Post-approval Change Management Protocols - Current Status and Next Steps on the Way towards a Global Tool

Dr. Markus Goese
Lead EU CMC Regulatory Policy
F. Hoffmann-La Roche Ltd, Basel - Switzerland
Presentation outline

• What is a PACMP?
• What are the benefits of protocols?
• What are the challenges?
• What is a CP?
• Expansion of the protocol concept (eCP)
• The Global context & way forward in ICH Q12
Question-1

• So what is a PACMP and what can be done with it?
Change Management Protocols in EU

- *Post-approval change management protocol (PACMP)* concept introduced in 2010 in EU through Variations Classification:

<table>
<thead>
<tr>
<th>Implementation of changes foreseen in an approved change management protocol</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
<th>Procedure type</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) The implementation of the change requires no further supportive data</td>
<td>1</td>
<td>1, 2, 4</td>
<td>IAIN</td>
</tr>
<tr>
<td>b) The implementation of the change requires further supportive data</td>
<td></td>
<td>1, 2, 3, 4</td>
<td>IB</td>
</tr>
<tr>
<td>c) Implementation of a change for a biological/immunological medicinal product</td>
<td></td>
<td>1, 2, 3, 4, 5</td>
<td>IB</td>
</tr>
</tbody>
</table>

**Conditions**

1. The proposed change has been performed fully in line with the approved change management protocol.

**Documentation**

1. Reference to the approved change management protocol.
2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.
3. Results of the studies performed in accordance with the approved change management protocol.
4. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA)
What is a PACMP?

• A PACMP 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.
**Reminder: Variation categories in the EU**
*Most variations for biologics are major (type II) changes*

<table>
<thead>
<tr>
<th>Category</th>
<th>Impact on quality, safety or efficacy?</th>
<th>Notification and implementation</th>
<th>Review time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type IA</td>
<td>None / minimal impact</td>
<td><strong>Notification</strong>: within 12 months after implementation</td>
<td>▪ 30 days</td>
</tr>
<tr>
<td>Type IA_IN</td>
<td>None / minimal impact</td>
<td><strong>Notification</strong>: immediate following implementation</td>
<td>▪ 30 days</td>
</tr>
</tbody>
</table>
| Type IB  | Minor potential impact; Classified by default, if change does not fall into another category | **Notification**: before implementation, but no formal approval  
**Implementation**: ‘tell, wait and do’ – MAH implements changes unless negative opinion received within 30 days | ▪ 30 days |
| Type II  | Major potential impact                  | **Notification**: EMA forwards positive CHMP opinion to EU Commission, and they amend the MA within one year  
**Implementation**: following CHMP opinion, without waiting for Commission approval | ▪ 60 days normally  
▪ 90 days for indication changes  
▪ 30 day for urgent safety issues |
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 Iain or IB

Source: EMA Questions and Answers on post-approval change management protocols
According to EMA PACMP Q&A:

- **Justification** that there is a recognized future need for the specific change within a reasonable timeframe.

- A detailed **description** of the proposed change.

- **Risk assessment** of the impact of the change on product quality.

- **Discussion on the appropriateness of the approved control strategy** to identify and manage these risks.
✓ **Description of the studies** to be performed, the **test methods** and acceptance criteria that will be used to fully assess the effect of the proposed change on product quality.

✓ For biologics, the approach to be used to demonstrate the **comparability of the pre-, and post-change product**.

✓ A **plan for stability studies** should be included, if appropriate.

✓ In case that the protocol describes **several changes**, a **justification** showing that the changes are related, and that a simultaneous review under a single protocol is meaningful.

✓ For small molecules, a **proposed reporting category** for step 2 (type IA or IB variation).
EU Experience: PACMPs authorised in the centralised procedure (last updated 22/05/2015, source: EMA)

<table>
<thead>
<tr>
<th>SCOPE</th>
<th>TYPE II</th>
<th>MAA</th>
<th>Line extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>New site for manufacture and/or QC testing of the drug substance</td>
<td>Bio: 12</td>
<td>Bio: 1</td>
<td>Che: 4</td>
</tr>
<tr>
<td>New site for manufacture and/or QC testing of the drug product</td>
<td>Bio: 18</td>
<td>Bio: 3</td>
<td>Che: 2</td>
</tr>
<tr>
<td>Change to the manufacturing process of the drug substance</td>
<td>Bio: 12</td>
<td>Bio: 2</td>
<td>Che: 1</td>
</tr>
<tr>
<td>Scale-up of the drug substance manufacturing process</td>
<td>Bio: 3</td>
<td>Bio: 2</td>
<td></td>
</tr>
<tr>
<td>Change to the preparation of a cell bank</td>
<td>Bio: 1</td>
<td>Bio: 2</td>
<td></td>
</tr>
<tr>
<td>Change to the manufacturing process of the drug product</td>
<td>Bio: 2</td>
<td></td>
<td>Che: 1</td>
</tr>
<tr>
<td>Change to the container closure system of the drug substance or drug product</td>
<td>Bio: 1</td>
<td></td>
<td>Che: 1</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Bio: 1</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>- 60 for biologics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 MAA, 49 Type II, 1 Extension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 9 for chemicals:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 MAA, 2 Type II</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: 4 PACMPs for biologics not included in the table were withdrawn (2 MAA, 2 Type II)

➡️ Limited use so far for chemical Drug Substance/ Drug Product
Why use a PACMP 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 implement CMC changes and place a product in distribution sooner than without the use of the PACMP procedure
  - Could also prove to be very useful regulatory tool in breakthrough/accelerated pathway scenarios, to supplement specific parts of initial dossier in a pre-agreed manner.
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
Some specific considerations for PACMPs

• The types of changes that could be included in a protocol depend on the complexity of the product and its manufacturing process, as well as the understanding that the company has gained about them.

• For a (biological) medicinal product where non-clinical/ clinical data are needed as part of the comparability exercise, a post approval management protocol will not be feasible.

• Change Management protocols are applicable to all types of applications, irrespective of the development approach that has been followed, i.e., traditional or enhanced;
  – However, it is expected that if the applicant has applied QbD principles during product development, then an increased product and process understanding is achieved, thus making it easier to predict the impact of a change on the active substance or finished product quality.
Question-2

• And what is a CP?
Comparability Protocols in the US


- Revision is on the FDA agenda of planned guidance to be published in 2015

- Overall, EU-PACMP and US-CP concept very similar
## Reminder: US Post-Approval Change Reporting Categories

<table>
<thead>
<tr>
<th>Submission Type</th>
<th>Potential impact</th>
<th>Product may be distributed</th>
<th>FDA Approval Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Approval Supplement (PAS)</td>
<td>Substantial</td>
<td>After approval</td>
<td>4 months</td>
</tr>
<tr>
<td>Changes Being Effected, 30 days (CBE-30)</td>
<td>Moderate</td>
<td>30 days after FDA receipt</td>
<td>6 months</td>
</tr>
<tr>
<td>Changes Being Effected (CBE)</td>
<td>Moderate</td>
<td>Immediately following FDA receipt</td>
<td>6 months</td>
</tr>
<tr>
<td>Annual Report (AR)</td>
<td>Minimal</td>
<td>No restrictions</td>
<td>180 Days</td>
</tr>
</tbody>
</table>

➤ First step of CP submitted with NDA/ BLA or as Prior Approval Supplement (PAS), second step allows for reduced reporting category if predefined criteria are met (e.g., CBE-30)
Example (US): Manufacturing Site Transfer of Product A from Site X to Site Y Leveraging ‘traditional’ CP

Defined business need

Submit CP describing site transfer acceptance criteria for product-site combination

Drug Substance Donor Site X

Product A

Execute transfer per defined requirements in CP

Drug Substance Receiving Site Y

CBE-30 Supplement with data demonstrating acceptance criteria met

- Time savings for US-CP-approach comparable to EU-PACMP, i.e. up to 5 months for site-transfer (product release to market)
Question-3

“CP + QbD Concepts” = ?
“CP + QbD Concepts” = Expanded Comparability Protocol (eCP)
**Expanded Comparability Protocol (eCP)**

- Term “eCP” was first introduced at the **US CASSS CMC Forum in July 2009** on QbD as concept for how to **manage lifecycle changes based on risk**

- **eCP leverages existing regulations for CPs**: move from one protocol for one change to an expanded protocol applicable to groups of similar changes (across products)

- **A range of QbD concepts (ICH Q8, Q9, Q10, Q11) can be applied**: leverages historical knowledge, **systematic risk assessment** and change requirements

- **Genentech’s drug substance manufacturing site transfer eCP proposal was accepted in FDA’s QbD pilot program in 2009**

- **Primary objective** of the site transfer eCP: **support the mobility of approved products to licensed drug substance facilities** within Roche/Genentech’s manufacturing network (“trans-BLA approach”: multiple products/ multiple sites)

- **Effectively leverages Quality Risk Management (ICH Q9)** and builds upon company’s knowledge/ experience with site transfers across products & **reduces number of regulatory submissions** of similar content, drives consistency
Concept of eCP to Support Multi-Product, Multi-Site Transfers

A network of Drug Substance Donor Sites

Submit eCP (PAS) describing acceptance criteria broadly for both Site and Product

A network of Drug Substance Receiving Sites

Potential Future Network Requirements

Execute transfer per defined requirements in eCP

CBE-30 Supplement with data demonstrating acceptance criteria met
Important questions to be asked:

→ What should be assessed in considering GMP or inspectional risk?

→ What should be tested to confirm comparability?

→ What are the impacts of ‘facility fit’ changes?

→ What products and facilities should be in scope?
**Snapshot: Site Transfer Risk Assessment**

*prospectively identified and assessed by team of experts*

<table>
<thead>
<tr>
<th>Process Step</th>
<th>Process Change</th>
<th>Hazard</th>
<th>Harm (Hazard Effect)</th>
<th>Severity</th>
<th>Hazardous Situations (Potential Causes of Hazard)</th>
<th>Preventative Controls</th>
<th>Occurrence</th>
<th>Detection Controls</th>
<th>Detection</th>
<th>PRN (SxO)</th>
<th>RPN (SxOxD)</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromatography (general)</td>
<td>Pool tank mixers are different</td>
<td>Localized product aggregation</td>
<td>Potential product quality impact (e.g., aggregate formation)</td>
<td>6</td>
<td>Different agitator design, improper controls around mixing</td>
<td>Batch record instructions</td>
<td>4</td>
<td>CofA testing, Batch record verification of mixing controls</td>
<td>4</td>
<td>24</td>
<td>96</td>
<td>Validation of mixing to establish mix times and speeds during Engineering run</td>
</tr>
<tr>
<td>Affinity Chromatography</td>
<td>In-line dilution of equil buffer (required due to buffer tank volumes)</td>
<td>Wrong concentration of equil buffer due to in-line dilution loaded on column</td>
<td>Process performance impact (yield loss). Minor shift in process performance/ product characterization. Potential product quality impact.</td>
<td>6</td>
<td>Equipment failure (e.g., conductivity probe, pump motor, flow meter)</td>
<td>Mixing ratio defined in automation, automation limits for conductivity, automation controls around equipment failure, calibration, PM, probe standardization procedures</td>
<td>2</td>
<td>Automation controls for conductivity prior to column going in-line, chromatogram review, pump alarms, equipment failure results in skid hold</td>
<td>2</td>
<td>12</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Risk Priority Number (RPN) is the product of the Primary Risk Number (PRN) and the score for probability of detection.

- **Subsequent step:** Risk Prioritization - Identified thresholds of risk acceptability incorporated in overall applicability to Site Transfer eCP
Main points accomplished:

- Agreed upon scope: products and facilities (scope excludes opportunistic process changes including changes to increase yield; included within scope: facility driven process modifications, eg. scale changes, disposables, raw material sourcing)

- Justified that historical knowledge of product characterization, stability & process performance is sufficient to support comparability with post-approval real-time stability commitment (successful demonstration of comparability using stress stability studies)

- Only licensed facilities in “a current state of GMP compliance” are allowed, so that Pre-Approval Inspection (PAI) may be waived

- Agreed future products and facilities could cross-reference the eCP if pre-defined criteria were approved

Overall: ability to quantify risk related to facility and process change:
eCP PAS approved in 2011 ✔, Subsequent drug substance transfers approved under eCP criteria with CBE-30 ✔
The Global context & way forward with ICH Q12
The Global context & way forward for PACMPs with ICH Q12

• It is planned that the upcoming ICH Q12 guideline contains a chapter describing *post-approval change management protocols* as an important tool for efficient lifecycle management.

• Based on current FDA and EMA guidance (showing a high degree of similarity), first draft of this chapter has been discussed & agreed during the Q12 EWG meeting in Fukuoka:
  – high-level contents is very much in line with the PACMP/ CP-principles, need for wider use & broader protocols confirmed
  – Swissmedic has PACMPs already in place

• PMDA/ MHLW have indicated their willingness to adopt the concept in Japan

➢ excellent foundation for protocol harmonization efforts under the lead of ICH
“The application file should contain a section summarizing the essential control strategy elements (at time of submission) learned from the science and risk-based pharmaceutical product development.

In addition, for all new registration dossiers, this section should also include a subsection on lifecycle management strategy (future planned changes) derived from the information/data submitted in the original application file (dossier). […] The section includes:

- **References to any post-approval change management protocols (PACMPs) contained within the dossier […]**

- **These protocols serve as main regulatory tool that describe future changes to the Established Conditions, the potential impact and reporting category of the change as well as the underlying data requirements for implementation”**
…to be continued @ next ICH meeting

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- Ingrid Markovic; FDA/CBER
- Yasuhiro Kishioka, PMDA
- Pierrette Zorzi, consultant
THANK YOU!

-- Questions?
Backups
Protocols in US-Regulation (BLA)

21 CFR 601.12(e) An applicant may submit one or more protocols describing the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. Any such protocols, or change to a protocol, shall be submitted as a supplement requiring approval from FDA prior to distribution of the product which, if approved, may justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.
Doing now what patients need next