Lifecycle Management of Pharmaceutical Products and ICH Q12 Concepts

NATIONAL REGULATORY CONFERENCE
KUALA LUMPUR, MALAYSIA – August 4, 2015

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Presentation Outline

- Challenges of global lifecycle management (LCM)
- Activities at ICH: Concepts of new Q12 guideline *“Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management”*
- Reflections on situation in the region
- Questions & Answers

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Challenges of global lifecycle management

The Blue Sky Vision

MOST PHARMACEUTICAL COMPANIES ARE OPERATING GLOBALLY

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

Regulatory content differences in original submission = first main cause for life-cycle complexity

Example Roche:

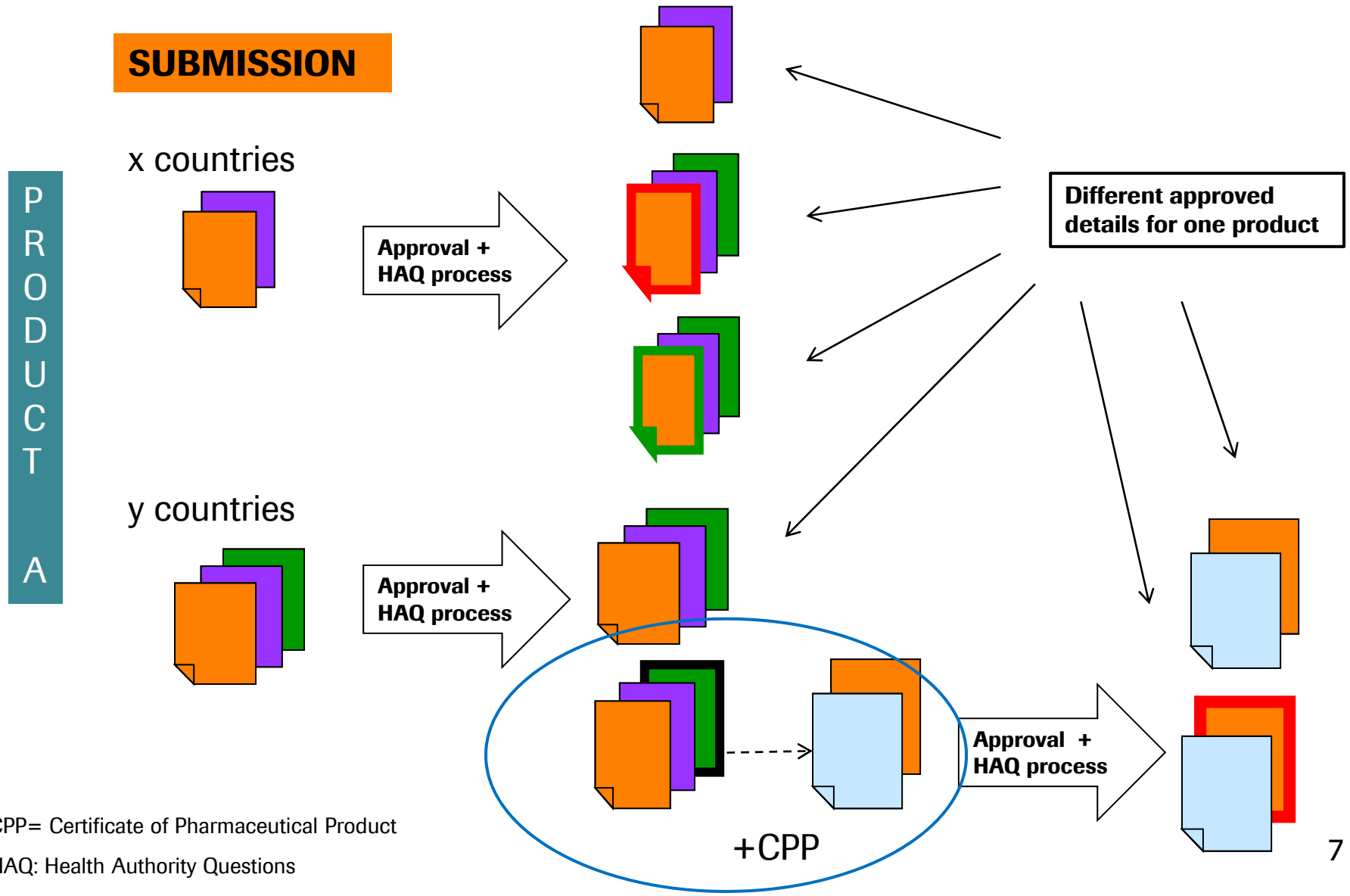
- Approximately 192 recognized states
  - Activities in ~140 countries

- Some countries accepting less detailed (CMC) information

but

- Observed trend towards introduction of country-specific or regional data in other countries:
  - Degree of detail
  - Declarations
  - Raw data
  - Submission of GMP documents – “paper inspections”

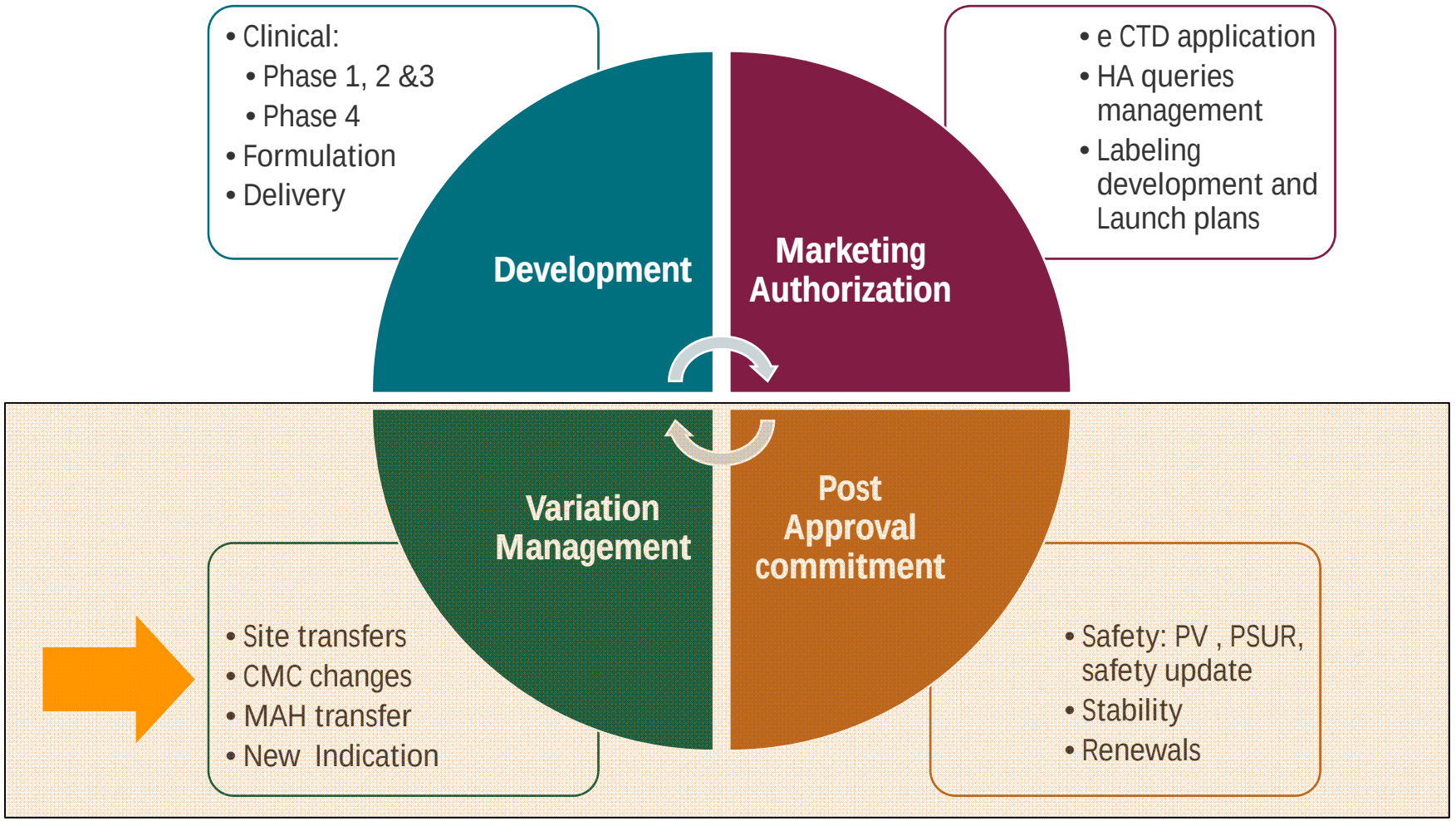
Approved details differ from country to country after Q&A compared to the submitted dossier



CPP= Certificate of Pharmaceutical Product

HAQ: Health Authority Questions

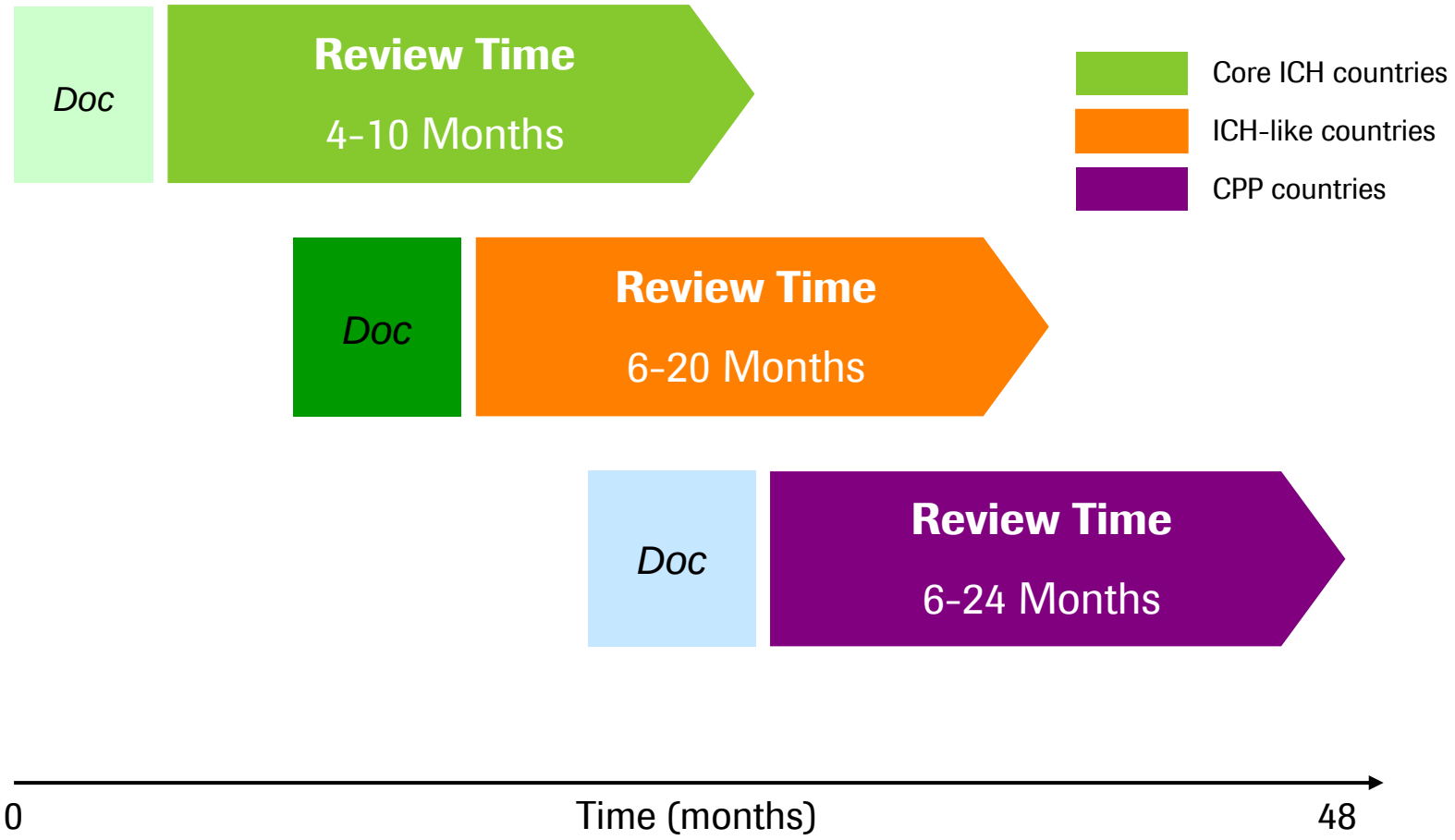
LIFE CYCLE MANAGEMENT OF A PHARMACEUTICAL PRODUCT



Introducing changes post-approval is an <u>essential</u> part of the lifecycle of a medicinal 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
- Fulfill increasing regulatory **agency requirements**

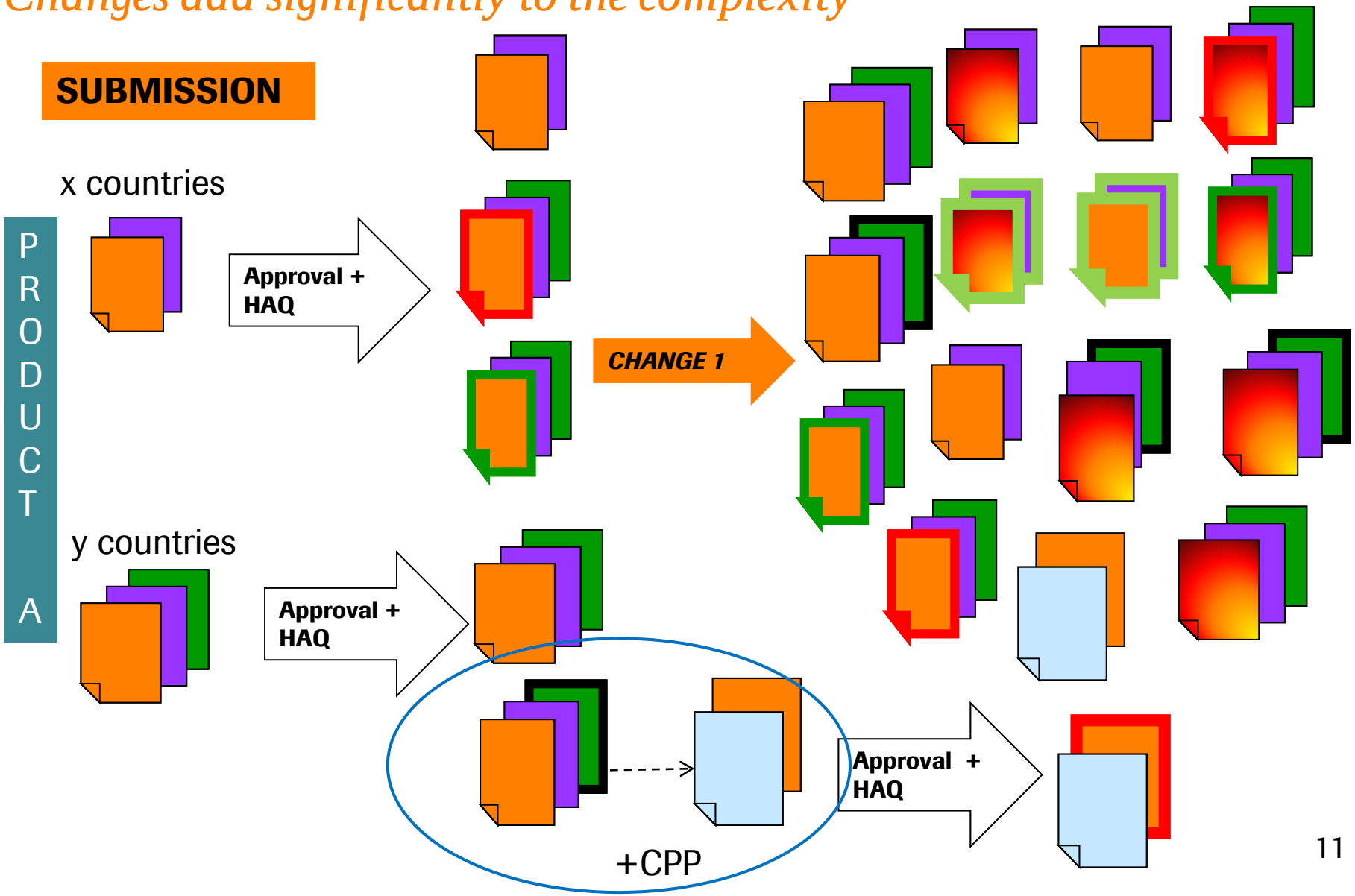
Bringing a post–approval change through the global systems can take years*



** example: manufacturing site-transfer for a biologic drug substance*

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

Changes add significantly to the complexity



Challenges to submit post-approval changes globally

Change classifications different or not available*

Country-specific requirements (e.g., stability, raw data)

Long/unpredictable approval timelines

Backlog due to high review demand at Health Authorities

CPP** or reference approval needed for submission?

Complex supply planning/ high bridging stocks

Drug shortage

Hinder innovation and continual improvement of process and product

Quality and safety

➔ **Need to Reflect on pragmatic solutions**

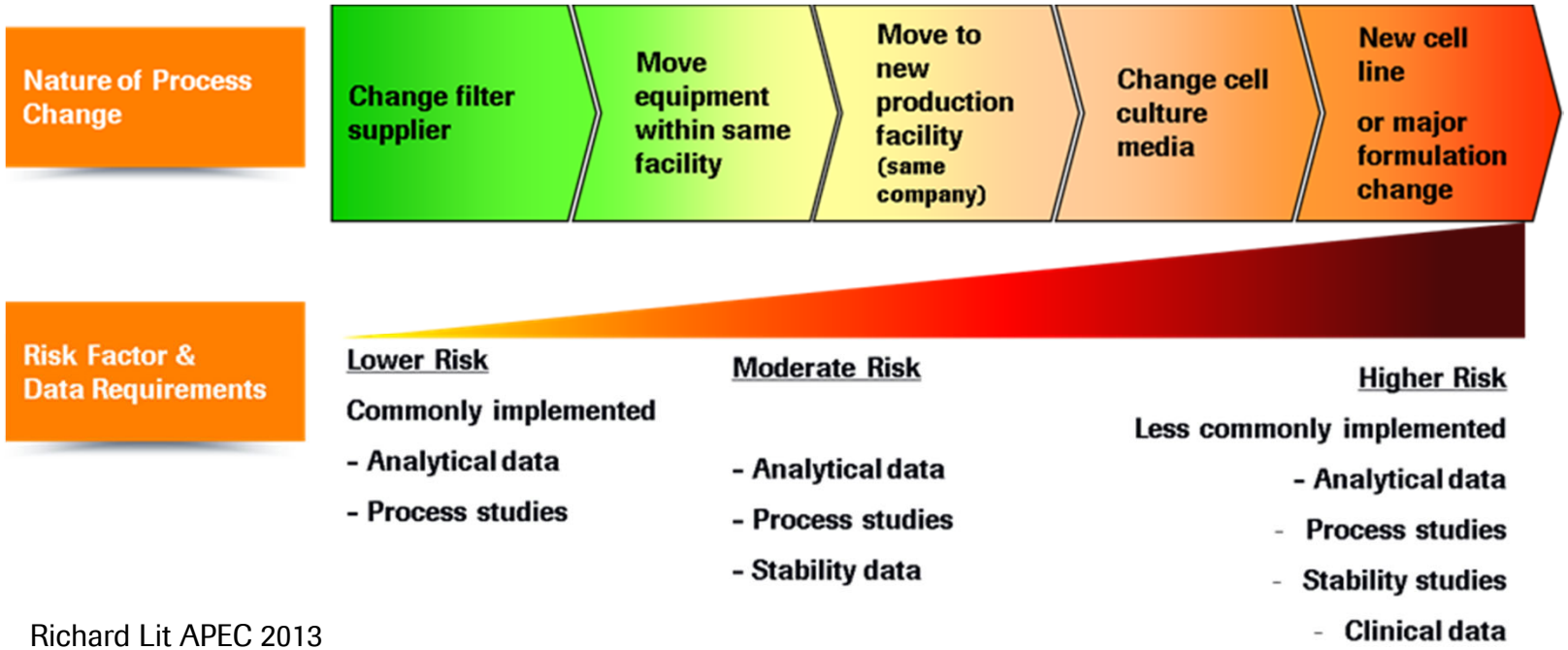
* Missing opportunities for Bundling, Annual Report and streamlining between different variation applications and renewal

** CPP= Certificate of Pharmaceutical Product

Key pillars to facilitate implementation of post-approval changes globally

- ***Change Classification concept***
- ***Procedural guidance incl. timelines***
- ***Documentation and data requirements*** *(remove GMP elements)*

Risk based approach (biotech example):



Richard Lit APEC 2013

Examples for guidelines on handling changes/ variations to an approved dossier

- **WHO** (currently for chemical drugs and vaccines)
- **EMA/ European Commision (EC)**
- **US-FDA**
- **Japan/ PMDA**

for chemical drugs and large molecules/ biologics

- **ASEAN** (currently for chemical drugs only)

Comparison of regional change categories

Risk	Approach/ Region	EU	US	Japan	WHO	ASEAN
Higher	«PRIOR APPROVAL»	Type II Variation	Prior Approval Supplement (PAS)	Partial Change Application (PCA)	Major Variation Vmaj	Type II Major Variation MaV
Moderate	«TELL, WAIT & DO»	Type IB Variation	Changes being effected in 30 days (CBE-30)		Minor Variation Vmin	Type I - Minor Variation-Prior Approval MiV-PA
	«TELL & DO»	Type IA_{IN} Variation	Changes being effected (CBE)		Immediate Notification IN	
Lower	«DO & TELL»	Type IA Variation	Annual Report (AR)	Minor change Notification (MCN), within 30 days after implementation/ shipping	Annual Notification AN	Type I - Minor variation-Notification MiV-N

Roche supporting 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

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LifeCycle* Management: *What is needed?*

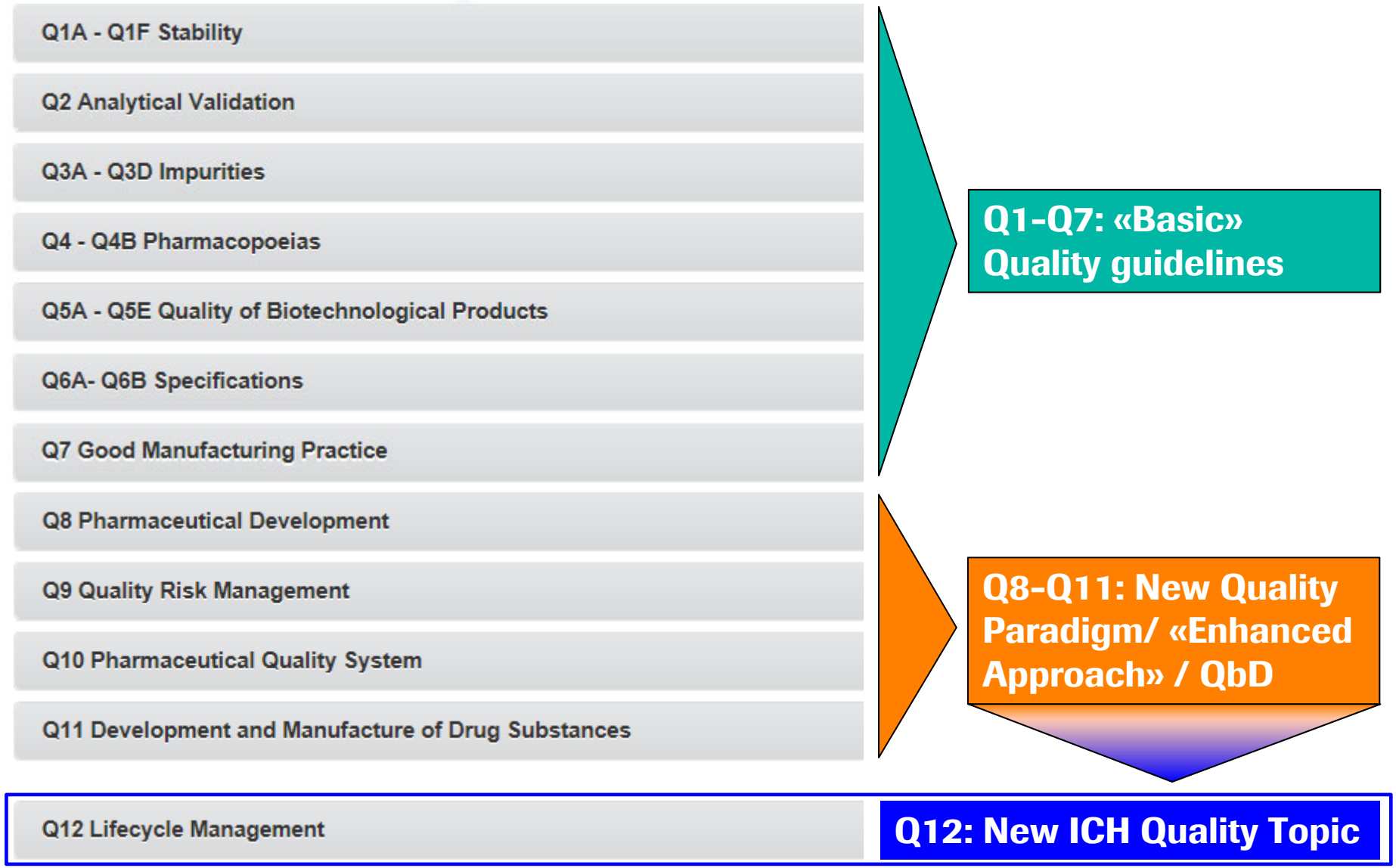
- **Desired state**

  A system that facilitates managing quality changes and continual improvement throughout the whole product lifecycle with an ***emphasis on post-approval/ commercial manufacturing***

*Product and Process LifeCycle:

Pharmaceutical Development → Technology Transfer → Commercial Manufacturing → Product Discontinuation

ICH Quality Guidelines incl. Q12

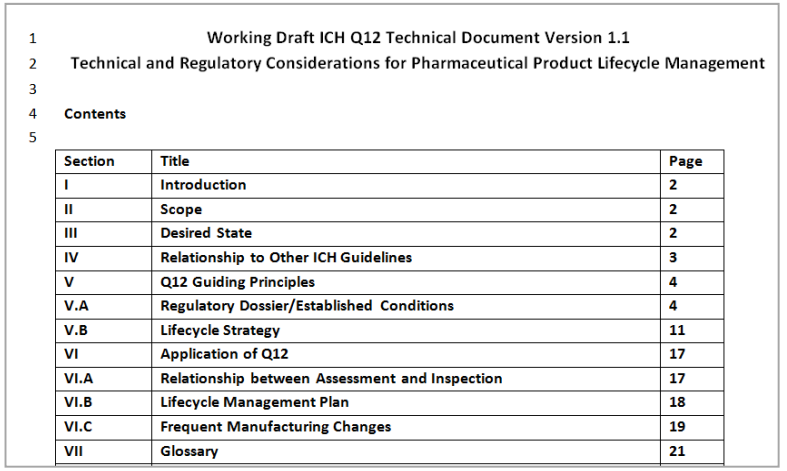


ICH Q12 – Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

- **ICH Q12 Expert Working Group**
  - Diversity of technical expertise (small and large molecule, development, manufacturing, quality and regulatory, assessors and inspectors)
  - Good collaboration, team commits to address difficult topics
  - Q12 EWG team members (current status):
    - **EU/EMA, EFPIA, Swissmedic, APIC, FDA, PhRMA, Health Canada, IGPA, BIO, MHLW/PMDA, JPMA, WHO, WSMI, DoH Chinese Taipei, DRA Singapore**

- **Scope of the Q12 Guideline:** All pharmaceutical products including currently marketed chemical, biotechnological and biological products

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

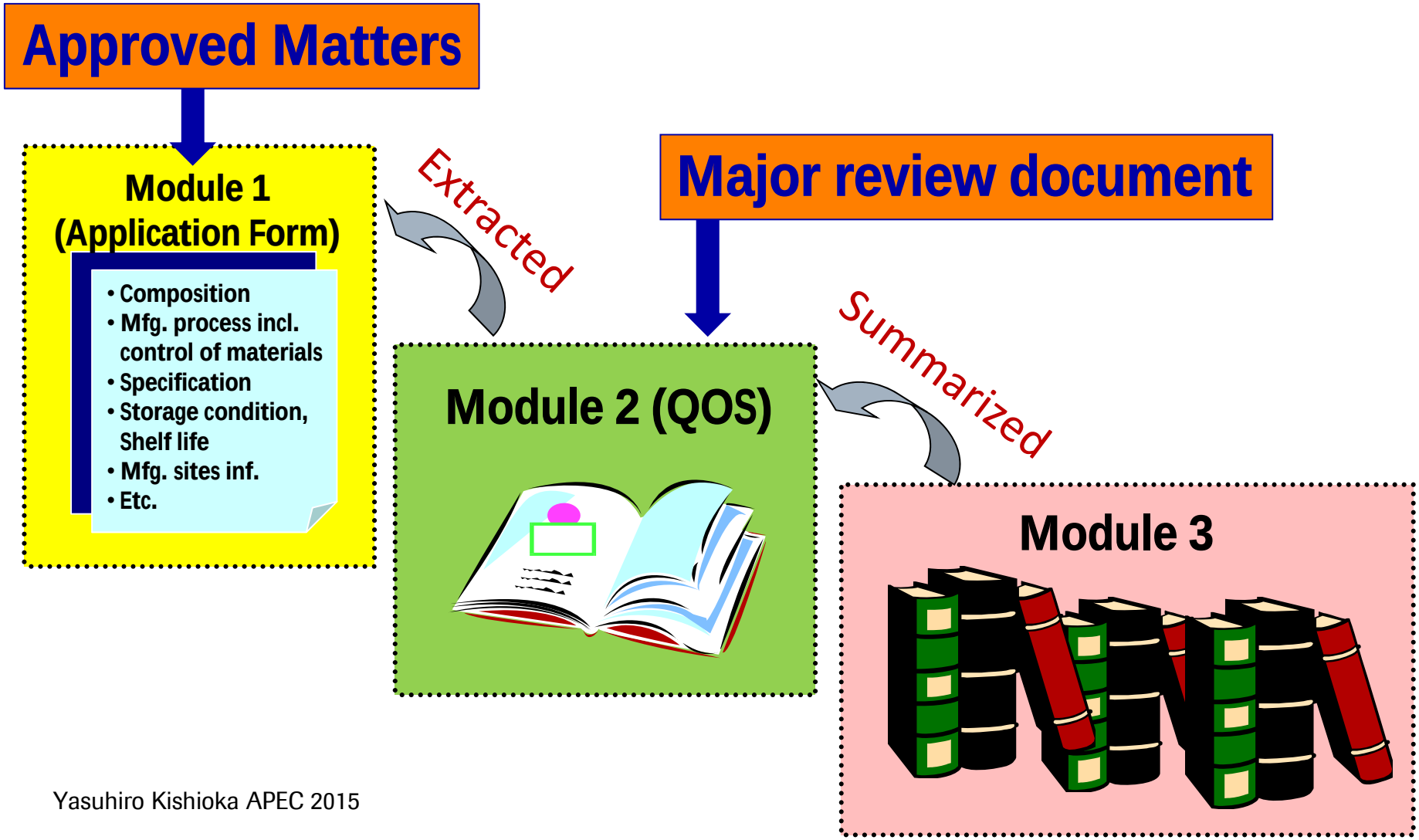


Working Draft ICH Q12 Technical Document Version 1.1
Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Contents

- Clarifying **established conditions** for manufacture and control based on risk, product type, development approaches, manufacturing experience, GMP status
- Development of **product lifecycle strategy**
- Provide **harmonized tools** to facilitate prospective changes over the product lifecycle, e.g. **change management protocols**
- Establish ICH **expectations** of assessment and implementation of **frequent manufacturing changes**

Example "Established Conditions" in Japan: Relationship between Application Form (AF) and CTD Documents (1/2)

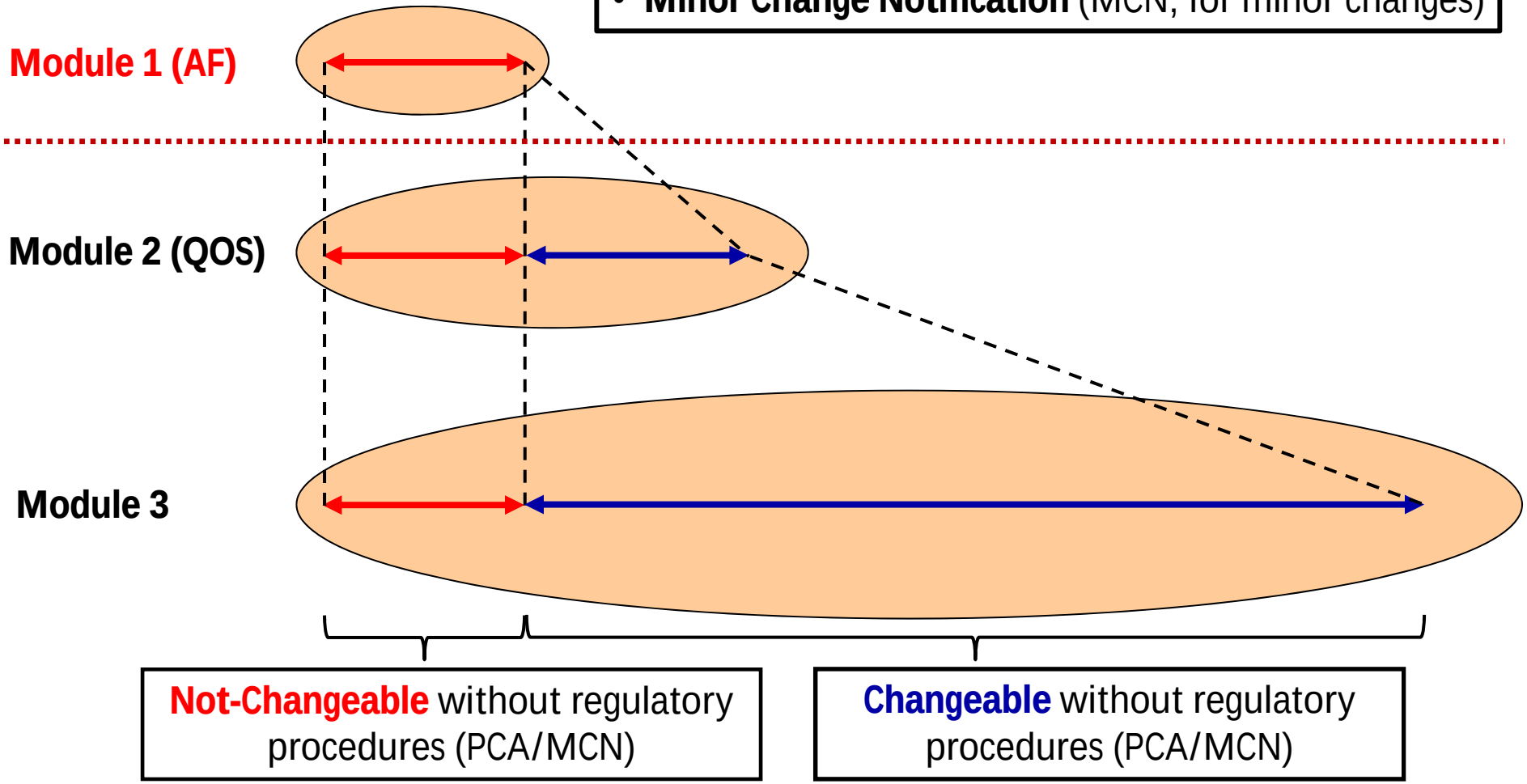


Yasuhiro Kishioka APEC 2015

Example "Established Conditions" in Japan: Relationship between Application Form (AF) and CTD Documents (2/2)

Legally binding

- **Partial Change Application** (PCN; for major changes)
- **Minor Change Notification** (MCN; for minor changes)

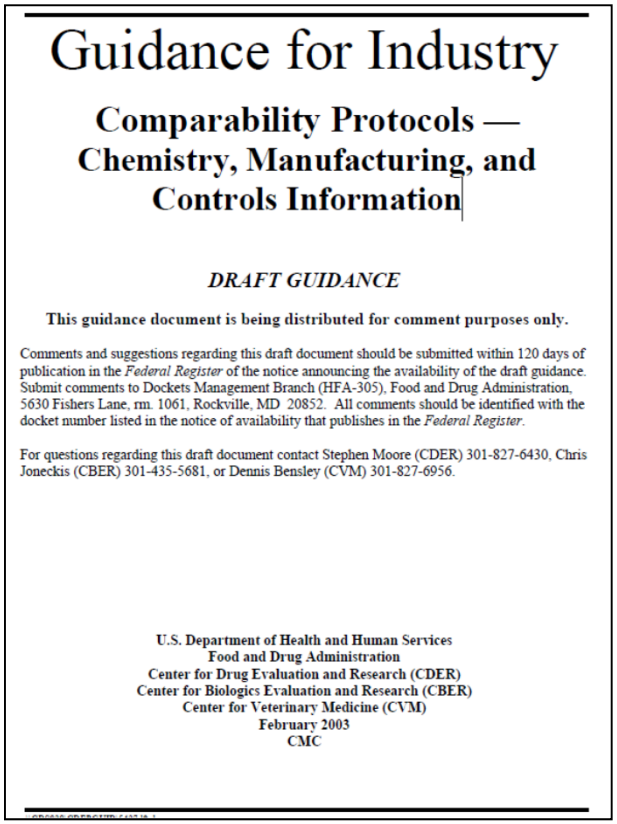


Established Conditions/ Regulatory commitments for Manufacture and Control

- Despite ICH M4/ CTD being in place for the marketing authorization application in the ICH regions:
  - there is **no harmonized understanding/ approaches to defining which information in the dossier is binding** and therefore requires a post-approval regulatory action when it is changed
  - ➢ Important: defining "Regulatory Commitments/ Approved Matters/ Established Conditions" to **clarify binding information and supportive details in dossier**
- Working definition of 'Regulatory commitment/ Approved Matters/ Established Condition' drafted in Q12 EWG, to be further discussed and improved:
  - *"…certain binding information concerning the manufacture and control… including description of the product, manufacturing process, facilities, specifications and other elements of the associated control strategy (e.g. storage conditions or shelf-life)"*
  - CTD sections containing regulatory commitments identified

Comparability Protocols (CPs)/ Post-approval change management protocols (PACMPs)

- US-FDA issued „*Draft Guidance for Industry Comparability Protocols - Chemistry, Manufacturing, and Controls*" in 2003 (based on ICH Q5E)
- EU introduced Post-approval change management protocols (PACMPs) in 2010
- **Overall, EU-PACMP and US-CP concept very similar; good starting point for ICH Q12**



Guidance for Industry

Comparability Protocols — Chemistry, Manufacturing, and Controls Information

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 120 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Stephen Moore (CDER) 301-827-6430, Chris Joneckis (CBER) 301-435-5681, or Dennis Bensley (CVM) 301-827-6956.

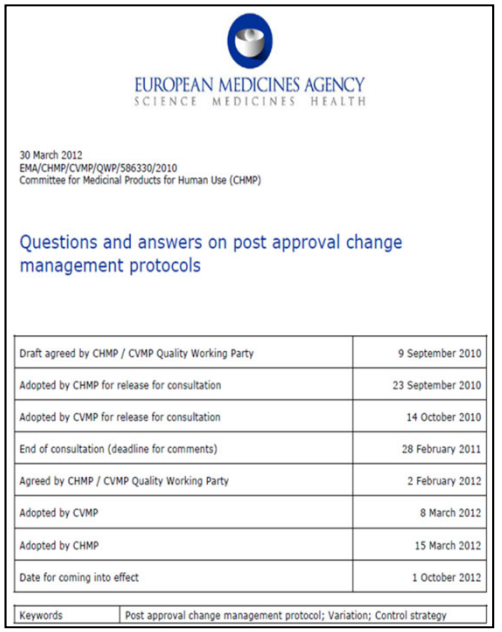
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)
February 2003
CMC

Post Approval Change Management protocols (PACMPs): Definition – EU example

- **A PACMP is a regulatory tool that describes specific change(s)** that a company would like to implement following marketing authorization and how these would be **prepared and verified**

- **A PACMP applies to all types of products** and incorporates a **science and risk-based approach** to evaluate impact of change(s) on product quality in a **proactive** manner

- PACMPs may be included in an original marketing authorization application (**MAA**) or be submitted as a stand-alone **type II-variation**; approved PACMPs can be modified via a type II (major change) or type IB (minor change) variation



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 March 2012
EMA/CHMP/CVMP/QWP/586330/2010
Committee for Medicinal Products for Human Use (CHMP)

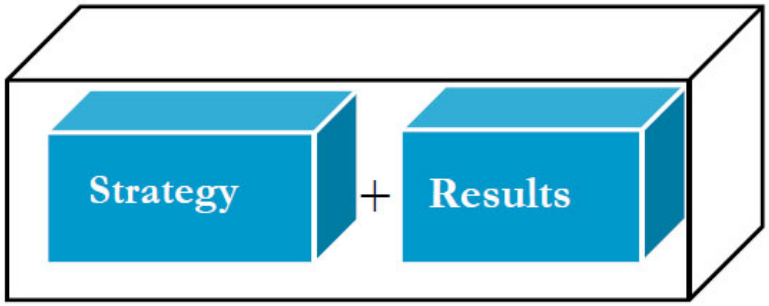
Questions and answers on post approval change management protocols

Draft agreed by CHMP / CVMP Quality Working Party	9 September 2010
Adopted by CHMP for release for consultation	23 September 2010
Adopted by CVMP for release for consultation	14 October 2010
End of consultation (deadline for comments)	28 February 2011
Agreed by CHMP / CVMP Quality Working Party	2 February 2012
Adopted by CVMP	8 March 2012
Adopted by CHMP	15 March 2012
Date for coming into effect	1 October 2012

Keywords	Post approval change management protocol; Variation; Control strategy

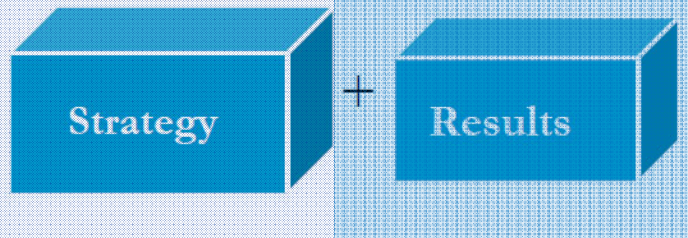
The principle of the Change Management Protocol: a 2-step implementation approach

«traditional» approach without PACMP:



Currently
Evaluation of a proposed variation as a 'whole' (Strategy + Results)

with PACMP:



Early Step 1:

Submission of a Change Management Protocol

Type II Variation

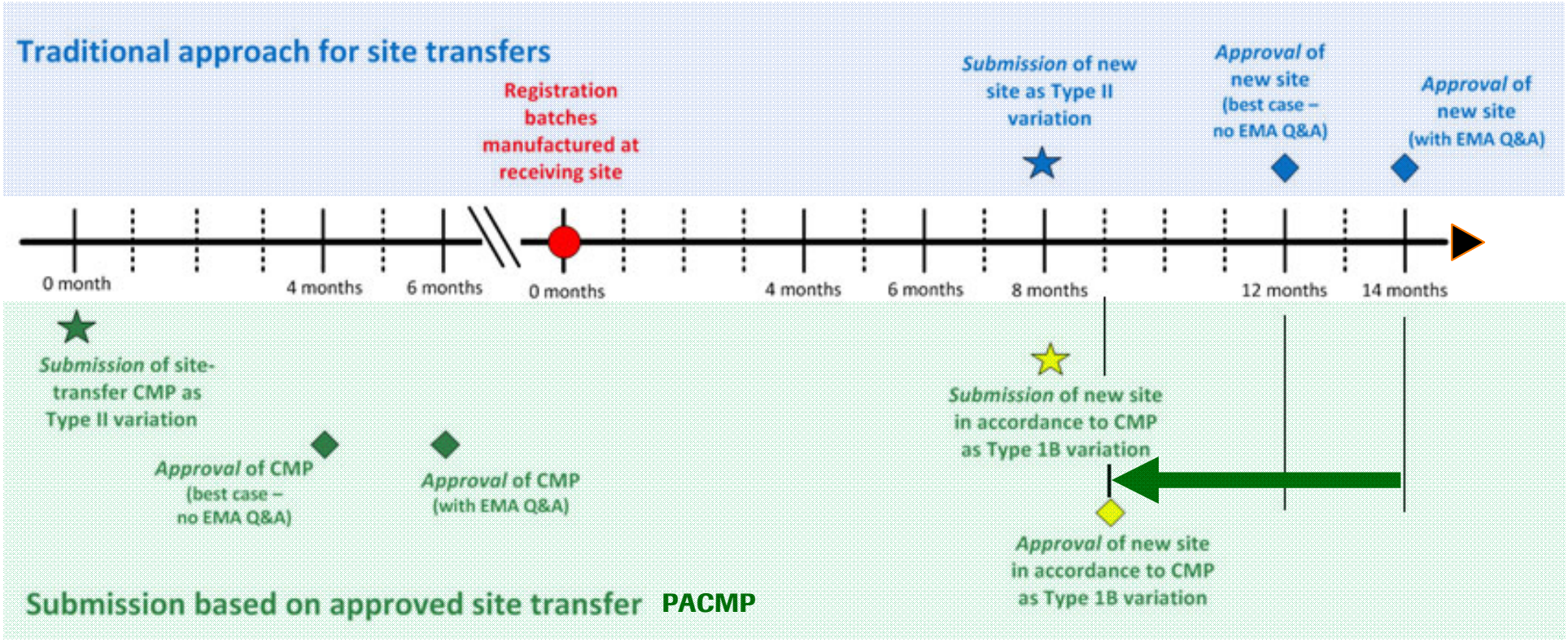
Fast Step 2:

Reporting of implementation of a change in accordance with an approved protocol

Type IA_{IN} or IB

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

Example (EU): Biologics DS manufacturing site transfer - Benefit of PACMP Approach vs. „Traditional“ Approach*



- **3-5 months faster approval of the site change using a PACMP**

**Note: approval timelines for type II variation in this scheme include positive CHMP opinion and Commission Decision*

Why use a PACMP/ CP approach?

- **Benefits:**
  - **Expedited review and/or inspection** at step 2 of PACMP procedure
  - **Reduced category for future reporting** of CMC changes covered by the approved protocol (but type IB default for biologics in EU)
  - **Predictability and transparency** in terms of requirements and studies needed to implement a change (approved protocol is an agreement between the sponsor and the HA)
  - **Faster implementation**, if the pre-determined criteria of the PACMP are met; use of the PACMP could allow an applicant to **place a product in distribution sooner**

Summary ICH Q12 – Opportunities for Harmonization and anticipated benefits

Opportunities: Enablers &Tools for Changes	Canada	EU	Japan	Switzerland	USA	Rest of World
Regulatory Oversight of All Changes (Assessment of Variations *or* GMP Inspection of PQS Change Management System)	✓	✓	✓	✓	✓	✓
Clearly defined Regulatory Commitments/Approved Matters/Established Conditions (in Dossier)	?	?	✓	?	?	?
Harmonized Post-Approval Change Management Protocols	X	✓	X	✓	✓	?
Tiered, Risk-based Regulatory Framework for Assessment of Variations to Marketing Authorisations	✓	✓	✓	✓	✓	?

BENEFITS

For Regulators: Facilitates appropriate, risk-based regulatory oversight; increased efficiency

For Industry: Increased manufacturing efficiency and opportunities for innovation & improvement

For Patients: Better availability and reliability of the supply of high quality pharmaceuticals

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- **Reflections on situation in the region**
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Reflections on situation in the region/ ASEAN

- The lifecycle management was traditionally managed by **renewal system**
- **After implementation of post-approval variation guidance** (which is based on science and risk-based approach) the **renewal system continues to exist**
- **Reflection:** Consider optimal operation for lifecycle management which is streamlined, non-duplicating and effective in protecting patients' safety to achieve:

  (1) optimal management of large volume of applications without duplication

  (2) Timely access of products to patients in need.

Global convergence of Lifecycle Management for Biotherapeutics – *recent WHO activities*

February 2014:

- IFPMA established a position paper on post-approval change requirements

- Procedural guidance for Biotherapeutics

May 2014 (Seoul meeting):

- Post-approval change management becomes high priority topic

October 2014 (Geneva):

- Guidelines for procedures and data requirements for changes to approved *vaccines* adopted

➔ High priority to build Biotherapeutics variation guidelines based on the existing vaccines principles as:

- Addition of an Annex to the *WHO Guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA* or
- As a standalone document

IFPMA: *International Federation of Pharmaceutical Manufacturers & Associations*

The WHO Guideline for Changes to Approved Vaccines may provide the Best Opportunity for Implementing Global Post-Approval Variation Requirements of Biotherapeutics

World Health Organization

WHO/BS.2014.2238
ENGLISH ONLY

Guidelines for procedures and data requirements for changes to approved vaccines

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this early draft is to provide information about the Guidelines for Procedures and Data Requirements for Changes to Approved Vaccines to a broad audience and to improve transparency of the consultation process.

These Guidelines were developed based on the outcomes and consensus of the WHO consultation convened in 2013 with participants from national regulatory authorities, national control laboratories, vaccine manufacturers and academia researchers and comments from the public consultation on WHO website in 2014.

The text in its present form does not necessarily represent an agreed formulation of the

Extract from WHO guideline for changes to approved vaccines

2. INTRODUCTION/ SCOPE

This document provides guidance for NRAs and MA holders on the regulation of changes to the original MA dossier or product licence for an approved vaccine in terms of: **(a) procedures and criteria for the appropriate categorization and reporting of changes; and (b) the data required to enable NRAs to evaluate** the impact of the change on the quality, safety and efficacy of the vaccine.

Additionally, the purpose of these WHO Guidelines is to assist NRAs in establishing regulatory procedures for post-approval changes to vaccines.

The guidance given below applies to the manufacture and use of approved prophylactic vaccines for humans. However, **the general principles set out in this document may also apply to other biological products.**

➔ **Proposal to expand the scope of the guideline to** ***Biotherapeutic products (prepared by rDNA technology)***

Extract from WHO guideline for changes to approved vaccines

Clear, risk-based procedural guidance and review timelines are proposed

Category	Supplement	Maximum Review Period
Quality Changes		
Major Quality Changes	**Significant potential to have an impact on Quality; Safety; Efficacy** **Prior Approval Supplement (PAS)**	**6 months**
Moderate Quality Changes	**Moderate Potential to have an impact on Q;S;E** **Prior Approval Supplement (PAS)**	**3 months**
Minor Quality Changes	**Minimal Potential to have an impact on Q;S;E** **Do not require notification to the NRA [1]**	**N/A**

[1] *Minor quality changes that are related to a moderate or major quality change should be included in the PAS if they have been implemented after the submission of a previous supplement for a moderate or major quality change.*

Extract from WHO guideline for changes to approved vaccines

Detailed dossier requirements are provided, e.g. for the drug substance and the final product

Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
2. Change to an antigen manufacturing facility:			
a. replacement or addition of a manufacturing facility for the antigen bulk, or any intermediate of the antigen	None	1-4, 6-8	Major
	1-4	2, 4-8	Moderate
b. deletion of a manufacturing facility or manufacturer for an antigen intermediate, or antigen bulk	5, 6	None	Minor

Conditions

1. The new manufacturing facility/suite is an approved antigen manufacturing site.
2. Any changes to the manufacturing process and/or controls are considered either moderate or minor.
3. The new facility/suite is under the same QA/QC oversight.
4. The proposed change does not involve additional containment requirements.
5. There should at least remain one site/manufacturer, as previously authorized, performing the same function as the one(s) concerned by the deletion.
6. The deletion should not be due to critical deficiencies concerning manufacturing (e.g., recurrent

Supporting Data

1. Evidence of facility GMP compliance.
2. Name, address, and responsibility of the proposed facility.
3. Process validation study reports.
4. Comparability of the pre and post-change antigen with respect to physico-chemical characterization, biological activity, and impurity profile. Occasionally, bridging non-clinical and/or clinical studies may be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis taking into consideration the quality comparability findings, the nature and level of the knowledge of the vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine use.
5. Justification for the classification of any manufacturing process and/or control changes as moderate or minor.
6. Description of the batches and summary of in-process and release testing results as quantitative data, in a

Key elements for biotherapeutics drug substance and drug product have to be included:

➔ Adapt description of relevant changes

➔ Adapt the respective conditions

➔ Adapt the respective supporting data for a given change, e.g. batch analysis data, stability standards (e.g., accelerated stability studies + not more than 6 months real-time data to maintain shelf-life…)

Important Update from latest APEC meeting June 2015 in Korea

- **Public commitment from WHO to pursue the development of a global guidance for post-approval variations for Biotherapeutics based on the vaccine principles**

- Addition of an Annex to rDNA guideline or
- as a standalone document
- Document expected late 2016/ early 2017

World Health Organization

Reflections on situation in the region/ ASEAN, cont'd

➔ Some proposals to make a link to the concepts outlined in this presentation:

- With the ASEAN variation guideline now in place, the renewal system should be purely administrative (cf. example EU, Singapore)
- Industry should commit to timely, comprehensive variation submissions of high quality
- HAs should ensure variations are managed through transparent guidance (comprising clear procedures [timelines], classification, documentation and data requirements -- **see WHO example**)
- **Interaction between industry and regulators should be built on trust and sharing responsibility – in the collaborative spirit of ICH Q12.**

Acknowledgements

- Susanne Ausborn, Roche
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- Sannie Chong, Roche
- Ai Ling Woo, Sheen Wei Wong; Roche Malaysia
- ICH Q12 EWG colleagues, especially Yasuhiro Kishioka, PMDA

Thank you very much!

Questions?

Doing now what patients need next