Table 18: ICH Q12- Regulatory insights, Successful Use of PACMP, Case Studies- What Worked, Didn't

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Key Words:

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Scope: In 2020, the ICH Guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management was first published. The guidance "provides a globally agreed framework to facilitate the management of such post-approval CMC changes in a predictable and efficient manner across the product lifecycle." The idea behind this document was to simplify the complex process of post-approval changes and improvements from all perspectives of this important process. The targeted result was to provide a clear path for implementation of improved technologies and continual improvement over the lifecycle of a drug.

This roundtable is designed to encourage different stakeholders in the process to discuss how the guidance within ICH Q12 are being interpreted and applied. We pose the following,

Questions for Discussion:

1. What have been the strongest benefits? How have they been most effectively achieved? Also, what might be some unforeseen complexities in applying the ideas described in the guidance?
2. Are there case studies that can be shared where ICH Q12 was implemented?
   a. How was it implemented?
   b. Who were the stake holders and the drivers within the company?
   c. What additional data was used to justify the identification of Established Conditions?
3. Have you implemented significant changes to your risk management system, development strategy, control strategy or quality system as a result of ICH Q12?
4. Have companies or regulators observed greater flexibility? Or do they perceive the possibility for greater flexibility to implement process changes?
   a. If so, how did you realize this additional flexibility?
   b. If not, what additional data or knowledge would be required to achieve this additional flexibility at the time of filing?

Discussions Notes:

Post Approval Change Management Protocol (PACMP)

- Attendees at the table introduced themselves, present at the table were a mix of Regulatory CMC and Analytical colleagues from various companies; therefore varied level of experience.
- The stakeholders within the company acting as drivers to enforce ICH Q12 tools are mainly the Regulatory functions, followed by the Quality functions. The other SMEs are being exposed to the tools and can see the benefits, esp. as it relates to the speed of approvals.
- Question asked if ECs are the main component of the PACMP. Answered that PACMPs are for prospective changes to be introduced along the lifecycle of the product, and follows an analogical format that requires data to be introduced and acceptance criteria. ECs are regulatory binding components of a change that requires submission/notification to the Health Agencies.

- Team discussed if the concept of the PACMPs are new and this was highlighted as not new for the US (due to the Comparability Protocol, (CP)). Companies discussed that they have submitted CPs and the documentation submitted was very extensively huge.
- When the PACMPs were introduced, the US companies thought this would reduce the volume of pages shared for the CPs.
- Pilot experiences of CPs in the US mentioned by US based companies.
- A Drug product site change using PACMP was submitted and numerous questions were asked by the Agency leading in the end to the submission being withdrawn. The technical teams in the end saw this as cumbersome and refrained from pushing back.
- Another attempt was shared in the form of a Prior Approval using CP to notify the Agency. The technical teams were on board and supported as needed. Approval was granted for this drug substance raw material change protocol with the subsequent downgrade to a CBE-30 from a PAS.
- Ensuring companies are prepared by collecting the required supporting data and outlining different situations is the best approach. EMA does not allow correction of quality issues.
- The question was asked about where to file classic validation protocol; this was highlighted to be filed under S.2.5 and not in the Regional section.
- Drug product site changes works better with EMA than with the US due to Inspections. It is easier to arrange Inspection times with the EMA than with the US FDA.
- The question was asked, how much change data is used in the Comparability Protocol? It was mentioned that the acceptance data and lab scale data, small scale characterization data will all support in justifying the change.
- The EU package shared to multiple sites in tech transfers proves beneficial as the Inspections from the EMA is faster so this helps to provide good knowledge of what you are planning to write in the submission package.
- It was discussed that companies have tried cross-product sharing for about approximately ten (10) different products using the one (1) CP.
- The types of changes that have been submitted included, change in supplier and process – this was submitted and was successfully approved. Changes for drug substance raw material changes were also submitted and successfully approved. Changes concerning facilities, higher aggregates and critical quality attributes have not yet been explored by the companies present at the table so they stated it would be interesting to see how this can be done.
- It is recommended for companies to evaluate the type of changes to define the need for submission in PACMPs. For example container closure system change will require stability data to support, is the time sufficient? Are changes too complex; so PACMPs can be used as a way to de-risk more complex changes.
- Challenges sighted includes the availability of PPQ batches at the initial stages, etc.
- Risk assessments of the change proving no impact or little impact to the product quality can aid to support the PACMP by proving comparability. It is recommended to always preempt the possible questions from the Agency and attempt to have the data upfront.
- It was mentioned that all companies have either attempted the submission of PACMPs or discussing to explore the submission of PACMPs for Initial Market Authorizations (IMA: NDA, BLAs). No company at the table has ever submitted a PACMP in the post approval stage to date. The benefits at the IMA stage are being discussed within companies and can be seen for the functions by leveraging experience within the company and prior knowledge of the types of changes to be explored for the type of product and the sites to be registered.

- Early planning of the changes to be included in the PACMPs can be difficult to determine, however, close communication with the cross-functional teams to advice on the strategy of using PACMPs. Regulatory colleagues are encouraged to further discuss with operation colleagues for awareness in a collective effort - the need for the early identification of the changes.

Established Conditions:

- It was discussed that Established Conditions (ECs) have been mainly submitted for the analytical procedure sections of regulatory dossiers. Companies have been partially implementing ECs within the dossiers and not in entirely.
- It has been proven to be challenging to downgrade the sections as most of the sections are already considered 'Established'.
- It was stated that the US FDA colour coded many M3 sections as a recent experience from one company. It proved conflicting with the different coding from various Agencies.
- Examples for Non-Established and Established changes were shared across the table.
- When writing sections, it is recommended to focus on the Established conditions and not include the Non-Established conditions as this could be extensive. The company's PQS should be equipped to properly manage the latter.
- It was mentioned that Pre-submission meetings can prove very beneficial for both Industry and Agency. It was said that Australia is open to this.
- The EMA legal framework does not accept Established Conditions to date. Cases where this was included in submissions and the agency asked to have it removed.
- Health Canada has advised to share ECs and PACMPs in the submissions and they will review.
- The Health Canada pilot concerning PACMP and Established Conditions can be leveraged for Industry to gain experience and to support adoption across Agencies in the future.
- The Japan and South Korea has already built ICH Q12 Tools in their infrastructure.
- Recommendation for the Agencies to work alongside each other to have more alignment; in conjunction to Industry attempting to coordinate submissions.