Optimising the management of post-approval changes for patients' timely access to medicines

The industry perspectives with a Pledge for Convergence

7th APAC, April 2018

Sannie Chong (Ph.D. FRSC)
Asia Pacific Tech Regulatory Policy
Roche Singapore Technical Operations

Outline

1. Challenges facing industries in post-approval change management
2. Case studies to illustrate the complexities
3. Reflection for pragmatic solution (global convergence) to optimise post-approval change regulations

Outline

1. Challenges facing industries in post-approval change management
2. Case studies to illustrate the complexities
3. Reflection for pragmatic solution (global convergence) to optimise regulations of post-approval variations

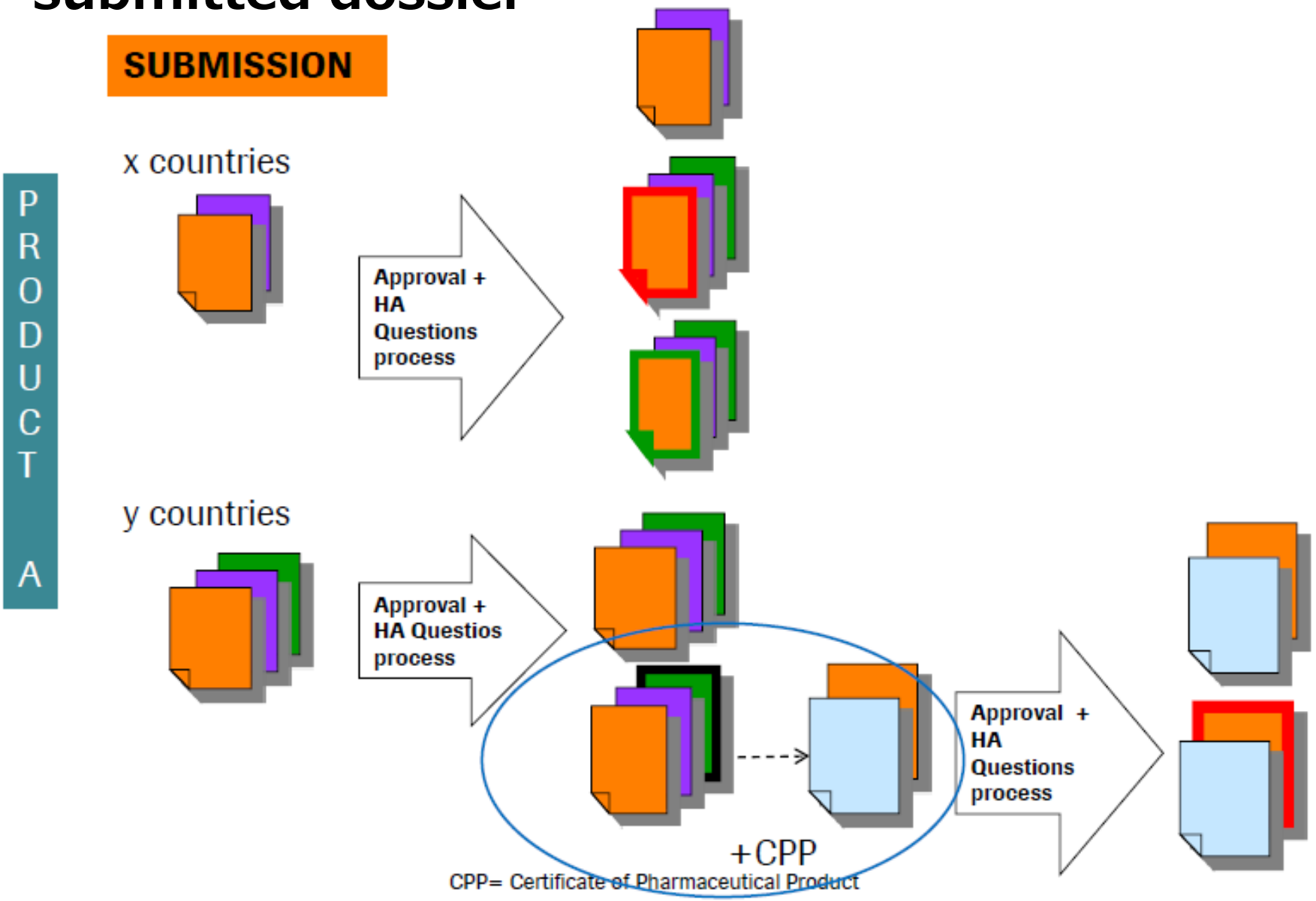
Pharmaceutical companies are operating globally and have global manufacturing sites

- Manufacturing sites across the world
- Global registration with Health Authorities
- Global supply chain
- Multiple sourcing strategy

The content differences at original submission are the first main cause for life-cycle complexity

- Activities in approximately 140 countries
- Two categories of CMC packages
  - ICH-like requirements
  - Countries asking for less detailed information
- Trend towards introduction of country-specific or regional data
  - Degree of detail
  - Certificates e.g. Certificate of Pharmaceutical Products (CPP)
  - GMP related documents - “paper inspections”
  - Raw data
  - Declarations, signature

Approved details differ from country to country after Q&A compared to the submitted dossier



One global submission can lead to several dossier versions approved in different countries

Represents one dossier (for one product)

- One global submission can lead to **multiple** separate registration dossiers with different content

➔ **Regulatory environment requires convergence**

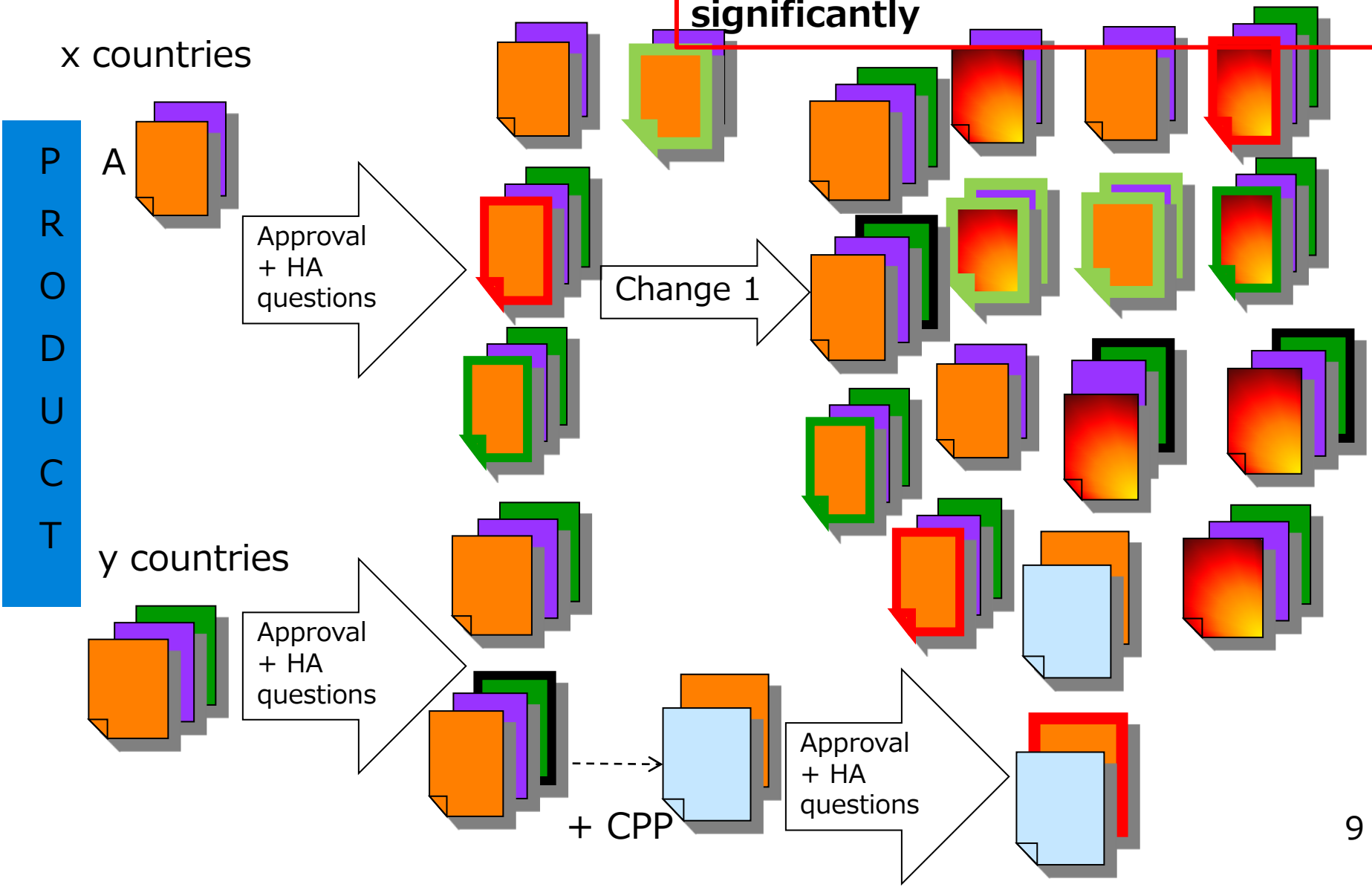
Introducing changes post-approval is an essential part of the lifecycle of a product

- Ensure market access and continuous supply of live-saving drugs to patients by reacting to supply demands
- Support continuous improvement and optimization of manufacturing process and quality of the medicinal products
- Remain state-of-the-art with manufacturing methods and analytical techniques
- Alignment with global safety reporting requirements
- Fulfill regulatory agency requirements

Approved details differ from country to country after Q&A compared to the submitted dossier

Roche

Changes add to the complexity significantly



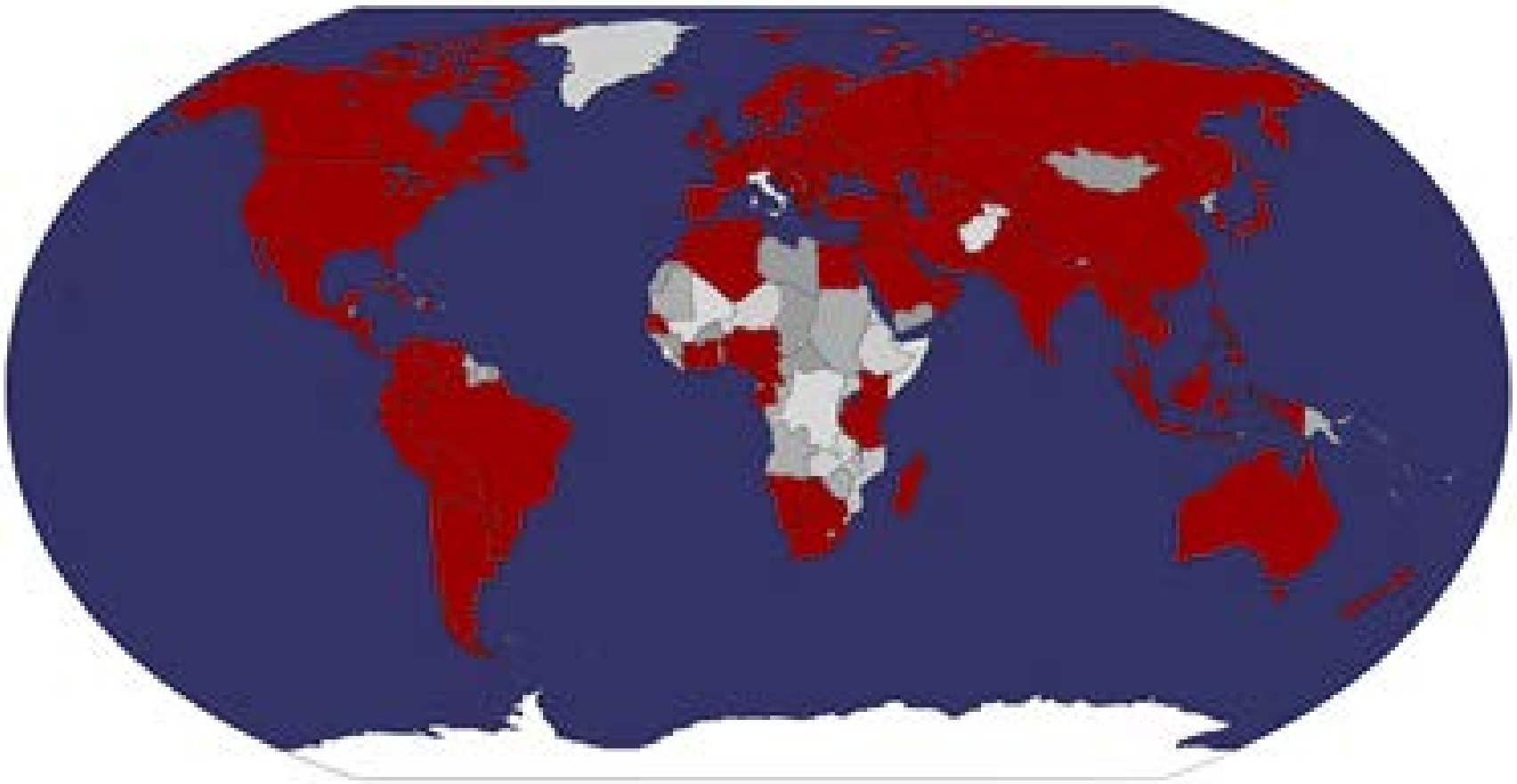
Outline

1. Challenges facing industries in post-approval change management
2. Case studies to illustrate the complexities
3. Reflection for pragmatic solution (global convergence) to optimise regulations of post-approval variations

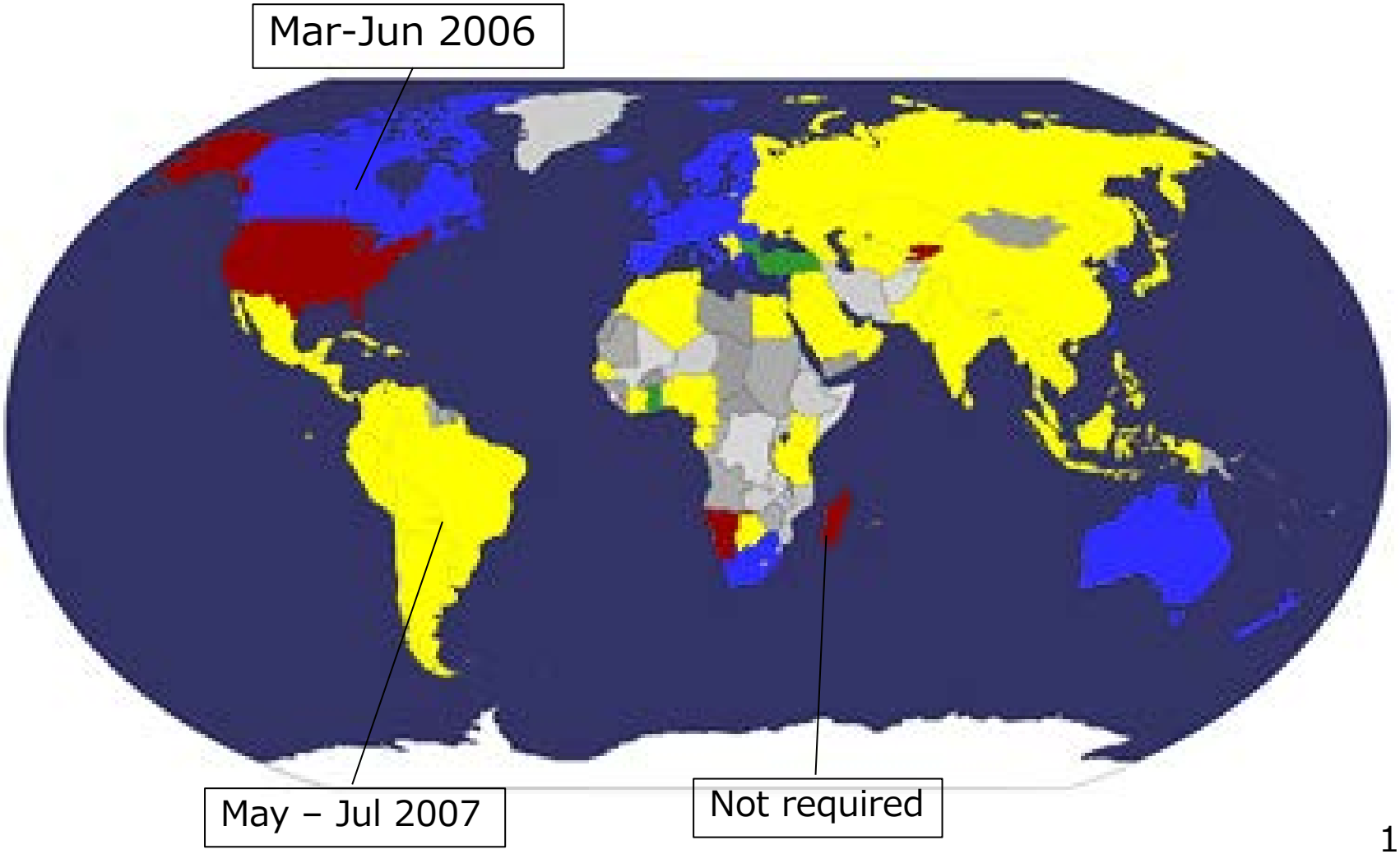
Case study:
Site addition

- Change description
  - Site change
  - Involves technology transfer of the Drug Product manufacturing process to an additional site

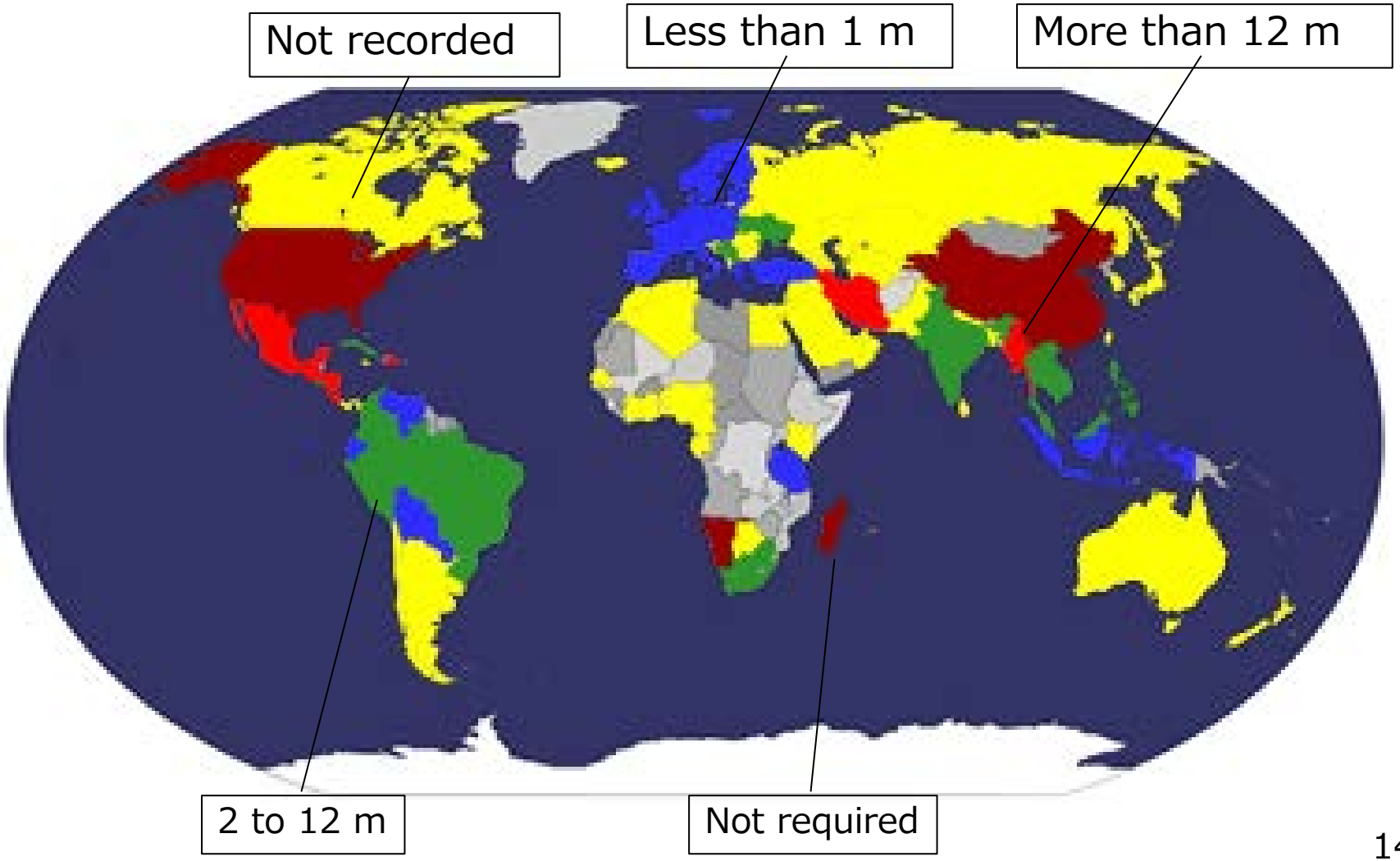
Case study
Product 2 is registered in 120 countries at the time of the Drug Product Site addition



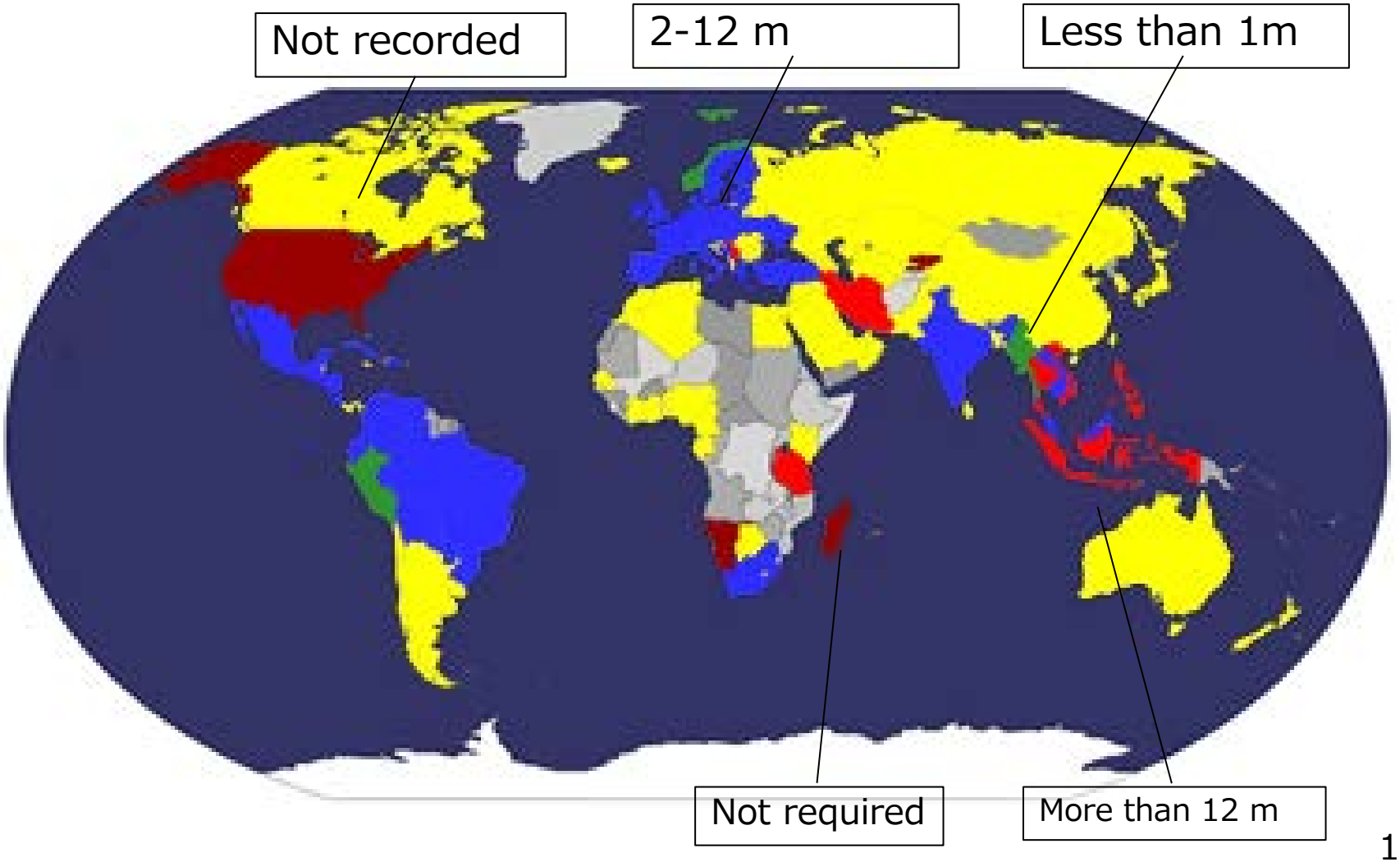
Case study:
The change was dispatched to all but three countries in 2 waves



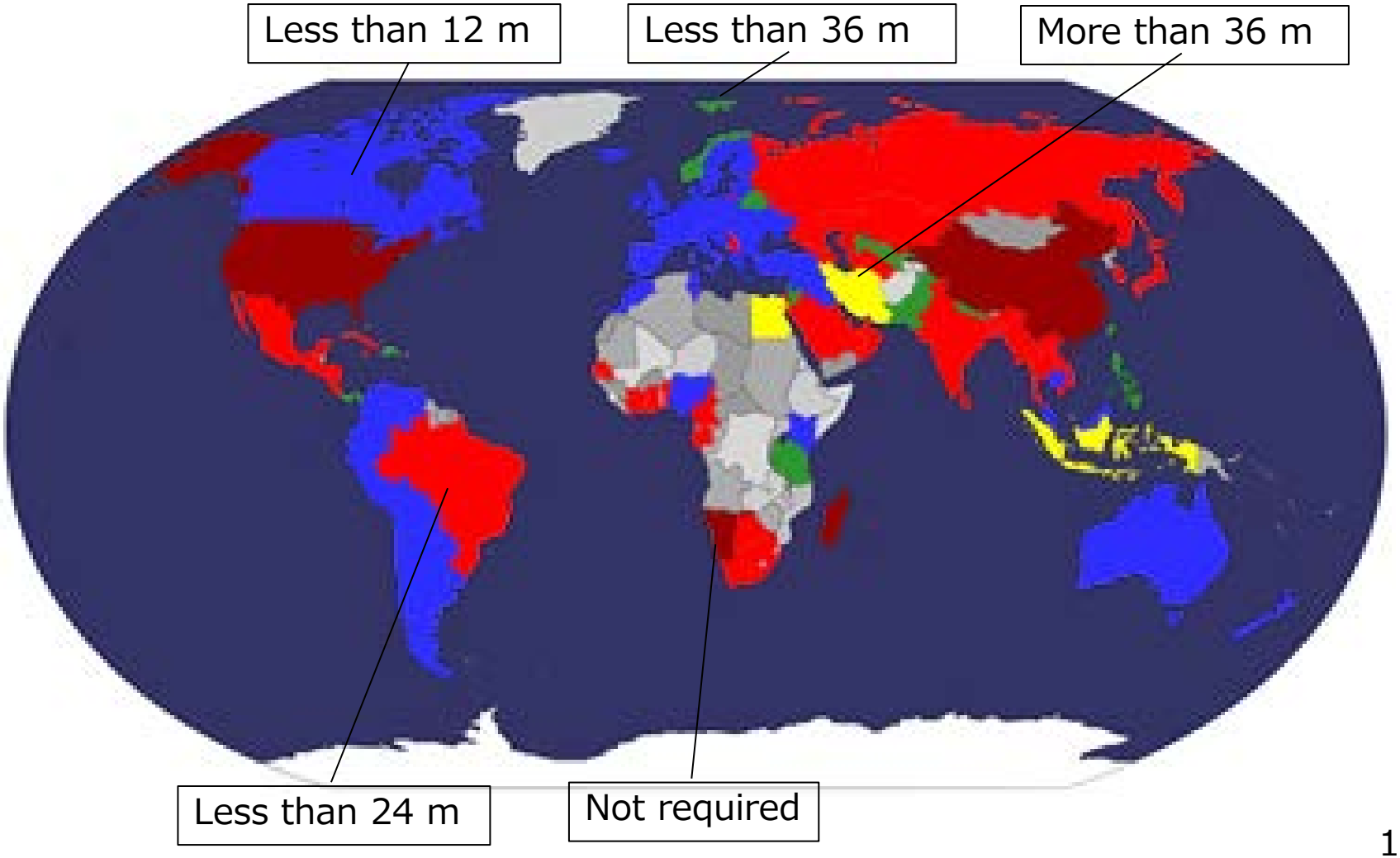
Case study: The actual submission was performed within 10 months by the majority of countries



Case study: The time from submission to approval – where recorded – varied substantially



Case study: A majority of countries approved in 24 months after dispatch but global implementation took 41 months



Increased Complexity: Site addition is a new registration instead of a post-approval variation

Site Change	1-Site-1 License
Regulatory Application	New registration
- Dossiers	Module 1-2-3
- Stability	ASEAN Stability requirement
- Shelf-life	At least 24 months
- CPP	Required
- GMP	Required
- Leaflet	Same
- Label for manufacturer	Applicable, individual
- Application Fee	Yes
- License fee	Yes
- Lead time	18 months
- Fast track regulation	Not available
- Expert	2x Quality experts
- Sample import and testing	Yes

Filing as "new registration" requires huge amour

Safety Changes
Impact of the Current Regulatory Landscape

- Information on the safe and effective use of medicine to benefit HCPs and patients
- It is therefore of utmost importance that information is kept updated, and rapidly accessible, throughout the lifecycle of a medicine, as new safety data emerge
- The approval process for safety labelling changes can be lengthy (up to 3 years)
- In addition, approval timelines are unpredictable and vary from *NRA to NRA

❑ Impact: Approval delays slow down HCPs and patients' access to up-to-date product information, including the latest approved Benefit-Risk profile of the product. In this case, delayed approvals also have direct consequences on pharmacovigilance procedures

❑ Impact: Unpredictable timelines further add to the complexity of the planning of updated labels on the market. This can potentially increase risks for patients whereby HCPs, and patients themselves, do not have access to the available information

❑ Impact: With much product information now being available over the internet – which patients across countries can access – the different approval timelines can create confusion and consequent product misuse/noncompliance.

*NRA: National Regulatory Authority

Outline

1. Challenges facing industries in post-approval change management
2. Case studies to illustrate the complexities
3. Reflection for pragmatic solution (global convergence) to optimise regulations of post-approval variations

Ongoing efforts for harmonization at regional and global levels

Global Regulatory standards

- Improvements in supply, quality and safety
- Better outcomes for patients
- Global access for innovative pharmaceuticals

Driving Global Regulatory Convergence

WHO guideline for PAC to biotherapeutic products

World Health Organization

Post ECBS Version
ENGLISH ONLY

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 17 to 20 October 2017

Guidelines on procedures and data requirements for changes to approved biotherapeutic products

Overview of WHO Guideline

http://www.who.int/entity/biologicals/expert_committee/PAC_highlighted_20_Oct_2017.HK.IK.pdf

Contents

WHO Appendix 1

Reporting categories and suggested review timelines

Quality changes		
Reporting categories	**Procedures**	**Suggested review timelines[1]**
Major quality changes	Prior approval supplement (PAS)	3–6 months
Moderate quality changes	PAS	1–3 months
Minor quality changes	Require notification to the NRA[a, b]	N/A
Quality changes with no impact	Do not require notification to the NRA	N/A

Safety, efficacy and product labelling information changes		
Safety and efficacy changes	PAS	10 months
Product labelling information changes	PAS	5 months
Urgent product labelling information changes[c]	PAS for urgent safety restrictions	Immediate implementation on receipt of supplement by the NRA
Administrative product labelling information changes	PAS	30 days
	Do not require approval prior to implementation[d]	N/A

WHO clear category and dataset based on risk

6.4 Quality changes with no impact

Quality changes that have no impact on quality, safety and efficacy of product may be implemented by the marketing authorization holder without prior review by the NRA. These changes must be retained as part of the manufacturer's GMP records or marketing authorization holder's product records, as applicable. These changes must comply with the applicable GMP requirements and must be available for review during GMP inspections. Examples of such changes include, but are not limited to:

- non-critical changes to the licensed application, including corrections to spelling mistakes, and editorial changes made to documents (such as validation summaries and/or reports, analytical procedures, standard operating procedures or production documentation summaries for added clarity) that have no impact on the quality, safety and efficacy of the product;
- replacement of equipment with an identical equipment;
- change in specifications for a compendial raw material, a compendial excipient, or a compendial container closure component to comply with an updated pharmacopoeial standard/monograph;

Comparison of change/reporting categories
Regional initiatives (e.g. ASEAN) can adopt WHO Guideline

Risk	Approach/ Region	EU	US	Japan	Canada	WHO	ICH Q12
Higher	«PRIOR APPROVAL»	Type II Variation (2-3m)	Prior Approval Supplement (PAS, 4m)	Partial Change Application (PCA, 12m)	Supplemental New Drug Submission (6m)	Major Variation (3-6m)	Prior approval
Moderate	«TELL, WAIT & DO»	Type IB Variation (1m)	Changes being effected in 30 days (CBE-30)	Minor change Notification (MCN, 1m)	Notifiable change (3m)	Moderate Variation (1-3m)	Notification moderate
	«TELL & DO»	Type IA_{IN} Variation	Changes being effected (CBE-0)	Non approved matter	Level 3 (annually)	Minor Notification	Notification minor
	«DO & TELL»	Type IA Variation (Annual report)	Annual Report (AR)				
Lower	GMP	PQS only	PQS only		Level 4 (On-site/GMP record)	With no impact (On-site/GMP record)	PQS only

WHO Guidelines recommending work-sharing and reliance

Implementation of new regulations should not affect product supply and access to products. Therefore, NRAs are strongly encouraged to establish requirements that are commensurate with their own regulatory capacity, experience and resources. NRAs of countries procuring products are encouraged to consider establishing procedures for the expedited approval of changes based on previous expert review and approval of the same changes by the NRAs of the countries where these products are licensed, or based on the decision of a recognized regional regulatory authority. If a change has been approved by another competent NRA, the NRA receiving the submission may choose to recognize this approval decision or may make an independent decision based on its own assessment. Foreign approval documentation may accompany the required information to support the change, as outlined in this document. The responsibility for the final regulatory decision on the approval of the change still lies with the receiving NRA (see section 8 and Appendix 1).

Singapore Health Sciences Authority's new route *Verification route (reliance approval) for PAC*

- Verification route with shorter timeline, which aims to:
  - enable greater leveraging of reference agencies' assessments
  - minimise duplication of effort
  - enhance process efficiency as part of HSA's on-going effort, in particular for effective life cycle management for registered medicinal products
- To qualify, the proposed variations must be:
  - identical to those approved by one of HSA's five reference agencies
  - accompanied by the proof of approval of that reference agency
  - (when required) approved product label of that reference agency
- **Not required to submit certificate such as CPP, or assessment report.**

Source: HSA MedProd Registration "Update on HPRG's Initiatives", Jun 2016, Q4 2017

How can ICH Q12 help to address the challenges mentioned before?

- **Categorisation of changes**: define a risk-based categorisation/ communication framework with the regulatory authorities for CMC changes
- Clarifying **established conditions**, i.e. stimulated by the Japanese Module 1 provides a clear understanding between firms and regulatory authorities regarding the necessary (binding) elements to assure product quality


ICH
harmonisation for better health

INTERNATIONAL CONCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT

Q12

Draft version

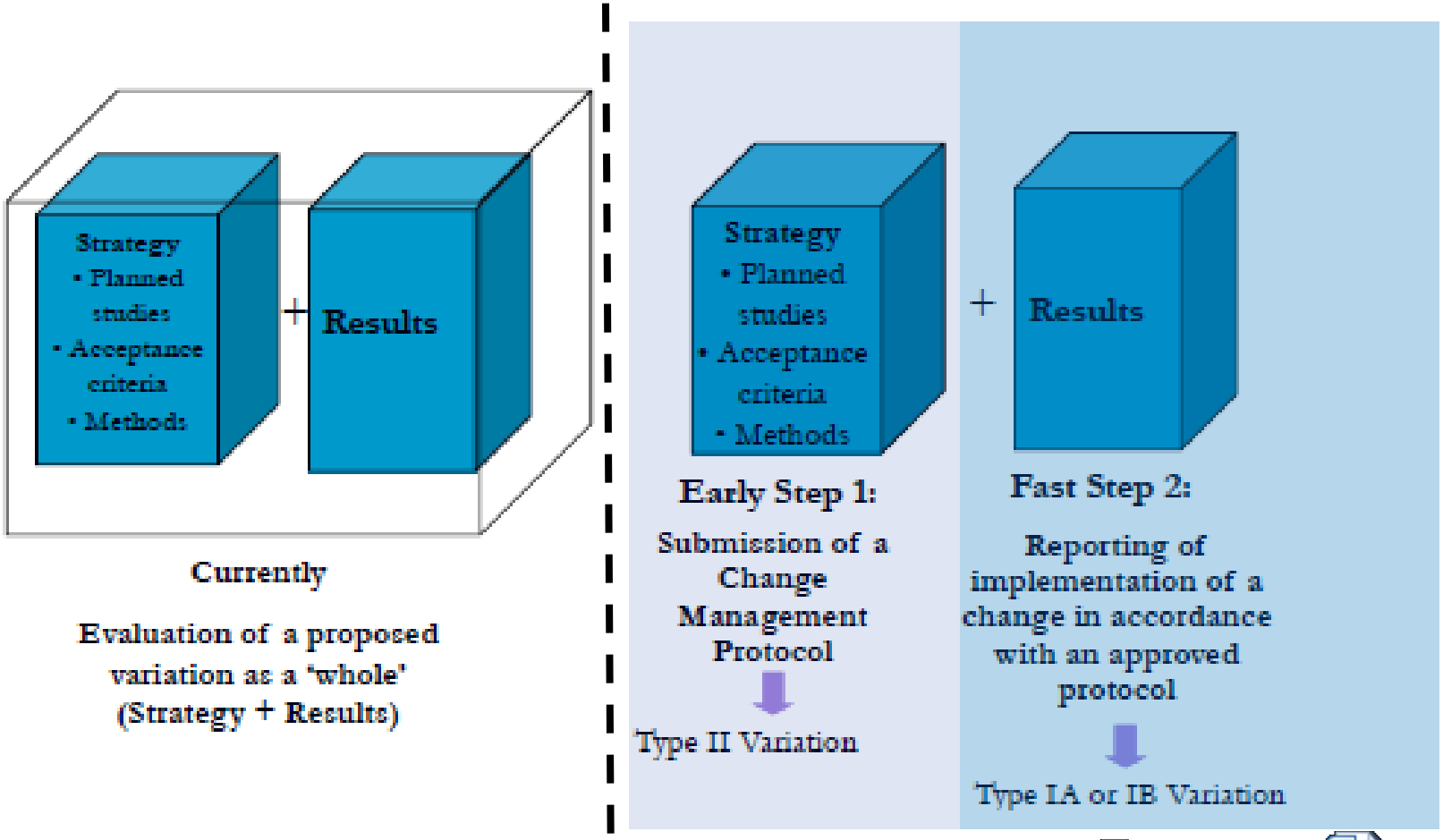
Endorsed on 16 November 2017

- Introducing **post-approval change management protocols (PACMP) globally** as a valuable regulatory tool to modify the filing category for changes based on prior agreement between the firm and regulatory authorities

Can be implemented together with (WHO) variation guideli

- Development of **product specific lifecycle management strategy**: central repository for the established conditions and the associated reporting category when making changes to established conditions

EMA principle of the Change Management Protocol: a 2-step implementation approach



Source: *EMA Questions and Answers on post-approval change management protocols*

Adobe Acrobat Document

Microsoft Word Document

Since 2012 defined in EMA Q&A:

Change managment protocol (CMP)

- Describes specific changes that the Marketing Authorisation Holder would like to implement following market approval and how these would be prepared and verified
- Incorporates a science and risk-based approach to evaluate impact of change on product quality
- Objective is more predictable and faster implementation of post approval changes and more global flexibility for change management

CMP is also mentioned in the WHO variation guideline

Similar concept also available in US

MHLW/ PMDA will launch a pilot program for CMP in Japan as of April 1st, 2018

Industry position papers on life cycle management

Roche

IFPMA position paper

EFPIA position
aper February 201

IFPMA

22 November 2016

efpia
European Federation of Pharmaceutical Industries and Associations

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

IFPMA Position Paper on the Handling of Post-approval Changes to Marketing Authorizations

Introduction

Following the initial launch and throughout a drug product's commercial life, changes that might impact the product's quality and safety profile will inevitably occur. These changes may include modifications to raw materials, analytical methods, suppliers, manufacturing equipment, processes and sites and are a consequence of continual improvement, implementation of innovative technologies, efficiencies of production or increases in scale to improve the availability of drug products for patients. Variations, also known as post approval changes, are necessary in order to comply with evolving regulatory requirements.

After receiving market approval, drug products are used in a wider population that brings further knowledge to its safety profile. It is important that such information is reflected in the product labelling in a timely manner for the benefit and safety of patients and healthcare professionals. Thus post approval changes to the originally approved dossier are an essential part of a product's lifecycle. Therefore, it is important that new product knowledge is managed in a structured and planned way to enable continual improvement, to encourage innovation, state of control, and to ensure uninterrupted product availability for patients.

Many drug products are managed globally throughout the commercial part of their lifecycle. However as regulatory systems develop and evolve worldwide, the requirements to submit and review post approval changes and implement safety labelling updates are increasing. As a consequence there is a growing potential for divergence, increased complexity and less predictability across markets. The major challenges with managing variations globally include the variable or unpredictable timelines and submission requirements across National Regulatory Authorities (NRAs) for review and approval. This leads to different implementation dates for changes thus increasing the potential for compliance issues as well as contributing to the complexity due to the need to manage multiple variants of

Concluding Remarks
IFPMA: Longer term solutions

Roche

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

Concluding Remarks
IFPMA: 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 (e.g. change 1-site-1-license to multi-sites-1-license, similar to what Taiwan FDA and Malaysia NPRA have achieved)

Concluding Remarks

Global convergence of post-approval change regulations: a «Win-Win» outcome

Harmonized post-approval regulations ➔ Adopt WHO guidelines (change classification, procedures, timeline) and ICH Q12 Change Mgt Protocol

Regulators	Industry	Patients
✓ Prioritize based on criticality of change ✓ Enable more efficient use of resources ✓ Focus on critical issues without compromising regulations' robustness (Consider Singapore HSA's best practice of reliance)	✓ Allow better planning and execution of changes ✓ Reduce risk of non-compliance ✓ Reduce complexity in supply chain	✓ Improved drug quality rapidly accessible to the market ✓ High quality standard maintained globally ✓ Ensure continuous market access
Reliable supply of high quality drugs to all patients GLOBALLY		
Enhance collaboration/knowledge sharing with other agencies		
Transparency		

Our appeal: Streamline current process (remove 1-site-1-licence similar to what Taiwan FDA and Malaysia NPRA have achieved)

Acknowledgements

- Susanne Ausborn, Wassim Nashabeh, Thomas Schreitmueller, Markus Goese and Kowid Ho - Roche / Genentech

- Hye Na Kang - WHO

Doing now what patients need next