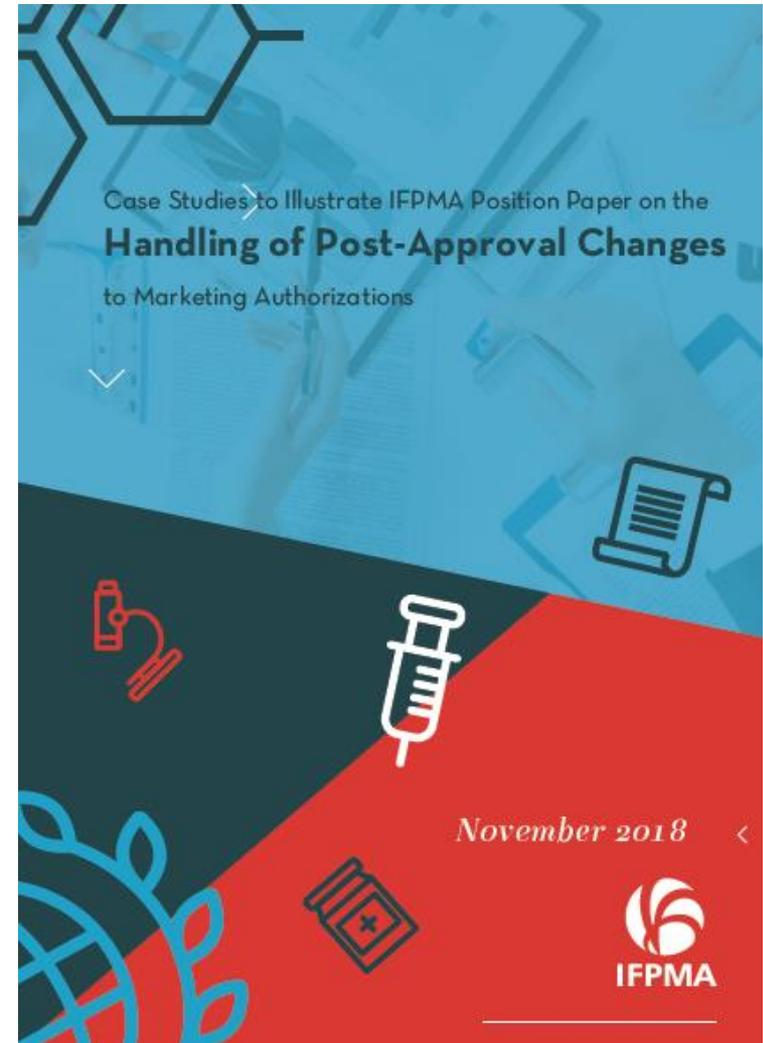


Case Studies to Illustrate IFPMA position paper on the Handling of Post-Approval Changes to Market authorizations

<https://www.ifpma.org/resource-centre/case-studies-to-illustrate-ifpma-position-paper-on-the-handling-of-post-approval-changes-to-marketing-authorizations/>



Problem statement

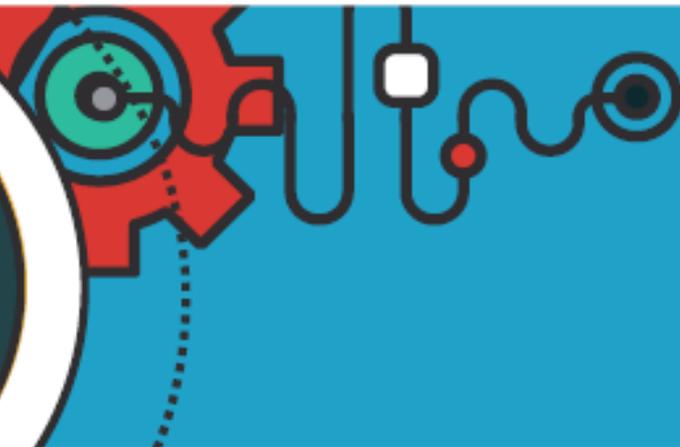
“Innovation is not just about bringing new medicines and vaccines to people; it covers also the continuous supply of these medicines, as well as reflecting advances in manufacturing and quality standards. Once a medicinal product reaches a market for the first time, Post-Approval Changes (PACs) are implemented throughout its life cycle to introduce manufacturing changes to enhance the efficiency of the process or sustain adequate supply. These activities contribute to ensuring innovative products remain accessible to patients worldwide”

However, the introduction of variations is regulated in a very diverse manner by national regulatory agencies (NRAs) worldwide, which causes unnecessary delays in implementation and unequal global availability



What is a Post-Approval Change?

Post-Approval Change (PAC) is the term used to refer to specific changes that a marketing authorization holder would like to make to an approved marketing authorization or license. These changes include, but are not limited to, changes in product composition, manufacturing process, quality controls, equipment, facilities or product labelling information.



Optimizing Post-Approval Change (PAC) Management for Timely Access to Medicines Worldwide – EFPIA position paper

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

1. Enhance robustness and efficiency of manufacturing process
2. Improve Quality Control (QC) techniques
3. Respond to changes in regulatory requirements
4. 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



Draft



Final



Optimising Post-Approval Change Management for Timely Access to Medicines Worldwide

Date: 08/02/2017

Version: 1.0

Executive Summary

Post-approval changes (PACs) to the registered information of authorised medicinal products, hereafter referred to as 'variations', are introduced routinely worldwide to: 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 continued effort is critical to continuously improve existing medicines and is, in many ways, as important as bringing new medicines to the market.

Once marketed, medicinal products are used more widely than the population in clinical development and this helps to refine knowledge of the product safety profile. For the benefit of patients and Health Care Professionals (HCPs), it is critical that such information is reflected in the product label in a timely manner, through variations to the prescribing information.

As regulatory systems develop and evolve worldwide, the requirements to submit and review variations in multiple markets are becoming even more complex. International collaboration and cooperation towards regulatory convergence has been recognised as the way to address the challenges of National Regulatory Agencies (NRAs) to address such increases in workload (see WHO working documents on Good Regulatory Practice - QAS/16.686). Industry believes that global convergence will provide a more efficient environment for the management of post-approval changes to Marketing Authorisations (MAs) worldwide, and will contribute to ensuring patients' continuous access to state-of-the-art medicines, and up-to-date product safety information. At the same time, industry acknowledges that more measures like advanced planning of changes at start of the life-cycle, more strategic combination of changes as well as transparent communication of supply challenges need to be taken from their side to contribute to complexity reduction. Ultimately, all of these activities will contribute to enhancing global public health.

This paper aims to describe the challenges with the current landscape for managing variations, and presents opportunities and recommendations for global convergence and improvement, in line with the World Health Organisation (WHO) guidelines. The paper addresses both quality variations (also referred to as Chemistry Manufacturing and Control, CMC) and safety label updates, and the recommendations aim to bring consistency and predictability to the global management of variations, whilst contributing to patients' timely access to quality medicines and the latest safety information.

What is this about?

6 real case studies describe the extensive process to go through to have innovative Post Approval Changes (PACs) implemented.

These 6 case studies highlight how patients across the world are being affected by unnecessary delays and access hindrance to enhanced quality medicines and vaccines.

CASE STUDY 1: Updating testing monographs to improve quality and harmonize testing requirements globally.

Issue:

This case study examines how a company who chose to update a drug's testing monograph in order to improve its quality had to navigate varying approval timelines due to different regulatory requirements, which increased the inventory and supply chain management complexity.

Solution:

Globally harmonized data requirements, along with consistent timelines for assessment and approval of these PACs should lead to improved predictability to manage them, thus reducing the risk of stock-outs, mix-ups and non-conformance to market applications.

CASE STUDY 2: Updating testing monograph to comply with harmonized pharmacopoeia chapter.

Issue:

Since there is no common classification system for PACs a product may undergo, classification varied from one country to another with some NRAs classifying the PAC as major, while other classified the PAC as moderate or minor.

Solution:

Classification of changes and supportive required documentation should be commensurate with potential patient risk, for the efficient use of both industry and regulatory resources, in particular for changes to comply with latest pharmacopoeial standards

CASE STUDY 3: Use of novel regulatory mechanism to address supply shortage related to quality issue.

Issue:

Supply shortages due to Quality issues

Solution:

This case study shows how the Post Approval Change Management Protocol (also known as Comparability Protocol) can reduce shortage time and resume reliable supply of medicines to patients within reasonable time limit. Implementation of these types of protocols allow for faster and more predictable implementation of PACs, as companies engage NRAs earlier in the evaluation of the strategy for the change and a later separate evaluation of the data produced based on the agreed upon strategy.

CASE STUDY 4: Multiple PACs to Vaccine Products.

Issue:

This case examines how vaccines can undergo a significant number of PACs submitted worldwide, whose complexity might require the involvement of multiple regulatory experts rather than a single one from a specific country. In the long run, vaccines journeys become very complex and unsustainable

Solution:

Greater emphasis on convergence, reliance, and harmonization in regulatory requirements are effective solutions that must be taken into consideration

CASE STUDY 5: Implementation of new facility to provide additional drug product manufacturing capacity at an existing site.

This case study discusses how improving global submission and approval processes can increase predictability and trust in approval timelines, which may prompt future investment and innovation in medicines and vaccines manufacturing.

CASE STUDY 6: Implementation of additional drug product testing site.

This case study highlights the importance of a common classification system that provides the opportunity for implementation of minor PACs by notification or tracked via internal product quality systems instead of prior approval.

Case Study 1: Updating testing monographs to improve quality and harmonize testing requirements globally

- Drug marketed >75 countries
- Drug is a dispersible tablet with a chemical ingredient as active substance
- Moderate changes consisting of tightening of specification limits and replacement of 2 older testing methods by 1 single improved testing procedure

»»» REQUIREMENTS VARIED

Change to drug product specifications

General Requirements all countries

- Updated Sections, 3.2.P.5.1, 3.2.P.5.2, 3.2.P.5.3, 3.2.P.5.4 and 3.2.P.5.6.
- Analytical comparison of 3 batches, current vs proposed.
- Certificate of analysis (CoA) for 3 batches.
- Testing Monograph/Control procedure.

Additional specific requirements

FOR ANALYTICAL COMPARISON 3 BATCHES

- Certificate of analysis (CoA) - 3 batches.
- Comparative validation data.
- Specifications, hand-signed (for Peru).
- Stability commitment (South Africa 1 batch).
- Reference country approval.
- Manually signed specification document (Peru).
- Letter of authorization (Chinese Taipei).
- Stability data as per ASEAN guideline on Stability Study of Drug Product (Singapore).

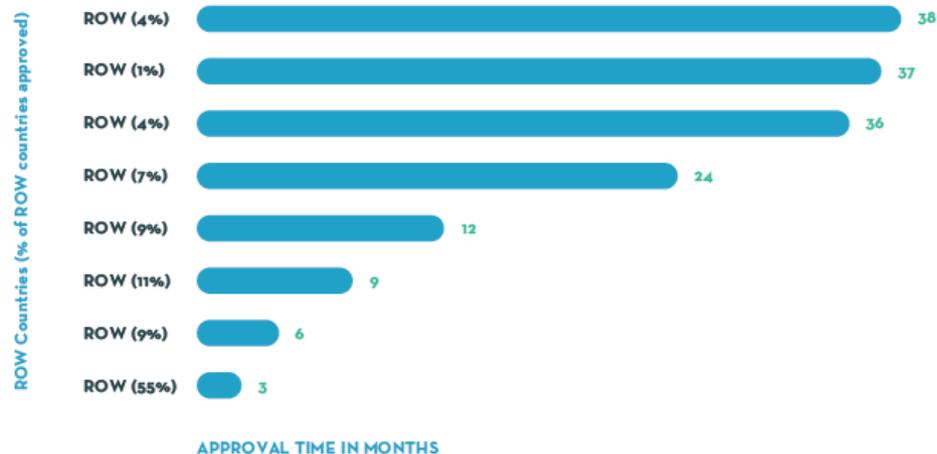


Case Study 1: Updating testing monographs to improve quality and harmonize testing requirements globally

REPORTING CATEGORY, APPROVAL TIME VARIED



REST OF THE WORLD APPROVAL TIMES VARIED FROM 3 TO +38 MONTHS



Case Study 1: Lessons learned and recommendations

Lessons

- A moderate change resulted in widely varying global approval timelines from 1 month to >3 years
- Increased complexity in the manufacturing and supply chain in order to sustain supply
- Resources spend which could have been spend elsewhere

Recommendations

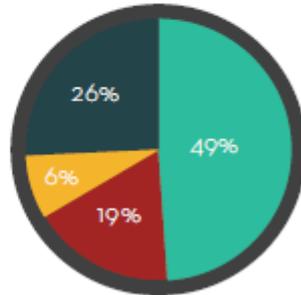
- Adoption of global, harmonized and consistent regulatory guidelines like the WHO PAC guidelines
- Clear and consistent timelines for assessment
- This will result in:
 - Decreased complexity in supply chain
 - Alleviated need for excess resources
 - Reduced risk for shortages
 - Encourage companies to adopt innovative technology

Case Study 2: Updating testing monograph to comply with harmonized pharmacopoeial chapter

- Drug marketed 100 countries
- Minor variation to comply with ICH Q4 Annex 6
- Product is powder and solvent for injection, 4 strengths, mono and multidose

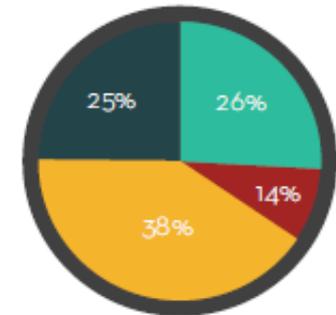
Classification categories for PACs
(Theoretical - at time of assessment)

- Major
- Moderate
- Minor
- None



Classification categories for PACs
(Actual by NRA - at time of submission)

- Major
- Moderate
- Minor
- None



Case Study 2: Updating testing monograph to comply with harmonized pharmacopoeial chapter

Change to pharmacopoeial method and related specifications - Product X

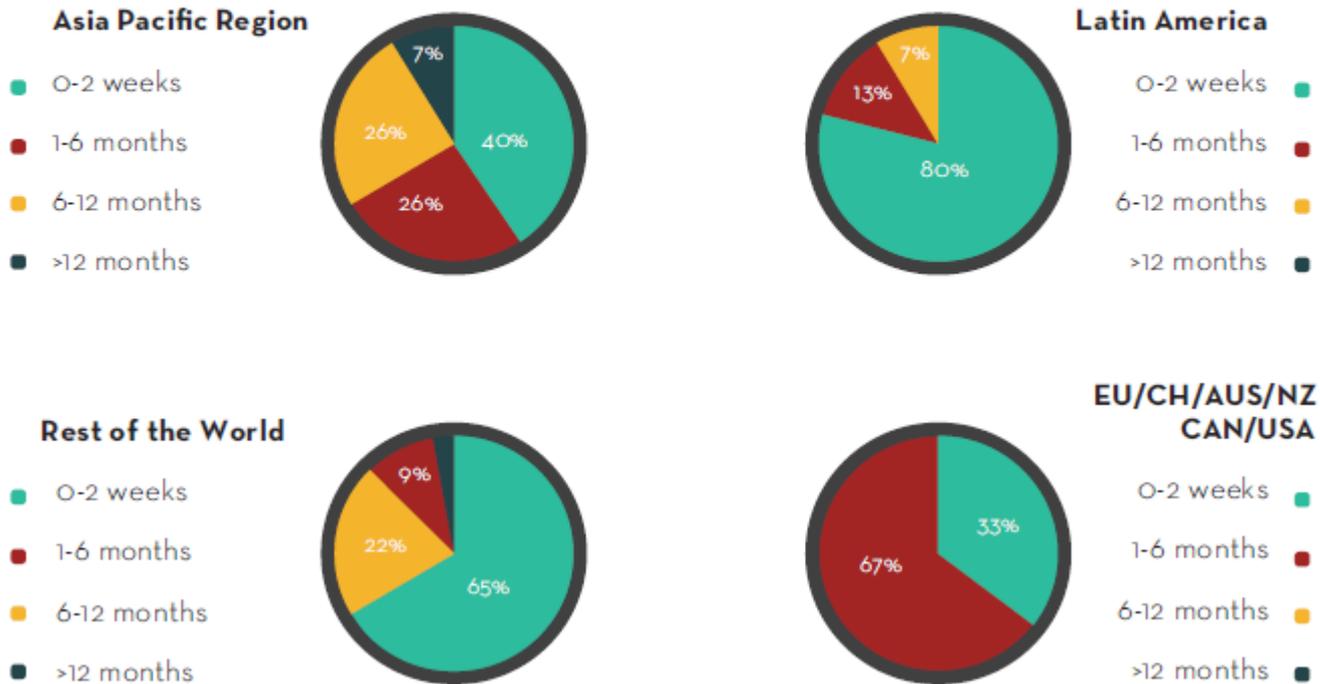
- General Requirements all countries**
- Updated Sections, 3.2.P.5.1, 3.2.P.5.2, 3.2.P.5.4, 3.2.P.5.6.
 - Comparative table of current and proposed specifications

- Additional specific requirements**
- SOP for control procedure.
 - Data and sample calculation.
 - Chromatograms for content by HPLC used for calculation.
 - Normative document update.
 - Certified Product Information Document update.
 - Certificate of Analysis (CoA) - 3 batches.
 - Specifications, hand-signed.
 - Reference country approval.
 - Stability data.



Case Study 2: Updating testing monograph to comply with harmonized pharmacopoeial chapter

In addition to varying classification categories for PACs and different country requirements, variable approval timelines were experienced leading to implementation delays.



Case Study 2: Lessons learned and recommendations

Lessons

- Even for a minor PAC intended to comply with the latest harmonized pharmacopeia and not affecting product quality it took up to 15 months to obtain global approval

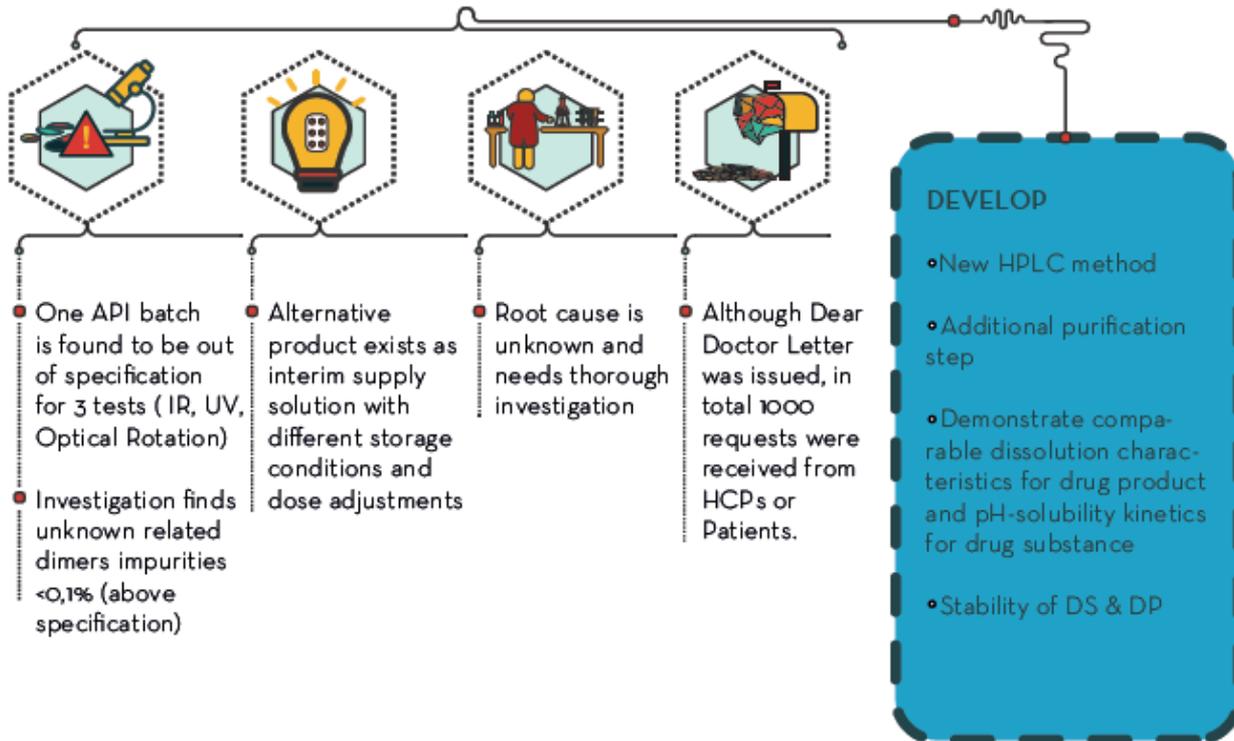
Recommendations

- Globally harmonized and risk based categorization of PACs
- Clear & consistent timelines for assessment
- The regulatory communication category, supporting information/documentation requirements, and associated time frame for evaluation should be commensurate with potential patient risk, for the efficient use of both industry and regulatory resources

Case Study 3: Use of novel regulatory mechanism to address supply shortage related to quality issue

- Drug marketed >8 countries and on WHO model list for Essential Medicine
- API supplier has issue with out of specification test result
- Several changes needed to be implemented

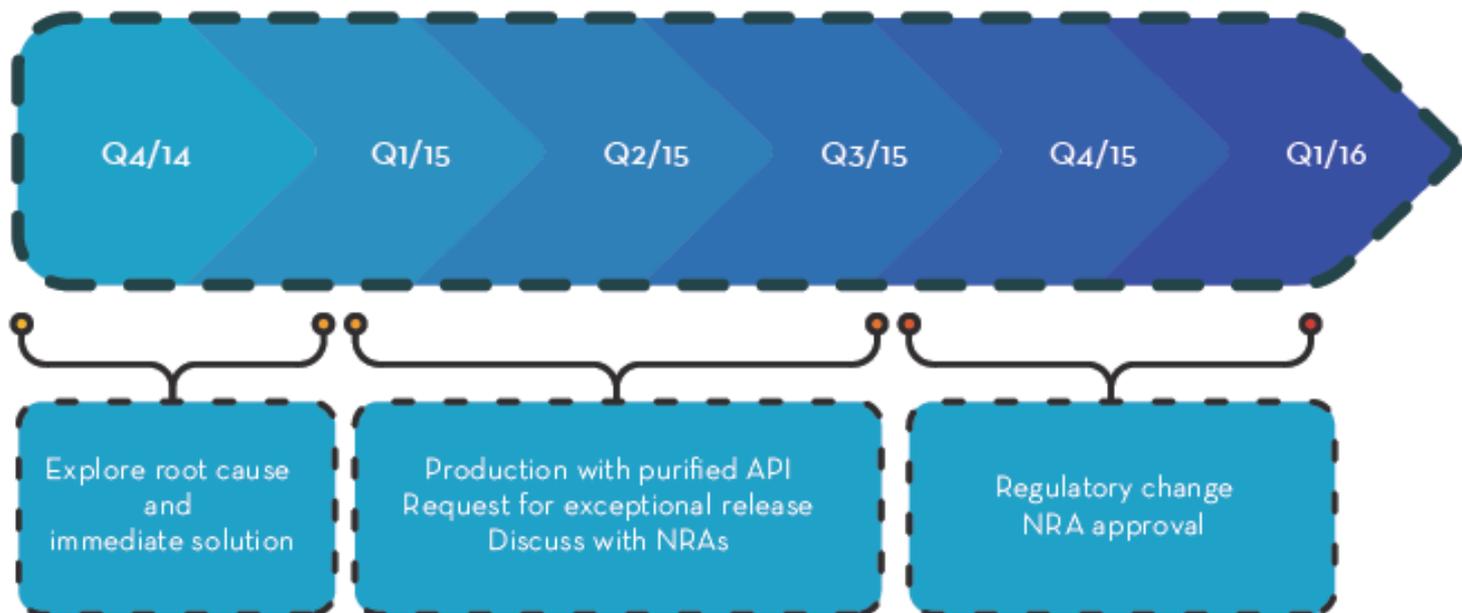
CHALLENGES



Case Study 3: Use of novel regulatory mechanism to address supply shortage related to quality issue

INVESTIGATION & REMEDIATION

Initial plan



Case Study 3: Use of novel regulatory mechanism to address supply shortage related to quality issue

REGULATORY STRATEGY OPTIONS

Option 1: Major variation (type II) upon Active Substance Master File update and stability (National)



Option 2: Post-approval Change Management Protocol (PACMP)



Option 3: Exceptional release with new updated specifications base on quality defect report (before regulatory submission) - one country

Case Study 3: Lessons learned an Recommendations

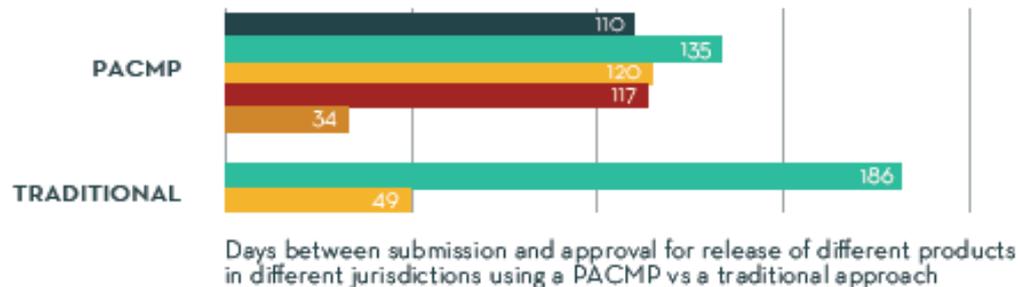
REGULATORY STRATEGY OPTIONS

The Benefits

- **Step-wise approach** which allows an **early evaluation** of the strategy for the change and a later provision of data (stability in particular).
- **Strategy discussed upfront in NRA meeting.**
- Based on the known changes to the manufacturing of API, NRAs could evaluate in close collaboration with Good Manufacturing Practices branch a **risk-based batch release.**

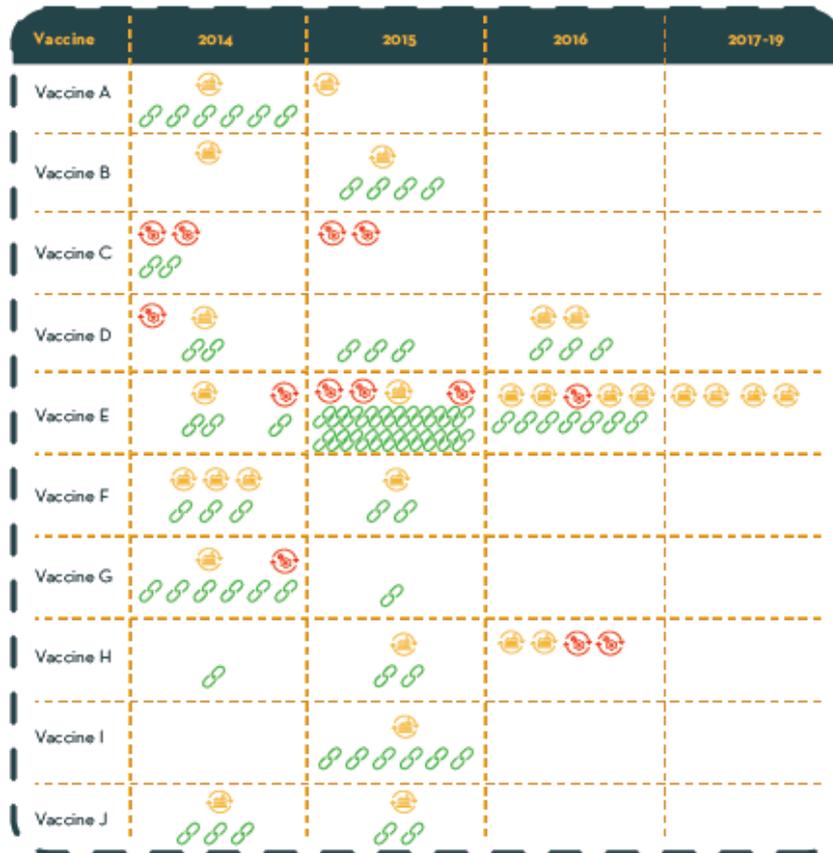
The Results

- Leads to **faster and more predictable implementation** of changes.
- **Decreased supply disruption and drug product available to patients sooner.**



Case Study 4: Multiple PACs to Vaccine Products

»»» MULTIPLE AND OVERLAPPING TECHNICAL CHANGES (Examples of Vaccine Products - a view from 2014/2019)



Legend

- Building/Site Change (to different country)
- Process change
- Other (e.g. specification, reagent, device)

- Each change can impact 50-100 licenses
- Results in 1000s of PACs filed every year
- A lot of PAC are related to manufacturing site changes and these can take up to 5 years for global approval
- Many PACs overlapping in time resulting in high intensity of supply chain management related to PACs with multiple versions of the same product being produced at the same time

Case Study 4: Lessons learned and Recommendations

- Regulators and Industry want to secure access for patients to high quality, safe and effective medicines and vaccines using process that are continuously improving to keep up to date
- Industry should continue to harmonize the way it presents the data to regulators
- Requirements and timelines should be harmonized
- Routine PACs that meet requirement of a defined protocol should be managed in the pharmaceutical quality system
- Greater emphasis should be put on reliance enabling regulator to specialize in certain areas

Case Study 5: Implementation of new facility to provide additional drug product manufacturing capacity at an existing site

- New building adjacent and connected to an existing and approved building
- To increase supply of 10 products manufactured there

The company invested in the facility to promote global production capacity and provide increased manufacturing control (through use of isolator technology), while minimizing potential supply issues. In the USA and EU, the company leveraged a PAC Management Protocol outlining specific criteria that would be met. However, no mechanism exists to leverage this kind of protocol in most markets, resulting in long approval timelines in many other jurisdictions

Operation of the original facility was extended for >3 years beyond the initial estimated closing date, resulting in increased staffing, maintenance, and technical challenges. Extended approval times magnify supply chain complexity, increasing risk of drug shortages or expired products, while delaying the implementation of process improvements.

Case Study 5: Lessons learned and Recommendations

- Harmonization with the WHO (and/or the ICH requirements) should lead to shorter and standardized review timelines, while improving review quality
- Harmonization efforts should consider the following:
 - Providing a framework which allows for utilization of Post-Approval Change Management Protocols globally
 - Providing standardized approval timelines, including options for accelerated approvals following reference country approvals
- Improving the global submission and approval processes provides increased visibility and confidence in approval timelines, thus encouraging future investment and innovation in drug manufacturing

Case Study 6: Implementation of additional Drug Product Testing Site

- Alternate drug product testing site (in addition to the existing) for parenteral monoclonal antibody
- New site already approved for testing other parenteral products and is GMP approved

- The addition of an alternate testing site allows for consolidation of quality control testing sites, an alternate testing lab for importation testing, while setting aside the need for an outside contract laboratory.
- Qualification for importation testing sites, including global approvals, would reduce the need for redundant testing.
- The addition of an alternate drug product testing site provides risk mitigation, supporting the company's ability to release product in the event of issues at the other testing site.

Case Study 6: Lessons learned and Recommendations

From the company's perspective, this PAC has minimal potential to impact product quality, considering that:

- No changes in testing or analytical methodology. All methods previously validated;
 - The receiving lab is currently approved for similar methods and products, has evidence of GMP compliance and is inspected regularly;
 - Internal procedures provide systems with adequate controls.
-
- Requirements for routine PACs have consistent requirements that can be defined by NRAs in advance of implementation.
 - These criteria and controls support assessment of the addition of a new drug product testing site as a minor risk change that should not require prior approval
 - NRAs should align to common classification systems that provide the opportunity for implementation of minor PACs by either notification only or tracked via internal product quality systems.

6 recommendations

1. **Common classification system** for PACs
2. **Clear and transparent timelines** for assessment and PAC implementation
3. Leverage regulatory mechanisms and tools to **streamline PAC review**
4. Enhanced and **proactive communication** between marketing authorization holders and national regulatory authorities
5. Enhanced communication and **collaboration** between NRAs, leading
6. Enhanced use of **electronic means** for timely access to updated product safety information to reliance and mutual recognition

Recommendations (1)

01



Common classification system for PACs:

IFPMA proposes the adoption of a **tiered, risk-based classification system** for PACs to marketing authorizations based on the principles outlined in the relevant WHO guidance. The use of **common classification systems** would facilitate consistent implementation of PACs by stipulating criteria for appropriate reporting to NRAs. Consistent implementation could be achieved through the classification of PACs 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 PAC founded on a well-documented assessment that is both science- and risk-based**.

02



Clear and transparent timelines for assessment and PAC implementation:

To strengthen the use of common classification systems, **clear and consistent timelines** should be identified for the regulatory assessment of PACs, specifically 3-6 months for major PACs and 1-3 months for moderate PACs, **in line with the WHO's guidelines** on PACs. Adherence by NRAs to the specified timelines for regulatory assessment is critical. **Implementing processes for expediting priority reviews that address an urgent need**, for example to prevent or alleviate a drug shortage or labelling information that addresses critical product safety updates, should be considered. In such instances, shorter review times should be anticipated. A common pragmatic definition of "market implementation" for PACs and agreed **common market implementation timelines** would unequivocally reflect the impact of each change and expedite the implementation of urgent PACs for the benefit of the patient. Market implementation should also **take into account efficient use of existing stock-material produced before the PAC was implemented**, when there is no quality or safety issue.

Recommendations (2)

03



Leverage regulatory mechanisms and tools to streamline PAC review:

Novel regulatory mechanisms and tools are becoming more widely available for PAC 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 PACs in a more predictable and efficient manner. Consistent, risk-based, tiered PACs systems for quality PACs 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 PAC burden for NRAs and industry are important.

04



Enhanced and proactive communication between marketing authorization holders and national regulatory authorities:

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 PACs, between the marketing authorization holders and NRAs across multiple geographic regions. Enhanced communication will provide for transparency, consistency, and predictability in regulatory outcomes and decision making.

Recommendations (3)

05



Enhanced communication and collaboration between NRAs, leading to reliance and mutual recognition:

IFPMA encourages collaboration and reliance on approvals from experienced NRAs to facilitate approval of moderate and major PACs based on previous experts' review resulting in shorter approval timelines, as outlined in the WHO's guidelines for vaccines and for biotherapeutics. NRAs should consider introducing processes to prioritize the handling of labelling PACs 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 PAC in the context of the local medical setting) this should be justified and notified to the applicant accordingly.

06



Enhanced use of electronic means for timely access to updated product safety information:

Electronic means to access product information should be gradually introduced, based on learnings from early-adopting NRAs. Timely access could be achieved through, for example, promoting the use of experienced NRAs' websites where up-to date approved labels/labelling are stored, maintained and easily accessible.