Lifecycle Management of Pharmaceutical Products and ICH Q12 Concepts

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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

One World

One Regulatory Standard
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

SUBMISSION

x countries

y countries

Approval + HAQ process

Different approved details for one product

CPP = Certificate of Pharmaceutical Product

HAQ: Health Authority Questions
LIFE CYCLE MANAGEMENT OF A PHARMACEUTICAL PRODUCT

- Clinical:
  - Phase 1, 2 & 3
  - Phase 4
  - Formulation
  - Delivery

- Development

- Marketing Authorization
  - e CTD application
  - HA queries management
  - Labeling development and Launch plans

- Variation Management
  - Site transfers
  - CMC changes
  - MAH transfer
  - New Indication

- Post Approval commitment
  - Safety: PV, PSUR, safety update
  - Stability
  - Renewals
Introducing changes post-approval is an essential 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.

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
- 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):
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 (currently for chemical drugs only)
- ASEAN (currently for chemical drugs only)
## Comparison of regional change categories

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

**Note:** The table outlines the regional change categories for different regions (EU, US, Japan, WHO, ASEAN) based on the type of variation (Type II, Type IB, Type IA, etc.). Each category specifies the approach and regional standards for managing changes in regulatory procedures.
Roche supporting efforts for harmonization at regional and global levels

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

Q1A - Q1F Stability
Q2 Analytical Validation
Q3A - Q3D Impurities
Q4 - Q4B Pharmacopoeias
Q5A - Q5E Quality of Biotechnological Products
Q6A - Q6B Specifications
Q7 Good Manufacturing Practice
Q8 Pharmaceutical Development
Q9 Quality Risk Management
Q10 Pharmaceutical Quality System
Q11 Development and Manufacture of Drug Substances
Q12 Lifecycle Management

Q1-Q7: «Basic» Quality guidelines

Q8-Q11: New Quality Paradigm/ «Enhanced Approach» / QbD

Q12: New ICH Quality Topic
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?

- 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)

Approved Matters

Module 1 (Application Form)
- Composition
- Mfg. process incl. control of materials
- Specification
- Storage condition, Shelf life
- Mfg. sites inf.
- Etc.

Module 2 (QOS)

Module 3

Major review document

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)

**Module 1 (AF)**

**Module 2 (QOS)**

**Module 3**

**Not-Changeable** without regulatory procedures (PCA/MCN)

**Changeable** without regulatory procedures (PCA/MCN)
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)


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

«traditional» approach without PACMP:

- Strategy
- Results

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

with PACMP:

- Strategy
- Results

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 IAIN 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
### Opportunities: Enablers & Tools for Changes

| Regulatory Oversight of All Changes  
(Assessment of Variations or GMP Inspection of PQS Change Management System) | Canada | EU | Japan | Switzerland | USA | Rest of World |
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<tr>
<th>Clearly defined Regulatory Commitments/Approved Matters/Established Conditions (in Dossier)</th>
<th>Canada</th>
<th>EU</th>
<th>Japan</th>
<th>Switzerland</th>
<th>USA</th>
<th>Rest of World</th>
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<table>
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<thead>
<tr>
<th>Tiered, Risk-based Regulatory Framework for Assessment of Variations to Marketing Authorisations</th>
<th>Canada</th>
<th>EU</th>
<th>Japan</th>
<th>Switzerland</th>
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### 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/ 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
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**

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**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*
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

<table>
<thead>
<tr>
<th>Category</th>
<th>Supplement</th>
<th>Maximum Review Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Changes</td>
<td></td>
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</tr>
<tr>
<td>Major Quality Changes</td>
<td>Significant potential to have an impact on Quality; Safety; Efficacy</td>
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<td>Moderate Potential to have an impact on Q;S;E</td>
<td>3 months</td>
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<td>Minimal Potential to have an impact on Q;S;E</td>
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<td>Do not require notification to the NRA</td>
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</tbody>
</table>

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:

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...)

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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
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.
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- ICH Q12 EWG colleagues, especially Yasuhiro Kishioka, PMDA
Thank you very much!

Questions?
Doing now what patients need next