

Case Studies to Illustrate IFPMA Position Paper on the Handling of Post-Approval Changes

to Marketing Authorizations



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PREFACE

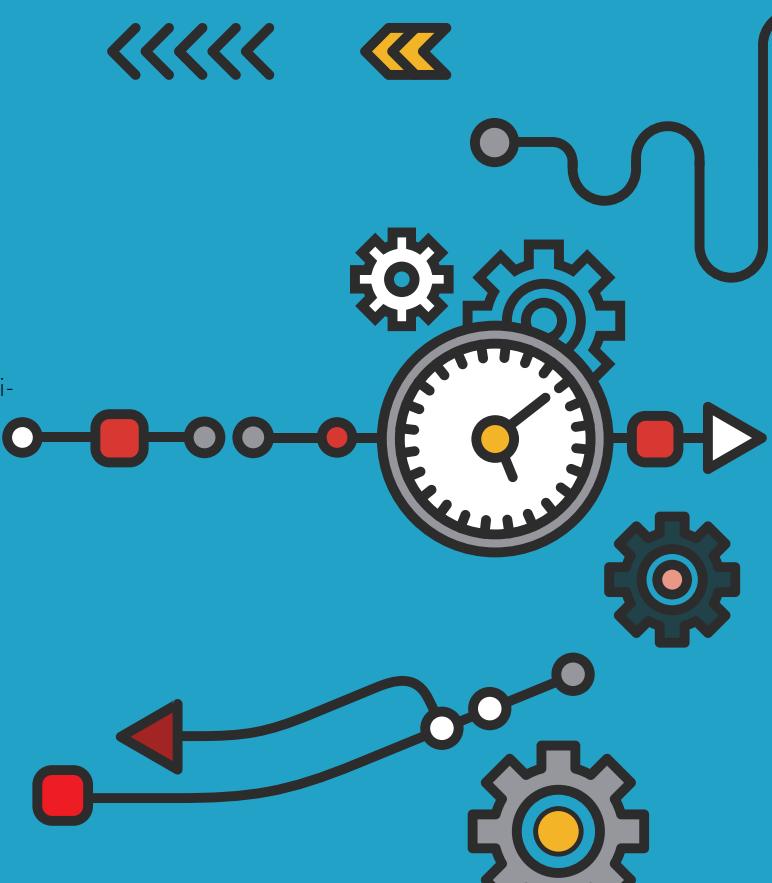
In the past few decades, the biopharmaceutical industry has contributed significantly to global health progress. Millions of people are benefiting from medical innovation and no one can contest today that people are living longer and healthier worldwide. It is the intense innovation by biopharmaceutical companies from the discovery of vaccines, to the development of novel medicines to combat deadly infectious diseases, cancer, and other life-threatening diseases that have brought us where we are today and will take us where we need to go tomorrow in achieving better health for all. Yet, in some therapeutic areas and geographic settings, progress is slow and remains incomplete. This is why we propose to collectively join efforts and work towards achieving the Sustainable Development Goal 3, so that all can benefit from innovation in health.

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. Also, once marketed, medicinal products are used by a greater population than that of the clinical development phase, which helps to refine knowledge about the product safety profile. For the benefit of patients and health care professionals, it is critical that such information is reflected in the product label in a timely manner, through variations to the prescribing information.

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.

This brochure describes the complexity with handling such regulatory activities, and the impact it has on access to such medicinal products. It is supported by six illustrative case studies aimed at raising awareness about the current challenges of PACs regulations and demonstrating how the consistent and predictable management of PACs can enhance public health overall. This represents an opportunity for all relevant stakeholders to partner and ensure patients' timely access to innovative medicines.

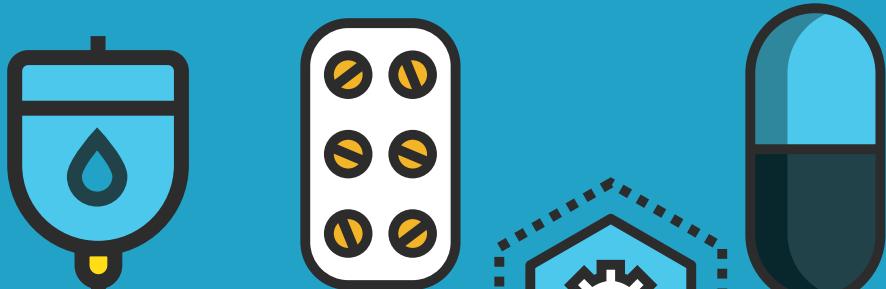
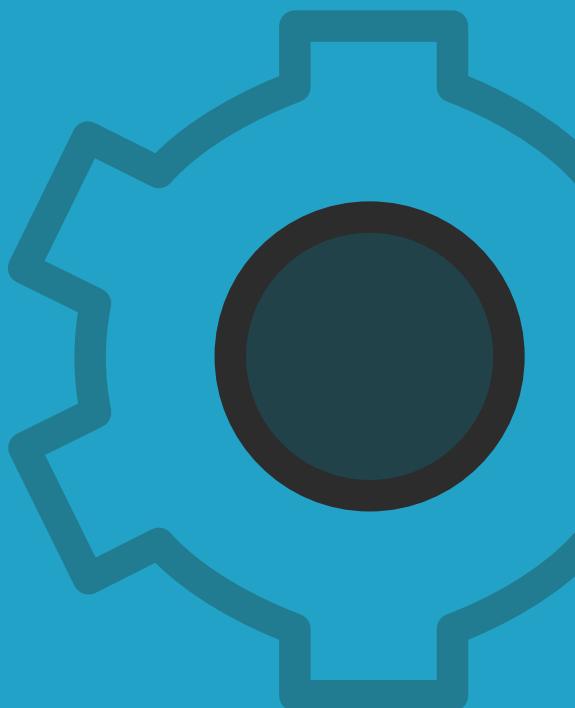
SDG3: "Ensure healthy lives and promote well-being for all at all ages."



INTRODUCTION

Pharmaceutical manufacturers face an increasing number of national regulations and procedures related to PACs. These regulations differ broadly in terms of requirements. Timelines for approval procedures may vary significantly between countries and are often hard to predict. This highly complex regulatory environment for globally applicable PACs represents a major challenge for the Industry in ensuring the uninterrupted supply of high quality, safe, and effective medicines and vaccines to patients around the world.

The purpose of this brochure is to raise awareness about the need for consistency and predictability of PACs regulations and procedures to ensure that medicines and vaccines continue to be delivered in a timely manner, safely, reliably, and efficiently to patients around the world throughout their life cycle.



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.



PROBLEM STATEMENT

Medicines and vaccines may reside on the market for decades. Uninterrupted supply is needed throughout the life cycle of these products while the quality, safety and efficacy are ensured. Changes are a normal part of a product's lifecycle. They may occur in raw materials, manufacturing processes, analytical methods, manufacturing sites, or any other information covered by the marketing authorization dossier. These are either voluntarily introduced by the company, as part of process improvements, changes introduced by the suppliers of materials used by the company or performed to comply with evolving regulatory requirements. PAC regulations provide oversight to ensure that they do not impact the quality, safety or efficacy of a medicine or vaccine. If these changes do however have an impact on the safety and efficacy of the product, this will be reflected on the product labelling information and may alter the uptake of the product. Thus, changes to product labelling information should be seen as an essential tool for an efficient risk-management approach throughout a product's lifecycle.

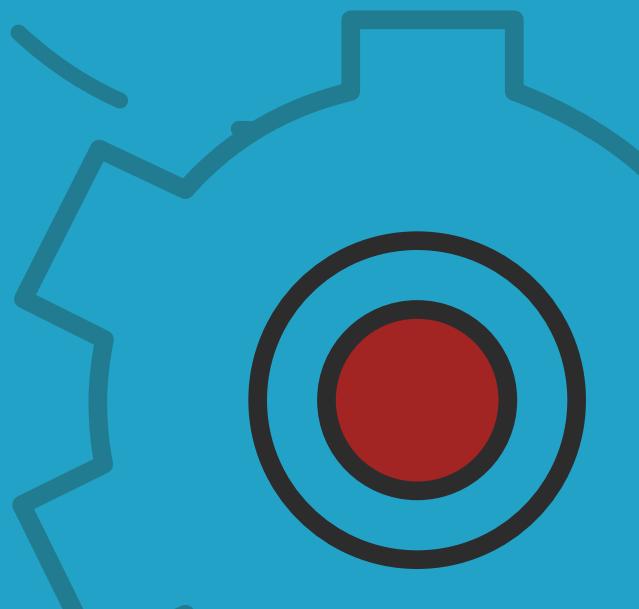
Most pharmaceutical companies nowadays operate globally or regionally, securing supply of medicines to patients in many different countries. PAC regulations however are country specific, and often with unique requirements. As regulatory systems develop and evolve worldwide, the requirements to submit and review PACs are increasing. As a consequence, there is a growing divergence of PAC regulations, causing increased complexity across countries.

Major challenges are posed notably by variable or unpredictable timelines across National Regulatory Agencies (NRAs) for change, review, and approval. To manage different implementation dates for the same PAC to a product while ensuring global market supply, companies have to manage multiple variants of the same product or have to keep multiple processes or test methods running for the same product. This dramatically increases supply chain complexity.

Major challenges are posed notably by variable or unpredictable timelines across NRAs for change, review, and approval. To manage different implementation dates for the same PAC to a product while ensuring global market supply, companies have to manage multiple variants of the same product or have to keep multiple processes or test methods running for the same product. This dramatically increases supply chain complexity, which in turn increases the risk of non-conformance to dossiers in certain countries and represents an increased risk of supply shortages.

Highly sophisticated processes, facilities, and equipment needed to manufacture pharmaceutical products require continuous improvements and updates, keeping them robust and state-of-the-art, and thus avoiding the risks of quality failure. The complexity of the current PAC regulatory landscape faced by the Industry is a limiting factor in driving these improvements and to manufacturing innovation.

As such, the lack of efficiency in PACs management is a major threat to the uninterrupted supply of high quality, safe, and effective medicines and vaccines to patients around the world. In our view, it is creating an unnecessary burden on companies and regulators alike, often with little benefit or even harm to patients.



EXECUTIVE SUMMARY

This brochure aims to give a brief overview of the current regulatory landscape surrounding PACs. It explores how PACs regulation can be challenging not only for regulators and manufacturers, but also and ultimately for patients. In order to illustrate this in a realistic manner, IFPMA has put together a series of case studies that describe the extensive process that some of our member companies had to go through to have innovative PACs implemented. This also helps IFPMA's Position Paper on the Handling of PACs to Marketing Authorizations.

Also, by collecting evidence and comparing efforts undertaken in this diverse set of regulatory requirements, the following 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.

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. 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 pharmacopoeial chapter.

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.

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.

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.

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.



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.

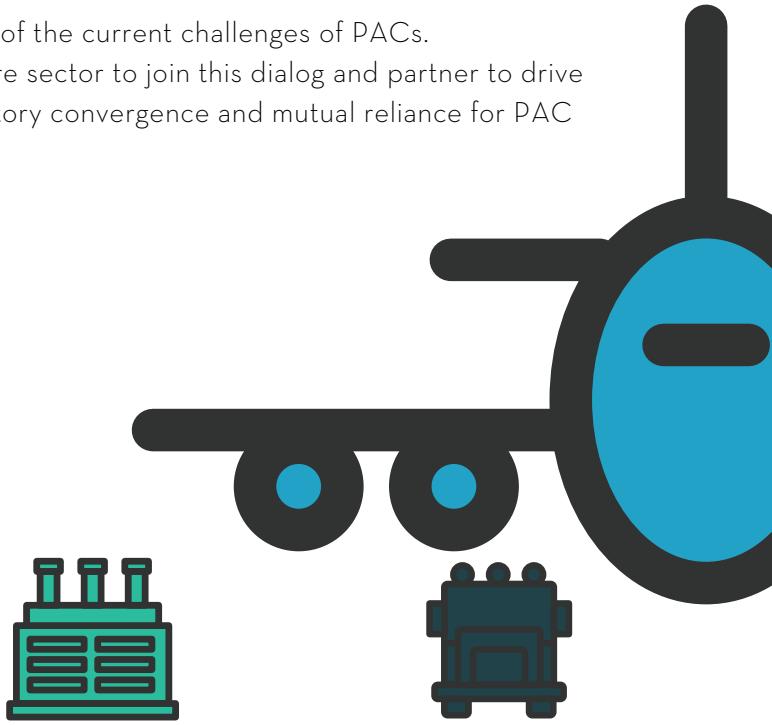
CASE STUDY 6: Implementation of additional drug product testing site.

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.



A CALL TO ACTION

This is a call to action to accelerate awareness of the current challenges of PACs. We encourage all stakeholders in the healthcare sector to join this dialog and partner to drive significant change towards international regulatory convergence and mutual reliance for PAC management. Patients worldwide rely on us!



case study

01



Updating Testing Monographs to improve quality and harmonize testing requirements globally



SITUATION

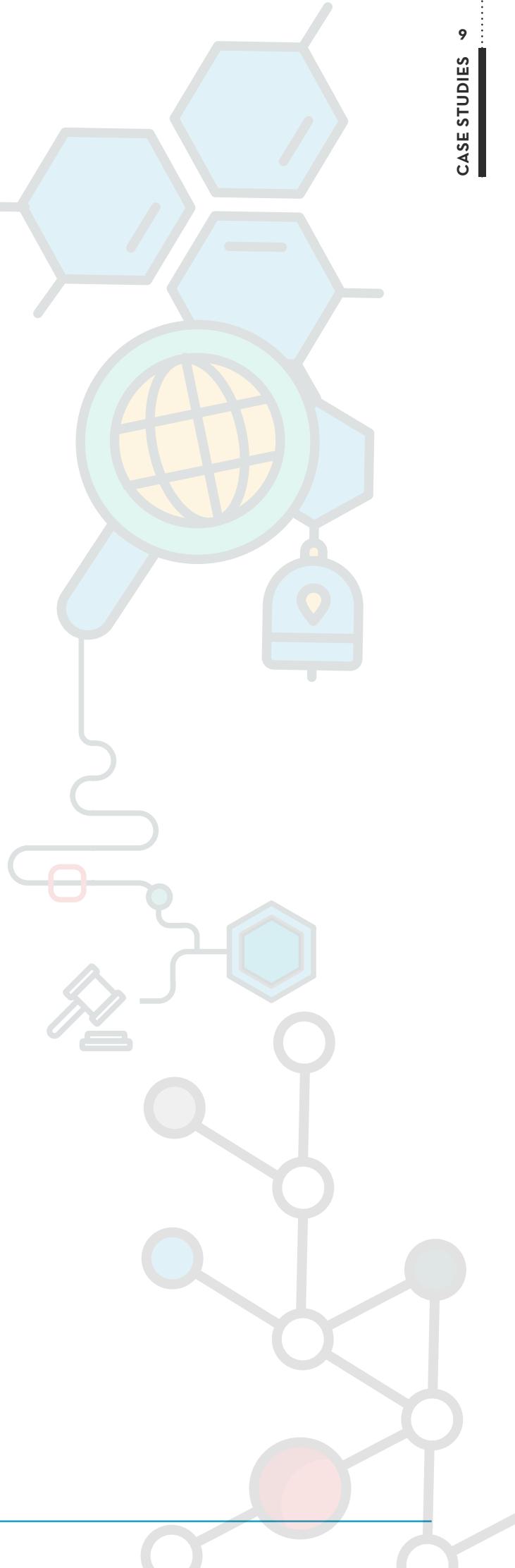
A medicine is marketed in over 75 countries worldwide to treat iron overload caused by blood transfusions in adults and children. The medicine is a dispersible tablet that contains a chemical ingredient as an active substance. Moderate changes were made to the drug's testing monograph in order to improve its quality and to harmonize testing requirements globally. These PACs consisted of a tightening of specification limits and replacement of two older testing methods by one single improved testing procedure.

STRATEGY

The global pharmaceutical company notified regulatory authorities in Europe, the USA, Japan and 53 other countries about the proposed PACs. In addition to submitting required documentation in all countries, which comprised an analytical comparison and updated sections of the original submission along with the new Testing Monograph, the company had to adhere to numerous additional requirements from various NRAs.

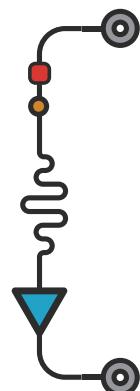
Additional requirements ranged from hand-signed documents to additional stability studies. In most countries, the PACs had to be notified and could be implemented without prior approval. Yet in some countries, the PACs had to be approved by the NRA prior to beginning implementation. Varying documentation requirements and approval requirements led to implementation delays varying from 1 month to more than 3 years.

To accommodate this variability, the company had to implement duplicate testing and duplicate release procedures until PACs were approved in all countries globally. The company also had to plan for additional inventory for the product released according to the old testing monograph, to ensure timely and reliable supply to patients in countries that had not yet approved the PACs.



LIFE CYCLE MANAGEMENT STUDIES QUALITY PAC

">>>> REQUIREMENTS VARIED

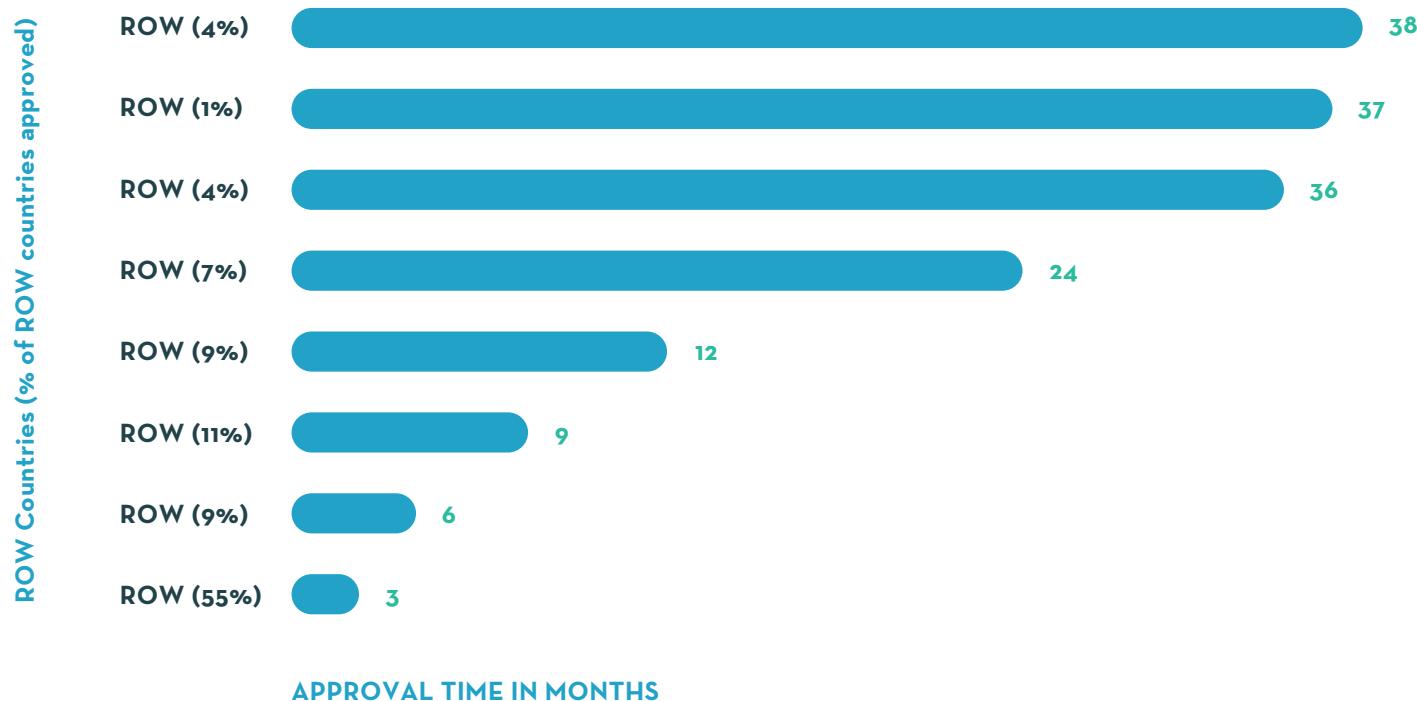


Change to drug product specifications	
General Requirements all countries	<ul style="list-style-type: none"> ● Updated Sections, 3.2.P.5.1, 3.2.P.5.2, 3.2.P.5.3, 3.2.P.5.4 and 3.2.P.5.6. ● Analytical comparison of 3 batches, current vs proposed. ● Certificate of analysis (CoA) for 3 batches. ● Testing Monograph/Control procedure.
Additional specific requirements	<p>FOR ANALYTICAL COMPARISON 3 BATCHES</p> <ul style="list-style-type: none"> ● 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).

">>>> REPORTING CATEGORY, APPROVAL TIME VARIED



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



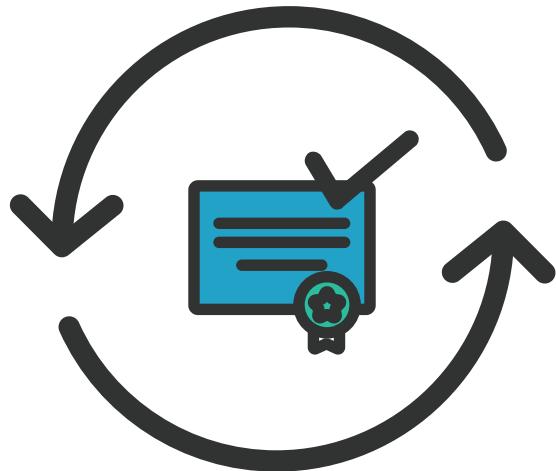
LESSONS LEARNED AND RECOMMENDATIONS

For a moderate change intended to improve a drug's quality, differences in reporting categories and data requirements resulted in widely varying global approval timelines, ranging from 1 month to more than 3 years. The measures the company had to implement to ensure sustained supply to patients globally during this extended period resulted in increased complexity in inventory and supply chain management, increasing risks of stock-outs, mix-ups and non-conformance to market applications. Resources needed to be re-allocated to mitigate these risks.

Globally harmonized and consistent regulatory approaches to PACs such as proposed in the World Health Organization's guidance on variations, along with clear and consistent timelines for assessment and approval of these PACs should lead to improved predictability to manage them. This convergence or harmonization of requirements will alleviate the need for excess resources, decrease complexity in managing global supply chains, reduce the risk of drug shortages and encourage companies to adopt innovative technology in order to supply drugs that are manufactured to the highest quality standards.

case study

02



Updating Testing Monograph to comply with a harmonized pharmacopoeial chapter



SITUATION

This PAC required a minor variation to comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q4 Annex 6 Harmonized Pharmacopoeial Chapter (uniformity of dosage units – mass variation) in line with the European Pharmacopeia <2.9.40>, United States Pharmacopeia <905> and Japanese Pharmacopeia <6.02>. This change affected several of the company's biological products including a recombinant protein marketed in more than 100 countries worldwide as powder and solvent for solution for injection (4 strengths and multiple monodose or multidose presentations).

The company therefore requested a PAC in the reference monograph for the finished product specification for uniformity of weight of the freeze-dried product to the European Pharmacopeia monograph 2.9.5 "Uniformity of Mass" in order to meet the harmonized chapter on "Uniformity of Dosage Units" for the European, USA and Japanese pharmacopoeias.

The company had to assess the PAC for possible reporting to regulatory authorities in Europe, the USA, Japan and 70 other countries, in accordance with possibly established regional regulatory mechanisms pertaining to pharmacopoeial PACs.

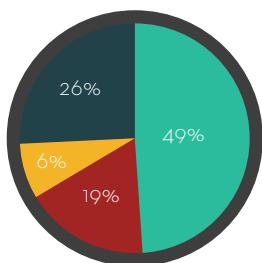
This PAC was further classified by NRAs at time of submission. Classification was highly variable from one country to another; the PAC was classified as "major" in 26% of the countries and as "moderate" in 11%, but in both cases prior approval was required before implementation. Other 38% of countries classified it as "minor", requiring only notification after implementation or without the need for any reporting in 25% of countries.

STRATEGY

Classification categories for PACs

(Theoretical - at time of assessment)

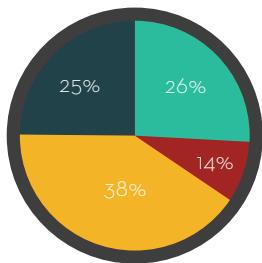
- Major
- Moderate
- Minor
- None



Classification categories for PACs

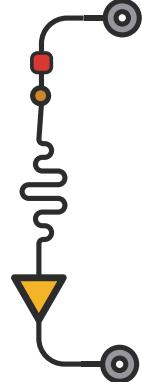
(Actual by NRA - at time of submission)

- Major
- Moderate
- Minor
- None



The marketing authorization holder could submit the same package affecting several products benefiting from a worksharing procedure in Europe. It consisted in appropriate updates to module 3 sections 3.2.P.5.1 (specifications), 5.2 (analytical method), 5.4 (batch analysis) and 5.6 (justification of specifications). Batch data was provided for three lots of each of the strengths as currently marketed.

This was considered sufficient to demonstrate that the test and limits can be appropriately applied to release testing. However, additional requirements for submission in other countries ranged from hand-signed documents to additional stability studies.



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

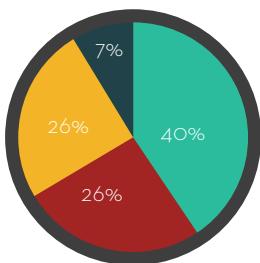
Additional specific requirements

- 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.

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

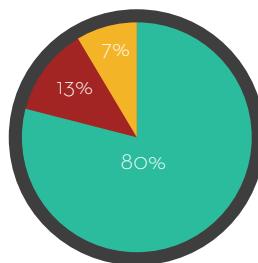
Asia Pacific Region

- 0-2 weeks
- 1-6 months
- 6-12 months
- >12 months



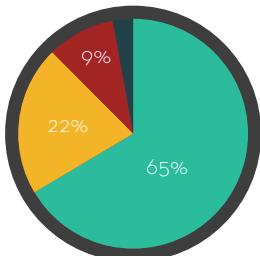
Latin America

- 0-2 weeks
- 1-6 months
- 6-12 months
- >12 months



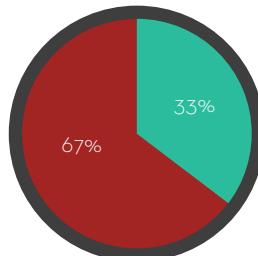
Rest of the World

- 0-2 weeks
- 1-6 months
- 6-12 months
- >12 months



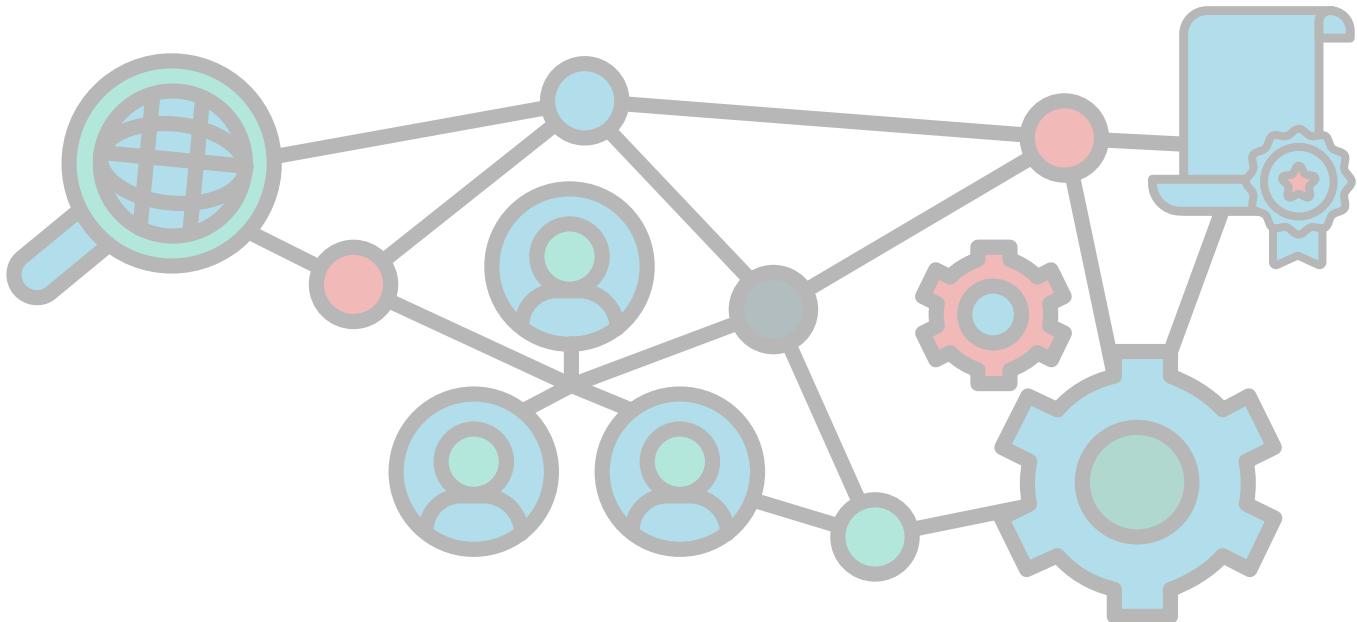
EU/CH/AUS/NZ CAN/USA

- 0-2 weeks
- 1-6 months
- 6-12 months
- >12 months



To accommodate this variability, the company had to implement duplicate testing and duplicate release procedures until the PAC was approved in all countries.

The company also had to cope with complexity in the lifecycle maintenance of various product strengths due to lack of dossier harmonization worldwide.



LESSONS LEARNED AND RECOMMENDATIONS

For a minor PAC intended to comply with latest harmonized pharmacopoeial requirements not affecting the product's quality or its benefit/risk profile, differences in reporting categories and data requirements resulted in widely varying global approval timelines, ranging from few days to more than 15 months.

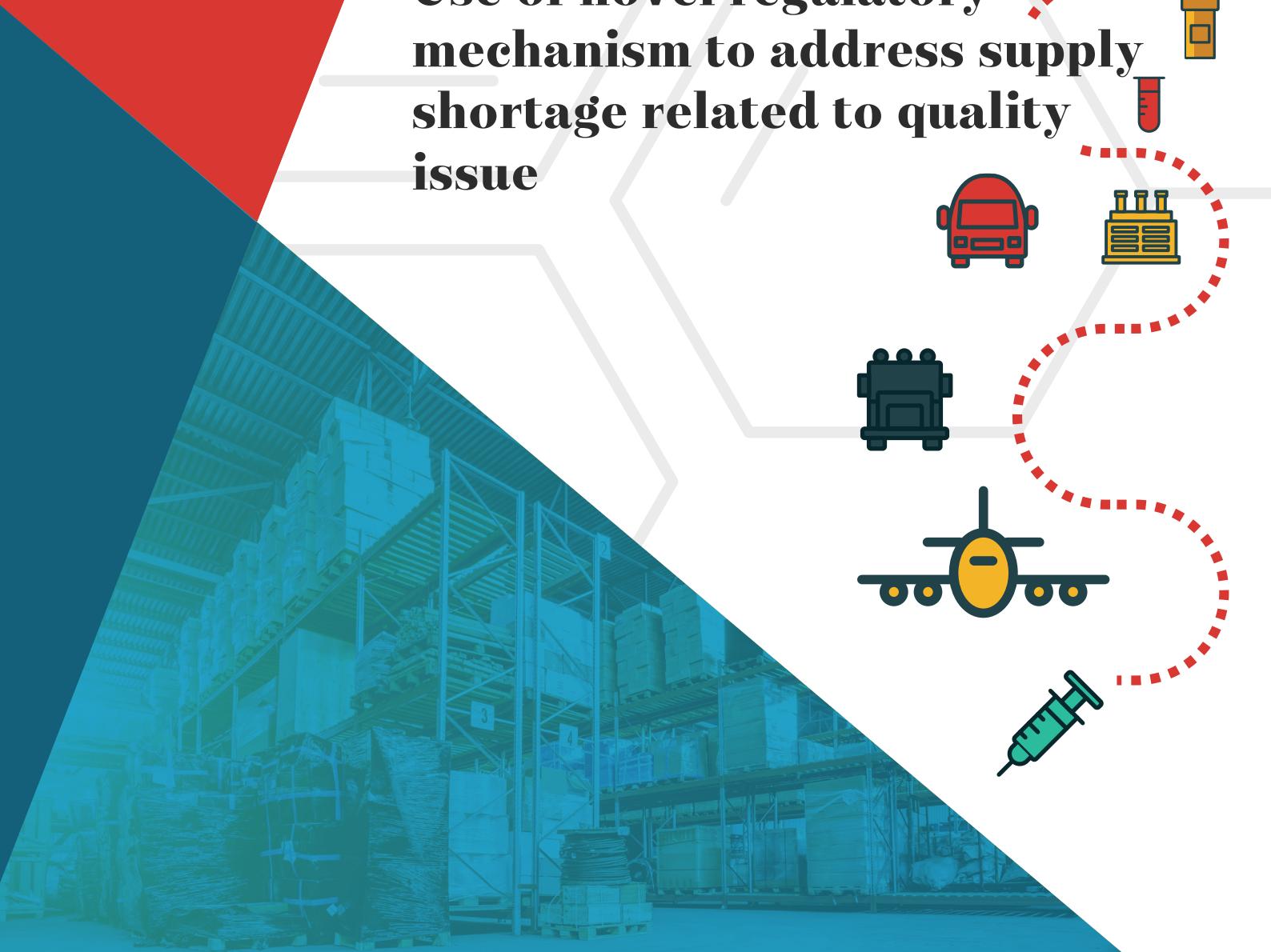
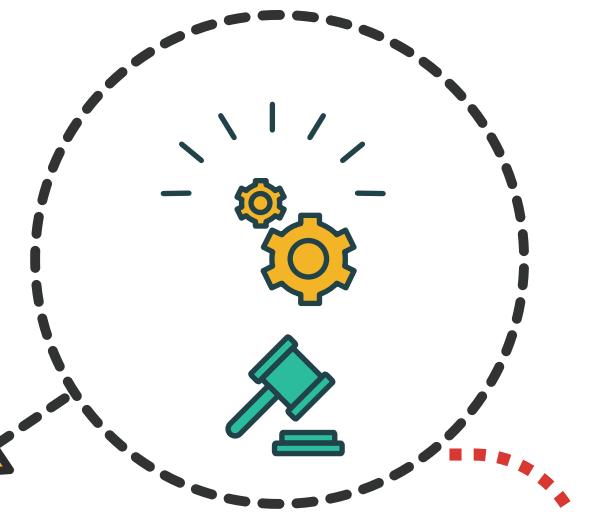
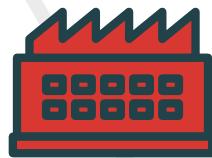
Globally harmonized and risk-based categorization of PACs, along with clear and consistent timelines for assessment as needed, should facilitate their management in a more predictable and efficient manner, allowing some minor PACs to be managed within product quality system without further reporting need.

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

03

Use of novel regulatory mechanism to address supply shortage related to quality issue



SITUATION

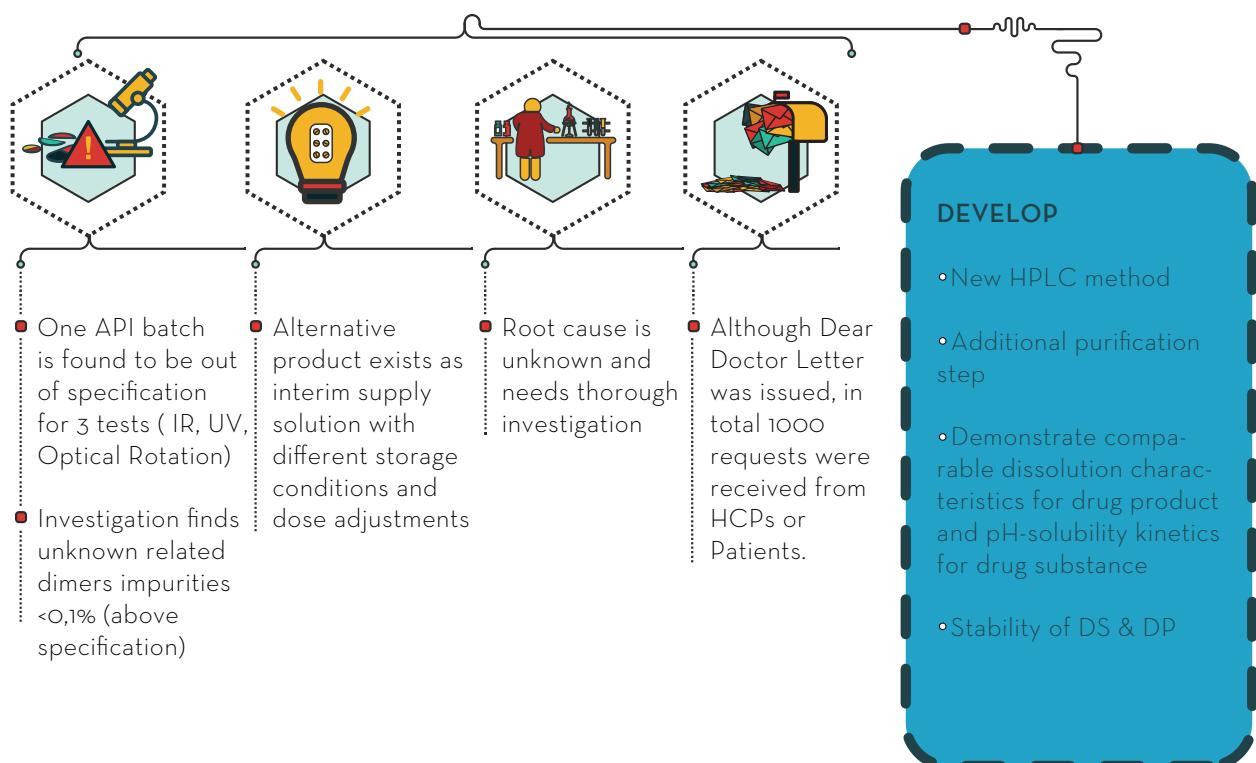
Drug A has been nationally registered and marketed since 1970, in more than 8 countries worldwide (in Europe, Latin America and Israel, at the time of this publication), imported in 4 additional countries and used as a substitution therapy in primary adrenocortical insufficiency (Morbus Addison's disease) and salt-losing adrenogenital syndrome in combination with a glucocorticoid. The medicine is a tablet that contains a chemical ingredient known as 9-Fluorohydrocortisone (fludrocortisone), with a spectrum of action equivalent to that of the natural mineralocorticoid aldosterone. It is classified as "life-saving drug" and included in the WHO's Model List of Essential Medicines. Drug A is the only approved fludrocortisone-containing medicinal product in its markets.

The company was informed by the only approved supplier of the active pharmaceutical ingredient about a shortfall in its availability. The shortfall had been caused by manufacturing

issues experienced by the supplier, leading to nonconforming active pharmaceutical ingredient for manufacturing the tablet.

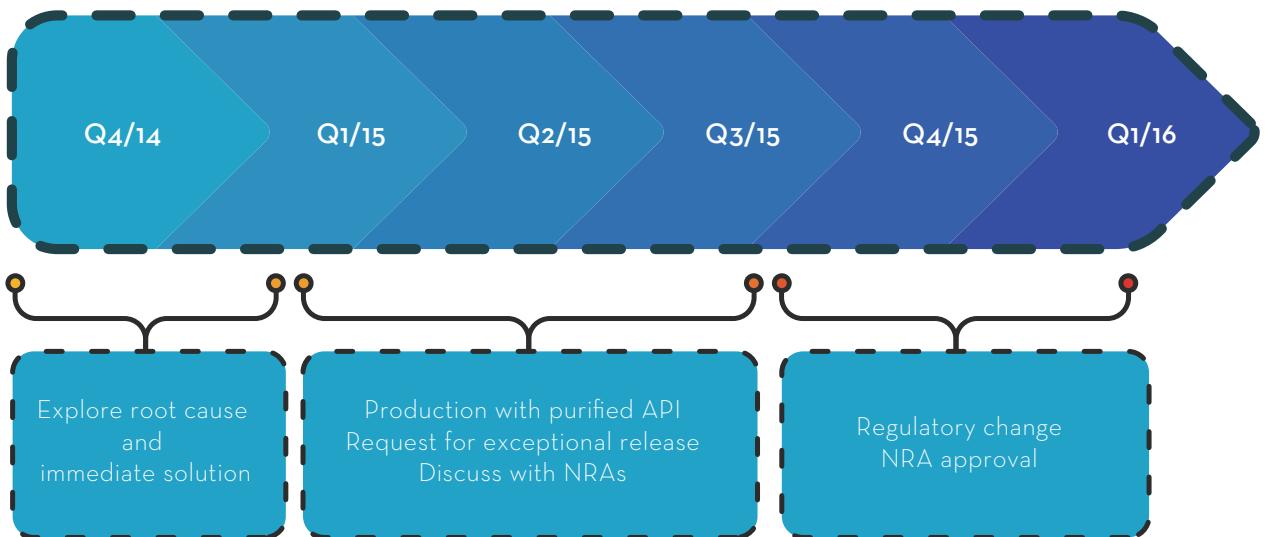
Investigation revealed the presence of new unknown impurities in the active pharmaceutical ingredient, above acceptable limits, although the finished product remained within the specifications acceptance criteria. As Morbus Addison's patients depend on a regular and sufficient supply of fludrocortisone, immediate measures and further root cause investigation were undertaken including searching for additional active pharmaceutical ingredient sources and finished product sources. To ensure continued patient support, a substitute medication has been distributed, depending on local regulations, to help bridge the time period until supply of medication would become available again. Relevant regulatory authorities needed then to agree upon several proposed remediation actions, including an additional step to purify the active ingredient to ensure that it could be resumed for production of tablets.

CHALLENGES



>>> INVESTIGATION & REMEDIATION

Initial plan



STRATEGY

The global pharmaceutical company as the marketing authorization holder and finished product manufacturer notified regulatory authorities in all concerned countries about the issue and the proposed PACs. In only one country, an exceptional release was agreed to allow continued patient treatment and supply based on a risk assessment from the quality defect report provided by the company.

In all other countries, the proposed PACs had to be approved by each NRA prior to implementation. A regulatory PAC submission was therefore required with a complete update of the Active Substance Master File from the currently approved dossier including manufacturing process description, process validation, characterization of reference standard and related impurities, control of drug substance, along with active pharmaceutical ingredient and finished product comparative batch analysis and stability data. Approval and related implementation timelines ultimately varied from 34 days to 186 days from country to country.

In order to reduce shortage time and resume reliable supply of their medication to patients as soon as possible, a regulatory tool -

Post-Approval Change Management Protocol

- was proposed during interaction with some NRAs and accepted by them whenever feasible in local regulations.

This regulatory strategy allows a 2-step approach for submission of PACs with an early evaluation of the strategy and risk assessment and a later, separate and quicker evaluation of the data produced based on the agreed strategy (as long as results are within expected range).

➡➡➡ 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



LESSONS LEARNED AND RECOMMENDATIONS

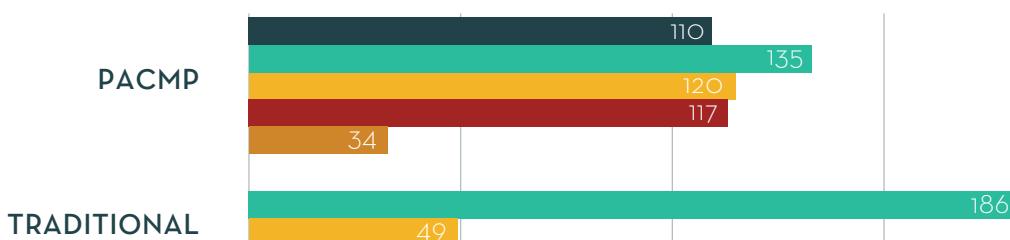
>>> REGULATORY STRATEGY OPTIONS

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.**



Days between submission and approval for release of different products in different jurisdictions using a PACMP vs a traditional approach

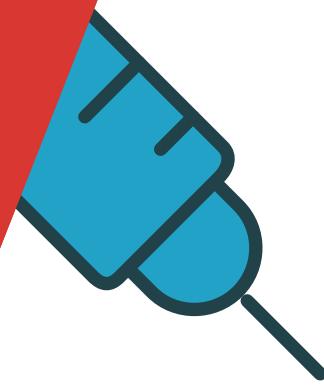
This regulatory strategy and related tool could lead to faster and more predictable implementation of PACs as well as mutual understanding and agreement of planning between the company and the respective NRA, and ultimately risk-based batch release, compared to classical approach waiting for the last stability data to implement the PACs.

The Post-Approval Change Management Protocol is a regulatory tool that provides predictability and transparency in requirements and studies to implement a PAC and its consequences. It allows early dialogue with assessors

and inspectors and was helpful to resume supply and access to quality medicines to patients in the context of critical shortage of an essential medicine.

case study

04

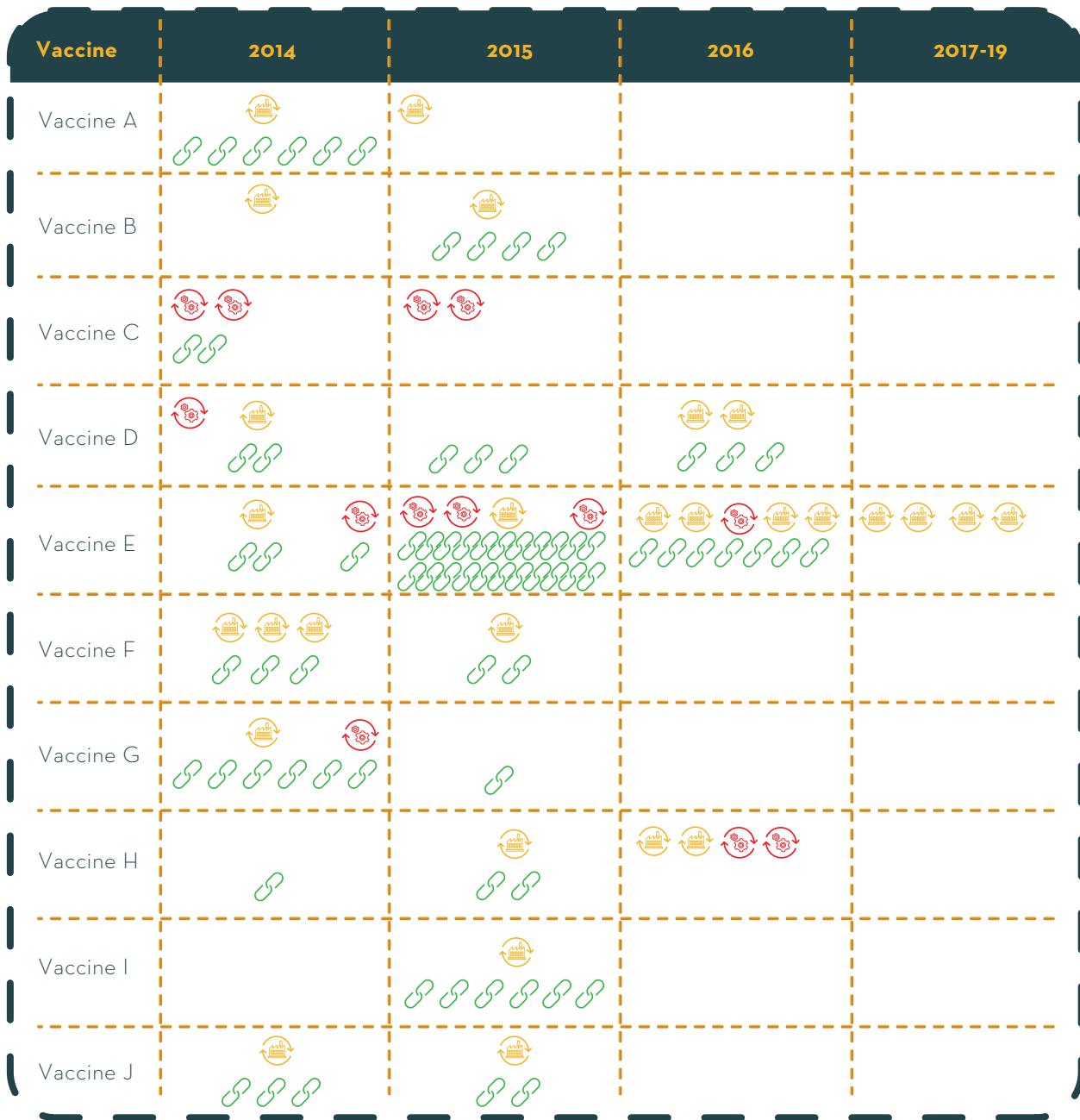


Multiple PACs to Vaccine Products



SITUATION

»»» 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)

Vaccines are biological products ranging from live viral vaccines to recombinant protein antigens, which can be formulated into larger combinations. They may also include an adjuvant to potentiate the immune response. To add to the complexity, vaccines have long life spans (e.g. recombinant hepatitis B vaccine was first launched in the 1980s); the result is that vaccine marketing authorisation licences need to be maintained for long periods. Moreover, as vaccines are biologicals, PACs to vaccine products have to be implemented more often, and these tend to be classified as major. In contrast to many pharmaceuticals, the same change can frequently be repeated across multiple products. In addition, a lot of vaccines are manufactured in global manufacturing chains resulting in complex supply challenges, which have the potential to impede timely delivery of vaccines worldwide.

The case study shown above is a snap-shot from 2013/2014 projecting the PACs needed for a range of vaccine products over 3-4 years. The PACs are broadly classified into those impacting buildings/sites, the manufacturing process, and others (such as specifications, reagents, devices).

STRATEGY

This case study shows that many vaccine products (often combinations) have multiple PACs in one year. Given that each change can potentially impact 50-100 licences worldwide (as vaccine products are often registered widely) it is easy to understand how a vaccine company can file for thousands of PACs each year.

This case study shows that many of the PACs involve manufacturing site and building PACs. As millions of doses of vaccines are produced to supply large immunisation programs, new sites of manufacture are often introduced to ensure supply of these doses and to maintain state-of-art processes. In total, across all the

products, 26 building/site PACs are shown (though many will be the same site, as the same building is used for multiple products). Given that such PACs often impact many licences, this represents approximately 1300-2000 building licence PACs alone around the world (based on 50-75 licences per product). As each new manufacturing site change can take around 5 years to be approved globally, in some countries patients won't have access to the product from the new site for at least the first five years after its first registration. This 5-year period is long enough for other PACs to be filed for maintaining state-of-the-art processes and innovation.

The result of this is that vaccine companies, in particular, submit multiple PACs to many licences worldwide that are overlapping or partially overlapping in time. A single change can be assessed numerous times by different authorities globally, each of them taking different times to assess and approve (in some cases, between 24 to 36 months). This requires high levels of supply chain management to track PACs in the product to ensure that the product released matches its registered details in a given country. It also means that multiple variants of the same product need to be produced and handled to ensure supply of vaccine products worldwide.



LESSONS LEARNED AND RECOMMENDATIONS

NRAs from different markets need to assess and approve PACs to vaccine products for use in their population. Vaccines are often used in young healthy populations so we must be assured that any change does not impact safety, quality or efficacy.

This case study however illustrates the significant number of PACs being submitted worldwide. A single regulator only sees a fraction of these PACs but the global picture is complex with multiple PACs at different stages. Ultimately, the regulator and the vaccine manufacturer aim to supply high quality, well tolerated and effective vaccines, manufactured using processes that are continuously improving to keep up to date.

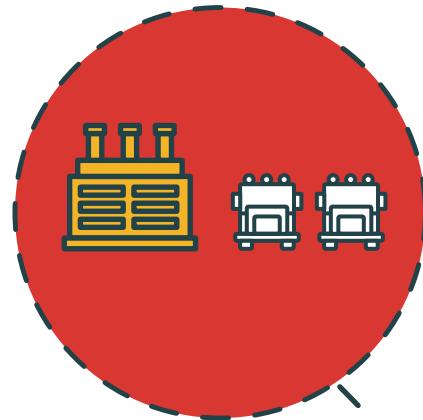
The current system and approach of submitting multiple PACs worldwide that are assessed repeatedly during a period of 3-5 years is not sustainable. We need to recognise that the industry needs to continue to work on harmonizing the way it presents data to regulators, but regulators, should also seek to converge requirements and align PACs requirements and timelines to enable PACs to be regulated whilst minimising the impact on continuous supply. There is a need for processes which allow routine PACs that meet the requirements of a defined protocol, to be managed in the pharmaceutical system.

A greater emphasis must be placed on creating opportunities for reliance on change assessments within groups of regulators, enabling regulators to specialise in certain product or disease areas. For vaccines, reliance is particularly important, considering that many NRAs start with chemical drug expertise and then move into vaccines. Relying on agencies that have vaccine expertise already is a great way of making vaccine regulation time and cost-effective, while allowing NRAs to develop their own specific expertise on other areas, and relying on other regulators for different products. Apart from trying to reduce the number of PACs we

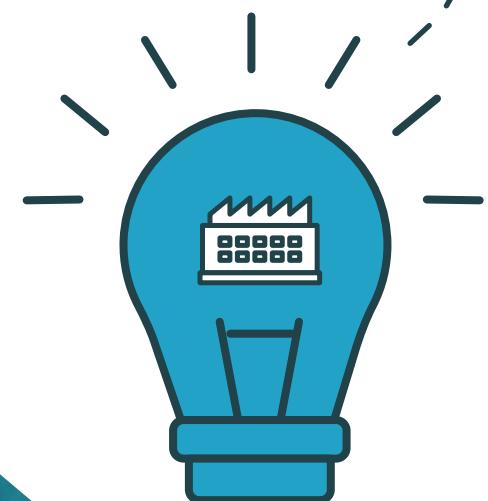
submit, we must also look for ways to make PAC management more predictable and less complex. This will allow us to make PACs without compromising efficient supply while fostering innovation, ultimately ensuring global access to safe and efficacious vaccines.

case study

05



Implementation of New Facility to Provide Additional Drug Product Manufacturing Capacity at an Existing Site



SITUATION

A global pharmaceutical company built an adjacent building (connected) to one of their currently-approved manufacturing buildings. This new building is intended to promote product supply, thus changing the current drug product manufacturing capacity. The new product fill-lines utilize isolator technology and provide additional levels of control for the aseptically-produced parenteral products. Once functional, this production facility can manufacture around 10 innovative globally distributed products.

STRATEGY

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 Post-Approval Change Management Protocol that outlined 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.



LESSONS LEARNED AND RECOMMENDATIONS

Given the long approval timelines in many jurisdictions and to promote adequate product supply in all markets, the company chose to maintain production in both the original and new manufacturing facilities. Operation of the original facility was extended for more than 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 (and product scrap), while delaying the implementation of process improvements.

Harmonization with the WHO (and/or the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) requirements should lead to shorter and standardized review timelines, while improving the quality of the review. 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.

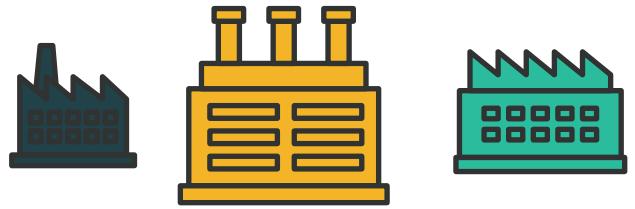
Improving the global submission and approval processes provides increased visibility and confidence in approval timelines, thus encouraging future investment and innovation in drug manufacturing.

case study

06



Implementation of Additional Drug Product Testing Site



SITUATION

A global pharmaceutical company added an alternate drug product testing site (in addition to the existing), for a commercially approved parenteral biologic product (monoclonal antibody). The additional testing site is owned and operated by the company and is currently approved to perform similar release testing for multiple other parenteral biologic products. The site is registered, inspected, and has been deemed compliant with the GMP in place, in numerous regulatory inspections.

STRATEGY

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.



LESSONS LEARNED AND RECOMMENDATIONS

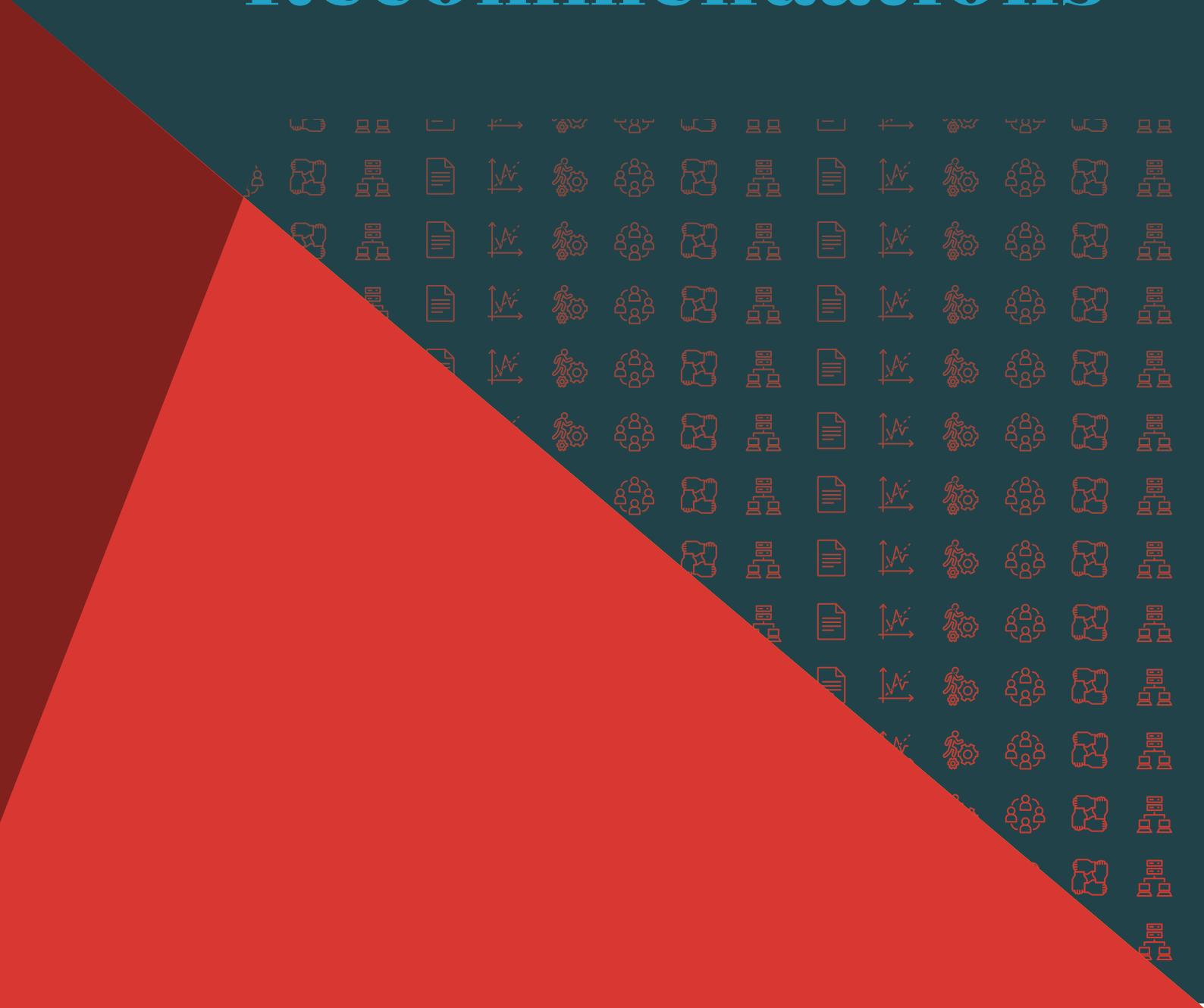
From the company's perspective, this PAC has minimal potential to impact product quality, considering that:

- There were no changes in testing or analytical methodology. All methods had been previously validated;
- The receiving lab is currently approved for similar methods and products, has current evidence of compliance with the current GMP, and is inspected regularly;
- Internal procedures (and current GMP and Product Quality Systems) provide systems with adequate controls.

Requirements for routine PACs (such as registration of an alternate test site) have consistent requirements (e.g. method transfer reports) 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 (and instead be provided as a notification similar to the US annual report or European Medicines Agency via Type 1A submissions).

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.

Recommendations



IFPMA recommends the worldwide implementation of consistent and harmonized regulatory approaches for the management of PACs. These should be proportionate to the impact that the change might have on product quality, safety, and/or efficacy. Specifically, IFPMA recommends adoption of the following:

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.

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.

05



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

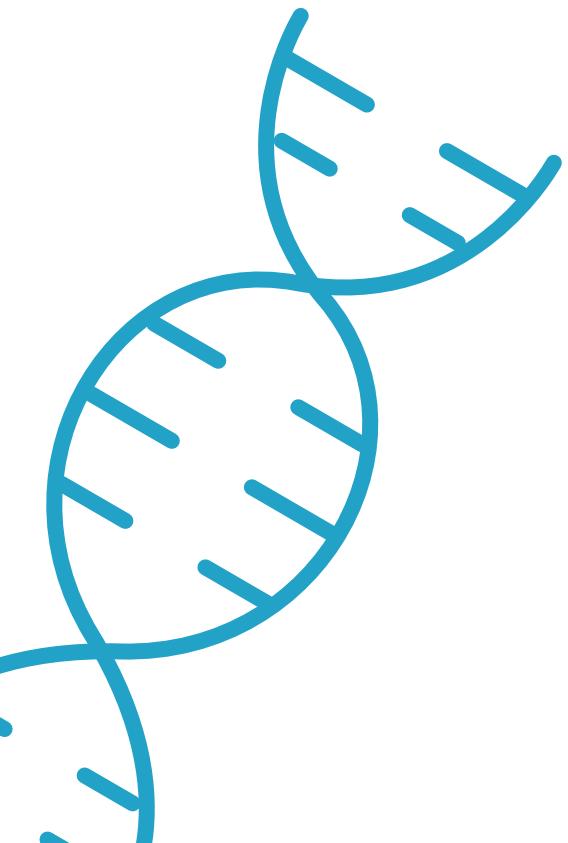
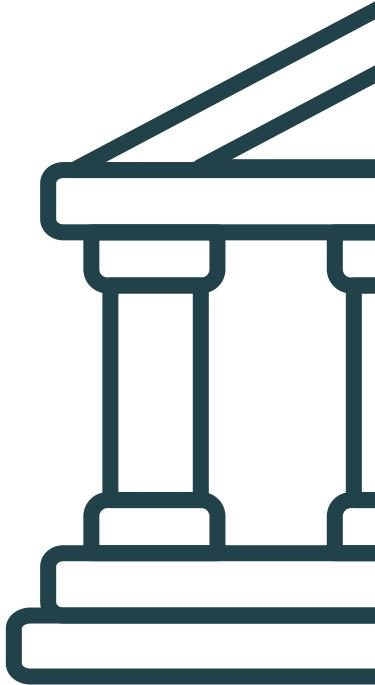
IFPMA encourages collaboration and reliance on approvals from experienced NRAs to facilitate approval of moderate and major PACs based on previous experts' review resulting in shorter approval timelines, as outlined in the WHO's guidelines for vaccines and for biotherapeutics. NRAs should consider introducing 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:

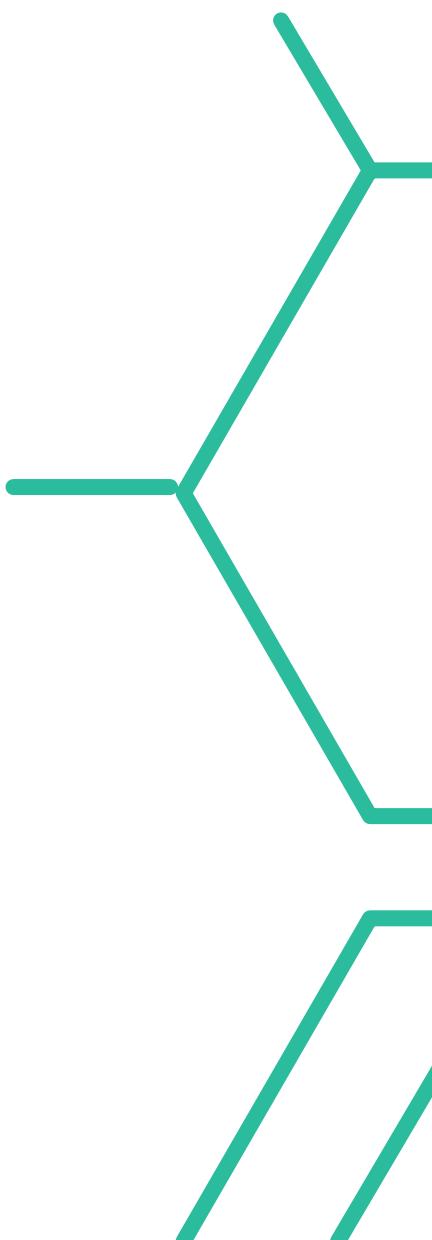
Electronic means to access product information should be gradually introduced, based on learnings from early-adopting NRAs. Timely access could be achieved through, for example, promoting the use of experienced NRAs' websites where-up-to date approved labels/labelling are stored, maintained and easily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

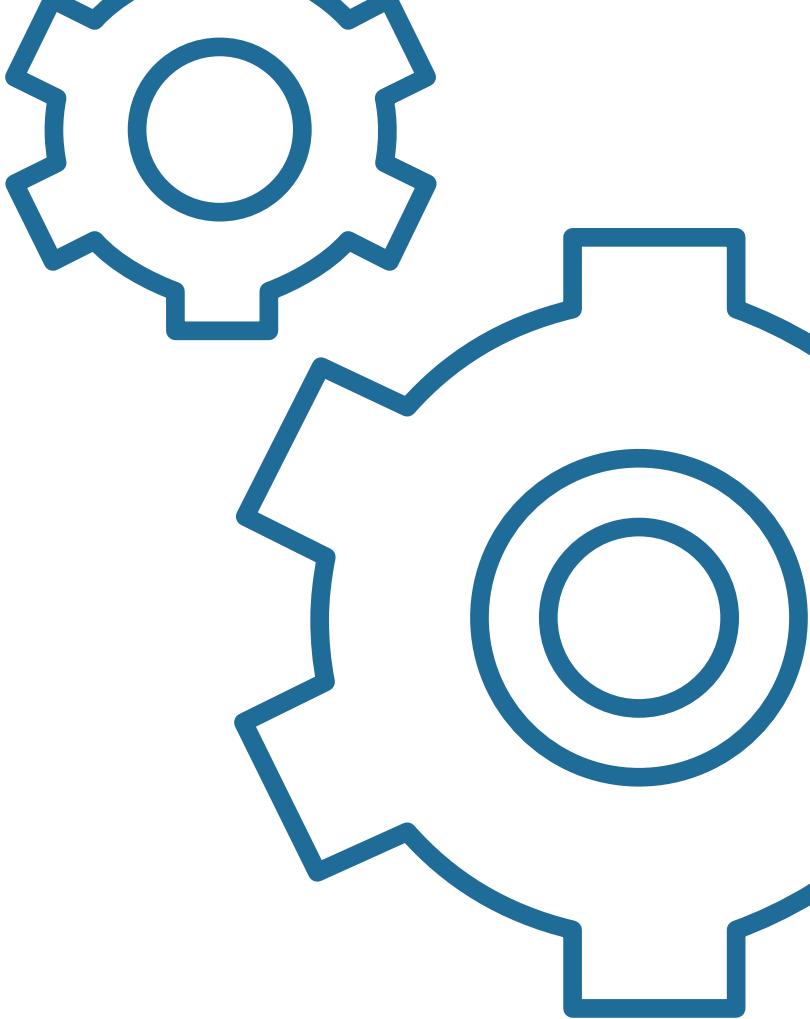
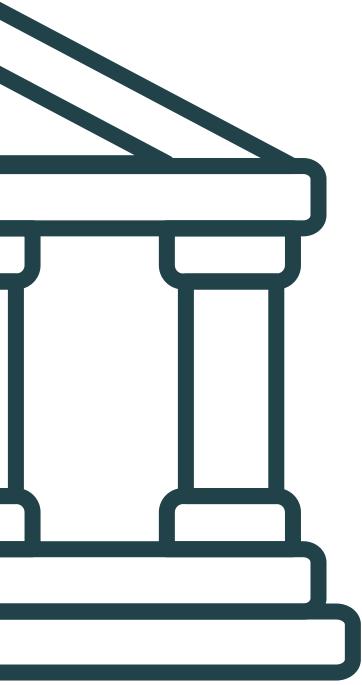


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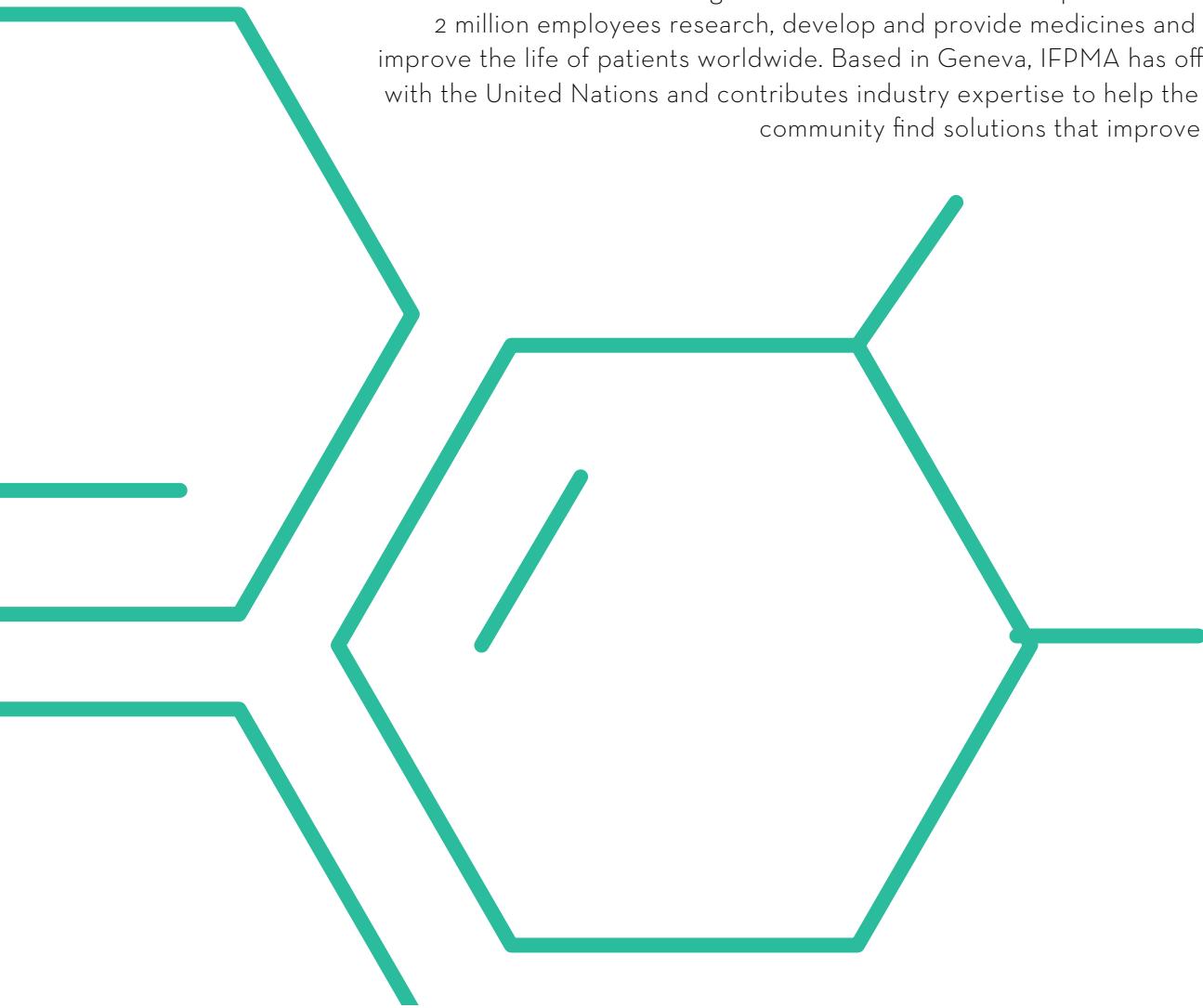


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IFPMA represents the research-based biopharmaceutical companies and associations across the globe. The research-based biopharmaceutical industry's 2 million employees research, develop and provide medicines and vaccines that improve the life of patients worldwide. Based in Geneva, IFPMA has official relations with the United Nations and contributes industry expertise to help the global health community find solutions that improve global health.





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