Post Approval Changes (PAC) are essential to the Life Cycle Management (LCM) of a medicine or vaccine:

- Enhance robustness and efficiency of manufacturing process
- Improve Quality Control (QC) techniques
- Respond to changes in regulatory requirements
- Upgrade state-of-the-art facilities

This effort is critical to continuously improve existing medicines and is, in many ways, as important as bringing new medicines to market.
### Observations

- **Heterogeneous classification systems**
- **Specific local requirements**
- **Unpredictable and variable approval timelines**
- **Divergent decisions by regulatory bodies**
- **Variable implementation periods**

### Impact

- Multiple approved variants of a product have to be managed adding significant complexity on the supply chain and increase compliance risk.
- Potential impact on submissions elsewhere.
- Resource consuming requests for regulators to have exceptions to maintain supply.
- Difficulty to plan submission and implementation may result in stock outs.
- Reduced ability to reply to country demands, which can be sudden, in a timely and predictable manner.

*CMC = Chemistry, Manufacturing and Control*
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<th>Observations</th>
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<tr>
<td>Approval process for safety label changes can be lengthy and unpredictable</td>
<td>Slower HCP and patient access to up-to-date product information resulting in increased risk to patient</td>
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<td>Variable implementation periods</td>
<td>Consequences on pharmaco-vigilance surveillance based on approved product information</td>
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<td>Different versions of the label can be accessible on the internet (in different markets) leading to HCP and patient confusion</td>
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Proposals for improvement

Heterogeneous classification systems
- Unified risk-based variation classification system
- Allow simultaneous submissions (i.e. grouping)
- Stimulate NRA to work together and converge

Specific local requirements
- Converge requirements and eliminate unnecessary submission of data

Unpredictable and variable approval timelines
- Clear procedural guidance + appropriate, aligned timelines
- Seek opportunities & solutions to enhance life cycle management

Divergent decision by regulators
- The above will optimise convergent decisions

Variable implementation periods
- Common implementation timnings for the new change

Safety labeling review and implementation process can be lengthy & unpredictable

Independent, dedicated & expedited process for safety updates

In the future, electronic labels could enable direct access to the most recent product information
Short to mid-term actions

Converge requirements through adoption of international standards (WHO) through a risk-based approach to the classification of variations, data requirements, and timelines.

Allow flexible implementation periods for technical and labelling variations

Dedicate resources for review and approval of safety labelling variations in an accelerated manner

Encourage exchange of knowledge between the review and inspection departments

Consider to focus resources to ensure that important public health aspects i.e. supervision of supply chain, counterfeits, pharmacovigilance, are in place. This may be more impactful than re-assessing a change already evaluated by other agencies.

Minimize the number of country-specific requirements
Longer term solutions

Implement best practices and principles from ICH Q12. Increasingly rely on the companies’ Pharmaceutical Quality Systems (PQS) to effectively manage minor changes without the need to file variations.

Stepwise Implement collaboration among regional NRAs that enables work-sharing, mutual reliance of assessments and, in the longer term, mutual recognition of approvals.

Implement broad acceptance of e-labelling and progressive deletion of paper leaflets in the pack, in line with information technology capability in countries worldwide.

Industry to improve planning of changes through the product life-cycle and seek to adopt new mechanisms, expected in the future, such as Post Approval Change Management Protocol.
“A more efficient landscape for the handling of post-approval changes to MAs worldwide will contribute to enhancing global public health by ensuring patients’ continuous access to state of the art medicines, and up-to-date product safety information. The potential benefits of alignment and harmonization include: reduced shortage/stockouts, faster access to product made with process improvements, and encouragement of new technologies.”