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Implementation of ICH Q12: Reviewers' perspective from the Health Canada pilot program on ECs and PACMPs

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Outline

- Steps for the implementation of ICHQ12
- Scope & Purpose of the Q12 pilot program in Canada
- Criteria used to select applications
- Pilot program timelines
- Reviewer's perspective
  - PACMP
  - ECs
- Q&A

Implementation timelines in Canada

- The Post-NOC Changes guidance document 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

  - **August 2021:** External consultation with stakeholders (120 days)
  - **January 2022:** **Training sessions** for the reviewers
  - **March 2022:** Launch of the **pilot program** (on ECs and PACMPs)
  - **February 2023:** End of the pilot program on ECs and PACMPs
  - **February/March 2023:** Finalization of the PNOCC guidance document
  - **May/June 2023:** Projected Implementation of ICH Q12 in Canada (Step 5)

Health Canada Q12 Pilot Program on ECs and PACMPs – Scope

Scope:

- Established Conditions (ECs) and Post-Approval Change Management Protocol (PACMPs)
- Biologics, radiopharmaceuticals and small molecules
- Submissions with 180 days review timelines
  - Supplements to New Drug Submission (SNDS) applications for **biologics** and **radiopharmaceuticals**
  - New Drug or Abbreviated New Drug Submissions (NDSs or ANDSs) or Supplements (S(A)NDSs) for **pharmaceuticals**

Health Canada Q12 Pilot Program on ECs and PACMPs – Purpose

Purpose:

- To allow Health Canada staff and industry to gain experience with Established Conditions and PACMPs prior to implementation of ICH Q12
- To get familiar with the ICH Q12 reporting categories nomenclature and the corresponding Health Canada's reporting categories described in the Post-NOC Change (PNOCC) quality guidance document
- Opportunity for increased interaction between Health Canada and applicant

Expression of Interest (EOIs) and Selection criteria

EOIs:

- Letter to request Expression of Interest (EOIs) sent on November 5, 2021
- Received 10 EOIs
- Deadline to submit applications in the pilot program : March 6, 2022

Selection criteria:

- Type of product (e.g., blood, vaccine, anti-cancer drug, pharmaceutical).
- Scope of application (e.g., the changes that are covered by the proposed protocol or manufacturing steps where ECs are proposed)
- Extent of sponsor's experience using ICH Q8-Q11 principles.
- Whether the proposed submission will be based on limited data or will use platform knowledge.
- Plans for any pre-submission meetings to take place prior to filing the submission for the ICH Q12 Pilot Program for ECs and/or PACMPs .

Health Canada Q12 Pilot Program on ECs and PACMPs – Applications

- Accepted 8 applications (S/NDSs) into the pilot program:
  - Mixture of small and large molecule and innovator and generic

Scope of the application	BRDD (Large molecules)	PDD (Small molecules)
Established Conditions (ECs)	2	2
Post-approval Change Management Protocols (PACMPs)	3	1

Health Canada Q12 Pilot Program on ECs and PACMPs - Timelines

Receipt of the applications in the pilot program:

- The submission of an EC and/or PACMP had to be received by HC no later than **March 6, 2022**.

Screening period:

- 45 days: **April 21, 2022**

Review period:

- 180 days: **October 20, 2022**
- Potential date for the end of pilot program

Current status:

- Review is completed for 3 large molecules and 1 small molecule and is still underway for 2 large molecules and 2 small molecules (PtC)
- Anticipate to complete the pilot program in **March/April 2023**

Reviewer's experience - PACMPs

Current status:

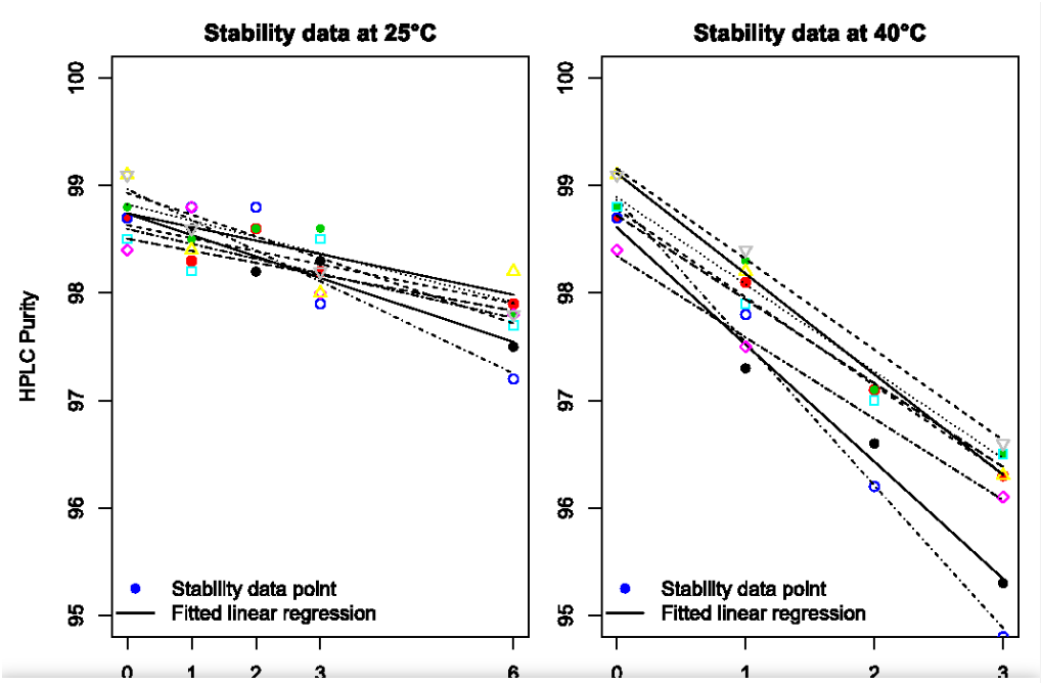
- Received 4 applications – All covered new manufacturing sites/suites
- Only one company requested a pre-submission meeting
- 3 Notices of Compliance (NOCs) and 1 Notice of Non-Compliance (NON)

Initial experience and learning:

- Protocols were well written in general.
- Proposals for the reporting category for Step 2 were reasonable
- Importance to justify the proposed comparability criteria as outlines in ICH Q5E and Q6B. The statistical approached must be justified.
  - With PACMP, at Step 1, we don't have any batch data.
  - For a NDS, S/NDS or Notifiable Change, even if the acceptance limits for the comparability assessment are larger than expected, there are batch analysis data we can rely for the assessment and may demonstrate that the comparability batch data are much tighter than the proposed limits.

Reviewer's experience – PACMPs (cont'd)

- Difficult to define the scope of a expanded PACMP
  - The scope of an expanded change protocol may cover multiple related products or manufacturing changes (e.g. facility changes).
  - Need to justify how the same comparability criteria apply to a class of products.



Reviewer's experience – Established Conditions

Current status:

- Received 4 applications covering drug substance and drug product
- No company requested a pre-submission meeting
- 1 Notices of Compliance (NOC) and 1 Notice of Non-Compliance (NON)
- Issued lot of clarifaxes and received several requests for Pause the Clock (PtC). Mainly about the justification of reporting categories for ECs and the PLCM document

Initial experience and learning:

- Applicant's approach to risk assessment and change management provide helpful context to established condition proposals
- Established conditions and reporting category proposals need to be scientifically justified and supported by risk assessment (or in compliance with post-NOC change guidance document)
- Risk assessment should consider holistic control strategy
- PLCM is a valuable tool for both applicant and Health Canada

Reviewer's experience – ECs (cont'd)

- ICH reporting categories vs Health Canada reporting categories.
- Some companies provided an addendum to the PLCM that included a rationale for the proposed ECs and the level of risk and to clarify the corresponding Health Canada reporting categories (worked well) .
- Explain the level of risk associated with each category. A change with Moderate risk needs to be filed as a Notifiable Change for Biologics. However, the associated reporting categories can be negotiated.
- Encouraged to include the following reporting categories table at the beginning of the PLCM.

Comparison between ICH and HC reporting categories

EC Risk	ICH Terminology	Health Canada*	
		BRDD	**PDD**
High	Prior Approval	Level I - Supplement	Level I - Supplement
Moderate	Notification Moderate	Level II – Notifiable Change	
Minor	Notification Low	Level III – Immediate Notification	Level III – Immediate Notification
		Level III – Annual Notification	Level III – Annual Notification
No / negligible risk	Not Reported (handled by PQS)	Level IV – Changes not reported	Level IV – Changes not reported

**** According to ICH Q12, ECs and their associated reporting categories can be negotiated.***

Reviewer's experience – PLCM document

- A complete list of proposed ECs, their reporting categories (if proposed), and the eCTD locations for their scientific justification should be included in the Product Lifecycle Management (PLCM) document in eCTD ***Section 3.2.R.8 - Product Lifecycle Management Information*** (to be available after the implementation of Q12 in Canada)

- Need to be referenced at the end of the CPID (hyperlink) under ***Regional Information - Product Lifecycle Management Information***

- Need to include CTD section to direct where to find the supporting data (including the Sequence number) – See next slide

Reviewer's experience – PLCM document

eCTD Section	Established Conditions *(Note that identification and justification of each EC is presented in the relevant eCTD section)*	Reporting Category When Making a Change to the EC
	The ECs below are to be implemented at the following sites: FEI xxxxxx FEI yyyyyy	
Seq 0001, 3.2.P.3.3, p. 4	The manufacturing process consists of the following sequence of unit operations: 1. Powder blending 2. Roller compaction 3. Tablet compression 4. Film coating	PAS
Seq 0001, 3.2.P.3.3, p. 44	**1. Powder Blending** The active substance and three excipients are mixed together. The following process parameters are defined as ECs.	
Seq 0003, 3.2.P.3.3, p. 45	Operating principle: Diffusion mixing	PAS
Seq 0001, 3.2.P.3.3, pp. 45–47	Equipment type: V-blender	Change to equipment of same operating principle: AR

Reviewer's experience – PLCM document

- As ECs may be proposed for the entire CMC sections or may be proposed for a subset of information provided in Module 3 (e.g., for an individual unit operation of the manufacturing process), it is recommended to include the following statement at the beginning of the PLCM document:

"It should be noted that if specific ECs or reporting categories are not proposed in a marketing application or for a specific section(s) of a marketing application, then ECs and associated reporting categories when making changes would be those that Health Authority typically considers to be ECs and the reporting categories follows recommendations contained in local guidance regarding post-approval changes"

Conclusion

- Post approval changes are taking years for worldwide approval slowing down implementation of changes and continuous improvements which can lead to drug shortages.
- ICH Q12 intends to harmonize lifecycle management to facilitate and encourage continuous improvement in pharmaceutical manufacturing through risk-based oversight
- Such improvements and resulting benefits can help to:
  - Ensure that patients reliably receive quality medicines over the lifecycle of the product
  - Mitigate drug shortages due to quality issues
  - Facilitate innovations in manufacturing
  - Reduce burden to regulators and industry
- This is based on a Change Management system within an effective and robust PQS which should contribute to a greater level of manufacturing control, which subsequently strengthens the confidence Regulatory Authorities have in a company's ability to consistently produce high quality products

Conclusion (cont'd)

- Significant progress made toward Q12 implementation in Canada
  - Need to complete the pilot program and finalize the revision of the post-NOC guidance document
- Helpful to add **information about the PQS** of the proposed site where ECs or PACMPs are proposed (e.g., inspection history by Health Canada, recalls and product quality defects, quality management maturity information where available)
- The **Cover Letter** should includes a brief narrative description and rationale of the change(s); including a statement whether or not specific ECs are proposed and whether or not post-approval changes will follow the recommendations in the post-NOC quality guidance document.
- Importance to have **pre-submission meetings** in order to receive preliminary feedback on the proposed approaches for the PACMPs, ECs and PLCM document. This will assist in the review of applications containing these elements.

Thank you!