Roundtable Session 2 – Table 11: ICH Q12- Global Implementation Challenges With PACMPs and Established Conditions

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Abstract:

The ICH Q12 guideline is intended to promote innovation and continual improvements in the biopharmaceutical industry through proactive communication of change plans and risk-based regulatory mechanisms for assessment and approval. The regulatory mechanisms such as Established Conditions (ECs) and Post-Approval Change Management Protocol (PACMP) are designed to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle.

The global implementation of ICH Q12 is promised to expedite post-approval product variations with consistent quality standards globally in the more efficient and predictable manner. However, the interpretation of ICH Q12 elements such as ECs and PACMPs differs between health agencies in practice. These differences include the assessment of information provided to justify ECs and non-ECs, the assessment of reporting category for the proposed change and the level of details provided in PACMPs. These differences greatly increase the complexity of global submissions following the ICH Q12 guideline and putting the promise to ensure uninterrupted and robust access to medicines at risk.

In this round table, we will share experiences and pain points with the global implementation with EC and PACMPs.

Discussion Questions:

1. What is your experience with preparing for quality modules in the dossier following ICH Q12? What are the pain points?

2. What questions have you received from health agencies regarding EC and PACMP? Are there common themes between different regions? What are the main differences and opportunities?

3. What information and the level of details have you provided to justify for non-EC? And what is the outcome?

4. How do you use PACMP to facilitate the introduction of new technologies in the future such as an alternative ID method or HPLC column change?

5. Even if you haven't formally submitted ECs/PLCMs/PACMPs, have the items in ICH Q12 (such as Appendix 1) reshaped how you approach a review (Regulators) or perform your change assessments (Industry)?

Notes:

- The Q12 working group started 10 years ago. The mission was to identify gaps that need to be closed and how to interpret which information is important and legally binding. The wording in the legislation is very broad. The term ECs in Q12 is new- and used to identify which elements need to be reported when making a change. It can be used for post approval supplements or new applications. It should help to identify the core quality elements and help to increase the overall predictability. Several tools where introduced with Q12, e.g. PACMP or PLCM for lifecycle where all important information can go in.
- The ICH Q12 approach was used for a new product to manage the lifecycle, reporting categories were provided. The received feedback was negative. More details including characterization data would be needed. A briefing book was sent along with the submission but it didn't discuss the EC details. Overall, the company would not use the EC strategy for novel products because of the potential negative impact on the submission / approvability.
- How does the industry implement Q12 if it is not used globally (currently only FDA)? It cannot be filed globally although it is more work during product development. It is only slowly rolling out. As of now it is unclear which countries will adopt what. Canada may be there by end of this year, Europe may take another five years as a new legislation is necessary. MHRA may adopt even earlier than EMA. PACMPs are used more extensively for more complex changes. Overall the cost / benefit ratio seems to be negative.
- EC is not the design space. The design space is not used in Q12 and cannot be used to identify ECs.
- Also M4Q gets revised now. Does this slow down the process? It is very little information available in M4Q R2. However, M4Q will contain all sections like the PLCM. Q12 Annex 1 states which sections should contain ECs.
- From agency perspective there are not enough submission which gives the impression the industry is not interested in the concept. This seems to be a big misunderstanding.
- Where do challenges come from? Internal challenges are the non-availability of resources. A different mindset is needed and many people are not there yet. The use of Q12 increases the sophisticated understanding but it takes time to get there.

- In general justifying non ECs is very difficult and the benefit is not seen by all participants. On top QA needs to buy-in on the concept regarding definition of criticality. The quality system needs to slightly adopt. This kind of assessment is not commonly used in QA and is also resource intense.
- One company has a dedicated working group for ECs which is existing for five years now. Again resources are a hurdle because the work is done during development and pays off only if a PAS is submitted. During the initial submission of a products it seems to be difficult and pre-alignment with the HA regarding reduced reporting categories is needed. Because of all this limitation the company did not file ECs yet. The next try will be with a monoclonal antibody where DS and DP processes are platform. There the EC implementation should be possible. Process understanding is key. Also analytics will be a topic.
- What is the benefit e.g. for analytics, process, or raw materials? The benefit would be the reduction of the reporting category in case of changes.
- Should the internal working group consist of cmc or process people? Representatives from each function should participate. The cmc department should lead the working group.
- The implementation of Q12 is mainly for advanced companies. The control strategy is CQA centered and helps to understand the risks. The assessment of criticality upfront increases the predictability of the outcome. The benefit of this effort comes very late. During lifecycle the workload should be less.
- Companies are still learning to use the PLCM document. PACMP is often used to address site transfers. Starting point are low risk pieces. In addition, the PLCM document is another document that needs to be maintained.
- The intent of the PLCM is also to enhance communication between companies and agencies.
- Is prior knowledge used to justify ECs? If there are similar processes e.g. for mAbs prior knowledge can be used in the justification.

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