

Industry Position Paper: Optimising Post-Approval Change Management to Facilitate Continuous Supply of Medicines and Vaccines of High Quality Worldwide

Joint Position from EFPIA, IFPMA and Vaccines Europe

Industry Position

Industry acknowledges its commitment to continue improving its strategic and predictive planning and proactive communication of changes to help facilitate global supply.

In addition, Industry believes that global regulatory convergence of post-approval changes to Marketing Authorisations (MAs) using science and risk-based approaches will enable a more efficient management of quality and supply improvements and will facilitate patients' access to innovative medicines and vaccines.

National Regulatory Authorities (NRAs) should: establish national or regional guidelines in line with international standards (with regard to a risk based classification of changes and standardization of requirements) [1, 2]; have clear procedural guidance including timelines; and implement reliance pathways to accelerate the approval of changes.

Key Points and Messages

| Tools for efficient PACs management | What is necessary to implement? |
|--|---|
| Reliance, Worksharing, and Recognition | Apply World Health Organisation (WHO) reliance principles to PACs [3, 4]. If a Certificate of Pharmaceutical Product (CPP) is required, then reliance should be applied, and the review shortened. |
| Convergence of administrative and national requirements | Reduction of national specific requirements adapted to the risk-level of the change. International Council for Harmonisation - Common Technical Dossier (ICH CTD) format should be used. |
| Risk based and harmonised categorisation of PACs | A common understanding of risk-based approaches (ICH Q12 and associated ICH guidelines Q8-Q11 and WHO Guidelines) with major, moderate, and minor classification allowing more changes to be managed in the Pharmaceutical Quality System (PQS). |
| PACs with defined approval timelines | Convergence regarding the classification of PACs with clear timelines (e.g. WHO timelines in PAC guidelines [major (prior approval) – maximum 6 months; moderate (notification) - maximum 3 months]). |
| Q12 tools: Post-Approval Change Management Protocol (PACMP) and the concept of Established Conditions (EC) | <p>ICH Q12 implementation based on science and risk-based approaches (including justification of a lower reporting category or no reporting if managed within the Pharmaceutical Quality System, PQS).</p> <p>For rapid benefit of ICH Q12, implementation of PAMCPs is recommended. This tool can allow an appropriate lower reporting category to enable the reporting of results after executing the protocol as agreed with Health Authorities.</p> |
| Defined common market implementation criteria | Pre- and post-change product versions should co-exist in the market during a transition period. |
| Health crisis preparedness plan | PACs review timelines for emergency applications must be accelerated (use of reliance). |
| Industry efforts | Continue improving strategic, predictive planning and communication of changes to help facilitate global supply; enhance PQS as an enabler to change implementation. |

Introduction

Post-approval changes (PACs) to the registered information of authorised medicinal products, are introduced routinely worldwide to enhance the robustness and efficiency of the manufacturing process, ensure timely supply in case of increased demand, improve quality control techniques, respond to changes in regulatory requirements and upgrade to state-of-the-art facilities. This continued effort is critical to prevent supply disruption and continuously improve existing medicines and vaccines and is, in many ways, as important as bringing new medicines and vaccines to the market.

Why it Matters

Changes to approved licenses are essential to maintain a continuous supply of high-quality medicines and vaccines. This becomes more important when the product development and registration process is accelerated to meet unmet medical needs, thus pushing changes that would typically be made during development into the post-approval setting.

The current global regulatory landscape for PACs has the following features:

- Inconsistent classification systems.
- Specific and supplementary local data and format requirements.
- Unpredictable and variable approval timelines [5].
- Divergent interpretation and decisions by regulators based on the same data.
- Variable implementation periods after completed regulatory action.

This can lead to:

- Duplication of effort by industry and regulators worldwide (receiving the same change application) which can result in additional time to review, an increase in the backlog of PACs and divert focus away from critical changes.
- Delayed submission and staggered approval times.
- Diverse or unpredictable change implementation periods after approval. This can have the unintended consequence of delaying or staggering submissions across markets especially those which have shared packs.

Ultimately these factors lead to challenges in managing inventories and supplying product due to staggering of approved regulatory in different countries and/or delays in change implementation until approved in all countries. This can result in a change taking 3 to 5 years to approve thus hindering innovation and increasing the risk of shortages.

Tools for efficient PACs management

Use of Reliance Practices Should be Maximised

Collaboration amongst regulators has been shown to be essential to make better use of available resources and to enable more efficient regulatory pathways leading to fast access of medicines and vaccines to patients [3].

Industry strongly supports the WHO position on the use of reliance (see definitions in glossary) [3] and its broader application throughout the full lifecycle of a product, including for GMP inspections and lot release [6, 7]. The following points are highlighted:

- Reliance should be applied across the life cycle of a product. As reliance has mainly been implemented for the initial marketing authorisation so far, we encourage use of this pathway for post-approval changes as well.
- Reliance can be applied using a CPP or other reference document, e.g. approval letter, in which case the PAC review of the reference agency should be recognised and approved locally in short time.
- Applicants need to assure regulators that products are essentially the same or sufficiently similar.
- Any differences with the reference country dossier supporting the PAC need to be explained and justified by the applicant.

- Reliance is not limited to geographically co-located countries and can be used across regions and markets globally.
- To facilitate reliance practice, convergence of requirements is a key enabler and a reduction of national specific requirements is important for longer term success (see next Section).
- Reliance may require information sharing between regulators (e.g., unredacted assessment reports) with the consent of the Sponsor, thus appropriate Memorandum of Understanding or Confidentiality Agreements may need to be in place to ensure that confidentiality is maintained.
- Regulators may need to adapt legislation to undertake reliance.
- Joint reviews help to increase capability through engagement and this in turn leads to increasing trust amongst regulators.
- Reliance can take various forms including Worksharing and ultimately Recognition pathways. This requires an assessment of convergence and determination of equivalence of country regulatory practice to issue formal agreements between the parties involved.

Requirements for the Submission of PACs Should be Converged

Data requirements for PACs should be adapted to the risk level and limited to those that are scientifically justifiable. We propose that data that can be verified during inspection should be eliminated e.g. Certificate of Analysis (CoAs), batch records, analytical raw data, cleaning validation, Quality Agreements, and testing samples when production sites are certified for Good Manufacturing Practice (GMP) compliance [8].

Industry encourages the adoption of the ICH CTD format/content for initial marketing authorisations as well as for PACs globally to drive towards a harmonized dossier throughout the life cycle (increasing the homogeneity among PAC dossiers), to facilitate and speed up the preparation and submission process.

Many countries still require GMP certificates, in addition to CPP which includes a statement on GMP, documents with original ('wet') signatures and additional administrative declarations, which duplicates information and create delays. Additional specific requirements (for which the content is already available in Module 3, e.g. CoAs, Transmissible Spongiform Encephalopathy (TSE)/ Bovine Spongiform Encephalopathy (BSE) certificates, declarations) can be eliminated.

Common Market Implementation (Quality Assurance, QA release) Time-Windows Should Be Defined and Agreed

Pre- and post-change product versions should co-exist in the market during a transition period.

- Flexible timelines are needed to ensure smooth transition and supply continuity of the post-change product version, whilst approval processes may still be on-going in other regions of the world. This is specifically important to accommodate the long lag time to supply global products with complex manufacturing processes e.g. produced in shared facilities to reduce potential supply chain disruption.
- The most effective system would be to allow grouping/bundling changes where needed and have common approval times and a common implementation definition across countries.

PACs Classification and Timelines Should be Converged and Common Risk-Based Approaches Adopted

A common regulatory understanding of risk-based approaches and risk-based classification of changes is essential for post-approval changes management.

Risk-based Classification

- Adopting a risk-based approach for assessing impact of post-approval changes correlated with a clear, tiered categorization of changes (depending on their potential impact on Quality/Safety/Efficacy) is essential.
- This is highlighted in the ICH Q12 chapter 2 and WHO guidelines on procedures and data requirements for changes). To provide a further breakdown of specific changes and data requirements, we recommend alignment with WHO's Guidelines on procedures and data requirements for changes [1, 2 and 9].

Timelines Linked to Risk-Based Procedures

- Maximum review periods for changes should be established - e.g. WHO guidance [2]: major changes (prior approval) maximum 6 months review; moderate changes (notification) maximum 3 months review.

Additional Risk-Based Considerations

- Finally building on the concept of reliance and risk-based approaches, the following should be implemented:
 - Changes with no impact on quality, safety or efficacy based on product knowledge and process understanding should be managed internally within companies' PQS without any reporting to NRAs as per ICH Q12 [10].
 - When already reviewed and approved in a reference country, a major or moderate change should be accelerated in the relying country via a verification or abridged pathway (i.e. a risk-based approach).
 - A verification /abridged review pathway should be based on the change package and evidence of acceptance i.e. a CPP or approval letter or notification confirmation from the reference country agency.
 - The risk classification for low risk changes should be unified e.g. based on WHO classifications, to enable the same annual report to be submitted globally.

Maximise the Use of Tools in ICH Q12 (Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management) [11]

The implementation of ICH Q12 introduces several important tools and related concepts which we believe can help to streamline technical change management based on process understanding and risk-based approaches [12]. The following elements are important:

- First, the establishment of change categories classified according to the level of risk providing a global standard classification approach.
- Second, introduction of the Established Conditions (EC) concept which enables aspects in the application to be identified that need to be reported if changed (based on quality impact), with the related reporting category.
- Third, a post-approval change management protocol (PACMP) approach. The use of a PACMP (which already exists under the WHO guideline and has been applied in other jurisdictions (e.g., United States of America (USA), European Union (EU)) for several years), should be strongly encouraged and utilised by the regulator and the applicant. As a full implementation of this approach, regulators should introduce an appropriate lower reporting category to enable the reporting of results after executing the pre-approved change protocol.
- Fourth, the possibility for the applicant to justify a lower reporting category of the change is permitted e.g. from prior approval to notification based on product and process understanding. This brings

benefits for the applicant and regulator leading to shorter regulatory review timelines allowing products with lower risk changes to be introduced more quickly.

- Finally, changes not required to be reported to regulators can be managed and documented within the PQS, and subsequently verified during inspection [11 and 13]. In addition, European Medicines Agency (EMA) has, since 2017, introduced a mechanism for working cell bank and reference standard changes to be managed using an approved qualification protocol without needing future repeated variations [14]. This approach should be adopted more widely.

Recommendation on ICH Q12 Implementation Approaches

To determine whether to prioritise implementation of ICH Q12 tools, we recommend to first consider the level of maturity of the PACs regulatory framework in place. The following factors are important in this assessment:

- if a risk-based approach and tiered categorization is in place,
- if ICH Q8-Q11 [15-18] are implemented [19, 20] and adhered to,
- or if some tools would necessitate adaptation of the national legal framework.

As an example, implementation of PACMP could be first introduced and harmonized based on experience and knowledge sharing from other mature NRAs (EMA and USA Food and Drug Administration, FDA).

Other Tools and Novel Approaches

Other tools and concepts are being used in addition to that referred above, that we believe can also have an impact. These novel tools can enable multiple changes to be assessed and approved at the same time. For example:

- Grouping/bundling the same change impacting multiple products, or multiple changes of the same product (as in EU).
- Matrix approaches to rationally reduce the number of lots required to support a manufacturing change for validation and stability e.g. for vaccine combination products (in WHO guidance [2]) can reduce the number of vaccines lots that are analysed. This in turn can lead to faster submission and approval timelines and less destruction of lots
- The stability data approach from ICH Q12 chapter 9 (three aspects highlighted: identifying the stability-related quality and shelf-life-limiting attributes; use of appropriate tools to evaluate the impact of the intended change (e.g. stability predictive models); and use of confirmatory stability studies post-change instead of submission of data as part of a regulatory change submission) [11].

Emergency Preparedness Considerations

The recent Covid-19 pandemic has led to a re-think in terms of how changes should be managed especially in an emergency [21]. Regulators and the pharmaceutical industry have made significant efforts to mitigate issues and to find innovative approaches to accelerate PACs. Such collaborative efforts should be continued.

We believe the following elements are particularly critical for major changes applied to therapeutics or vaccines, such as addition of new manufacturing sites in the context of technology transfer to expand manufacturing capacity in a short timeframe:

- PACs review timelines for emergency applications should be accelerated, with suitable timelines given.
- Transparent communication and coordinated dialogue amongst stakeholders are critical elements for success.
- Finally, rather than having multiple reference authorities in an emergency procedure consideration should be given to limit to the first market where the relevant change package has been submitted and approved by a reference authority.

Final Remarks

Regulatory oversight is critical to ensure that high quality and effective medicines and vaccines are available in a country. Regulators and the pharmaceutical industry have a collective responsibility to assure an uninterrupted supply of compliant, safe and efficacious medicines and vaccines to patients globally. As regulatory systems are strengthened worldwide, the requirements to submit, review and approve changes in multiple markets are becoming more complex.

Regulators as well as Industry believe that, the regulatory process for managing post-approval changes needs to be significantly simplified to facilitate global supply of medicines and vaccines. This can be achieved with consistent, harmonized and clear classifications and adherence to timelines, increased reliance between regulators and the use of novel regulatory and scientific tools. International collaboration and cooperation towards regulatory convergence is a good way to address the increasing workload challenges of NRAs (see WHO Annex 11 to 55th report 'Good regulatory practices in the regulation of medical products' [22]).

We acknowledge that more efforts need to be made by the Industry to reduce the complexity of managing post-approval changes. These measures include advanced planning of changes at start of the lifecycle, more strategic combination of changes as well as transparent communication of supply challenges to regulators.

The development of products under accelerated conditions to address the pandemic is resulting in higher numbers of post-approval changes. Expanding reliance pathways to PACs can facilitate global supply to patients worldwide.

Action by all stakeholders is required to develop an efficient change management system that contributes to enhancing global public health.

Annex

➤ Some definitions

Definitions of Reliance mechanisms: In this paper we primarily refer to three reliance pathways in the context of PACs, i.e.:

- **Reliance.** This is defined by WHO [3] as *'The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others.'*
- **Work-sharing.** This is defined as *'A process by which NRAs of two or more jurisdictions share activities to accomplish a specific regulatory task.'* [3]
- **Recognition.** This is defined as *'Acceptance of the regulatory decision of another regulator or trusted institution. Recognition should be based on evidence that the regulatory requirements of the reference regulatory authority are sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement (whereby [nation] states recognize and uphold legal decisions taken by competent authorities in another member state).'* [3].

Definitions of ICH Q12 regulatory tools [11]:

- **Post Approval Change Management Protocols (PACMP)** is a description of specific changes that a company would like to implement during the lifecycle of the product and how these would be prepared and verified. This allows early evaluation of the change strategy to enable planning of future change(s) by the applicant during the lifecycle of a product. PACMPs would require approval by the regulatory authority, and the conditions and acceptance criteria outlined in the protocol must be met in order to implement the change(s).
- **Established Conditions (EC).** ECs are legally binding information considered necessary to assure product quality. Consequently, any change to ECs necessitates a submission to the regulatory authority.

➤ Glossary of terms

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| BLA | Biologics Licence Application |
| BSE | Bovine Spongiform Encephalopathy |
| CPP | Certificate of Pharmaceutical Product |
| CTD | Common Technical Document |
| ECs | Established Conditions |
| EMA | European Medicines Agency |
| FDA | Food and Drug Administration (United States of America) |
| GMP | Good Manufacturing Practice |
| ICH | International Council on Harmonisation |
| MAA | Marketing Authorisation Application |
| MAs | Marketing Authorisations |
| NRAs | National Regulatory Authorities |
| PACs | Post-Approval Changes |
| PACMP | Post-Approval Change Management Protocol |
| PQS | Pharmaceutical Quality System |
| QA | Quality Assurance |
| TSE | Transmissible Spongiform Encephalopathy |
| WHO | World Health Organisation |

➤ References

[1] - WHO Annex 3—Guidelines on procedures and data requirements for changes to approved biotechnological products WHO Technical Report Series N° 1011, 2018

[2] - WHO Annex 4: Guidelines on procedures and data requirements for changes to approved vaccines WHO Technical Report Series N° 993, 2015

[3] - Good Reliance Practices in regulatory decision-making: high-level principles and recommendations. WHO Drug Information, Vol 34, No. 2, 2020 (Annex 10)

[4] – Statement from Global Regulators on the Value of Regulatory Reliance (2021). Link - Statement from Global Medicines Regulators on the Value of Regulatory Reliance | International Coalition of Medicines Regulatory Authorities (ICMRA) (accessed November 2021)

- [5] – Hoath C., Chang L., Ramalingam Iyer K., Kutza J., Murray S., Smith H. and Payne R. (2016). Post-approval Changes for Biopharmaceutical Drug-Substance and Drug-Product Manufacture: Regulatory Complexity and Impact. December 2016. *BioProcess International* (bioprocessintl.com)
- [6] - Position Paper – Best Practices for In-Country Testing and Sample Management (October 2020) [Position Paper - Best Practices for In-Country Testing and Sample Management - IFPMA](#)
- [7] - IFPMA Position Paper on Regulatory Reliance (June 2019) <https://www.ifpma.org/resource-centre/ifpma-position-paper-on-regulatory-reliance/>
- [8] - Position Paper – Best Practices for In-Country Testing and Sample Management (October 2020) [Position Paper - Best Practices for In-Country Testing and Sample Management - IFPMA](#)
- [9] - General guidance on variations to multisource pharmaceutical products (Annex 10, WHO Technical Report Series 996, 2016)
- [10] – Ramnarine E., Vinther A., Bruhin K., Tovar C. and Colao M.P. (2020). Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS) - Through Enhanced Science and Risk-Based Approaches Industry One-Voice-of-Quality (1VQ) Solutions. *PDA Journal of Pharmaceutical Science and Technology* May2020, *pdajpst.2020.011734*; <https://journal.pda.org/content/early/2020/05/28/pdajpst.2020.011734>
- [11] - ICH Q12 (Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management) – all ICH Q Guidelines at: [ICH Official web site](#) [ICH Official web site](#)
- [12] – ICH Q12 Training materials (Module 0 to module 7):
https://database.ich.org/sites/default/files/ICH_Q12_IWG_TrainingMaterial_Modules0-7_2021_0611.zip
- [13] - PIC/S Recommendation document titled “How to Evaluate and Demonstrate the Effectiveness of the Pharmaceutical Quality System with regard to Risk-Based Change Management”, PI 054-1.
- [14] - European Medicines Agency post-authorisation procedural advice for users of the centralised procedure (29 October 2021). Specific sections - 7.2.7. How should I submit a new working cell bank (WCB)? (Classification category B.I.a.2 a) New Jun 2017 and 7.2.8. How should I submit a new reference standard for a biological medicinal product? New Jun 2017. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-post-authorisation-procedural-advice-users-centralised-procedure_en.pdf
- [15] - ICH Q8 (Pharmaceutical Development)
- [16] - ICH Q9 (Quality Risk Management)
- [17] - ICH Q10 (Pharmaceutical Quality System)
- [18] - ICH Q11 (Development and Manufacture of Drug Substances)
- [19] – ICH Q8/Q9/Q10 Training material: <https://ich.org/page/presentations>
- [20] – ICH Q11 Training material:
https://database.ich.org/sites/default/files/Q11_TrainingDeck_Final_2018_0522.pdf
- [21] - ICMRA stakeholder workshop on Enabling Manufacturing Capacity during the Covid-19 pandemic (link to slide deck): http://www.icmra.info/drupal/sites/default/files/2021-07/covid-19_manufacturing_capacity_ws_presentation.pdf
- [22] - WHO Annex 11 to 55th report ‘Good regulatory practices in the regulation of medical products’