European Federation of Pharmaceutical Industries and Associations

Draft ☐ Final ✱

18 April 2019

Optimising Post Approval Change Management for Safety Labelling Updates in the Middle East Region

This document is aligned with and builds on the principles of the EFPIA position paper: "Optimising Post-Approval Change Management for Timely Access to Medicines Worldwide".

http://www.efpia.eu/media/25953/efpia-post-approval-change-position-paper_final_feb2017.pdf.

What are safety labelling updates (SLUs) and how do they benefit patients?

A safety labelling update is an update to any safety section in the label which is clinically meaningful. The World Health Organisation definition is:-

Safety and efficacy change: In the context of this document, safety and efficacy changes refer to changes that have an impact on the clinical use of the biotherapeutic product in relation to safety, efficacy, dosage and administration, and that require data from clinical or post-marketing studies, and in some instances clinically-relevant nonclinical studies, to support the change.

The benefit risk profile of innovative products changes over time as more data about the product in "real-life" clinical settings becomes available. This leads to the need to update the product information to advise health care professionals about the best way to care for their patients. At the beginning of an innovative product's life cycle such changes can be frequent, on the scale of several SLUs per annum for the first few years. The frequency of such updates support patient safety effectively in those regulatory environments where the health authority review processes are adequately resourced and optimised. Where the resources are stretched, or the review processes are not aligned with international standards then regional review processes can, and do, unnecessarily delay updates to the product information thus potentially impacting patient safety.

Current environment for managing SLUs in the Middle East region

From the survey described in the EFPIA MERN position paper, industry obtains marketing authorisations in the region using product information as approved by a reference regulatory authority and for updating the safety and efficacy elements of registered product information. It is also evident that approvals for a given SLU in the ME region can take up to 18 months after said SLU is approved by a reference regulatory authority.

This is not optimal for patient safety in the region and it is noted and highly recognized that few NRAs already use notification process, and some have taken necessary actions to accelerate approvals of SLU.

The minimum realistic time line for implementation of a safety update for a Middle East country requiring reference approval compared with the reference country itself is outlined below covering both National Regulatory Authorities' (NRAs) review timelines & Implementation timelines:


EFPIA Brussels Office
Leopold Plaza Building ✱ Rue du Trône 108
B-1050 Brussels ✱ Belgium
Tel: + 32 (0)2 626 25 55 ✱
www.efpia.eu ✱ info@efpia.eu

Reference Country

Country requiring reference approval minimum timelines:

In summary, patients in the region can receive an updated label up to 30 months after identification of the safety concern and up to 18 months later than patients in the reference country. This gap is further extended in the cases of local filing restrictions e.g. inability of company to submit because a previous variation (whether CMC or SLU) is still under review by the health authority.

The reasons for such delays can differ from country to country, but reflect the difficulties faced by industry and regional health authorities. The EFPIA MERN survey identified the following limiting factors to rapid implementation in the region were identified:

- Requirement for legalized CPP
- Requirement for local approval before implementation
- Queuing for appointment to submit the application / limited numbers of appointments
- Long timelines for variation approval process
- Close-down periods of National Regulatory Authorities for receipt of variations
- Inability to submit the update application if a variation, renewal or baseline e-CTD application for the same product is still ongoing
- Shared pack implementation complexity (many companies use multi-country packs, waiting for all countries sharing a pack to approve and implement a SLU can mean additional work for industry and health authorities in the form of “grace period” applications, special import permits etc).

As can be seen above, introducing a SLU post-approval change across several markets takes too long from the patient safety perspective. As regulatory systems evolve, the requirements for manufacturers to manage variations in multiple markets are becoming more and more complex. The regional regulatory environments remain overall unpredictable and disharmonised, and industry believes that more can be achieved by adopting a unified risk-based approach to reviewing SLUs, and further synchronise timelines and converge data packages. These efforts will provide a more efficient way to manage post-approval SLUs, and contribute to ensuring patients’ continuous access to up to date safety information for state of-the-art medicines.

Variation requirements and assessment steps generate a heavy burden on NRAs as well. To address NRAs’ challenges with this increased workload, the World Health Organisation (WHO) recognises the

benefits of international collaboration and cooperation towards regulatory convergence - see e.g. WHO working documents on Good Regulatory Practice (QAS/16.686).

At the same time, industry acknowledges that it can also contribute, through e.g. where possible advanced planning of SLUs at the start of the life-cycle and more strategic combination of changes. Ultimately, all of these activities will contribute to enhancing global public health. This paper presents the current challenges, opportunities and recommendations for convergence, to bring consistency and predictability to the management of SLUs in the region, and in accordance with the WHO guidelines.

2. Recommendations

EFPIA wishes to recommend a set of actions to facilitate SLUs management, noting that some of these are already enacted in some ME NRAs' guidance.

High Priorities

Prioritization of safety labelling update with prior approval by reference agency using facilitated pathways

- Using the concept of reliance and simplifying the review procedure
- Approval procedures for submission of SLUs, after reference country approval, should be:
    - Tell & Do or notification to support alignment with reference label. Otherwise inconsistencies will drive complex dependency issues and confusion to Health Care Professionals (HCP) and patients

Important Update: Some National Regulatory Authorities (NRAs) are starting to use abridged or verification reviews during the initial marketing authorization application (e.g. Saudi Arabia, Egypt, Jordan, UAE) based on the availability of approval by reference regulatory agencies. Such NRAs are encouraged to apply the same principles for approval of SLUs relying on the regulatory decision made by the reference country without further review (immediate implementation)

Classification of SLUs and procedural guidance

- Converge requirements through the adoption of international standards for risk-based classification of SLUs, consequent procedure approval type should be notification only.
  In specific cases where NRA will still need to conduct a review, then to consider a reasonable review timeline (e.g. max. 1-3 months).
- To streamline the process of implementation and shared pack management across the ME
  The recommendation would be to follow the principles outlined in:
    - EU Variation guideline (2013/C223/01) (for small molecules – see WHO guidelines below for other products)
    - WHO guideline on procedures and data requirements for changes for approved vaccines
    - Draft WHO guideline on procedures and data requirements for changes to approved biotherapeutic products

Resources

- With the application of the reliance and risk-based classification (above), SLUs could be handled through administrative notifications, allowing agencies to focus resources on major quality variations (having no prior approval by reference agency) and new introductions/ innovation.
- SLU submission should be exempted from compulsory submissions appointments and should not be subject to close-down periods of NRAs
- Build capacity for review & relevant committee meetings to allow for timely approvals


EFPIA Brussels Office
Leopold Plaza Building ✱ Rue du Trône 108
B-1050 Brussels ✱ Belgium
Tel: + 32 (0)2 626 25 55 ✱
www.efpia.eu ✱ info@efpia.eu

• Promote the creation and use of NRA's website where approved labels are stored, maintained and accessible.
Strategic management of changes or activities • Submission and review of SLUs should not be limited by ongoing other variations such as CMC, renewals or baseline eCTD application. • Encourage exchange of knowledge between the review and inspection departments to prevent drug shortages.

Dossier Content
• Minimize the number of country-specific requirements such as CPPs and local artworks
• Harmonize requirements across ME
• Content to be limited to:
  ○ Notification Letter with SLU description
  ○ Approved Reference Country Label
  ○ Word Document showing the updated label
  ○ Comparison of new and existing label
• Remove the need for the legalization of documentation
• Leverage use of Reference Agency website for verification of approved labels.
• Consider commitments (post-approval) to allow for timely approval and implementation of SLU

3. Conclusion

After reviewing the current regulatory landscape in the Middle East region in terms of Safety Labelling Updates Management, EFPIA MERN has identified opportunities for simplification and harmonization of the Review-Approval-Implementation Process in alignment with WHO recommendations for good regulatory practice, global convergence and processes simplification that ensures continuous patient access to safe, well tolerated, high quality and compliant medicines.

The EFPIA MERN recognizes and welcomes the efforts undertaken by many NRAs of the Middle East region that yielded simplified, faster procedures through notification process and reliance on reference agency/ label approval. Not only will this ensure timely safety labeling updates but also faster implementation in all countries with quicker access of the most updated label to Health Care Professionals and patients.


EFPIA Brussels Office
Leopold Plaza Building ✱ Rue du Trône 108
B-1050 Brussels ✱ Belgium
Tel: + 32 (0)2 626 25 55 ✱
www.efpia.eu ✱ info@efpia.eu