

Global Trends in Lifecycle Management

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Presentation Outline

- Background – Trends in Lifecycle Management
- Tools to help managing post-approval changes
 - Risk-based regulatory framework
 - Q12 tools
 - Common format
 - Work sharing
- Closing remarks

Background – Global Trends in Lifecycle Management

- Lifecycle management of therapeutic products, including vaccines, are very challenging
- Each time a new drug is approved, associated post-approval changes are made :
 - Optimize the process
 - Increase the scale of production (scale-up, new manufacturing sites)
 - Decrease the cost of production
 - etc...
- This results in an increase in drug applications filed to the National Regulatory Agencies (NRA)
- How to manage this increase in post-approval changes in a context of resources limitation?

Risk-based regulatory framework

- To optimize the management of post-approval changes, a regulatory framework which use a risk-based approach should be implemented for the categorization of these changes
- Such approach have been described in two WHO guidelines:
 - *WHO Guidelines on Procedures and Data Requirements for Changes to Approved Biotherapeutic Products*
 - *WHO Guidelines on Procedures and Data Requirements for Changes to Approved Vaccines*

WHO guidelines for post-approval changes

WHO position

- The regulation of changes to approved biopharmaceutical products (BTPs) is key in ensuring that products of consistent quality, safety and efficacy are marketed after they receive authorization or licensure.
- If a National Regulatory Authority (NRA) so desires, these guidelines may be adopted as definitive national requirements.
- It is possible that modifications to this document may be justified due to risk–benefit and legal considerations specific to each NRA.
 - In such cases, it is recommended that any modifications should not alter the principles outlined in these guidelines.
- *NRAs are encouraged to apply the concept of work sharing or to use collaborative approaches when reviewing post-approval changes.*

WHO PAC guidelines for BTPs



World Health
Organization

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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**

Proposed guidelines

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 proposed WHO document on *Guidelines on procedures and data requirements for changes to approved biotherapeutic products* to a broad audience and to improve transparency of the consultation process.

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee. Written comments proposing modifications to this text **MUST** be received **by 15 September 2017** in the Comment Form available separately and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Department of Essential Medicines and Health Products (EMP). Comments may also be submitted electronically to the Responsible Officer: Dr Hye-Na Kang at email: kangh@who.int.

The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide, second edition" (KMS/WHP/13.1).

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Categories for Quality Changes - Appendix 2 and 3

- Changes are categorized on the basis of a risk analysis.
 - Has a proposed change of the manufacturing process or the control strategy an impact on the quality attributes (i.e. identity, strength, purity, potency) of the drug product?
 - If so, what is the potential impact on the safety or efficacy of the product?
 - Depending on the risk level identified, the change is categorized as
 - Major quality change
 - Moderate quality change
 - Minor quality change
 - Quality changes with no impact

Procedures for Quality changes 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

¹ The review timelines are established by taking into consideration the country or regional situation and the capability of the NRA.

Examples of Quality Changes - Appendix 2 and 3

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
29. Change in the storage conditions for the drug substance, involving:			
a. addition or change of storage condition for the drug substance (e.g. widening or narrowing of a temperature criterion)	None	1–4	Moderate
	1, 2	1–3	Minor
Conditions			
1.	The change is not necessitated by recurring events arising during manufacture or because of stability concerns.		
2.	The change consists in the narrowing of a temperature criterion within the approved ranges.		
Supporting data			
1.	Proposed storage conditions and shelf-life.		
2.	Updated post-approval stability protocol and stability commitment.		
3.	Justification of the change in the labelled storage conditions/cautionary statement.		
4.	Results of stability testing (i.e. full real-time/real-temperature stability data covering the proposed shelf-life generated on at least three (3) commercial-scale batches).		

- the **conditions to be fulfilled** in order for a given change to be classified as major, moderate or minor (if any of the conditions outlined for a given change are **not fulfilled**, the change is automatically considered to be at the **next higher** reporting category – e.g. if any of the conditions recommended for a moderate quality change are not fulfilled, the change is considered a major quality change);
- the **supporting data** for a given change, either to be submitted to the NRA and/or maintained by the MA holder (if any of the supporting data outlined for a given change are not provided, are different or are not considered applicable, **adequate scientific justification** should be provided).

Tools to help manage workload associated with post-approval changes – ICH Q12

- This ICH guideline entitled “**Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management**” has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. ***It provides a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle***
- Implementation of this new ICH Guideline will ***promote innovation and continual improvement*** in the biopharmaceutical sector and ***strengthen quality assurance and reliable supply of product***, including proactive planning of supply chain adjustments.

ICH Q12 tools - Established Conditions (ECs)

- ECs are legally binding information judged necessary to assure product quality and can be proposed & justified (within the existing regulatory framework) or are otherwise indicated by existing regulation & guidance; ***any change to an EC necessitates a formal regulatory submission.***
 - EC essentially means “communicate the change”
- The number of ECs, & how narrowly defined, depends on product & process understanding, characterization, development approach & potential risk to product quality.
- ECs may be proposed for the entire CMC sections or may be proposed for a subset of information provided in Module 3 (e.g., for an individual unit operation of the manufacturing process).
- ***Changes to non-ECs don't need to be reported (Managed within the PQS)***
- Based on “Highly-functioning” PQS

ICH Q12 Tools - Post Approval Change Management Protocols (PACMP)

- PACMP provides predictability and transparency in the requirements and studies needed to implement a change; may address one or more changes for a single product, or may address one or more changes to be applied to multiple products.

A two-step process:

Step 1

- ***Submission of a written protocol***
 - o proposed change(s) with rationale(s)
 - o risk management activities
 - o proposed studies and acceptance criteria to assess the impact of the change(s)
 - o other conditions to be met
 - o the proposed reporting category
 - o any other supportive information
- ***Approved by regulator in advance of execution***

ICH Q12 tools - Post Approval Change Management Protocols (PACMP)

Step 2

- Carry out tests and studies outlined in the protocol
- If results/data generated meet the acceptance criteria in the protocol and any other conditions are met, submit this information to the regulatory authority according to the category in the approved protocol
- Depending on the reporting category, approval by the regulatory authority may or may not be required prior to implementation of the change.

Organization of the submission (ICH M4Q)

M4 : The Common Technical Document

- The agreement to assemble all the Quality, Safety and Efficacy information in a common format (called CTD - Common Technical Document) has **revolutionised the regulatory review** processes, **led to harmonised electronic submission** that, in turn, enabled implementation of good review practices. For industries, it has **eliminated the need to reformat** the information for submission to the different ICH regulatory authorities.

The Quality section of the Common Technical Document (M4Q)

- provides a Harmonised structure and format for presenting CMC (Chemistry, Manufacturing and Controls) information in a registration dossier. The table of contents includes sections on Drug Substance and Drug Product. A new section on Pharmaceutical Development has been included to replace the Development Pharmaceuticals Report (currently a part of the EU submission requirements). Also, a new CMC summary document, the Quality Overall Summary, has been developed.

Other tools to help manage post-approval changes

- Use of foreign decision (Reliance)
- Use of foreign review
- Work sharing (e.g. ACCESS)
- ICMRA pilot program on collaborative assessments of CMC submissions

Concluding remarks

- Number of post-approval changes keep increasing years after years
- Not all post-approval changes require prior approval
- Industry and Regulators all have limited resources so there is a need to focus the oversight to changes with the greatest risks (Major and Moderate risks)
- The others may be notified or implemented and managed by the PQS
- Strongly encourage to use a risk-based regulatory process as described in the WHO post-approval changes guidance documents
- We all work to provide faster access of drugs to patient, therefore it is strongly encouraged to use :
 - Reliance
 - Foreign review
 - Work sharing
 - ICH Q12 tools

Thank you!

