



Post-authorisation procedures

Změny registrace po uvedení přípravku na trh

REGISTRACE LÉČIVÝCH PŘÍPRAVKŮ OD A DO Z

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Agenda

- **Types of post-authorization procedures**
- **Changes of MA in general**
- **Variations**
- **Other important life cycle events**
- **Key takeaways**

Types of post-authorisation procedures

- Variations
- Line Extensions
- Transfer of Marketing Authorisation
- Renewal
- Duplicate Marketing Authorisation
- Withdrawal

Why Do Changes Matter?

- | | | |
|--|--|-------------------------|
| <ul style="list-style-type: none"> • Ensures safety, quality, and efficacy • Keeps HAs and patients informed • Legal requirement to maintain marketing authorization up to date and in compliance | <ul style="list-style-type: none"> • For whom it is important that the variations are being submitted and approved? <ul style="list-style-type: none"> • Regulatory • Manufacturing • Quality • Clinical/Medical • Commercial • Marketing • ... | <p>...whole company</p> |
|--|--|-------------------------|

Variation & its types

- Simple definition: A change to an already approved medicine.



- Variation is a change in regulatory documentation already assessed by a Health Authority

- Examples:

- Changing the manufacturing site
- Updating the product label
- Adding a new indication

- Type IA:** Minor, often admin, “no” impact, “tell and do”
 - Type IA_{in} (IA_{in}) – immediate submission

- Type IB:** Minor to moderate, “tell, wait and do”

- Type II:** Major, needs full review, “tell, wait and do”

- Line extensions:** Significant change requiring a separate application pathway & life cycle (“tell, wait and do”)



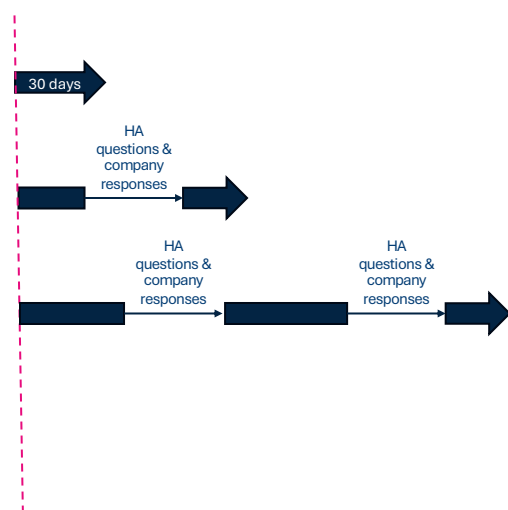
Timelines

- Type IA:** Immediate implementation, notify within 12 months
 - No questions from HA

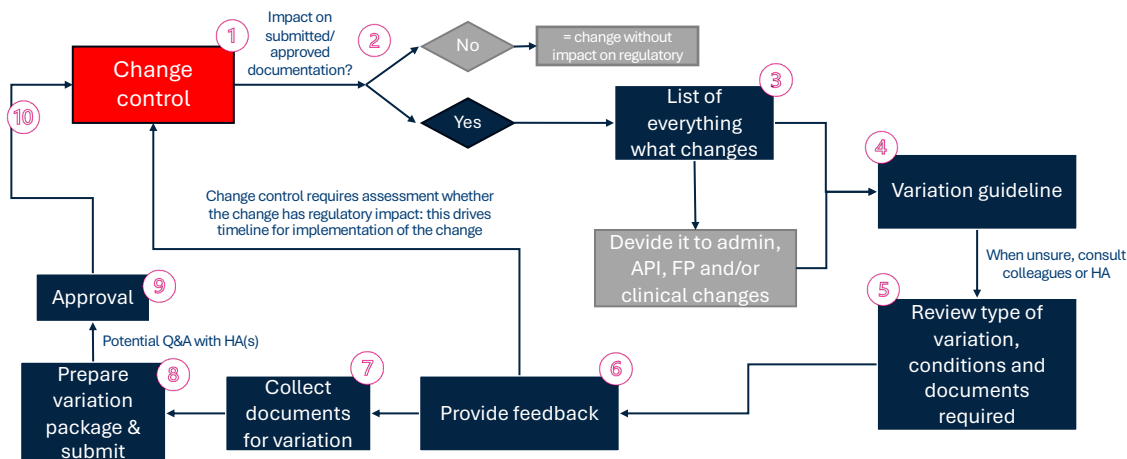
- Type IB:** 30-day review
 - Questions from HA

- Type II:** 60–90 days (can vary)
 - Questions from HA

- Grouping:** variation with the most complex classification is driving the timeline of whole grouping



How to Classify a Variation (+ follow up steps)



How to read the variation guideline?

Annex				
TOPIC / SCOPE OF CHANGES				
A. ADMINISTRATIVE CHANGES				
B. QUALITY CHANGES				
I. Active Substance				
a) Manufacture				
b) Control of active substance				
c) Container closure system				
d) Stability				
e) Design Space				
II. Finished Product				
a) Description and composition				
b) Manufacture				
c) Control of excipients				
d) Control of finished product				
e) Container closure system				
f) Stability				
g) Design Space				
III. CFP/TSE/monographs				
IV. Medical Devices				
V. Changes to a marketing authorisation resulting from other regulatory procedures				
a) PMF/VAMF				
b) Referral				
c) Change management protocol				
C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES				
I. Human and Veterinary medicinal products				

B.II.b) Manufacture				
B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type	
a) Secondary packaging site	1, 2	1, 3, 8	IA _{ES}	
b) Primary packaging site	1, 2, 3, 4, 5	1, 2, 3, 4, 8, 9	IA _{ES}	
c) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products.			II	
d) Site which requires an initial or product specific inspection			II	
e) Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products.	1, 2, 3, 4, 5, 6, 7, 8, 9		IB	
f) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products manufactured using an aseptic method excluding biological/ immunological medicinal products.	1, 2, 3, 4, 5, 7, 8		IB	

Conditions
1. Satisfactory inspection in the last three years by an inspection service of one of the Member States of the EEA or of a country where an operational Good Manufacturing Practice (GMP) mutual recognition agreement (MRA) exists between the country concerned and the EU.
2. Site appropriately authorised (to manufacture the pharmaceutical form or product concerned).
3. Product concerned is not a sterile product.
4. Where relevant, for instance for suspensions and emulsions, validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.
5. Product concerned is not a biological/immunological medicinal product.

Documentation
1. Proof that the proposed site is appropriately authorised for the pharmaceutical form or product concerned, i.e.: For a manufacturing site within the EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMP database will suffice once the public version is operational. For a manufacturing site outside the EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority. For a manufacturing site outside the EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EEA. A reference to the EudraGMP database will suffice once the public version is operational.
2. Where relevant, the batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated and the validation data presented, or validation protocol (scheme) to be submitted.
3. The variation application form should clearly outline the "present" and "proposed" finished product manufacturers as listed in section 2.5 of the (Part IA) application form.
4. Copy of approved release and end-of-shelf life specifications if relevant.
5. Batch analysis data on one production batch and two pilot-scale batches simulating the production process (or two production batches) and comparative data on the last three batches from the previous site; batch data on the next two production batches should be available on request or reported if outside specifications (with proposed actions).
6. For semisolid and liquid formulations in which the active substance is present in non-dissolved

Notes
In case of a change in or a new manufacturing site in a country outside the EEA without an operational GMP mutual recognition agreement with the EU, marketing authorisation holders are advised to consult the relevant competent authorities first before making the submission of the notification and to provide information about any previous EEA inspection in the last 2-3 years, and/or any external EEA inspection(s), including inspection, alert, product, category.

For example: https://www.ukh.sk/buxus/docs/Registracie/Tlaciva/classification_guideline_adopted.pdf

Submission Basics

- **Where to submit:** EMA, national authority, or via worksharing
- **Format:** eCTD (or national format)
- **Grouping:** More variations (related to each other) submitted together
- **Annual Reporting:** submission of minor changes together, once a year (or a defined period)
- **Worksharing:** submission of more variations together across several MAs

Key Documents

- Cover letter
- Application form & Annexes
- Supporting documents depending on the change
 - Module 3 change:
 - updated CTD sections of Module 3
 - update/addendum to QOS
 - Module 4/5 change:
 - updated or additional study reports etc.
 - Update/addendum to relevant M2 sections
 - Safety change: PV (and labelling) documentation in M1
 - Labelling change: updated SmPC/PIL/mock-ups...

“Present-Proposed”

- Most important for explaining the change
- Describes status as is = “**present**”
- Describes future status, once the variation will be approved = “**proposed**”
- In eAF
- Must be simple, but detailed

Implementation date & period

• Implementation date

- When the change takes effect
- Important for all variations as from this date onwards, only new status should occur
- Needs to be reported to HA for IA variation type

• Implementation period

- Transition period between old and new status
- Depends on variation type and approval date
- Up to 6 months from approval
- Once new status occurs, no turning back
- For safety updates no or short implementation period

Legal basis and further reading

Previous EU Guideline for Classification of Variations

- Until **15 January 2026**, marketing authorisation holders must continue to follow the **existing guideline**:
- **Title:** *Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008*
- **Legal Basis:** [Commission Regulation \(EC\) No 1234/2008](#)
- **CMDh Procedural Guidance:** [CMDh – Variation Procedure](#)

Current guideline

- A **revised guideline** entered into force on **15 January 2026**, following the updated **Regulation (EU) 2024/1701**, which became applicable on **1 January 2025**.
- **Legal Basis:** [Commission Regulation \(EC\) No 2024/1701](#)
- **Transition guidance:** [EMA – Guidance on the application of the revised variations framework](#)



- More flexibility for grouping
- Expanded worksharing possibilities
- Simplification of several procedural pathways
- Increased lifecycle management efficiency
- Better support for innovation and supply continuity

Other Important Lifecycle Procedures

Line Extension

- New strength
- New pharmaceutical form
- New route of administration
- Treated separately from standard variations

Renewal

- Confirmation that benefit-risk remains positive
- Usually based on accumulated experience with the product

Transfer of MA

- Change of MAH
- Sale or acquisition of product portfolio
- Requires regulatory approval

Duplicate

- Additional MA based on the same dossier and product

Withdrawal

- Withdrawal of an MA, i.e. requesting to cancel its validity
- = End of the life cycle)

Key Takeaways

- ☐ Every medicinal product continues to evolve after approval.
- ☐ Variations are only one part of post-authorisation lifecycle management.
- ☐ Regulatory requirements must be considered before implementing changes.
- ☐ The right classification is the foundation of every successful submission.
- ☐ Regulatory Affairs does not work alone. Lifecycle management is a team effort.
- ☐ Understanding the process is important. Understanding the impact is essential.

**Approval gets a product onto the market.
Lifecycle management keeps it there.**