

IFPMA Position Paper on the Handling of Post-approval Changes to Marketing Authorizations

Introduction

Following the initial launch and throughout a drug product's commercial life, changes that might impact the product's quality and safety profile will inevitably occur. These changes may include modifications to raw materials, analytical methods, suppliers, manufacturing equipment, processes and sites and are a consequence of continual improvement, implementation of innovative technologies, efficiencies of production or increases in scale to improve the availability of drug products for patients. Variations, also known as post approval changes, are necessary in order to comply with evolving regulatory requirements.

After receiving market approval, drug products are used in a wider population that brings further knowledge to its safety profile. It is important that such information is reflected in the product labelling in a timely manner for the benefit and safety of patients and healthcare professionals. Thus post approval changes to the originally approved dossier are an essential part of a product's lifecycle. Therefore, it is important that new product knowledge is managed in a structured and planned way to enable continual improvement, to encourage innovation, state of control, and to ensure uninterrupted product availability for patients.

Many drug products are managed globally throughout the commercial part of their lifecycle. However as regulatory systems develop and evolve worldwide, the requirements to submit and review post approval changes and implement safety labelling updates are increasing. As a consequence there is a growing potential for divergence, increased complexity and less predictability across markets. The major challenges with managing variations globally include the variable or unpredictable timelines and submission requirements across National Regulatory Authorities (NRAs) for review and approval. This leads to different implementation dates for changes thus increasing the potential for compliance issues as well as contributing to the complexity due to the need to manage multiple variants of products/processes. International collaboration and cooperation towards regulatory convergence has been recognized as an appropriate regulatory mechanism which could address the NRAs' challenges with managing the associated increase in workload.

IFPMA believes that global regulatory convergence, such as work sharing between NRAs, as well as reliance on assessments by Stringent Regulatory Authorities¹ (SRAs), will provide a more efficient and predictable environment for the management of post approval changes to

¹ *Stringent regulatory authority (SRA): a regulatory authority which is: (a) a member of the International Conference on Harmonization (ICH) (as specified on www.ich.org); or (b) an ICH observer, being the European Free Trade Association (EFTA), as represented by Swissmedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time). WHO Technical Report Series, No. 961, 2011, Annex 11*



marketing authorizations (MAs) worldwide. This global regulatory convergence will also contribute to ensuring patients' continued access to quality medicines and up-to-date product safety information. Ultimately, it will contribute to enhancing global public health.

This paper presents IFPMA's initial proposals on the commercial part of lifecycle management. It proposes how post approval changes related to quality and safety label updates could be managed more efficiently.²

Proposal

Implementation of Quality Post Approval Changes

- IFPMA recommends the implementation of consistent and harmonized regulatory approaches for the management of global post approval changes that are based on assessing the potential of a change to have an impact on product quality, safety and/or efficacy. Therefore IFPMA proposes the implementation of a tiered, risk-based classification system for variations to MAs based on the principles outlined in the relevant World Health Organization (WHO) guidance:
 - Guidelines on procedures and data requirements for changes to approved biotherapeutic products (Annex 3, WHO Technical Report Series No. 1011, 2017)
 - Guidelines on variations to a prequalified product (Annex 3, WHO Technical Report Series 981, 2013)
 - Guidelines on procedures and data requirements for changes to approved vaccines (Annex 4, WHO Technical Report Series No. 993, 2015); and
 - General guidance on variations to multisource pharmaceutical products (Annex 10, WHO Technical Report Series 996, 2016).
- The use of common classification systems would facilitate consistent implementation of post approval changes by stipulating criteria for appropriate reporting to NRAs. Consistent implementation could be achieved through the classification of post approval changes into 'major' or 'moderate' categories that require regulatory assessment and approval before implementation; classification into a 'minor' category may require only notification or no reporting dependent upon certain conditions. In addition, companies should be permitted to demonstrate an appropriate classification for a post approval change founded on a well-documented assessment that is both science- and risk-based.
- To strengthen the use of common classification systems, clear and consistent timelines should be identified for the regulatory assessment of post approval changes, specifically 3-6 months for major changes and 1-3 months for moderate changes, in line with WHO guidelines on post approval changes. Adherence by NRAs to the specified timelines for regulatory assessment is critical. NRAs should consider implementing processes for

² N.B. It is intended that these proposals will be further developed and elaborated as IFPMA engages with relevant NRAs.



expediting priority review that address an urgent need, for example to prevent or alleviate a drug shortage or labelling information that addresses critical product safety updates. In such instances, shorter review times should be anticipated.

- IFPMA encourages collaboration and reliance on approvals from SRAs^{3,4} to facilitate approval of moderate and major post approval changes based on previous experts' review as outlined in the WHO guidelines for vaccines and for biotherapeutics (draft).
- Novel regulatory mechanisms and tools are becoming more widely available for post approval change management and should be recognized for their role in improving assessment efficiency. The development of the new ICH Q12 guideline (Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management) is an example of one initiative that intends to provide a framework to facilitate the lifecycle management of post approval chemistry, manufacturing and control (CMC) changes in a more predictable and efficient manner. Consistent, risk-based, tiered variations systems for quality changes that include regulatory mechanisms and tools and use of an effective pharmaceutical quality system to facilitate product lifecycle management and a potential reduction in the post approval change burden for NRAs and industry are important.
- More proactive communication of a product's lifecycle management strategy with NRAs is encouraged and may be a useful mechanism to facilitate a mutual understanding of post approval commitments and planned changes, between the MAH and the NRA across multiple geographic regions.
- A common definition of "market implementation" for post approval changes and agreed common market implementation timelines would unequivocally reflect the impact of each change and expedite the implementation of urgent changes for the benefit of the patient.

Implementation of Post Approval Change Safety Labelling Updates

Patients and healthcare professionals deserve timely access to the most up to date safety information, and implementation of such labelling changes would benefit from a faster and more efficient process. The following considerations could contribute to achieve this goal:

- NRAs should consider introducing processes to prioritize the handling of safety labelling variations, in a more predictable and expedited manner. This may be achieved through a procedure whereby the original approval (in the reference country) is recognized within a reasonable and specified timeframe by other NRAs. Labelling submission requirements should also be aligned to those in the reference country. Where a NRA may require more time to review, (e.g. to assess the change in the context of the local medical setting) this should be justified and notified to the applicant accordingly.

³ *Good review practices: guidelines for national and regional regulatory authorities. (WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth report. Geneva, World Health Organization. Technical Report Series No. 992, 2015, Annex 9 (in preparation)).*

⁴ *Good review practices: guidelines for national and regional regulatory authorities (WHO Drug Information, Vol. 29, No.1, 2015)*

International Federation of Pharmaceutical Manufacturers & Associations	Ch. Des Mines 9 P.O. Box 195 1211 Geneva 20 Switzerland	Tel: +41 22 338 32 00 Fax: +41 22 338 32 99 www.ifpma.org
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- Electronic means to access product information should be gradually introduced, based on learnings from early adopting NRAs. This could be achieved through, for example, promoting the use of trusted authoritative NRA websites where up to date approved labels/labelling are stored, maintained and easily accessible.

Conclusion

A product can reside in the commercial phase for more than 15 years post-launch, during which time patients should benefit from uninterrupted supply and any product improvements that may be introduced. This will also contribute to NRAs and industry commitments to public health.

The regulatory change management systems to implement quality changes and update safety label information should be more predictable and consistently implemented across all countries globally to facilitate innovation, and ensure a continuous state of control, and timely availability of drug products. IFPMA believes consistent implementation can be achieved through:

- Consistent, risk-based, tiered variations systems for quality changes that include regulatory mechanisms and tools and use of an effective pharmaceutical quality system to facilitate product lifecycle management and a reduction in the post approval change burden for NRAs and industry;
- Expedited approval of certain variations that are of significant benefit to patients, e.g. to prevent/alleviate drug shortages or improve safety;
- Clear and transparent regulatory assessment timelines and adherence by NRAs;
- Transparency, consistency and predictability in regulatory outcomes and decision making;
- The development of closer harmonization and specialization of NRAs, where possible, leading to reliance and potential mutual recognition; and
- Enhanced use of electronic means for timely access to updated product safety information.

IFPMA believes implementing such measures will lead to improved transparency, consistency and predictability in regulatory outcomes and decision making, as well as resulting in an appropriate level of regulatory oversight. This will benefit patients, regulators and industry globally by contributing to the sustainable supply of medicines and vaccines.

IFPMA supports WHO, NRAs and key stakeholders in their continuing efforts to work together to improve the effectiveness of regulatory systems worldwide thereby ensuring continuous availability of safe and effective drug products.