

Reference Document on Post-Approval Change Management Protocols (PACMPs)

This paper describes the concept of Post-Approval Change Management Protocols (PACMPs), its current adoption and implementation status worldwide, and benefits.

It specifically addresses the mid to long term recommendation of the EFPIA MERN 2017 position paper on “Optimising the management of Post-Approval Changes for patients’ timely access to medicines in the Middle East region” i.e.:

- Industry to improve planning of changes through the product life-cycle where possible and seek to adopt new mechanisms that are expected in the future such as Post Approval Change Management Protocol (PACMP) as a valuable regulatory tool to modify the filing category for changes based on prior agreement between the firm and regulatory authorities.

1. What are Post-Approval Change Management Protocols (PACMPs)?

Definition: a Post-Approval Change Management Protocol (PACMP: EU and ICH Q12 terminology) or Comparability Protocol (US terminology) is a comprehensive plan for assessing the effect of a proposed change or multiple (related and consequential) CMC only (chemistry, manufacturing and controls) post-approval changes on the quality of a product (identity, strength, purity, potency, performance and stability).

Content: it describes specific change(s) that the sponsor would like to implement, in a first MAA, or during the life cycle of a product (through a Type II variation in the EU, or a Prior Approval Supplement (PAS) in the US), and how the impact can be verified. Based on the product process understanding and risk assessment of the potential impact of the change on the quality of the product, a PACMP would include studies, specific tests, and the acceptance criteria that demonstrate the lack of negative impact of the proposed CMC changes on the product quality.

Regulatory process: a PACMP provides for a step-wise approach to the assessment of the change(s), i.e.

- Early step 1: evaluation of the strategy for the change(s);
- Later Step 2: separate evaluation of the data produced, based on the agreed strategy.



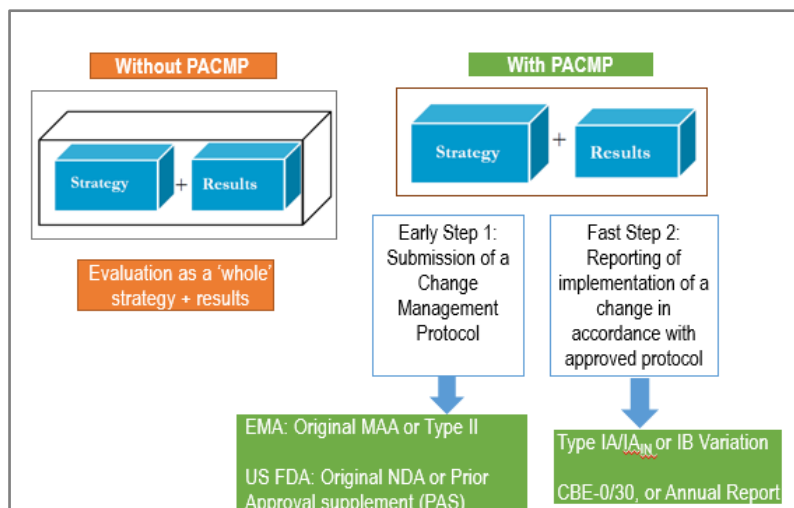


Figure 1: comparison of the process to assess and implement a change through a standard procedure (without PACMP) and using a PACMP.

2. A well-established procedure with a defined scope

Country level adoption: the concept of PACMP has been in application in the EU and US for over 10 years and was more recently introduced in Switzerland, South Africa and Japan (pilot for post-approval only).

- US FDA Pharmaceutical Quality/CMC - First introduced in 2003
- EU 2010 Variations classification (sections B.I.e and B.II.g) and [EMA Q&As of March 2012](#)

WHO adoption: more recently, WHO embedded the concept in the following Annexes:

- [Annex 3](#): GL on procedures and data requirements for changes to approved Biotherapeutic products - 2017
- [Annex 4](#) GL on procedures and data requirements for changes to approved Vaccines - 2014

ICH adoption: finally, it is one of the concepts being introduced by the ICH Q12 Guideline to expedite regulatory approval of a change - see ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management and Annex which provides illustrative examples - [Final Q12, November 2019](#). ICH Q12 was subsequently adopted by EMA/CHMP in March 2020 - see: [EMA Q12 webpage](#).

Scope of application

Products and applications types: PACMPs can be applied to all products types, i.e. small and large molecules, including vaccines, and in a first marketing authorisation application or a subsequent variation.

Scope of the change: PACMPs strictly apply to CMC only changes, i.e. it is not possible to submit a PACMP where non-CMC data including non-clinical, clinical and/or immunogenicity data would be required to support the change.



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3. Benefits of implementing PACMPs

Key messages

- PACMPs provide predictability regarding the information required to support a CMC change and the type of regulatory submission based on prior agreement between the MAH and regulatory authority.
- Broader acceptance of PACMPs worldwide will also facilitate the use of reliance across Agencies¹, where a similar regulatory package is submitted, and to harmonisation of dossier content and subsequent variations data packages (Module 3).
- PACMPs can also facilitate CMC acceleration, where regulatory initiatives allow for acceleration of the clinical development programme (EU PRIME, US and China Breakthrough Designation and Japan Sakigake, Orphan Drugs) and for specific product types such as oncology and pandemic therapies. This clinical acceleration adversely impacts on the ability of the CMC programme to deliver on all aspects of the normally anticipated submission content. The use of PACMPs to manage changes in the immediate post-launch period in a transparent, predictable and efficient manner can contribute to the timely global access of these much needed products to patients and security of supply.
- PACMPs have the potential to reduce the lead time to implement a change across markets, thus supporting continuous supply and availability of medicines to all patients globally.

While PACMPs require a thorough understanding of the concerned products and processes, the business benefits are significant, especially where used to introduce broad protocols covering multiple changes e.g. multi-site protocols for DS (Drug Substance) or DP (Drug Product) and/or multiple products.

From a regulatory CMC perspective, the stepwise approach is expected to lead to a faster and more predictable implementation of changes post-approval, since the MAH will have obtained agreement from the Regulatory Authorities about the proposed strategy and tests to verify the effect of the change on product quality. Typically, the variation category designated for reporting changes under an approved post approval change management protocol is at least one category lower than would normally be the case, i.e.

- ✓ In the EU: from a Type II to a Type IB or IA for Biologics, and from a Type IB to a Type IA² for small molecules, where no supporting data need to be reviewed (EU classification B.I.e.5a and B.II.g.5c).
- ✓ In the US: from a PAS to either a Change Being Effective in 30 days (CBE-30 days), or a CBE-0 or an Annual Report.

PACMPs bring predictability to the acceptability of a change, and to the data requirements for justifying a change, especially when the requirements are uncertain, or a novel approach is proposed, providing several additional benefits to introducing PACMPs, including:

- ✓ Opportunity to pro-actively engage with Health Authorities (HAs) prior to implementing a change, and towards securing faster approval time and subsequent implementation;
- ✓ Increased regulatory certainty through enhanced predictability in data requirements and timelines;

¹ WHO [Good Reliance Practices, June 2020](#)

² Type II: 'Tell, Wait for Approval (60 to 90 days); Type IB: 'Tell, Wait 30 days and Do' and Type IA: 'Do and Tell'



- ✓ Multiple use, provided that the PACMP remains relevant and up to date at the time of filing the implementation step (MAH responsibility);
- ✓ Support continuous process improvements.

Furthermore, PACMPs can provide significant assets to HAs and patients access as follows:

- ✓ Support expanding markets, through accelerated addition of (multiple) manufacturing sites;
- ✓ Reduction of lead time to approval of a change (or submission of changes which rely on reference country approval as a pre-requisite to filing), thus increasing supply management efficiency, and preventing shortages.

Annex 1: Definitions

- **ICH Q12 definition of a Post-Approval Change Management Protocol (PACMP):** a PACMP is a regulatory tool that provides predictability and transparency in terms of the requirements and studies needed to implement a change as the approved protocol provides an agreement between the MAH and the regulatory authority – see section 4.1 of the [ICH Q12 GL](#) for further details.
- **EU/EMA definition of a Post-Approval Change Management Protocol (PACMP):** a PACMP describes specific changes that a company would like to implement during the lifecycle of the product and how these would be prepared and verified. It is a step-wise approach in the assessment of changes, which allows an early evaluation of the strategy for the change and a later separate evaluation of the data produced based on the agreed strategy. Such a stepwise approach is expected to lead to faster and more predictable implementation of changes post-approval, since the MAH will have obtained agreement from the Regulatory Authorities about the proposed strategy and tests to verify the effect of the change on product quality.
- **US FDA definition of a Comparability Protocol (CP):** a CP is a comprehensive, prospectively written plan for assessing the effect of a proposed CMC post approval change(s) on the identity, strength, quality, purity, and potency of a drug product or a biological product (i.e., product), as these factors may relate to the safety or effectiveness of the product (i.e., product quality) - first introduced in 2003 – revised in 2016.

Annex 2: External References: position papers and Agencies guidelines

- [EFPIA position paper](#) ‘Optimising Post-Approval Change Management for Timely Access to Medicines Worldwide, Feb. 2017 and EFPIA Middle East Regulatory Network (MERN) [version](#) of the above position, Nov. 2017.
- [ICH Q12 GL](#) on Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, and [Annexes](#), which provides examples of PACMPs, and the EU [implementation](#) note, March 2020.
- EU: Variations Classification guidelines ([2013/C 223/1](#)) and [EMA Q&As](#) on PACMPs.
- US: [DRAFT FDA guidance](#) on Comparability Protocols for Human Drugs and Biologics: CMC information.
- [WHO Annex 3](#) (TRS 2011 of 2017) [GL on procedures and data requirements for changes to approved bioterapeutics](#).
- [WHO Annex 4](#) [GL on procedures and data requirements for changes to approved vaccines](#).



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Annex 3: Questions & Answers

- **How does a PACMP differ from a Design Space (DS) approach?** a PACMP can provide wider change opportunities with less information up front. Experience with registered DSs is that the regulators have a high expectation for information supporting the success at the commercial site, in the initial filing. Another key difference is that a change within an approved DS does not need regulatory reporting, while a change supported by an approved PACMP will trigger reduced reporting. Evaluation of the Pharmaceutical Quality System (PQS) will remain the same whatever the change category.
- **What is an Established Condition (EC)?** this regulatory concept is also being introduced by ICH Q12. It aims to delineate the aspects in the application that need to be reported when changed. This way, items which are not included in ECs (supported by appropriate data) can be changed under the PQS, with no reporting. ECs are legally binding information (or approved matters) considered necessary to assure product quality. Thus, any change to ECs necessitates a submission to the regulatory authority.



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