Question and answer document pertaining to variations for medicines for human use
Version 2.8 (31 January 2022)

Contents

General questions

Q 1.1 – When did the amended Variation Regulation 1234/2008 (as amended by Regulation 712/2012) enter into force?

Variation Regulation (EU) No. 1234/2008 entered into force on 1 January 2010 and was amended with the entry into force of Regulation (EU) No. 712/2012. The Variation Regulation has therefore been in force since 4 August 2013 for products in the mutual recognition procedure and the centralised procedure, as well as for products which have been authorised purely* through the national procedure.

* This question and answer document from the MEB uses the following terms 'purely national procedure' or 'purely national authorisation' to indicate that this concerns a medicine authorised via a national procedure, without a procedure of mutual recognition.

Q 1.2 – A marketing authorisation is used as a starting point to define when grouping or worksharing is possible. What exactly is meant by a marketing authorisation?

There is no definition of a marketing authorisation at a European level. Each competent authority applies its own system. In some countries separate marketing authorisations are issued per strength and pharmaceutical form. In other countries a marketing authorisation is issued that includes all strengths and pharmaceutical forms.

Within the CMDh it has been agreed that for MRP/DCP products, all strengths and/or pharmaceutical forms of a product will be considered as a single marketing authorisation, e.g. NL/H/1234/001-004 are 4 different strengths and/or pharmaceutical forms that form part of one single marketing authorisation.

The definition used of marketing authorisation is not the same as the definition of a global marketing authorisation. It should be noted that the concept of the global marketing authorisation was developed for data exclusivity purposes only, and is therefore not used in relation to the Variation Regulation.

- Therefore informed consent authorisations do not fall under the same marketing authorisation as the basic product.
- The same applies to duplex authorisations and duplicate dossiers which do not fall within the same marketing authorisation as the basic product.

Although the MEB often provides a separate RVG number per strength and pharmaceutical form, the MEB also uses this definition of marketing authorisation at the background in the internal database, and this definition may therefore also be used for grouping/worksharing of purely national authorisations (see also Q.3.1).

Q 1.3 – Does Variation Regulation 1234/2008 (as amended by Regulation 712/2012) also apply to homeopathic and herbal medicinal products?

The following types of products are not included in Variation Regulation 1234/2008 (as amended by Regulation 712/2012) for the processing of variations:

1) Herbal medicinal products that are authorised as traditional herbal medicinal products in accordance with Art. 42, section eight of the Medicines Act.*
2) Homeopathic medicinal products that are authorised in accordance with Art. 42, section three of the Medicines Act.
3) Homeopathic medicinal products that are authorised in accordance with Art. 42, section four of the Medicines Act.

All other medicinal products, including herbal medicinal products, fall within the scope of Regulation 1234/2008 (as amended by Regulation 712/2012).

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 Botanicals department. If desired, the applicant can contact the Regulatory Project Leaders of this department prior to submission.

A discussion has been started in a European context to develop a clarification of the classification of the various changes for homeopathic products, analogous to Variation Regulation 1234/2008 (as amended by Regulation 712/2012). For the time being the variations are being evaluated by the national regulatory authority.

* See also question 5 of the Q&A on TRADITIONAL HERBAL MEDICINAL PRODUCTS on the CMDh website (www.hma.eu/20.html).

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 compulsory, 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 must the variation application form be filled in?

The variation application form has been published on the website of the Commission (see volume 2B of the Notice to Applicants; http://ec.europa.eu/health/documents/eudralex/vol-2/).
The European Medicines Agency and CMDh have together drawn up the European Medicines Agency/CMDh explanatory notes on Variation Application Form (human medicinal products only)(see http://www.hma.eu/96.html).
This document includes instructions for completing the form correctly. Many of these instructions are also of importance for variations for the purely national procedures.

Q 2.3 – How must 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 three situations in which the applicant cannot allocate the number on its own, but must request it from the RMS or CMDh secretariat/Reference Authority before submission:

- a grouped application for type IA variation(s) that relates to more than one marketing authorisation where the Netherlands is the RMS for all products concerned;
- a supergrouped IA variation that relates to more than one marketing authorisation with different RMSs (see CMDh BPG Chapter 6, which clarifies for which IA variations this is possible);
- a worksharing application.

The procedure number for a grouped application for type IA variations can be requested using a digital form on the MEB website (see https://fd8.formdesk.com/collegeterbeoordelingvangenees/variations-2). The CMDh secretariat will provide the applicant with a variation number for a worksharing application after acceptance.

In order to apply for a supergrouped type IA variation with the MEB (NL) as lead member state, you need to send a letter of intent by email to Ms Kora Doorduyn-van der Stoep at WerkgroepVariatie@cbg-meb.nl. For the template of this letter of intent, see the CMDh website: http://www.hma.eu/265.html.
You **do not** have to submit a separate application for a procedure number for these supergrouped variations via the above-mentioned form or the MEB website.

In the case of a worksharing procedure with MEB (NL) as the desired Reference Authority for both

- products authorised via an MRP/DCP procedure with more than 1 reference member state (RMS) and/or only purely national marketing authorisations of the same product in several member states,
- as well as purely for products for which the Netherlands is the RMS,

you should send a letter of intent to Ms Kora Doorduyn-van der Stoep at WerkgroepVariatie@cbg-meb.nl.
See also the MEB website: https://english.cbg-meb.nl/topics/mah-variation and for the template of the letter: http://www.hma.eu/265.html).

Q 2.4 – When must I submit the translations?

For a purely national procedure, Dutch-language text proposals must be submitted immediately upon submission for all variations.
For the MRP variation procedure, a distinction is made between type IA/IB variations on the one hand and type II variations on the other. Chapters 3, 4 and 5 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) states the following:

- For type IA and type IB variations, the national translations must be sent together with the submitted variation procedure.

- For type II variations, the national translations must be submitted no more than 7 calendar days after completion of the type II variation by the RMS.
- For worksharing procedures with only type IB variations, the national translations must be sent together with the submitted variation procedure.

Q 2.5 – Which language must be used for the product information to be submitted in MRP/DCP when the Netherlands is the only remaining member state (i.e. when there are no longer any other concerned members states involved in the procedure)?

According to the CMDh's interpretation of the legislation and regulations, the mutual recognition (MR) rules (Commission Regulation (EC) 1234/2008, Article 1 Subject matter and scope) apply to variations and renewals even when only one member state remains in the MRP or DCP, because the product has also benefited from the MR/DC procedure.
At the end of the procedure, the RMS must lay down the English-language texts for the summary of product characteristics (SmPC), package leaflet (PL) and labelling. This is among others required as the product information and public assessment report needs to be uploaded to the MRI Product Index. Therefore, English-language texts must be submitted and assessed, even for products where the Netherlands is the only remaining member state following the withdrawal of the marketing authorisation in the other member states (CMS).

Q 2.6 – When must 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 are submitted, these mock-ups must be submitted together with the 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 additional documentation. The MEB applies the principle that the application should be complete from the outset. 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 must be submitted simultaneously with the start of the national implementation phase.
See also the MEB policy document concerning marketing authorisations without Dutch translations of the product information and/or mock-ups (https://www.cbg-meb.nl/documenten/beleidsdocumenten/2020/01/01/meb-41).

Q 2.7 – In the case of a variation, should I submit an eCTD per strength and/or pharmaceutical form, or per marketing authorisation?

When submitting the initial marketing authorisation application, it is up to the applicant to decide whether to make a separate eCTD per strength and/or pharmaceutical form 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 must be followed through in all subsequent submissions after the initial marketing authorisation application.

Q 2.8 – Where can I find more information about eCTD and variations?

Relevant information about the eCTD is published on the eSubmission website (see http://esubmission.ema.europa.eu). Information on this subject is also published by the CMDh (http://www.hma.eu/277.html).

Q 2.9 – 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?

Variation Guidelines/Chapter 5 of Volume 2A of the Notice to Applicants (http://ec.europa.eu/health/documents/eudralex/vol-2/) states the following on this subject: "the holder will be requested to revise its application and to complete it in accordance with the requirements for a major variation of Type II application. Following receipt of the valid revised variation application, a Type II assessment procedure will be 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 sequence number and the original case number in order to prevent a fee being charged twice.

Q 2.10 – Can I submit multiple single variations with a single cover letter?

A single variation is one variation which is provided on a single variation application form, with a single set of underlying documentation. If more than one single variation is submitted, it will **not** be possible to send in a single cover letter accompanied by two variation application forms and two sets of underlying documentation (in other words as a kind of package).
Each single variation must be submitted as follows:

- cover letter per single variation;
- variation application form per single variation;
- underlying documentation per single variation.

It goes without saying that the applicant in the above situation must therefore submit a single cover letter per single variation and a single eCTD sequence. It is preferable for the eCTD to be submitted via the Common European Submission Platform (CESP). Alternatively, it can be submitted on a CD or DVD. In that case each single variation must be submitted on a separate CD or DVD.

Q 2.11 – Can the head office sign the variation application form if the local affiliate in the Netherlands is the marketing authorisation holder?

The variation application form states the following:

Name and address of the MA holder[5]:	Name and address of contact person[6]:
	Title, first name, surname
Company name	Company name
Address	Address
Telephone number:	Telephone number:
E-mail:	E-mail:

[5] For worksharing or grouped variations affecting more than one MA, indicate the MA holder to be used as reference MA holder for the handling of the procedure.

[6] As specified in section 2.4.3 in Part IA/Module 1 Application Form. If different, attach letter of authorisation. For worksharing or grouped type IA variations affecting more than one MA, a single contact should be designated for the application (see also Signatory box below).

The option is offered to have an applicant (i.e. not the MA holder) submit the variation. The variation application form must be signed by the applicant, and it is possible for the applicant's contact person to do this (i.e. not the MA holder). In footnote 6 of the variation application form the option is given that someone other than the MA holder may act as contact person, and that may be organised in one of two ways:

1. The contact person has already been mentioned in section 2.4.3 of module 1.2 (the application form of the initial application), or
2. a letter of authorisation is submitted for this specific variation.

Questions concerning Grouping and Worksharing

Q 3.1 – Is it possible to submit the same variations for several products in a single variation procedure, and to apply grouping and worksharing to purely national procedures?

As of 4 August 2013, purely national authorisations fall within the scope of Variation Regulation 1234/2008 (as amended by Variation Regulation 712/2012). The following grouping or worksharing procedures are possible:

- Grouping within a group of MRP/DCP authorisations OR within a group of purely national authorisations (several MAs* of 1 MAH are possible in the case of IA variations).
- Grouping of type IB/type II or grouped variations within a group of purely national authorisations of the same MAH.
- Worksharing with MRP/DCP, central products and purely national authorisations or combinations of these.

*1 marketing authorisation (MA) includes all strengths and pharmaceutical forms of a given product.

Q 3.2 – When must an annual report be submitted?

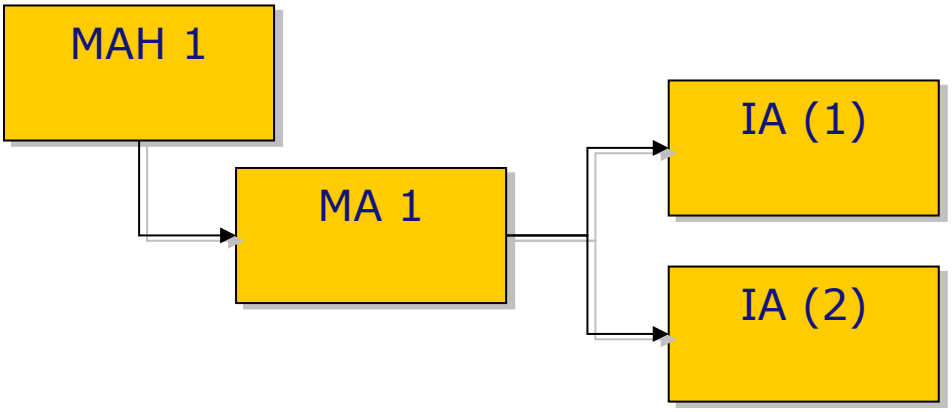
An annual report is another name for a grouped application in which only type IA variations have been included. This can be a grouped application concerning a single marketing authorisation or a grouped application concerning more than one marketing authorisation, provided that all variations are applicable to all MAs.
It is **not** permitted to include MRP/DCP as well as purely national authorisations in a single grouped variation with several MAs (see also Q.3.1).
An annual report must be submitted no more than 12 months after implementation of the first implemented type IA variation. It is up to the applicant to decide when to submit an annual report. One option is to collect type IA variations until a type IA variation immediate notification is implemented and then to submit all type IA variations as a grouped application.
It is not compulsory to save up all type IA variations in the form of an annual report; applicants may also submit type IA variations separately.

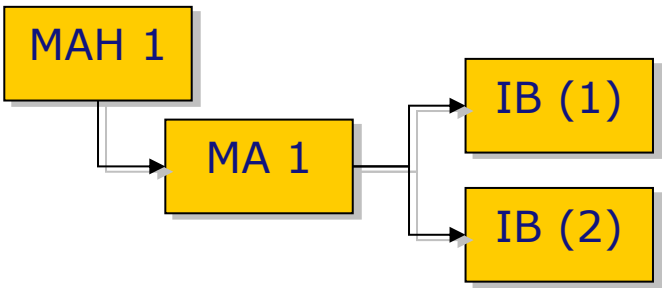
Q 3.3 – How should I submit the documentation in the case of grouping?

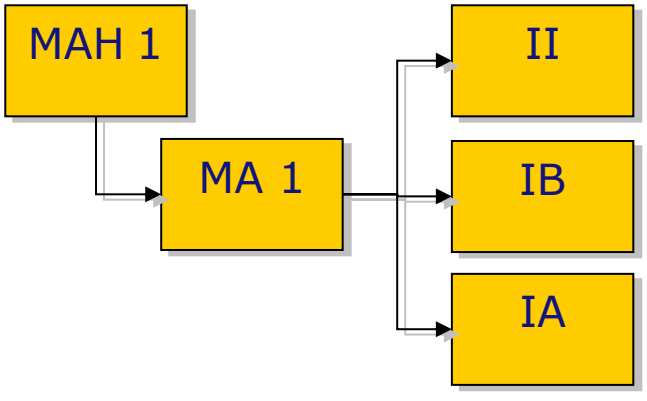
There are two different types of grouping:

Grouping within one marketing authorisation

Firstly, it is possible to submit several variations concerning a single marketing authorisation as a grouped application. A few examples are provided below.







The highest type of variation determines the type of the group: in the above example the application will be processed as a type II.

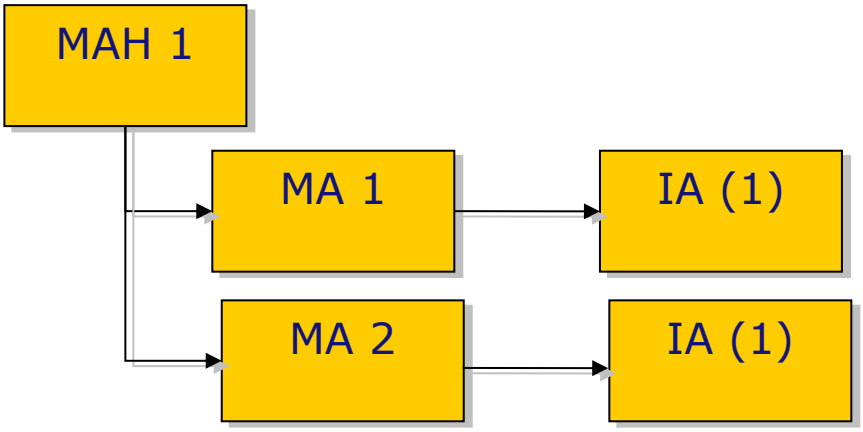
The application then consists of:

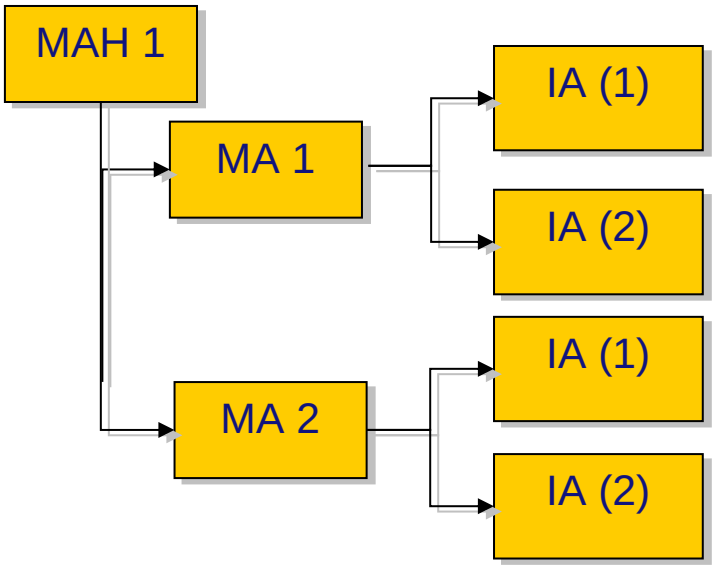
- One cover letter;
- One variation application form;
- For type IA variations: a copy of the relevant page(s) of the Variation Guideline (Chapter 5 of Volume 2A of the Notice to Applicants), indicating that the conditions have been with and/or the required documentation has been submitted.
- For type II variations: a copy of the relevant page of the Variation Guideline (Chapter 5 of Volume 2A of the Notice to Applicants).
- For type IB variations: a copy of the relevant page of the Variation Guideline (Chapter 5 of Volume 2A of the Notice to Applicants), if available;
- The accompanying documentation. If applicable, the section headings and section numbering of the CTD format should be used (so not appendices 1, 2, 3, etc.).
- In the event that the changes result in a change to the SmPC, package leaflet and/or labelling texts (modules 1.3.1, 1.3.2 and/or 1.3.3), both a clean and a track changes version must be submitted.
- In the event that the variations also lead to a change in the mock-up(s), this/these must be submitted.

If a grouped application consists of a type II, type IB and a type IA variation, all three variations must be listed on the same variation application form.
For grouping variations with a line extension see Q.4.3.

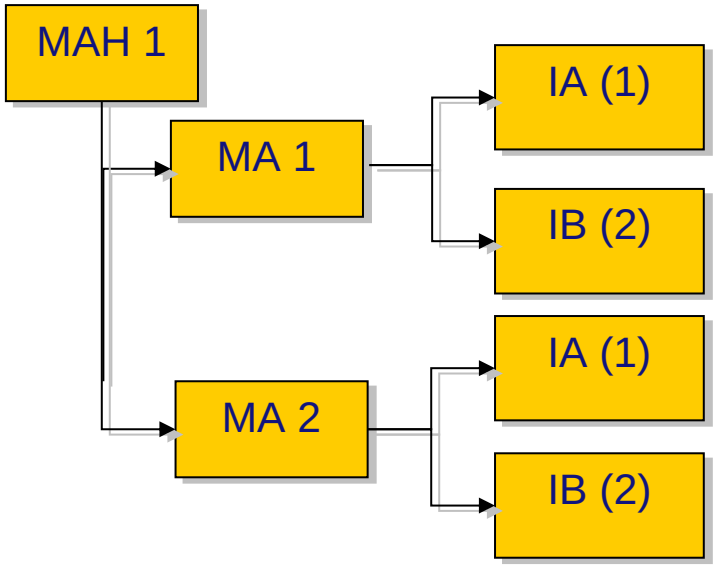
Grouping concerning more than one marketing authorisation

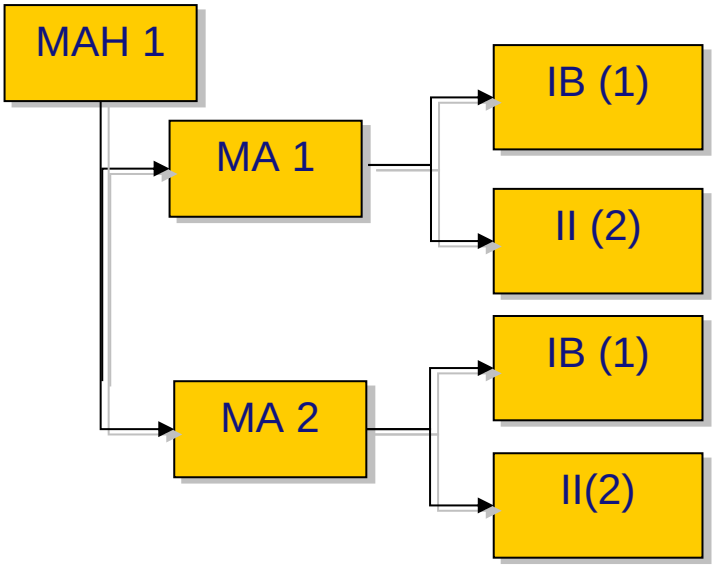
It is also possible to submit one or several variations concerning more than one marketing authorisation as a grouped application for the same MAH. This is only possible for MRP/DCP products in the case of type IA(in) variations. In the case of purely national authorisations this is also possible for type IB/type II and grouped variations. A few examples are provided below:


MAH 1
MA 1
IA (1)
MA 2
IA (1)


MAH 1
MA 1
IA (1)
IA (2)
MA 2
IA (1)
IA (2)

Purely national products, e.g.:





The application then consists of:

- One cover letter;
- One variation application form;
- A copy of the relevant page(s) of the Variation Guideline (Chapter 5 of Volume 2A of the Notice to Applicants), indicating that the conditions have been with and/or the required documentation has been submitted.
- The accompanying documentation. If applicable, the section headings and section numbering of the CTD format should be used (so not appendices 1, 2, 3, etc.).
- In the event that the changes result in a change to the SmPC, package leaflet and/or labelling texts (modules 1.3.1, 1.3.2 and/or 1.3.3), both a clean and a track changes version must be submitted.
- In the event that the variations also lead to a change in the mock-up(s), this/these must be submitted.

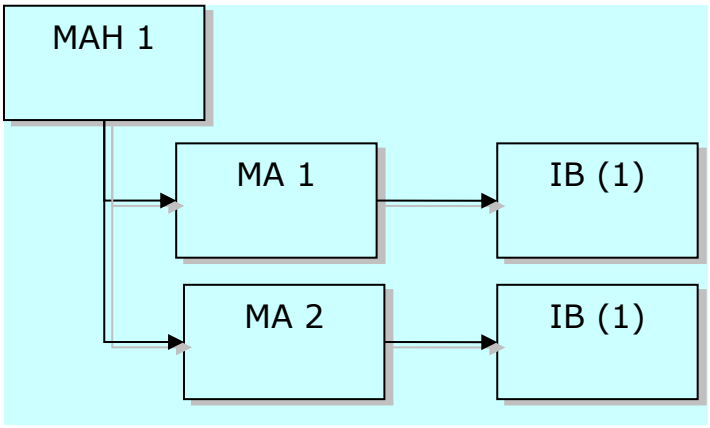
Again, in this case all submitted variations must be listed on the same variation application form. There is, therefore, only one variation application form. The same cover letter and variation application form must be included in each eCTD. It is preferential for the submission to take place via CESP. If eCTDs are submitted by post on several CDs or DVDs, they must be submitted to the MEB together in a single package (a single envelope or box).

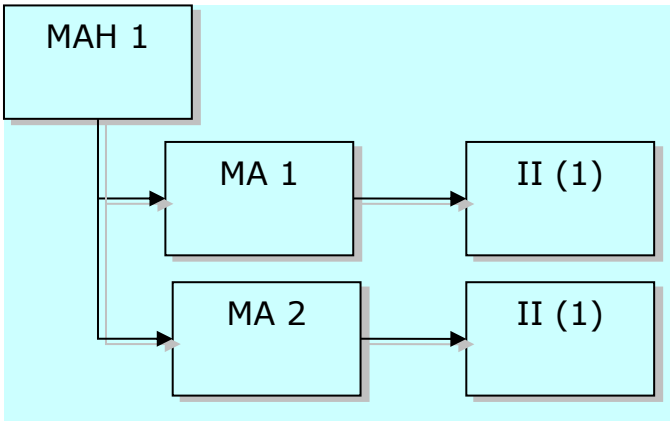
Q 3.4 – Is it necessary to request advice from the MEB before submitting a grouped variation?

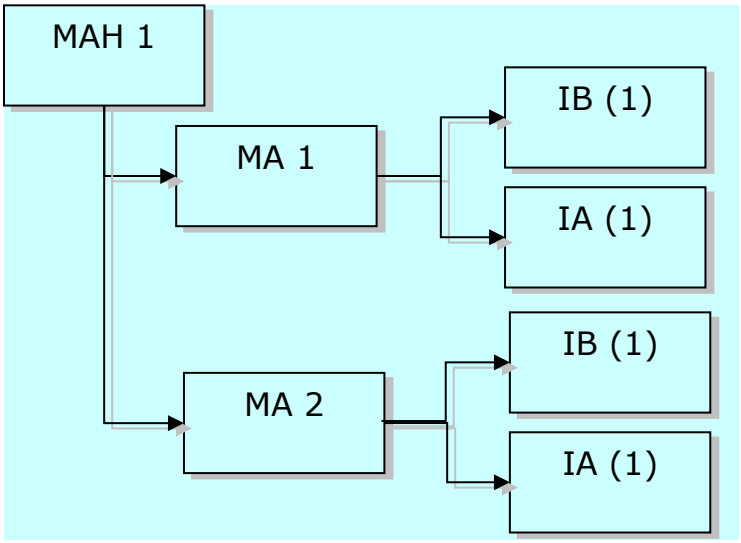
When submitting a grouped variation, the applicant must always provide a justification for the grouping in the variation application form. To this end, the applicant can refer to the examples given in Annex III of the Variation Regulation or those in the *Examples for acceptable and not acceptable groupings for MRP/DCP products* document published on the CMDh website (https://www.hma.eu/96.html). If the grouping is 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, while 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, by using the contact form available via https://english.cbg-meb.nl/contact, with 'variations' in the subject line.

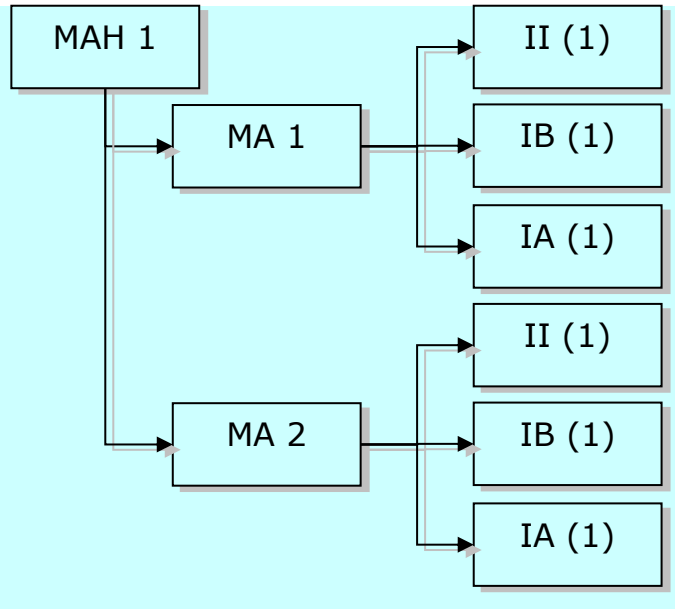
Q 3.5 – How should I submit the documentation in the case of worksharing?

Worksharing involves one or more variations concerning more than one marketing authorisation, of which the highest variation is a type IB or a type II. A few examples are provided below:


MAH 1
MA 1
IB (1)
MA 2
IB (1)


MAH 1
MA 1
II (1)
MA 2
II (1)


MAH 1
IB (1)
MA 1
IA (1)
IB (1)
MA 2
IA (1)



Worksharing of type IB/II or grouped variations of type IB and type II variations of a purely national authorisation is also possible, if this is submitted in several countries, for example if a grouped IB/I variation for an MA of an MAH is submitted in several countries. The MAH should send a letter of intent to the CMDh secretariat (see Chapter 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)

The application then consists of:

- One cover letter
- One variation application form
- For type IA variations: a copy of the relevant page(s) of the Variation Guideline (Chapter 5 of Volume 2A of the Notice to Applicants), indicating that the conditions have been with and/or the required documentation has been submitted
- For type II variations: a copy of the relevant page of the Variation Guideline (Chapter 5 of Volume 2A of the Notice to Applicants)
- For type IB variations: a copy of the relevant page of the Variation Guideline (Chapter 5 of Volume 2A of the Notice to Applicants), if available
- The accompanying documentation. If applicable, the section headings and section numbering of the CTD format should be used (so not appendices 1, 2, 3, etc.).
- In the event that the changes result in a change to the SmPC, package leaflet and/or labelling texts (modules 1.3.1, 1.3.2 and/or 1.3.3), both a clean and a track changes version must be submitted.
- In the event that the variations also lead to a change in the mock-up(s), this/these must be submitted.

Again, in this case all submitted variations must be listed on the same variation application form. There is, therefore, only one variation application form. The same cover letter and

variation application form must be included in each eCTD. It is preferential for the submission to take place via CESP. If eCTDs are submitted by post on several CDs or DVDs, they must be submitted to the MEB together in a single package (a single envelope or box).

Q 3.6 – Must all countries involved have approved all products for grouping concerning more than one marketing authorisation and for worksharing?

In the case of **grouping** concerning more than one marketing authorisation of MRP/DCP products it is not necessary for the RMS and CMSs to be the same for all products concerned. However, applicants are requested to group products where only 1 country acts as RMS (see also Chapter 6 of the CMDh BPG; http://www.hma.eu/96.html). An exception to this is formed by administrative variations (A category) known as the super grouping of type IA variations, see the aforementioned Chapter 6.
The CMS can vary per product or marketing authorisation (as also applies to initial marketing authorisation applications). In that case the CMS must receive only eCTDs for the strength and pharmaceutical forms that have been approved in the relevant CMS (see the CMD BPG on use of eCTD in MRP/DCP; (http://www.hma.eu/277.html).

In the case of **worksharing**, one or more variations are submitted for a group of marketing authorisations and that group can consist of MRP/DCP, central products and/or purely national authorisations that have been authorised in several countries. In the case of worksharing no request is made to make groups only of products that have the same RMS. It is possible that a group consists of 20 marketing authorisations, of which 5 have been centrally authorised, 14 via MRP/DCP and 1 via a purely national authorisation. Of these 14 MRP/DCP marketing authorisations only 10 could have been authorised in the Netherlands.
However, the same package must be sent to the Reference Authority and to all relevant member states. The relevant member states may therefore receive information on products that have not been authorised in that particular member state. In these cases the cover letter must clearly state which products (and therefore which eCTDs) apply to each member state.
For Worksharing variations involving no centrally registered products (CAPs), the 'Cover letter for Variation Applications in the Mutual Recognition Procedure' can be used as published by CMDh (https://www.hma.eu/265.html). For Worksharing variations with both CAPs and MRP products the standard EMA cover letter can be used, see question 4 of the Q&A on the EMA website (https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/worksharing-questions-answers).

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 CMDh Best practice guide for the submission and processing of variations in the mutual recognition procedure (see http://www.hma.eu/96.html).

National authorisations, type IA/IB/II variations

The list of product types can be found on the MEB website (see https://english.cbg-meb.nl/topics/mah-fees-and-product-types).

- 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, in other words 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 periods 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 2nd assessment round. Type IB variations must be approved by the MEB before you are allowed to implement the changes. However, just as in the case of Type IA notifications, for Type IB variations you receive any required amended marketing authorisation and/or the notice of change to the SmPC afterwards, in other words after approval. This administrative process takes place within 6 months after approval. However, the MEB aims to finish the process within 60 days.

For type II variations, the MEB applies three different timelines: 50, 164 or 194 days. These periods appear to deviate from the MRP timelines, but in these national procedures the clock starts directly after the receipt of the application and likewise restarts right after the 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 three timelines

- Type II safety: 50 days (30 days for the 1st round and 20 days for the 2nd round. No separate implementation round to follow after this 2nd round).
- Type II quality or type II other: 164 days (14+60 days for the 1st round, 60 days for the 2nd 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 1st round, 70 days for the 2nd 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. The applicant states the date on which the change was implemented on 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 the start of the variation. 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 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 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 receive the date of approval from the case manager by letter or email.

Date of approval of type IB and type II variations for MRP/DCP products:
At the start of the procedure the applicant receives the timetable from the RMS by email. After approval you 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 the 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 date as sent by the RMS.

Information regarding the implementation of type IB and type II variations for MRP products is also included in the CMDh Best practice guide 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 Question 4.4 in this 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 must a propose a time frame on the variation form within which the proposed change will be implemented. 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 6 months is acceptable. If a longer period is proposed, this needs to be justified. 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.

[1] This often includes changes to the SmPC in the sections 'Contra-indications', 'Special warnings and precautions for use', 'Interactions', and 'Adverse effects', in particular as a result of 'Urgent Safety Restrictions'.

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, which does not include a proposed moment for implementation is invalid and cannot be processed.

If no explicit approval of the implementation date will be send by the MEB, the proposed date may be considered accepted along with the approval of 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, 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.

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)).

> **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 is submitted on 1 March 2010 and the company had already implemented the type IA variation on 1 February 2010. In the SmPC the date is stated as 1 February 2010 and in the package leaflet as February 2010. The MEB processes this type IA variation on 29 March 2010, but leaves the date of (1) February 2010 in the SmPC and package leaflet as it is.

Questions concerning specific variations

Q 5.1 – What can I do to submit a change of name and/or address of marketing authorisation holder or change of product name in NL as correctly as possibly?

For products authorised via a mutual recognition procedure and where the Netherlands is the CMS, for which a variation number A.1 or A.2 is being submitted (change of name and/or address of marketing authorisation holder, or change of product name) that applies to the situation in the Netherlands, you are requested to clearly state this in the letter. This makes it easier for the MEB to differentiate these variations from the many hundreds of submitted changes of name and/or address that do not apply to the situation in the Netherlands.
This separate notification in the cover letter is not required for a change concerning a purely national procedure or a procedure for which the Netherlands is the RMS.

Q 5.2 – How should a change of manufacturer be submitted?

According to the guideline, a variation must be submitted for every step taken by a manufacturer in order to prevent any confusion regarding which steps are taken by a manufacturer. In order to avoid misunderstandings, marketing authorisations holders are kindly requested, in the event of changes to manufacturers, to provide information on all authorised manufacturers and the new situation with regard to all manufacturers. The variation application form must therefore not only list the new manufacturer, but also provide a complete overview (so not an empty section under ‘present’ and only listing the new manufacturer under ‘proposed’). You can limit yourself to the manufacturers performing a certain step. If a change is made to the manufacturer of the active ingredient, you only need to provide an overview of all manufacturers of the active ingredient and not of the manufacturers of the finished product or the manufacturers responsible for batch release.

Q 5.3 – Is the deletion of a strength and/or pharmaceutical form a variation?

The Classification Guideline lists variation C.1.7 ‘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 authorisation number, the marketing authorisation holder must submit a deletion request (see https://english.cbg-meb.nl/topics/mah-withdrawal-of-a-marketing-authorisation).

Q 5.4 – What does the MEB expect in case of a Type II C.I.2.b variation if the reference product is not harmonised or no longer has marketing authorisation?

As indicated in the answer to Question 3.23 of the CMDh Q&A on variations (https://www.hma.eu/20.html), the classified type IB C.I.2.a variation may only be used to implement changes to the product information in line with that of the reference product, if the latter is harmonised.
If the reference text is not harmonised, the changes must be submitted as Type II C.I.2.b variations. In accordance with the aforementioned Q&A, the marketing authorisation holder is expected to substantiate *for each change* why it has been decided to align the product information with a particular reference text. Therefore, a proper Overview should include a list of the differences between the reference texts and provide substantive arguments *for each change* as to why it has been decided to bring this element of the product information in line with a particular reference text.
For the sake of completeness, please note that withdrawal of the marketing authorisation of the reference product in a particular member state is not a valid argument to *fully align* the product information with that of another member state by means of a C.I.2 variation. Category C.I.2 is intended for making a change in product information following a *change* in the product information of the reference product.