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Bureau of Policy, Science and International Programs
Therapeutic Products Directorate
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Via email to hc.policy.bureau.enquiries.sc@canada.ca

Dear Sirs/Mesdames,

The International Society for Pharmaceutical Engineering (ISPE) would like to submit comments on the draft revised guidance documents on Post-Notice of Compliance (NOC) Changes – Quality. ISPE appreciates the opportunity to review these important revisions to Health Canada's guidance framework, particularly as they pertain to the implementation of ICH Q12. ISPE commends Health Canada on the manner in which they have looked to implement the tools and thinking behind ICH Q12 into the Canadian Post-Notice of Compliance Changes guideline. In particular, the positive way in which the concepts for both Post-approval Change Management Protocol (PACMP) and Established Conditions (ECs) have been reflected in Section 2 of the draft, which aligns well with ICH Q12. ISPE notes the adoption of science- and risk-based principles to justify ECs and to reflect this in appropriate reporting categories alongside the existing detailed change annexes. This flexibility in approach is welcomed by the industry.

ISPE would like Health Canada to consider the following high-level comments for the subsequent drafts of these guidance documents.

- The newly added change category of "Level II - Immediate Notifications (minor quality change)" is a considered a positive addition to the available regulatory tools. However, there is a lack of clarity around timings of submission. Line 97 & 237 of the Framework document state that an Immediate Notification needs to be submitted "…within 15 days of the date when a batch manufactured using those changes is first released to the Canadian market". This wording is not clear if Immediate Notifications can be submitted before the 1st impacted batch is released in Canada, or if the Sponsor needs to hold off on notifying Health Canada until the batch is released.
- In Section 2 "Guidance for Classification – Reporting Categories" of the Overall Quality document, and throughout the guidance, it would be helpful to align the Canadian reporting levels to those in ICH Q12. Inclusion of a summary table, for example, would be helpful. This would help to ensure consistency in application of ICH Q12 versus local reporting classification. In addition, mention is made of reflecting the reporting category in the body of CTD e.g., Module 3 (Section 3, Line 255, 256). While justification of the proposed reporting category could be provided in Sections 3.2.S and 3.2.P of Module 3 in CTD, the

explicit local reporting category should be reserved for the PLCM in Module 3.2.R to prevent regionalization of large parts of Module 3.

- Section 3, 3, “Pharmaceutical Development and Quality By Design” of the Overall Quality document appears to be taken directly from the predecessor guideline (Section 3.7). Whilst a design space is not a mandatory element of ICH Q12, there are still parallels to production of knowledge and understanding using science- and risk-based approaches (a knowledge space) and it would be helpful if these were discussed here. In particular, the use of elements mentioned in ICH Q8 and Q11 to develop the knowledge space for drug product and drug substance is considered a key element in establishing and, alongside ICH Q9, quality risk management justifying established conditions. We recommend that Section 3.3 includes discussion of the application of the science- and risk-based approach as well as use of quality risk management to justify proposals in post approval submissions and documentation. It would be appreciated if Health Canada would reflect on the wording of this section to take account more accurately of the language related to existing flexibilities described in ICH Q8 and Q11 with consideration of ICH Q12.
- Section 3.10 “Stability Testing” of the Overall Quality document makes no mention of the strategies outlined in ICH Q12 (Section 9 of ICH Q12) around stability studies and the use of science- and risk-based principles in the design of stability studies used to re-confirm the original retest period or shelf-life following a change. It would be beneficial if this section was revised to include relevant text on stability outline in ICH Q12.

ISPE is an individual membership Society of more than 18,000 professionals in 90-plus countries involved in the manufacture of pharmaceuticals and related products. The attached comments were developed by an international team of ISPE subject matter experts under the auspices of ISPE’s Product Quality Lifecycle Implementation (PQLI)® initiative which was formed in 2009 to provide guidance on practical implementation of the concepts described in ICH guidelines, focusing on Q8, Q9, Q10, Q11 and Q12.

We appreciate the opportunity to submit these comments for your consideration. Please advise if you would like ISPE to further support draft content or conduct further reviews of content on this topic.

Respectfully,

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