paper
  - A chapter-by-chapter description with salient points
  - Key principles and conclusions

- A second look at the chapters - how they developed & thoughts on various associated consequences & challenges:
  - The value of high-level harmonization on risk-rationalized categorization of manufacturing changes requiring communication with the regulator
  - “Established Conditions” and their potential for leveraging “regulatory relief”
  - A possible new life for Post-Approval Change Management Protocols
  - Potential for ICH Q12 to have significant value post-implementation, within and beyond current ICH jurisdictions, through regulatory convergence

- Implementation considerations and closing remarks

ICH
harmonisation for better health

ICH Q12
Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

May 2018

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

Legal Notice

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Outline

- **Objectives and Scope**
- **Key Sections**
  - Categorization of Changes
  - Established Conditions
  - Post-approval Change Management Protocol
  - Product Lifecycle Management
  - Pharmaceutical Quality System and Change management
  - Relationship Between Regulatory Assessment and Inspection
  - Post-Approval Changes for Marketed Products
  - Annex
- **Considerations**
- **Key Principles**
- **Conclusions**

Guideline Objectives

- Objectives* include:
  - …**Harmonize change management**…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**…

*From the ICH Q12 concept paper

Scope of ICH Q12

- Pharmaceutical drug substances (i.e., active pharmaceutical ingredients) and pharmaceutical drug products
  - Includes marketed chemical and biotechnological/ biological products
- Drug-device combination products that meet the definition of a pharmaceutical or biotechnological/biological product
- Does not include changes needed to comply with Pharmacopeial monographs

Categorization of Changes - Chapter 2

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

- 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 lowest risk changes are only managed and documented within the PQS and not reported to regulators, but may be verified on routine inspection

Established Conditions – Chapter 3

- **ECs are legally binding information (or approved matters) 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, but is provided to share with regulators the development and manufacturing information at an appropriate level of detail, and to justify the initial selection of ECs and their reporting category

Established Conditions – Chapter 3 (2)

- **ECs in a submission are either implicit or explicit:**
  - Implicit ECs are elements that are not specifically proposed by the marketing authorisation holder (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
    - Appropriate when either the proposed EC or reporting category is different than regional guidance or regulation
    - Not required, but if proposed, should be justified

Established Conditions – Chapter 3 (3)

ECs and the role of risk:

- The extent (number of ECs and how narrowly they are defined) of ECs will vary based on a number of factors, including:
  - product and process understanding
  - characterization
  - the firm's development approach, and
  - potential risk to product quality

Established Conditions – Chapter 3 (4)

ECs for manufacturing processes:

- Generally include unit operations and the sequence of steps
- Considering the overall control strategy, include those inputs (e.g., process parameters, material attributes) and outputs (may include in-process controls) necessary to assure product quality:
  - critical process parameters (CPPs, as defined in ICH Q8(R2))
  - key process parameters (KPPs)
    - parameters of the manufacturing process that may not be directly linked to critical product quality attributes, but need to be tightly controlled to assure process consistency as it relates to product quality

Established Conditions – Chapter 3 (5)

ECs for manufacturing processes fall on a continuum based on extent of development:

- 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).

Established Conditions – Chapter 3 (6)

ECs and reporting category for changes:

- After identifying ECs, MAH proposes reporting category for post-approval changes
- May follow existing regional regulations and guidance or propose alternate reporting category
- Reporting category is dependent on the potential risk to quality
  - Risk assessment activities should follow approaches described in ICH Q9
  - Consider the overall control strategy and any possible concurrent changes

Post-Approval Change Management Protocol – Chapter 4

- A post-approval change management protocol (PACMP) provides predictability and transparency in the requirements and studies needed to implement a change
- May address one or more changes for a single product, or may address one or more changes to be applied to multiple products
- A PACMP may be submitted with the original Market Authorization Application or subsequently as a stand-alone submission (supplement/variation)

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
  - 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 this information 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 (PLCM) – Chapter 5

Product Lifecycle Management (PLCM) document

- Serves as a central repository for ECs, reporting category for making changes to approved ECs, PACMPs (when proposed), and any 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
- Intended to enable transparency and facilitate continuous improvement

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

Submitting the PLCM document

- Initial PLCM document is submitted with the original Market Authorization Application, or
- with a supplement/variation for marketed products where defining ECs may facilitate regulatory change management.

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.
- Location is based on regional recommendations.

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

- 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 – Chapter 7

- Encourages communication between assessors and inspectors to facilitate implementation of Q12

Post-Approval Changes for Marketed Products – Chapter 8

- Q12 regulatory tools/enablers are applicable to marketed products
- Addresses frequent CMC changes, with intent to incentivize continual improvement
- Includes:
  - Structured approach for changes to analytical procedures
    - If approach is followed and all criteria met, the analytical procedure change can be made with immediate or other post-implementation notification, as appropriate, to the relevant regulatory authorities.
  - Principles for determining data requirements for stability where needed to support CMC changes

Post-Approval Changes for Marketed Products – Chapter 8 (2)

Structured Approach for Analytical Procedure Changes

Out of Scope

- Procedure where the specification does not adequately reflect the complex information provided by the method. For example:
  - Procedures for which only a subset of the peaks are identified and specified (e.g., assay for identity by peptide map)
  - The specification acceptance criteria include a general comparison to a reference standards beyond specified peaks (e.g., “comparable to reference standard”)
- Change(s) to a test method based on a biological/immunological/ immunochemical principle or a method using a biological reagent (e.g., bioassay, binding assay, ELISA, testing for viral adventitious agents).
- Changes to predictive models used with multivariate methods.

The flexibility provided by the “structured approach” may not be available in all regions and in all situations; some specific changes may require prior approval as defined in regional guidance.

Post-Approval Changes for Marketed Products – Chapter 8 (3)

Structured Approach for Analytical Procedure Changes

In order to use the "Structured Approach," a set of principles should be met.

Principles:

- High level description of the "new" and "old" methods should be same (e.g., chromatography with spectroscopic detection)
- Demonstrate equivalency or better through validation studies
- System suitability requirements should be established for the revised method
- No change to acceptance criteria (unless allowed by regional regulation)
- Approach may not be used if toxicological or clinical data are required as a result of the method change

Annex

- Step 2 guideline is currently published as a “core guideline” and accompanying “annex”
- Annex contains illustrative examples of:
  - Defining established conditions
  - Postapproval change management protocols
  - Product lifecycle management document

Examples are provided for illustrative purposes and are intended only to suggest how the principles in Q12 could be applied. They are not intended to serve as a binding template and other approaches may also be acceptable.

Considerations

- 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 (ECs) 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.

Key Principles

This guideline:

- Introduces a harmonized risk-based categorisation system for managing post-approval CMC changes under ICH framework
- Provides clarity to distinguish ECs and supporting information in a regulatory submission, encouraging continual improvement and innovation
- Enables planning and implementation of future changes to ECs in an efficient and predictable manner by using PACMP
- Introduces the PLCM document as a key communication tool – 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 for marketed products

Conclusions

ICH Q12

- Provides a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner
- Intended to demonstrate how increased product and process knowledge can contribute to a reduction in the number of regulatory submissions.
- With effective implementation of Q12 tools and enablers, should increase industry's ability to manage many CMC changes effectively under the firm's PQS with less need for extensive regulatory oversight prior to implementation.
- Tools and enablers build on the concepts of product and process understanding (ICH Q8 and Q11), application of risk management principles (ICH Q9), and an effective pharmaceutical quality system (ICH Q10).

ICH Q12 reached Step 2b on November 16, 2017 and has been published for public comment

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Can Q12 overcome previous disappointments?

- Will new “transformational” approaches be broadly accepted & used?
- Can Q12 establish new paradigms and provide “regulatory relief” that Design Spaces couldn’t?
- It seems that concerns about non-critical parameters, extensive data requirements, time & costs of development may have all contributed to the limited creation and/or acceptance of Design Spaces.

BUT

- What indicators are there that the regulators involved, or the associated concerns, have changed? Or that existing regulations will not present barriers?
- It’s hard to imagine that if the already industry-regulator-harmonized design space paradigm didn’t work, that something “softer” (less well defined?), based on “confidence” in the MAH’s product experience, knowledge management and quality system, will be accepted as grounds for extensive regulatory relief.

There is still work to do!

Categorization of manufacturing changes requiring communication with the regulator (1)

- Categorization exists in all current ICH member regulatory jurisdictions with varying reliance on regulations versus guidance
- Categories rationalized according to risk to patient (or product/process)
- Systems not harmonized r.e. number of categories, data expectations, timeframes for review
- All jurisdictions include at least one category requiring prior-approval and at least one category requiring notification
- Flexibility can be captured by indicating that if certain “conditions” are met regarding a change, the reporting requirement drops (or, conversely, if not met the reporting requirement moves up)

Categorization of manufacturing changes requiring communication with the regulator (2)

- The use of formal submission/reporting categories is currently, and will continue to be, the “workhorse” approach to accomplish manufacturing changes in ICH-member, and ICH-observant, regulatory jurisdictions, and is not described in current ICH guidance
- It is an enabler (perhaps essential) for the adoption (best use?) of Post-Approval Change Management Protocols
- Exemplification in Q12 will make the guideline more relevant to a broader group of regulatory jurisdictions; and may help encourage broader use, and high-level harmonisation, of risk-based reporting categories in those jurisdictions

- It provides for high-level “connection” with new WHO guidance, “Guidelines on procedures and data requirements for changes to approved biotherapeutic products”

Established Conditions and the potential for leveraging “regulatory relief” (1)

- EC essentially means “communicate the change”
- EC becomes associated with a reporting category
  - Pre-approval (upper, lower), Notification, Annual Report
  - In Japan only one “Pre”, one Notification & and no submitted Annual Report
- Do already marketed products have ECs?
  - Negotiated EC versus Default EC (captured in regulation/guidance)

- For analytical methods, some ECs could (perhaps) be method outcomes rather than method parameters
- Other “outcome-based” approaches may be possible for manufacturing process unit operations

BUT

- Can a significant change captured in existing regulation and guidance really be negotiated to be “off the radar”?

Established Conditions and the potential for leveraging “regulatory relief” (2)

- Link “negotiated” EC to “negotiated” reporting category during submission review?
- Based on what?
  - “High-functioning” PQS, + knowledge, + experience, + “je ne sais quoi”?
- Need “score card” for consistency (inter-agency, -division, -review team)
  - But inter-agency harmonization presents major challenge
- How is “agreement” captured? (for sharing with inspectors, other agencies)
- Even using a score card, if “agreement” can be specific to MAH, product, manufacturing site - and be different between regulatory jurisdictions, disharmony will increase

Established Conditions and the potential for leveraging “regulatory relief” (3)

- Existing regulation/guidance would have to defer to the negotiated reporting category
- Regulatory screening of submission for correct reporting category gets very complicated!
- Identifying (and correcting) reporting errors may present a problem if notifications are not formally screened

BUT

- How about implementation via “multi-element” PACM Protocols?
  - Based on a currently acceptable regulatory mechanism (now expanding)
  - Details are captured and assessable
  - Could be shared with, and possibly accepted by, other jurisdictions

A possible new life for PACM Protocols

- Currently under-used wherever use is possible
- Concept/use to become adopted by remaining ICH members via ICH Q12
- Chance to harmonize approach amongst ICH members (to extent possible)
- Multi-element PACM Protocols could give “more bang for the buck”
  - Same change across multiple products?
  - Same change across multiple sites?
- MAH can choose not to use the PACMP, without penalty

Potential for longer-term downstream effects within and beyond current ICH jurisdictions

- “ICH-ing” reporting categories, ECs & PACMPs will encourage broader adoption
- Possibility for ICH-independent harmonization and regulatory convergence
- For smaller agencies – possibility for “benchmark-agency”-based acceptance of 1st step of PACMPs with national/sovereign/accountable decision at 2nd step?

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HPFB Implementation WG to consider Impacts/implications for Health Canada

- Implement PACM Protocols - with new guidance (& regulation?)
- Consider formally “negotiated ECs” versus existing guidance
  - How to maintain fairness and consistency between agencies, between divisions and between review teams in the absence of a harmonized “rating guide”?
  - Consider changes to content of CPID (Certified Product Information Document)
- Modify Post-NOC Changes guidance where applicable to reflect ICH Q12 (& consider convergence possibilities)
- Formalize “Immediate Notification” reporting category
- Evaluate and address impact on resources including anticipated reduction in revenue from industry submission fees:
  - Reduction in number of SNDSs and associated fees resulting from downgrades to NC (via PACMP, or negotiated EC + lower category)
  - Possible reduction in total number of pre-approval submissions (SNDS + NC) if some are downgraded to Notifications
  - Possible shift in use of resources towards PACMPs and NCs (however, initial impact may be low)

Negotiated ECs and PACM Protocols will cause confusion in Reporting Categories

Reporting categories for similar changes, and how suitability or comparability is demonstrated, will not always follow PNOCC guidance and will differ from sponsor to sponsor, from product to product and from site to site. How can we help address screening/verification challenges and sponsor errors regarding reporting category used to communicate a change?

- What about a revised HPFB Submission Form in which the sponsor clearly explains the basis for the category of communication being used?
  - Refer to category interpreted from PNOCC guidance; and if already confirmed through prior contact with HPFB
    - Perhaps identify category already used in another major regulatory jurisdiction, with hope for convergence
  - Refer to a PACM Protocol that captured agreed downgrading of category
  - Refer to specific submission in which the category for that type of change was negotiated and agreed

Current focus of EWG drafting groups

- Approaches to training, and training materials to aid implementation
- Refining and/or adding examples for the appendix
- Product Specific Life-Cycle Management Strategy. What will it look like and where will it be placed in CTD? (Japan will keep “Approved Matters” in Module 1).

Current timeframe & milestones

- June 2017: Step-1 Document (Step-2 via ICH Assembly approval) then release for public comment (release was delayed until early 2018)
- Meetings via teleconference to address ongoing work
- Latest comment period ends in December, 2018 (HC = Mar 2 to Aug 26)
- Interim meeting planned in February, 2019
- June 2019 ~~November 2017~~: Finalize Step-4 Document

High-level goals for ICH Q12

- It should have practical utility and meet the needs of small and large companies using "traditional" and "enhanced" manufacturing approaches; and be of value to new and currently marketed products.

- It should capture what is functionally already harmonized, and whatever more we can achieve, with regard to multiple mechanisms to accomplish manufacturing change.

- It should create a framework that will foster ICH-process-independent regulatory harmonization and convergence; and have value beyond current ICH parties/members.

Health Canada ICH-Q12 EWG participants

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