RECOMMENDATIONS TO APPLY REGULATORY "RELIANCE" FOR THE EVALUATION OF POST - APPROVAL CHANGES

FIFARMA

Abbreviations in this document

CMC-PAC	Chemistry and Manufacturing Controls-Post-approval Changes
DSUR	Development Safety Update Report
eCPP	Electronic Certificate of Pharmaceutical Product
ECSPP	Expert Committee on Specifications for Pharmaceutical Preparations
eGMP	Electronic Good Manufacturing Practice
FIFARMA	Federación Latinoamericana de la Industria Farmacéutica
GMP	Good Manufacturing Practice
GRelP	Good Reliance Practices
GRP	Good Regulatory Practices
ICH	International Council of Harmonization
ML	Maturity Level
NRA	National Regulatory Authority
PAC	Post-approval changes
PAHO	Pan American Health Organization
PANDRH	Pan American Network for Drug Regulatory Harmonization
PACMP	Post-Approval Change Management Protocols
PSUR	Periodic Safety Update Report
RA	Regulatory Authority
WHO	World Health Organization

Post-approval changes (PAC) for medicinal products have increased rapidly in recent years, and faster than national regulatory authorities (NRAs) can reliably cope with. This is both a concern and a challenge for Latin American countries. The World Health Organization (WHO) has recently published two documents that will be critical for countries' regulatory system strengthening activities, including regulatory cooperation, convergence and transparency.

Good Regulatory Practices (GRP) and Good Reliance Practices (GRelP), published as Annexes 10 and 11 in the 55th report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) (WHO Technical Report Series 1033) [1], aim to support countries in improving the oversight and regulation of medicines and health products, and to promote greater collaboration between regulators, both regionally and internationally, to leverage resources more efficiently and ensure that quality health products reach people faster.

This document has been developed to focus only on chemical manufacturing controls (CMC), and legal administrative changes according to WHO definitions.

Quality and Legal Post-approval changes (PAC) to Medicinal Products: The Impact to the Supply Chain, and How Reliance can Help Minimize This Risk

As science progresses, there are increasing numbers of therapeutic innovations that generate a greater number of PAC on a global scale. These require frequent changes to adapt to the dynamic nature of supply chains. The discovery of more than one therapeutic indication for a drug is becoming more-and-more common, but the limited resources available to regulatory authorities (RAs) to monitor these may add unseen complications which can result in significant delays in the approval process. This potentially threatens product supply to some markets and might directly affect patient access to therapy. Such interruptions to ongoing therapy could have serious consequences, including death in some situations. As a result, there is a need to develop increasingly agile and reliable mechanisms to assess and authorize requested PAC [2, 3].

The purpose of this document is to provide recommendations to manufacturers and to RAs for improved decision-making processes aimed at implementing reliance and making it more efficient and, thereby, speeding up the approval process where appropriate.

PAC

The main reasons for which drug supply may be affected by a PAC:

- The country or region's demand cannot be covered by the supply chain (production capacity) of the manufacturing site;
- Contingency situations may require the addition of alternative supply sources;
- The development of safer and more effective formulations may be necessary;
- The manufacturing site may have surpassed the regulatory timelines established in the country of origin to implement the change and, therefore, risks its manufacturing authorization.

When a new product is manufactured in bulk, it undergoes adjustments in its specifications that are considered PAC that require approval prior to implementation. Launch must wait for the approval of such changes. This becomes even more critical when manufacturers implement International Council of Harmonization (ICH) Q12, which includes regulatory tools and enablers with associated guiding principles that should enhance industry's ability to manage PAC, since such changes may be part of the conditions stipulated within the original registration that do not require subsequent submission in the country of origin [4].

The availability of key performance indicators within Regulatory Agencies, aligned to GRP, is important as it provides transparency and is a tool for continuous improvement related to efficiency and efficacy [5].

Challenges of managing PAC in Latin America and the Caribbean:

The management of PAC in Latin America and the Caribbean faces various challenges, particularly for small states with limited resources [6], that do not allow effective evaluation and conclusion by the RAs. These include:

- **Approval times and human resources:** The NRAs allocate most of their human resources to the evaluation of new registration applications, with the intent of offering more alternatives to patients. This generates an accumulation (backlog) of pending PAC applications which has increased in recent years [2].

- **Lack of harmonization in regulations:** As ICH members, Brazil and Mexico are the only two countries in Latin America that have a defined classification for PAC based on risk or impact to product quality, efficacy and safety. These are aligned with the classification established by the US Food and Drug Administration and the European Medicines Agency. However, according to available published data, we observe a significant time investment in the assessment of PAC in Brazil for 2021 [4]

- **Lack of specific regulation for PAC:** Most countries in the region do not apply a risk-based classification of PAC, with different requirements for low-risk versus higher-risk developments. Indeed, changes are assessed under the same level of criticality and a complete technical dossier must be presented. This impacts the immediate filing of changes until the specific documentation for the country is available, particularly when a complete stability study is required.

- **Differences in implementation times and stock depletion terms:** Once approved, PAC must be implemented within the terms and timeframe established in the regulations of the manufacturing country. When this time expires it may compromise (delay) the approval to other countries to which the product is exported for marketing. The lack of defined regulations for the assessment and endorsement of PAC which are permitted by Regulatory Agencies makes it difficult to plan the implementation of the change process. As this does not allow compliance with the regulations of the manufacturing country or importing country, it may result in two types of critical situation:

1. Product destruction due to the inability to deplete product stock prior to the change. This happens because the exporting country establishes that the change must be implemented within a few months after approval.
2. Lack of product stock since the manufacturing country must implement the change to preserve its Good Manufacturing Practice (GMP) certification.

In addition, the implementation of ICH Q12 for regulatory agencies of reference could be another element that will have an impact on the supply in other countries.

How we can incorporate Reliance into our PAC assessments:

According to the WHO, "reliance" occurs when a regulatory system uses information and/or evaluations performed by a different institution to reach its own decisions. It is important to have clear criteria in the selection of trusted partners/products. There are many ways to make these decisions, but many rely on an assessment of the regulatory system to perform certain functions very well. The Pan American Health Organization (PAHO) uses the term "trusted authority" to describe this concept. (Please refer to the 2018 Pan American Network for Drug Regulatory Harmonization [PANDRH] Conference concept note on reliance principles for a more comprehensive discussion on this topic [7]).

Before making recommendations, it is necessary to define a similar product. According to the WHO, reliance can only be practiced if "...the medical product being assessed is essentially the same as that submitted to the reference NRA". (1)

Because some common misconceptions may arise, we suggest that:

Product similarity does NOT mean
• Identical manufacturing sites or suppliers.
• Identical records or documentation.
• Identical indications or use conditions worldwide.

To understand the concept of product similarity, a risk and science-based approach should be applied to 'product sameness' to ensure the applicability of regulatory reliance and maintenance of the supply chain.

Transparency between the parties is a key principle for GRP, as well as being fundamental for effective reliance.

Federación Latinoamericana de la Industria Farmacéutica (FIFARMA) 'members' commitment to effective regulatory convergence in Latin America

Companies that are members of FIFARMA recognize that there is a role for the industry, not only in the implementation of GRP, but also in how to ensure that the processes contributing to the product life cycle are maintained and made as efficient as possible. This helps NRAs to have a formal process that facilitates PAC and acknowledgement procedures.

Recommendations

Stringent RAs may apply dynamic post-approval pharmacovigilance and surveillance mechanisms:

- Performing on-site GMP inspections, verifying the effective implementation and execution of internationally-applied principles, such as ICH Q9 (Quality Risk Management [8]) and ICH Q10 (Pharmaceutical Quality System [9]) guidelines;

- Market surveillance and control. Being able to follow scheduled changes as manufacturing transfers. Post-marketing surveillance activities, including, among others, import and export control, changes to marketing authorizations and the fight against counterfeiting;
- Updating equipment that impacts product portfolios;
- Updating manufacturing processes, in-process controls and finished product controls;
- Vigilance. Collection and evaluation of related information regarding the safety of medicines and their adverse events and the ability to make regulatory decisions from the information obtained.

For the proper implementation of ICH Q12 guidelines by manufacturers, we recommend considering PAC previously approved by a stringent RA in order to reduce approval times and resource investment by Latin American RAs.

It is important to point out that the adoption of a reliance or unilateral recognition mechanism is recommended for PAC. This is provided that the sponsor requested the use of such a reliance mechanism in an application for a product like the one registered; both in the country where reliance is intended to be used, as well as in the process where the NRA has defined that reliance can be used. For such purposes, it is necessary for NRAs to issue a formal reliance mechanism and establish in which applications it will be adopted. It is also important to keep in mind that it is critical to set clear accountability goals, including around how the process will work, and how long it will take. Processes with little feedback, or that take an unjustifiable amount of time, discourage legitimate companies and deny patient access to products.

When filing their submission, we recommend that applicants include Post-Approval Change Management Protocols (PACMP) in their registration application in compliance with local regulations, along with a justification that suggests the use of reliance to the authority.

The optimized analysis procedure for PAC of general products may be adopted when the following requirements are met.

Industry should submit:

- Approval, acceptance, acknowledgement letter or email from the Reference Authority selected for the unilateral recognition procedure, if the authority issues it.
- Dossier with the sections affected by the change according to the local regulations.
- Letter requesting the implementation of reliance or unilateral recognition mechanism.
- Justification of any changes between the product approved by the reference agency and the product of the country where the change is submitted, according to WHO's Good Reliance Practices [1], or the reasoning that supports the differences in the classification of the change by the agencies involved.

Selecting trusted / reference authorities:

It is ultimately up to the individual NRA and their government to determine the appropriate trusted/reference authority. However, the decision needs to be informed by data rather than reputation or historical international alignments.

Supplemental documentation for PAC:

Some NRAs may request additional documentation for pharmaceutical products other than those provided to the selected trusted/reference authority. This is not recommended under use of reliance for PAC because the preparation of this additional information, including translation, requires time and resources which can cause unnecessary delays in submission of these documents, which will ultimately impact patient access to important products.

Requirements that the National Regulatory Authority (NRA) must meet with the Reference Agency:

- Approval, acceptance, acknowledgement letter or email issued by the reference agency.

Note: Public Assessment Reports are not issued for all PAC. We recommend relying on Approval Letters issued by the Reference Authority for all changes (except New Indications and Line Extensions). This is consistent with good practices referred to under Annex 1 of the WHO GRelP Guideline for processing PAC.

Additionally, we recommend that ICH Latin American RAs Brazil and Mexico adopt the ICH Q12 guideline (TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT [4]) to ensure supply continuity for new therapies that will be submitted in the short-term.

The **Reference Regulatory Agencies*** for this document are the following:

1. Authorities with which NRAs have signed cooperation agreements or a memorandum of understanding.
2. Reference Regulatory Agencies designated by the PAHO.
3. Authorities listed by the WHO at Maturity Level 4 (WLA ML 4).
4. Strict authorities according to Technical Report 1003 of the WHO.

The list mentioned in point 3 is not yet published by the WHO and the list mentioned in point 4 will cease to be valid once the WLA ML 4 mentioned in point 3 in the description above is designated.

KEY MESSAGES

As science progresses, there are increasing numbers of therapeutic innovations that generate a greater number of PAC on a global scale.

The management of PAC in Latin America and the Caribbean faces various challenges, particularly for small states with limited resources [6], that do not allow effective evaluation and conclusion by the RAs. These include: approval times and human resources, lack of harmonization in regulations, lack of specific regulation for PAC and differences in implementation times and stock depletion terms.

The adoption of a reliance or unilateral recognition mechanism is recommended for PAC. This document contains recommendations on how to apply reliance for PAC.

This paper provides a list of items for consideration by reference authorities, including: Authorities with which NRAs have signed cooperation agreements or a memorandum of understanding; reference Regulatory Agencies designated by the PAHO; Authorities listed by the WHO at Maturity Level 4 (WLA ML 4); and strict authorities according to Technical Report 1003 of the WHO.

This document has been developed to focus only on chemical manufacturing controls (CMC), and legal administrative changes according to WHO definitions.

Bibliographic references:

1. WHO Expert Committee on Specifications for Pharmaceutical Preparations. WHO Technical Report Series 1033 (55th report; 2021). Available from https://apps.who.int/iris/bitstream/handle/10665/340323/9789240020900-eng.pdf

2. Pan American Health Organization. Regulatory System Strengthening in the Americas. Lessons Learned from the National Regulatory Authorities of Regional Reference. Washington DC, April 2021. Available from https://iris.paho.org/handle/10665.2/53793

3. World Health Organization (2021). Evaluating and publicly designating regulatory authorities as WHO listed authorities. Geneva. Available from https://www.who.int/publications/i/item/9789240023444

4. European Medicines Agency (2017). ICH guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management. Available from https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q12-technical-regulatory-considerations-pharmaceutical-product-lifecycle-management_en.pdf

5. Rodriguez H, De Lucia ML. A Proposal of a Combined Convergence Regulatory Strategy Applied to Post-Approval Changes by Latin American Countries, Reducing Workload and Allowing Continuous Improvement to Guarantee the Quality, Safety, and Efficacy of Medicines. Front Med (Lausanne) 2021;8:768376. doi: 10.3389/fmed.2021.768376.

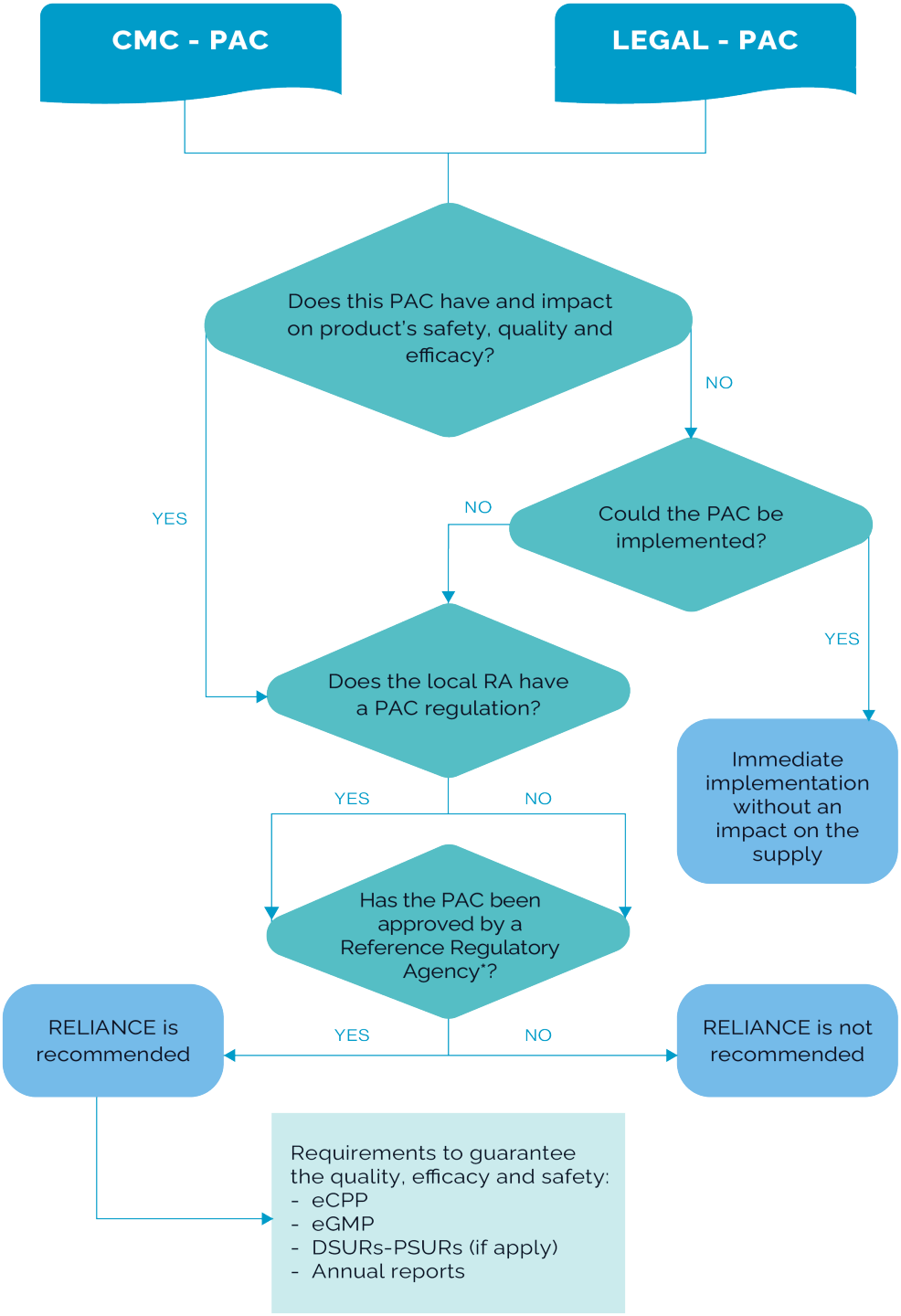
6. Regulatory System Models for Small States/Markets with Limited Resources. Concept Notes and Recommendations. Ninth Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH). San Salvador, 24 to 26 October 2018. Available from https://iris.paho.org/handle/10665.2/52387

7. Regulatory reliance principles: concept note and recommendations. Ninth Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH). San Salvador, 24 to 26 October 2018. Available from https://iris.paho.org/handle/10665.2/51549

8. ICH Harmonised Tripartite Guidelines. Quality Risk Management: Q9. 9 November 2005. Available from https://database.ich.org/sites/default/files/Q9%20Guideline.pdf

9. ICH Harmonised Tripartite Guidelines. Pharmaceutical Quality System: Q10. 4 June 2008. Available from https://database.ich.org/sites/default/files/Q10%20Guideline.pdf

Flowchart: Post - Approval Changes (PAC) Reliance Implementation



CMC-PAC: Chemistry and Manufacturing Controls-Post-approval Changes; DSUR: Development Safety Update Report; eCPP: Electronic Certificate of Pharmaceutical Product; eGMP: Electronic Good Manufacturing Practice; PAC: post-approval changes; PSUR: Periodic Safety Update Report.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