



Updates in post-approval regulatory affairs procedures

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Agenda

- **Post-approval regulatory activities**
- **EU regulatory framework shift**
- **New variation guideline**
- **IA & annual cycles**
- **Life cycle management approaches (PACMP, PLCM)**
- **Key takeaways**

Post-Approval Landscape



- Activities to
 - maintain a product on the market: variations, renewals, commitments
 - expand its market potential: duplicates, MA transfers
 - correct or conclude the life-cycle: withdrawals
- Variations are most frequent activity and drive most of the workload and complexity.

EU Regulatory System in Transition: What Has Changed?

- New Variations Regulation & Guideline (2024/1701)
- Emerging lifecycle tools (PACMP, lifecycle planning)
- Emergency and public threat activities included in legislation
- ATMPs, combination products and digital submissions considered
- Broader legislative context:
 - EU Pharma Package
 - Biotech Act
 - Critical Medicines Act & Shortages initiatives

We are not seeing isolated updates but a shift in how lifecycle is managed.

Variations Guideline: From Static List to Dynamic Framework

- The EMA Variation Regulation ([EC 1234/2008](#), concerning variations to marketing authorisations for medicines, is the legally binding EU law defining the variation procedure and the types of changes allowed. The significantly amended [\(EU\) 2024/1701](#) became applicable on **January 1, 2025**.
- The new EMA Variation Guideline [C/2025/5045](#) published September 22, 2025, provides detailed instructions on how to apply the regulation and clarifies documentation requirements and classification categories and applies to all new variations submitted from **January 15, 2026**.



The system is no longer only about knowing the rules but also understanding how they evolve.

Key updates in the guideline

Categories and classification

- Revised variation categories: the previous A (administrative), B (quality), C (safety/efficacy/pharmacovigilance), and D (specific changes to Plasma Master Files and Vaccine Antigen Master Files) are now E, Q, C, and M, respectively.
- Detailed justification is now required for unclassified Type II variations.
- Safety-related Type II variations must be implemented immediately.
- Reclassification of some variations (biologics etc.).
- Additional variation classifications for ATMPs, combination products and electronic submissions.
- References to veterinary products have been removed.

Submission procedure

- Annual bundling of Type IA variations is now allowed through super-grouping or an annual report.
- Mandatory work-sharing for minor Type IB variations affecting multiple marketing authorisations (CP, DCP/MR, National) is required.
- From January 2025, all variations (including extensions) must be submitted via the [IRIS digital platform](#).
- The guideline emphasizes flexibility in managing minor variations and improved coordination across multiple marketing authorisations owned by the same MAH.

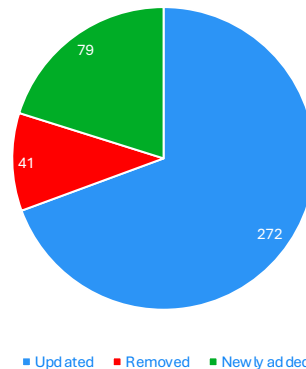
Tools and documentation

- Introduction of new tools:
 - Post-Approval Change Management Protocol (PACMP) for pre-agreed change pathways and
 - the Product Lifecycle Management Document (PLCM) for ongoing MA oversight.
- Detailed documentation requirements for changes to active substances, excipients, or medical device components.
- Emergency update flexibility is provided for human vaccines addressing public health emergencies in the EU (influenza & Covid-19).

Familiar structure but different logic underneath

- What stayed the same:
 - Structure of classification (albeit renamed)
 - IA / IB / II structure
 - “present vs proposed”
- What changed:
 - clarified conditions
 - restructured classifications
 - additional transparency in borderline cases
- Areas with most changes:
 - quality / manufacturing
 - safety-related labelling
- Increase in clarity (but also complexity)

Variation classifications summary



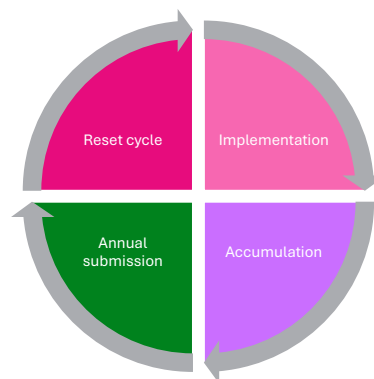
The guideline is clearer but not simpler.

Where It Really Changes How We Work

- IA annual reporting possibility & bundling IA variations
 - submission ≠ implementation
 - reporting = structured notification
 - IA changes are no longer ‘small changes’ and require structured tracking
- Worksharings
- Lifecycle planning tools (PACMP, PLCM)
- Planning vs. reacting

IA Annual Cycles

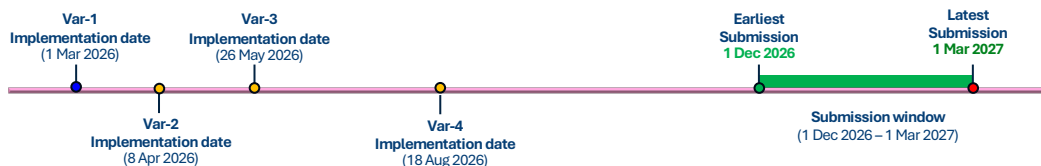
- IA variations are not to be submitted separately anymore
- Annual reporting of IA variations
- Start of cycle:
 - Is linked to MA and previous submission
 - Has a defined reporting window
- One cycle per MA
- Challenges:
 - Multi-country portfolios
 - Tracking - global vs local responsibility
 - Interaction with grouping
 - Handling of late IA changes & overlapping cycles



Success depends on tracking the cycle, not the individual variation.

Type IA Variations: Annual Update Rule

- Annual Update (“Type IA Annual Update”)
 - Submission timing: between 9 – 12 months after the oldest implementation date included
 - The “reporting year” is anchored to implementation date, not submission date
 - The reporting year is moving, resetting the period after the submission and starting with next implementation date
- Example of 9-12 Month Rule:
 - Variations implemented: 1 Mar, 8 Apr, 26 May, 18 Aug 2026
 - The oldest implementation (1 Mar 2026) sets the clock
 - Grouped IA submission between 1 Dec 2026 (9 months) and 1 Mar 2027 (12 months)
 - All later variations (Mar to Jul) can be included, but the reporting window still depends on the first change
- Exemptions / Alternative Submissions
 - Grouping: As part of an acceptable grouping together with IAIN, IB or II
 - Super-grouping: One or more Type IA variations across multiple MAs from the same MAH
 - Resubmission: When a single Type IA in an annual update was refused and must be resubmitted to comply with the 12-month rule
 - Exceptional immediate submissions (duly justified):
 - Needed to mitigate a shortage, agreed with MSSG (Executive Steering Group on Shortages & Safety)
 - Immediate dossier update required by EMA due to public health concern/emergency
 - Needed before a routine site inspection or a MAH transfer
 - Third country requests proof of EU acceptance (e.g., CPP or reliance program, shortage mitigation)



Post-approval Change Management Plan: Planned Changes

- Pre-agreed change plan with HA(s)
- Particularly useful for:
 - Complex manufacturing changes
 - Repeated complex/type II changes
 - Biologics, advanced therapies...
- Benefits:
 - Reduced uncertainty in data expectations
 - Reduced timelines for the change in future
 - Reduced fees for the change in future

Type II variation without PACMP:



Type II variation with PACMP:



Faster, more structured variation Type II execution

Product Life Cycle Management (PCLM) Concept

- Not always formalized, but:
 - structured lifecycle planning
 - anticipating changes
- Applies especially to:
 - biologics
 - complex portfolios
- Connected to:
 - PACMP
 - IA planning
 - grouping strategy
- It is NOT
 - a regulatory requirement
 - a formal submission
 - a complex system

Example (data only for illustration):

Area	Planned Change	Timing	Regulatory Approach
Manufacturing	New DP site	2027	PACMP + Type II
Manufacturing	New DS site	2027	PACMP + Type IB
API	New raw material supplier	2026	IB / grouping
Labelling	Safety update	ongoing	IB / II
Labelling	Indication extension	2027	II
R&D	New pharmaceutical form	2028	Line Extension

The product lifecycle becomes something you design not react to.

Key Takeaways

- EU regulatory framework shifts in mindset
- Variations system is becoming dynamic
- IA annual reporting requires active planning and very organised tracking
- PACMP (and PLCM) shifts work before submission
- New Pharma Legislation and other initiatives will bring further updates/changes into the framework
- Regulatory should move from handling changes to managing lifecycle