# Question and answer document pertaining to variations for medicinal products for human use (Version 3 June 2026)

## Contents

**General introduction**

- The Q&As should be considered as supplementary to the CMDh Q&As on variations, the CMD Procedural Guidance documents pertaining to variation applications and the *Guidelines on the details of the various categories of variation, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 (*'Variation Guideline') on the EC website.
- For information about the eCTD and eSubmissions in general, see the CMDh website (https://www.hma.eu/human-medicines/cmdh/procedural-guidance/esubmissions.html), the MEB website (Submission via CESP | Medicines Evaluation Board) and the EMA website (http://esubmission.ema.europa.eu/).
- This question and answer document from the MEB uses the terms 'purely national procedure' and 'purely national marketing authorisation' to indicate that this concerns a medicinal product that has been granted a marketing authorisation via a national procedure in the Netherlands, and not via a DCP/MRP.
- The definition of a marketing authorisation for MRP variations is stated in the CMDh Q&A on variations 1.4. For the definition of a marketing authorisation for purely national products in the Netherlands, the MEB uses the same reasoning for variations: all RVG numbers belonging to a group of marketing authorisations with the same active substance, including line extensions of these authorisations. Authorisations obtained via duplex applications or informed consent applications do not fall under the same marketing authorisation for variations for purely national marketing authorisations.

### Q 1.1 – Does Variation Regulation 1234/2008 (as amended) also apply to homeopathic and herbal medicinal products?

The following types of products are **not** included in the Variation Regulation 1234/2008 concerning the examination of variations:

1) herbal medicinal products that are authorised as traditional herbal medicinal products in accordance with Section 42(8) of the Medicines Act;*
2) homeopathic medicinal products that are authorised in accordance with Section 42(3) of the Medicines Act.
3) homeopathic medicinal products that are authorised in accordance with Section 42(4) of the Medicines Act.

All other medicinal products, including herbal medicinal products, fall within the scope of Regulation 1234/2008 (as amended).

Applications for changes to the authorisation conditions for the above-mentioned product groups (traditional herbal medicinal products and homeopathic medicinal products) are evaluated by the Novel Foods Unit (BNV).

For the agreements for variations for traditional herbal medicinal products in Europe, see CMDh Q&A 5 on **Traditional Herbal Medicinal Products.**

## Questions concerning the submission of a variation

### Q 2.1 – What has to be stated in a cover letter?

The CMDh has published a template cover letter for variations (see www.hma.eu/265.html). The use of this template is not mandatory but is strongly recommended for variations for MRP/DCP products. The MEB has also published recommendations for the cover letter on its own website (See https://english.cbg-meb.nl/topics/mah-cover-letter).

### Q 2.2 – How should variation numbers be allocated in the mutual recognition procedure?

A clarification of how MRP numbers must be allocated for products authorised through the MRP/DCP is provided in the *CMDh Best practice guide for the submission and processing of variations in the mutual recognition procedure*, Chapter 1 *CMDh BPG for the allocation of the mutual recognition variation number for Type I Notifications, Type II Variations Grouping and Worksharing* (see http://www.hma.eu/96.html).
There are two situations in which the applicant cannot allocate the number on its own but should request this from the chosen RMS/Reference Authority before submission:

- super-grouped IA variations;
- worksharing variations.

Such requests should be sent by email to WerkgroepVariatie@cbg-meb.nl, together with the relevant Letter of intent (see Variations | Medicines Evaluation Board).

### Q 2.3 – When should I submit the translations?

For a purely national procedure, Dutch-language text proposals should be submitted immediately upon submission for all variations. See also the MEB policy document 'MEB policy concerning marketing authorisations without Dutch translations of the product information and/or mock-ups' (MEB 41: MEB policy concerning marketing authorisations without Dutch translations of the product information and/or mock-ups | Policy Document | Medicines Evaluation Board).
For the MRP variation procedure, a distinction is made regarding when translations should be submitted between type IA/IB variations on the one hand and type II variations on the other. See chapters 3, 4, 5 and 7 of the *CMDh Best practice guide for the submission and processing of variations in the mutual recognition procedure* (see http://www.hma.eu/96.html).

### Q 2.4 – Which language should be used for the product information to be submitted in MRP/DCP when the Netherlands is the only remaining CMS (i.e. when there are no longer any other concerned Member States involved in the procedure)?

At the end of the procedure, the RMS should finalise the texts for the summary of product characteristics (SmPC), package leaflet and labelling in the English language. This is required for various reasons, including with regard to both the product information and the public assessment report to be uploaded on the MRI Product Index. To this end, English-language texts should first be submitted and assessed, even for products where the Netherlands is the only remaining Member State (as RMS) following the withdrawal of the marketing authorisation in the other concerned Member States (CMS).

### Q 2.5 – When should I submit mock-ups?

In the event that a type IA or IB variation also leads to changes in the package leaflet and/or labelling text (module 1.3.2 and/or 1.3.3) for which mock-ups need to be submitted, these mock-ups should be submitted together with the variation application. This allows the case to be closed upon approval of the variation, as the mock-ups do not need to be submitted separately.
For a type IA variation, it is not possible to submit supplementary documentation during the procedure. The application should in principle be complete from the start. However, the MEB does make an exception for mock-ups. Therefore, non-submission of a mock-up with a type IA variation will not result in the type IA variation being declared invalid. If mock-ups have not been submitted, the MEB will issue a request for this to be done.
In the event that a type II variation also leads to changes in the package leaflet and/or labelling text (module 1.3.2 and/or 1.3.3) for which mock-ups are submitted, these mock-ups should be submitted simultaneously with the start of the national implementation phase.
See also the MEB policy document 'MEB policy concerning marketing authorisations without Dutch translations of the product information and/or mock-ups' (MEB 41: wwwwMEB policy concerning marketing authorisations without Dutch translations of the product information and/or mock-ups | Policy Document | Medicines Evaluation Board).

### Q 2.6 – In the case of a variation, should I submit an eCTD per strength and/or pharmaceutical form, or per marketing authorisation/general information about the eCTD?

When submitting the initial application for a marketing authorisation, it is up to the applicant to decide whether to make a separate eCTD per strength and/or pharmaceutical form or to make an eCTD containing all strengths and/or pharmaceutical forms. The eCTD guidance (see http://esubmission.ema.europa.eu/) states that, once the decision has been made, it should be followed through in all subsequent submissions after the initial application for a marketing authorisation. This page also contains general information about eSubmissions.
Information on this subject can also be found on the CMDh website (http://www.hma.eu/277.html).

### Q 2.7 – During the validation of an unforeseen type IB variation, a decision can be taken that the change is actually a type II variation. Should the variation then be resubmitted from scratch?

The Variation Guidelines/Chapter 5 of Volume 2A of Notice to Applicants (EudraLex - Volume 2 - Public Health - European) states the following in this context: " the holder is asked to amend their application and to complete it in accordance with the requirements for a major variation of Type II. Once the valid revised variation application has been received, a major variation of Type II assessment procedure is initiated."
The idea is that the variation application is supplemented with the necessary additional information, including an updated overall summary (module 2.x). The variation is processed under the same serial number (but the annotation 'IB' in the procedure number is changed to 'II') and under the original case number.

## Questions concerning super grouping, worksharing and grouped variations

See CMDh Best Practice Guides chapters 6 and 7 (https://www.hma.eu/human-medicines/cmdh/procedural-guidance/variation.html).

### Q 3.1 – Is it necessary to request advice from the MEB before submitting a grouped variation?

When submitting a grouped variation, the applicant should always provide a justification for the grouping of various variations in the variation application form, unless it concerns grouping of multiple IA variations.
To this end, the applicant can refer to the examples given in Annex III of the Variation Regulation (1234/2008/EC) or those in the *'Examples for acceptable and not acceptable groupings for MRP/DCP products'* document published on the CMDh website (https://www.hma.eu/96.html). If the grouping is in line with these examples, it is not necessary to contact the MEB beforehand about the planned submission. However, it may be the case that the grouping is not covered by the examples mentioned, even though there are sound arguments for grouping the variations to be submitted. In that case, you should submit your substantiated proposal to the MEB for advice beforehand using the contact form (https://www.cbg-meb.nl/contact, with 'variations' in the subject line).

## Questions concerning implementation and timelines for approval

### Q 4.1 – Which timelines apply?

**Mutual recognition procedure, type IA/IB/II variations**

The marketing authorisation holder always receives a confirmation of receipt of the application. Additional information about timelines can be found in the respective *CMDh Best practice guide for the submission and processing of variations in the mutual recognition procedure* (see http://www.hma.eu/96.html).

**National marketing authorisations, type IA/IB/II variations**

The list of product types can be found on the MEB website (see https://www.cbg-meb.nl/onderwerpen/hwwv-producttypes-en-tarieven).

- For type IA variations, the MEB applies 60 days (30 days for the validation and 30 days for any administrative change to the marketing authorisation that might be required). In the case of a Type IA notification, you therefore receive the amended marketing authorisation and/or the notice of change to the SmPC afterwards, so after you have implemented the change in your own systems and after the MEB has declared your notification to be valid.
- For type IB variations, the MEB applies the same timelines as for type IB variations via MRP: 30 days for the validation and assessment, 30 days for any clock-stop period and 30 days for the second assessment round. Type IB variations should be approved by the MEB before you are allowed to implement the changes. However, just as in the case of Type IA notifications, you receive any required amended marketing authorisation and/or the notice of change to the SmPC afterwards for type IB variations, so after approval.

This administrative process takes place within six months after approval. However, the MEB aims to finish the process within 60 days.

For type II variations, the MEB applies two different timelines: 164 or 194 days. These timelines appear to deviate from the MRP timelines, but in these national procedures, the clock starts directly after receipt of the variation application and likewise restarts right after receipt of the answer. In an MRP variation, the clock is only restarted once the RMS distributes the Final Variation Assessment Report, and the assessment is performed whilst the clock has been stopped.
For type II variations, the MEB applies the following timelines:

- type II quality or type II other: 164 days (14+60 days for the first round, 60 days for the second round and 30 days for the final round. No separate implementation round to follow after the final round);
- type II new indication: 194 days (14+60 days for the first round, 70 days for the second round and 50 days for the final round. No separate implementation round to follow after the final round).

### Q 4.2 – Implementation (i.e. actual processing) of changes and date of approval of variations

Type IA variations are notified **after** the change has been implemented by the MAH. The applicant includes the date on which the change was implemented in the variation application form. This is the only way in which the applicant notifies the authorities of the implementation of a type IA variation.
Type IA variations (national and MRP) are declared valid/not valid by no later than 30 days after start of the procedure. No formal approval takes place, and for that reason, there is no date of approval either. In the event of a change to the product information, the implementation date stated by the company applies as the date of approval of the product information. The MEB includes this date in the product information (see also question 4.4).

Type IB variations for purely national marketing authorisations may only be implemented 30 days after the start date of the procedure, unless the MEB sends a notice to the applicant within those 30 days. If the applicant does not receive a notice, day 30 as stated in the confirmation of receipt of the variation will also apply as the date of approval.
Type II variations for purely national marketing authorisations may only be implemented once they have been notified and the applicant has received a notice of approval from the MEB. In the case of these variations, you will receive the date of approval from the MEB by email.

Date of approval of type IB and type II variations for MRP/DCP products:
At the start of the procedure, the applicant will receive the timetable from the RMS by email. After approval, you will receive a notice from the RMS containing the End of Procedure (EoP) date. This date is the approval date stated in the product information.
If the Netherlands is CMS and the product information does not change, the MEB will **not** send any national confirmation of the completion of these variations. The national approval date then corresponds to the EoP (end of procedure) date as sent by the RMS.

Information about the possibility to implement the changes of type IB and type II variations for MRP products is also included in the relevant *CMDh Best practice guides for the submission and*

*processing of variations in the mutual recognition procedure* (see http://www.hma.eu/96.html) and in the *Questions and Answers on Variations* document (http://www.hma.eu/20.html). . See also Q&A 5.2 in the latter document.

The policy outlined below applies to **all** products authorised by the MEB (including parallel import products and replica marketing authorisations).

For type IB and type II variations, the applicant should propose a time frame on the variation form within which the proposed change will be implemented. Alternatively, the applicant can opt for implementation with the next scheduled production run or propose a date of implementation.

In general, implementation within a period of six months is acceptable. If a longer period is proposed, a justification should be provided. Changes which relate to safety or correct use of the product,[1] or to a key quality aspect, should be implemented as quickly as possible. This will be assessed on a case-by-case basis.
In exceptional, severe cases, additional measures may be necessary, which may be determined after consulting with the Inspectorate and the marketing authorisation holder.

An application for a change to the dossier that does not include a proposed moment for implementation is invalid and cannot be processed.

In instances in which no explicit approval is sent, without notice to the contrary, the proposed implementation moment may be considered approved along with the rest of the application. If the proposed implementation date is not approved, this will be noted explicitly in the MEB's correspondence.

**Q 4.3 – It is possible to group a line extension with a type IB or type II variation. Can the type IB or type II variation be implemented before completion of the line extension?**

If the applicant decides to group a type IB or type II variation with a line extension of that product, this will be processed as a single application with a single start date and end date. This means that the approval for the type IB or type II variation is provided only once the line extension has been approved. The timelines of a new marketing authorisation application will therefore be applied.

**Q 4.4 – The Variation Regulation offers marketing authorisation holders the possibility to implement a change before the MEB has processed a new SmPC or package leaflet administratively. What date should be entered for section 10 of the SmPC and section 6 of the package leaflet?**

For type IA variations, the CMDh has agreed to the following (see Question 5.5 of the *Question & Answer document*; http://www.hma.eu/96.html).

[1] This often includes changes to the SmPC in the sections 'Contraindications', 'Special warnings and precautions for use', 'Interactions' and 'Adverse reactions', in particular as a result of *Urgent Safety Restrictions*

**Question 5.5**
*In case a type IA or type IAIN variation affects the package leaflet, how should the 'Date of revision of the text' be detailed in the printed version of the package leaflet?*
**Answer:**
For Type IA and IAIN variations, the 'Date of revision of the text' will correspond to the implementation date (i.e. when the Company internally approves the revised product information). (See also Question 5.2)

The MEB follows this agreement.

For type IB and type II variations, the CMDh has not made any agreements. The MEB applies the following agreements for reporting the date of revision in section 10 of the SmPC and the date of approval in the package leaflet in both the Word versions and the printed versions of the SmPC and package leaflet.

MRP products:
- type IB variation: the date when the RMS approves the type IB variation;
- type II variation: the date when the RMS approves the type II variation.

National products:
- type IB variation: day 30 after the start of the procedure. If the variation is approved and implemented before day 30, the date on which the SmPC is adopted counts as the approval date in section 10;
- type II: the date on which the MEB approves the type II variation.

Therefore, the MEB will not overwrite this date with a later date if the MEB processes the new SmPC and package leaflet later. An example is given below to illustrate this.

A national type IA variation was submitted on 1 March 2024, and the company had already implemented the type IA variation on 1 February 2024. The date is stated as 1 February 2024 in the SmPC and as February 2024 in the package leaflet. The MEB processed this type IA variation on 29 March 2024 but left the date of (1) February 2024 in the SmPC and package leaflet unchanged.

## Questions concerning specific variations

### Q 5.1 – Is the deletion of a strength and/or pharmaceutical form a variation?

The Variation Classification Guideline lists variation C.7 ‘deletion of a pharmaceutical form or strength’ as a type IB variation. However, the following footnote is included: *In cases where a given pharmaceutical form or strength has received a marketing authorisation which is separate to the marketing authorisation for other pharmaceutical forms or strengths, the deletion of the former will not be a variation but the withdrawal of the marketing authorisation.*
If the marketing authorisation holder wishes to delete a strength or pharmaceutical form of a product, and this strength or pharmaceutical form has its own marketing authorisation number, the marketing authorisation holder should submit a request to withdraw this marketing authorisation (see Withdrawal of a marketing authorisation | Medicines Evaluation Board).