Final Business Plan
Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
dated 28 July 2014
Endorsed by the ICH Steering Committee on 9 September 2014

1. The issue and its costs

- *What problem/issue is the proposal expected to tackle?*

  There is currently a lack of a harmonised approach on technical and regulatory considerations for lifecyle management. While the concepts in ICH Q8, Q9, Q10 and Q11 provide opportunities for a more science and risk-based approach for assessing changes across the lifecycle, several gaps exist which limit full realisation of intended benefits. The envisioned post-approval 'operational flexibility' has not been achieved. The main emphasis to date has focused on early stages of the lifecycle (i.e., development through launch).

  A similar focus is urgently needed for the commercial manufacturing phase in order to fill the gaps in the implementation and fully realize the opportunities promised by ICH Q8 toQ11. For example, lack of alignment has led to confusion on the necesssary information and level of detail in the dossier and its impact on change management and regulatory reporting. The lack of harmonised approaches for technical and regulatory aspects for lifecycle management has hindered the anticipated innovation and continual improvement in the pharmaceutical and biotechnology sector. An ICH harmonised approach on technical and regulatory considerations for lifecycle management will benefit industry, regulators and patients by supporting continued assurance and supply of high quality product.

- *What are the costs (social/health and financial) to our stakeholders associated with the current situation or associated with "non action"?*

  Without the development and implementation of these guidelines it would be anticipated that resource / costs for implementing post-approval changes would continue to remain at current levels and continue to increase. Continual improvement would continue to be sub-optimal, leading to less efficient processes remaining in place and other quality-related problems remaining unresolved. There would be a continued risk of supply disruption associated with these factors leading to drug shortage in some instances, and therefore resources / costs related to management of theses issues by regulators and industry will remain at current unacceptable levels.

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2. Planning

- *What are the main deliverables?*

  An ICH Guideline on lifecycle and change management that is intended to work with ICH Q8 to Q11 Guidelines and will provide a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more, transparent and efficient manner across the product lifecycle. Adoption of this guideline will promote innovation and continual improvement, and strengthen quality assurance and reliable supply of product. It will allow regulators (assessors and inspectors) to better understand, and have more confidence and trust in, a firm's Pharmaceutical Quality System (PQS) for management of post-approval CMC changes.

- *What resources (financial and human) would be required?*

  It is anticipated that such a harmonised Guideline (to *Step 2*) could be developed within an 18-month period, assuming input of 18 man-days per expert working group member for essential meetings over this period and 24 man-days of input from an appointed Rapporteur. Additional input would be expected from observers. Progression to *Step 4* is anticipated to be less resource intensive.

- *Timeline and Milestones*

Adoption of topic by Approval of ICH Steering Committee to develop concept paper	June 2014
Agreement of Concept Paper and Business Plan by IQDG	July 31 2014
Adoption of Concept Paper and Business Plan by Steering Committee	September 9, 2014
First EWG meeting (Lisbon, Portugal)	November 2014
Second EWG meeting	June 2015
Third EWG meeting	November 2015
Adoption of *Step 2* Document	2Q 2016
Adoption of *Step 4* Document	2Q 2017

3. The impacts of the project

- *What are the likely benefits (social, health and financial) to our key stakeholders of the fulfilment of the objective?*

  It is envisaged that the development and implementation of this new guideline would deliver a number of benefits for industry, the regulatory authorities and patients:

  - Harmonise change management, leading to better availability and reliability of the supply by enabling companies and regulators to manage CMC changes in a more transparent and efficient manner across the product lifecycle
  - Facilitate risk-based regulatory oversight and optimisation of resources for review and inspection
  - Assist industry in maintaining dossier conformance while facilitating continual product and process improvement

- Emphasize the use of the control strategy as a key component of the regulatory commitment to facilitate linking the dossier, continual improvement and regulatory inspections
- Enhance use of regulatory tools for prospective change management (e.g. Post-Approval Change Management Protocol (PACMP), comparability protocols, application form)
- Help assure supply reliability by enabling strategic management of CMC changes which could mitigate shortages related to manaufacturing and quality issues
- Support continual improvement of the manufacturing process and the control strategy which can result in decreased product variability
- Increase manufacturing efficiency
- Facilitate the introduction of innovations
- Support implementation of the validation lifecycle concept
- Enable control strategy lifecycle (e.g., model maintenance, analytical lifecycle)

In summary, the main drivers include: a more strategic approach to Lifecycle Management (LCM) across the product lifecycle, an opportunity to focus on science and risk based approaches for the assessesment post-approval changes with the appropriate level of regulatory oversight, encouraging Companies to develop and register more enhanced Quality by Design (QbD) approaches (supporting fuller implementation of Q8, Q9, Q10 and Q11), encouraging and providing companies with tools to introduce more innovative approaches to manufacturing across the ICH regions.

- *What are the regulatory implications of the proposed work – is the topic feasible (implementable) from a regulatory standpoint?*

  This guideline is not intended to introduce new requirements necessitating changes to the regulations in the regions.

  Different mechanisms for regulatory review of changes exist in the three ICH regions, and there will remain regional differences on how information in the dossier relates to reporting requirements (e.g. changes to be reported, information required for review, assessment timelines). Nevertheless the guideline is intened to clarify current expectations and optimise the use of the relevant regulatory tools in each of the regions.

4. Post-hoc evaluation

- *How and when will the results of the work be evaluated?*

  From an industry perspective, implementation of this Lifecycle Management Guideline will help to foster a quality improvement culture. An industry wide study identified continual improvement as one of the leading factors needed to build capabilities to drive quality excellence.

  In the EU, it is anticipated that application of the guideline could result in an increase in the use of PACMPs and consequently more Type IA or Type IB variations, rather

than Type II variations. There could be reduced problems with drug shortages and increased manufacturing effciciency and innovation, although these improvements would be difficult to measure.

In Japan, it is anticipated that this guideline could facilitate reviewers' decision of post approval chages. As the results, the number of minor change matters in the application form could be increased and the number of partial change applications could be reduced. It could also facilitate the activities for continual improvement though the activities would be difficult to measure.

For FDA, application of the guideline is expected to facilitate risk-based change management by industry, leading to increased product quality assurance and availability. Additionally, it will enhance FDA's risk-based regulatory decision making, resulting in more efficient and effective resource utilisation.

Health Canada follows a risk-based approach to manage post-approval changes and expects the industry to take greater responsibility in managing post-approval changes. The regulatory oversight will be commensurate the risk posed by the type of product and the proposed post-approval change

Swissmedic expects that the new guideline facilitates a risk based review of post approval changes. Thus, on the industry's side, implementation of innovations could be accelerated significantly.

It is important to note that providing a quantitative assessment of the potential impact of this proposed guideline is difficult due to the wide variety of approaches that could be taken by both industry and regulators. However, it is clear that the predominant financial impact of the proposed guideline to both industry and regulators is reduction in cost. While the exact reduction in cost may vary from agency to agency and company to company, the magnitude of impact is significant.