Roundtable Session – Table 2 – To PACMP or Not to PACMP

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Abstract:
From their initial introduction in 2010 to their inclusion as regulatory tool in ICH Q12 in 2020 to today, PACMPs have gained in relevance and in frequency of use for the CMC lifecycle management of biologics products.

While PACMPs have the power to considerably improve speed, predictability and transparency of requirements for the implementation of CMC changes, they are not without caveats to MAHs and regulators alike.

This roundtable invites MAHs and regulators to share their views on advantages and disadvantages of PACMPs, to discuss on CMC changes which may or may not be suitable for PACMPs and to highlight challenges frequently observed with the submission or review of PACMPs.

Discussion Questions:

1. How frequently do you use PACMPs or do you see PACMPs being submitted? How popular is a PACMP based regulatory strategy within your company?

    - Diverse industry experience in PACMP applications: some companies are using this tool since years, other have limited experience and are at a stage of exploration
    - The benefit to use a PACMP approach may not be obvious to companies in some instances.
    - Regulators see submission of PACMPs on a regular basis for biologics products

2. PACMPs require a step 1 submission/review/approval of the PACMP, followed by the step 2 implementation submission/review/approval. In which situations is this extra work justified? In which situations is a direct submission of a PAC more efficient?

    - A PACMP submission requires more than the description of a high-level concept
    - A PACMP submission requires a sound level of certainty within the company's cmc strategy about the change → extra work is well justified because company get change derisking as well as regulatory predictability, in addition to increased speed for the implementation of changes.
    - If there is a high need for future flexibility a PACMP is not the tool to go→ submission of a PAC more efficient
    - For regulators assessing a PACMP is per se a challenge as assessors are assessing something that has not yet happened- if the change description is poor, the future acceptance criteria can be hard to review
    - EMA Q&A document provides helpful guidance when to chose a PACMP approach
    - Approved PACMPs might be used to feed into reliance procedure allowing facilitation of a global change even in countries not so familiar with the concept

2. What types of post approval changes (PAC) would you consider specifically suitable for a PACMP approach? What types of PACs would you not consider suitable for a PACMP approach?
    - Well described manufacturing or testing site changes are the most common changes seen in PACMPs
    - With the overall downgrading of variations with the update of the variations guideline, PACMPs for simple changes may not offer a significant benefit anymore. The benefit of a PACMP will be more obvious for complex changes and /or multi-use/mutli product PACMPs.

4. Multi-use PACMPs and multi-product PACMPs present specific challenges. Are they taking the PACMP concept a step too far or are they specifically valuable?

- Multi-use PACMPs are considered more challenging than multi-product PACMPs due to the fact that they are extending further into the future and are more liable to changes. Nice examples about introduction of a novel analytical method platform across several products have been described. Prior knowledge is in such cases very important.
- Multi-product PACMPs must specifically describe an intended change and the subsequent deliverables/acceptance criteria. In order to suit multiple products, PACMP might be too generic and might lack the clarity on deliverables and acceptance criteria. Overly generic PACMPs will be difficult to review and to accept. Prior knowledge is key for multi-product PACMPs in order to show applicability/potential for implementation for the products in the scope.
- Multi-product PACMPs require platform approaches for the products in scope. Analytical methods are currently closest to platform applications.

5. What are the main challenges and obstacles encountered when submitting/reviewing PACMPs (step 1)? What are the main issues when implementing a PACMP controlled PAC (step 2)? If you could change one aspect of the PACMP process/rules, what would it be?

- For regulators high-level description of the intended change is not sufficient
- For step 2 implementation is with a minor variation only, on the regulator's side there is usually limited time to review these, and yet, the data package submitted can be extensive. Assessors need to rely on the fact that the protocol was pre-approved and did cover all relevant acceptance criteria
- Justified deviations from the initial PACMP are possible but need to be highlighted either as a change to the PACMP or transparently within implementation potentially requiring an upgrading into a higher variation category.
- PACMPs are used in reliance procedure. Broader awareness of the PACMP concept, e.g. shared by experienced agencies, will help to drive timely approvals of global post-approval changes