Roundtable Session – Table 3 - New EU Variation Classification - Experience to Date

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Abstract:

The recent revision of the EU Variations framework entered into force on 15 January 2026. Based on Commission Delegated Regulation (EU) 2024/1701 amending Regulation (EC) No 1234/2008 and the updated Variations Classification Guideline introduces a shift towards science- and risk-based approach to lifecycle management of medicinal products.

The reform aims to streamline post-authorisation change management by simplifying procedures, reducing administrative burden, and improving regulatory efficiency in response to increasing product complexity and volume of variations. Central to the revision is a refined risk-based classification system, where variations are assessed proportionately according to their potential impact on quality, safety, and efficacy, with substantial review of variation classification especially for Biologicals medicinal products. The updated guideline modernises classification categories and documentation requirements, reflecting scientific and technological advances.

Key changes also include the introduction of lifecycle management tools aligned with ICH Q12 (e.g., PACMPs) and enhanced grouping and worksharing mechanisms.

Overall, the revised framework aims for a more streamlined, predictable, and efficient implementation of post-approval CMC changes, while maintaining robust regulatory oversight and promoting innovation and supply continuity.

In this roundtable, participants will share their experience and perspectives on the revision and exchange best practices and opportunities for further streamlining

Discussion Questions:

1. Where do you see the greatest opportunities for simplification in the revised variations framework and what impact does this have on your lifecycle management strategies?
2. Which change categories or product classes benefit most from the revision?

3. What are the key challenges your organization anticipates in adapting to a revised variations framework (e.g., global alignment, internal processes, regulatory expectations), and how can these be effectively managed?
4. How can companies best leverage new tools such as PACMPs and PLCM to optimize their global CMC change management strategies?
5. How can international reliance on the new variation classification framework be further strengthened?

Notes:

Introduction & Objectives

The roundtable was attended with representatives from the pharmaceutical Industry, who are mostly involved in managing lifecycle changes across various geographic regions for biotechnological products as well as EU regulators from EMA and national competent authorities. The roundtable discussion opened with shared expectations from participants, centered on:

- Exchanging challenges and opportunities related to the implementation of the variation guideline.
- Discussing the interpretation and classification of changes.
- Addressing the use and challenges of the annual report framework.

EMA opened with a positive overall impression of the experience with the implementation of the new variation guideline implementation across CAPs and NAPs, noting progress in several areas while acknowledging remaining challenges.

The round table generated fruitful, informal, and open-minded discussions, with regulatory and CMC practical experiences illustrated by concrete industry cases. The following key discussions emerged:

Super Grouping — A Welcome New Procedural Tool

One of the highlights of the discussion was the introduction of super grouping as a new procedural mechanism:

- Appreciated by industry, as it allows a single procedure to cover multiple products simultaneously.
- Considered straightforward and efficient, facilitating the rollout of international submissions supported by CPPs.
- Perceived as a clear benefit for companies managing multi-product, multi-market portfolios.

Challenge identified: Some companies have over-interpreted the classification framework and applied higher variation categories than necessary, particularly for changes related to manufacturing transfers. This tendency toward over-classification adds unnecessary regulatory burden.

Mitigating measures proposed:

- The Q&A document should be leveraged to help avoid misclassification.
- Companies should consider requesting informal feedback from EMA Quality specialists to clarify interpretation before submission.
- EMA informed that alongside the implementation accumulated experience is evaluated in order to assess the need for additional guidance.

Variation Classification — Challenges & Observations

- A decrease in Type II variations has been noted by EMA, suggesting correct classification of the variation guideline of many scopes for biologicals that suggest reduced criticality of certain changes (i.e. 1B variations).
- However, some misclassifications persist (e.g., filtration changes classified as minor instead of major).
- Performing validation is considered a signal warranting a Type II variation classification.
- Stakeholders highlighted that in their view, risk of misclassification persists at the boundary between Type IA and Type IB, with some Type IA changes already implemented being retrospectively upgraded to Type IB creating significant operational and regulatory consequences amplified by the international roll out. The cut-off between Type IA and Type IB also remains a grey zone with uncertainty in interpretation.
- Many countries rely on EU decisions and dossiers (via CPP) for their own regulatory processes.
- The **9-month implementation period** for certain changes may create **timing challenges** for international rollout, particularly when other markets expect simultaneous or near-simultaneous implementation.
- Further clarity and harmonization on annual reporting expectations were flagged as a need.
- Prior to the guideline revision, EMA conducted an experience-collection exercise to guide the revision of conditions and enable downgrading of certain changes, based on risk-based/science-based principles— this was acknowledged positively.

- **Analytical suitability** for analytical procedures was identified as an ongoing challenge, with practical regulatory CMC experience and case studies shared among participants.

PACMP & PLCM

- The downgrading and new classification options enabled by PACMP were positively received by industry.
- However, PACMP remains underutilized globally, as it has not been fully adopted by all regulatory authorities outside the EU.
- A key mechanism to increase PACMP uptake is to include PACMPs (in 32R) in the initial Marketing Authorization Application dossier (MAAs) from the outset.
- PACMP does not yet delivered its full benefit for global submissions due to this inconsistent international adoption.
- PLCM tools are not used by industry, representing an underutilized opportunity for streamlined lifecycle management.

GMP vs. Dossier Relevance

A significant discussion point concerned the boundary between GMP-covered elements and dossier-relevant information:

- It was considered that Article 5 reports that GMP related information should be removed from the dossier
- There is a recognized grey zone in drawing the line between what is GMP-relevant and what requires dossier inclusion (e.g., process models, manufacturing descriptions) which should have consequence in the assessment of changes and dossier maintenance.
- Maintenance of older dossiers is particularly challenging, as legacy files often contain detailed manufacturing descriptions that may now be considered GMP-relevant rather than dossier-relevant creating inconsistency over countries MAA and maintenance burden.