

Health Canada Implementation of ICH Q12: CMC Changes

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CASS CMC Strategy Forum
July 2021



ICH-Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

- Key Sections and tools
 - Categorization of Post-Approval CMC Changes
 - Established Conditions
 - Post-approval Change Management Protocol
 - Product Lifecycle Management Document
 - Pharmaceutical Quality System and Change Management
 - Relationship Between Regulatory Assessment and Inspection
 - Structured Approaches for Frequent Post-Approval Changes
 - Stability Data Approaches to Support Evaluation of CMC Changes

Categorization of Changes

- Current Alignment

Convergence toward risk-based categorization of post-approval changes is encouraged as an important step toward achieving the objectives of ICH-Q12. (Some changes do not need to be reported). Such a system would include the Prior-approval and Notification categories for regulatory communications with one or more levels in each case:

Health Canada regulatory framework is compatible

- Multiple risk-based communication/reporting categories are available
 - Prior approval submission
 - Notification and/or Annual Report
- Post Notice of Compliance Changes Guidance (PNOCC) document
 - Comprehensive guidance regarding: category, conditions, data expected
- Framework allows for flexibility to move between categories (an enabler)
 - If certain conditions for change are met (captured in PNOCC guidance)
 - When linked to a Post Approval Change Management Protocol
 - To accommodate negotiated Established Conditions and Reporting Categories

Categorization of Changes

- Update of the PNOCC guidance document

Introduction of “Immediate Notification” category

- Introduction of the Level III – Immediate Notification reporting category will allow the notification of changes in a timely manner of the changes that have been downgraded from S/NDS or NC to a Level III change using the ICH Q12 tools and concepts.
- This reporting category also includes changes to established conditions (ECs) when reporting categories have been negotiated to be classified as immediate notification rather than a higher typical reporting category.
- Other examples of Immediate Notifications are included in the product-specific companion documents
- Applicable to both BRDD and TPD.
- Level III form will be updated to include the Immediate Notification.
- Sponsors are to notify Health Canada of the change within 15 days of the date when the manufactured product is first released to the Canadian market.

Updated reporting categories

ICH terminology	Health Canada	
	<u>BRDD</u>	<u>TPD</u>
Prior Approval	Level I - Supplement	Level I - Supplement
	Level II - Notifiable Change	
Notification Moderate	Level III - Immediate Notification	Level III - Immediate Notification
Notification Low	Level III - Annual Notification	Level III - Annual Notification
Not Reported	Level IV – Changes not reported	Level IV – Changes not reported

Established Conditions

- Current Alignment

Health Canada regulatory framework is essentially aligned/compatible

- Fully endorse regulatory flexibility deriving from
 - Fewer ECs and/or better focused ECs;
 - Rationalized/justified lower reporting categories
 - Mixed formats: “proposed/justified” ECs and “default to guidance” ECs

Concept of Established Conditions *has been introduced* in the PNOCC guidance document

Challenges:

- Will benefit from greater experience with proposed/justified ECs
- How to manage regulatory affairs complexity introduced by proposed / justified ECs & associated reporting categories that differ from ECs & associated reporting categories evident from guidance documents?
- **Cover letter** should be clear about whether or not the post-approval changes are filed using Q12 tools.
 - To inform/orient regulatory affairs staff
- Maintaining consistency in reaching decisions
- Training of evaluators and regulatory affairs officers

Post Approval Change Management Protocols

- Update of the PNOCC guidance document

- Concept of PACMP **has been introduced** in the PNOCC guidance document
 - A PACMP can be provided in the original new drug submission.
 - Otherwise, a new protocol, or a change to an existing one, requires submission of a supplement and issuance of a NOC prior to implementation because it may result in a lower reporting category for the changes covered in the PACMP once the actual comparability data are submitted (if reported as a Level II change).
 - For a minor quality change that results from the execution of a PACMP, the change should be notified **immediately after implementation**.
 - For changes which are common for multiple related products and facilities, an expanded change protocol can be proposed.
 - The scope of an expanded change protocol may cover multiple related products or manufacturing changes (e.g. facility changes).
 - Health Canada recommends that comparability protocols be submitted in eCTD **section 3.2.R.8** with the PLCM document.

Product Lifecycle Management Document (PLCM)

- Current Alignment

Health Canada is partially aligned

- Concept is well understood – we have our CPID (Certified Product Information Document)
- Concept of PLCM ***has been introduced*** in the PNOCC guidance document:
 - Health Canada recommends that the PLCM document be provided in tabular format in eCTD **section 3.2.R.8**, with specific references to the submission sequence, eCTD section number, and page number where each EC's scientific justification can be found.
 - An updated PLCM document should be included in post-approval submissions for CMC changes. The updated PLCM document should capture the change in ECs and other associated elements (reporting category, commitments, PACMP).
 - The PLCM should also be provided as an Appendix to the CPID.

Implementation timelines

- The PNOCC has been updated to incorporate the ICH Q12 tools and concepts (i.e., Established Conditions, post-approval change management protocol, product life cycle management document), including the addition of the “Immediate Notification” reporting category
 - **July 2021:** External consultation with stakeholders (90 days)
 - **October 2021:** Finalization of the PNOCC guidance document
 - **October/November 2021:** Launch of the pilot program
 - **January 2022:** Training session for the reviewers
 - **February/March 2022:** Implementation of ICH Q12 in Canada (Step 5)

