Optimising the management of Post-Approval Changes for patients' timely access to medicines in the Middle East region

This position paper is aligned with and builds on the principles of the EFPIA position paper: 'Optimising post-approval changes management for timely access to medicines worldwide, v1 of 8th Feb. 2017: http://www.efpia.eu/media/25953/efpia-post-approval-change-position-paper_final_feb2017.pdf.

What are post-approval changes (PACs) and how do they benefit patients?

Post-approval changes (PACs) to the registered quality (or CMC, i.e. Chemistry, Manufacturing & Control) information of authorised medicinal products, hereafter also referred to as 'variations', are introduced routinely worldwide to: react to increasing supply demand, enhance the robustness and efficiency of the manufacturing process; improve quality control techniques; respond to changes in regulatory requirements; and upgrade to state-of-the-art facilities.

This part of the product life cycle is, in many ways, as important as bringing new medicines to the market, as it provides patients with continuously enhanced medicines.

Current environment for managing PACs worldwide

Introducing a CMC post-approval change across several markets worldwide can take years. 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 classifying CMC changes, and further synchronise timelines and converge data packages. These efforts will provide a more efficient way to manage post-approval changes worldwide, and contribute to ensuring patients' continuous access to state-of-the-art medicines.

A comparison of post-approval change guidelines across 3 regions show that the concept of risk-based approach to change classification (considering the potential impact on quality, safety and efficacy) applies in some regions already (see Table 1 overleaf). Nevertheless, some disparities still occur around the process, timelines and data requirements.


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Table 1: Comparison of post-approval change guidelines across 3 regions

Risk based classification	EU *	WHO *	GCC
High	Type II major Variation **60 days****	Major Variation **180 days*****	Type II Variation **No set timelines**
Moderate	Type IB minor Variation 'Tell, wait **30 days** & do'	Moderate Variation **90 days*****	Type IB Variation **120 days**
Low	Type IA minor Variation 'Do & tell Type IA_{IN} **Immediate Notification** Type IA **within 30 days**	Minor **notification********	Type IA Variation **within 60 days**

* with option for grouping and work-sharing

** review timeline, which can be reduced to 30 days in case of urgent safety matters, or extended to 90 days in case of grouping

***recommended by WHO

*** timelines defined by the local NRAs

Variation requirements and assessment steps generate a heavy burden on National Regulatory Agencies (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. advanced planning of changes at the start of the life-cycle, more strategic combination of changes, as well as transparent communication of supply challenges. 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 CMC/quality variations in the ME region, and in accordance with the WHO guidelines.


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1. Managing CMC changes in the ME region

In the ME region, the following challenges for managing CMC variations have been identified throughout the process:

Classification	• Heterogeneous classification systems of CMC changes across countries

Submission process and content	• **Process:** below apply to specific ME countries (not all):
	  ○ The obligation to submit each change individually is very burdensome, especially for minor ones
	  ○ The non-acceptance of parallel submissions increases the complexity of supply planning
	  ○ The systematic request for appointment in some countries adds to the backlog and delay in processing submissions.
	• **Content:** country specific requirements further generate variability across the submissions, and add to the unpredictability; below apply to specific ME countries (not all)
	  ○ Provision of a legalized Certificate of Pharmaceutical Product (sometimes only from country of origin) ;
	  ○ Need for inspections, site registration (prior or at same time of variation submission);
	  ○ Additional documents to what is contained in the CTD, including the provision of extensive raw data (e.g. stability raw data, long-term stability data); specific local documents in the form of declarations/ statements; legalization of documents
	  ○ Non-acceptance of commitments in certain countries.

Review	• Unpredictable and variable review timelines, often driven by a full re-assessment, despite the availability of the reference country approval • Non-acceptance of dual sourcing • Requirements of sample provision and potential retesting as part of approval process etc.
Decision	• Divergent decisions across regulatory agencies
Implementation	• Variable implementation periods across markets

2. Recommendations

EFPIA recommends the following set of actions, with a view to initiate the discussion with competent authorities in the ME region:

High Priorities

Prioritization of changes with prior approval by reference agency using facilitated pathways, i.e.:

- Introducing the concept of reliance

Some NRAs are starting to use abridged or verification reviews during the initial marketing authorization application (e.g. Saudi Arabia, Egypt, Jordan), based on the availability of approval by stringent regulatory agencies. Such NRAs are encouraged to apply the same principles for approval of post-approval changes relying on the regulatory decision made by the reference country without further review

Subsequent and less stringent procedures for implementing changes, after reference country approval, would thus apply:

  - Tell & Do for minor changes
  - Tell, Wait & Do for major changes **with a defined 'waiting' time e.g. 30 days**

Note: where reference country approval is legally required, the Certificate of Pharmaceutical Product (CPP) or the decision granted by the reference agency shortly prior approval (not at submission) should serve that purpose.

Classification of changes and procedural guidance

- Converge of requirements through the adoption of international standards for risk-based classification of changes, and consequent procedure approval type while defining reasonable review timelines (e.g. max. 3 months for moderate changes, 6 months for major changes). 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
  - 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), more changes could be handled through administrative notifications, allowing agencies to focus resources on major variations (having no prior approval by reference agency)
- Remove compulsory submissions appointments, and provide optional appointments for critical changes
- Build capacity for review & relevant committee meetings to allow for timely approvals

Strategic management of changes or activities

- Accept bundling of changes, parallel/ supplemental submissions of other variations that come along or activities that are part of or a pre-requisite for the variation approval such as site registration.
- Encourage exchange of knowledge between the review and inspection departments

Dossier Content

- Minimize the number of country-specific requirements
- Reduce the need of legalized documentation (leveraging GMP certificates by stringent inspectorates which demonstrate compliance with international GMP standards)
- Harmonise dossier content across the ME
- Leverage commitments (pre-or post-approval) to allow timely approval and implementation of changes (e.g. with re to stability data requirements)


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In line with global harmonization initiatives led by ICH and WHO, we would recommend the following mid to long-term actions also:

Mid to Long-term
• Implement in a stepwise manner efficient collaboration among regional NRAs that enables harmonization of dossier content, work-sharing, mutual reliance of assessments and, in the longer term, mutual recognition of approvals (in line with WHO working documents on Good Regulatory Practice (QAS/16.686)).
• Implement best practices and principles from International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q12. Increasingly rely on the companies' Pharmaceutical Quality Systems (PQS) to effectively manage minor changes without the need to file variations.
• 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.

3. Conclusion

Industry believes that, where properly planned and executed, post-approval change management activities will ensure continuous patient access to safe, well-tolerated, high quality and compliant products.

Convergence of regulatory requirements, through increased collaboration amongst NRAs, both within the Middle East region and globally will contribute to meeting that objective. Reliance on regulatory decisions by stringent agencies as recently introduced for new drug applications in Saudi Arabia, Egypt and Jordan should be considered for the relevant products variations as well.

Furthermore, cross-functional talks within NRAs (e.g. inspectors and assessors) should be encouraged to optimise the use of regulatory resources and prevent drug shortages.

Together, these measures will contribute to the ultimate goal to facilitate timely and continuous access to medicines throughout the region and globally.


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