National FAQ on variations

1/10/2015 – version 3

Important remark:

In case of questions about the Regulation (EG) Nr 1234/2008 on Variations, it is also advisable to have a look at the following documents of the CMDh:

- Q&A document on variations (http://www.hma.eu/20.html)
- List with examples of accepted and non-accepted groupings (http://www.hma.eu/96.html)
- the list of published Article 5 Recommendations (http://www.hma.eu/293.html.)

The principles described herein also apply to the authorised medicines through the national procedure.

1. Glossary

- **CMDh:** Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human
- **Labelling:** label and packaging (Word document)
- **MA**: marketing authorisation: all strengths and pharmaceutical forms of a particular product
- **MAD:** marketing authorisation document
- **PSMF:** Pharmacovigilance system master file
- **RMS:** Reference Member State
- **SmPC:** summary of product characteristics

2. Questions linked to the submission of variations

Question 2.1
When submitting a IA/IB variation affecting the SmPC, PIL and/or labelling, the adapted texts (in Word version) should be submitted in the national languages. What should be submitted when the authorization procedure has not yet been dealt with at national level and consequently there are no texts available we can rely on?

Answer:
The last submitted version in the ongoing dossier is used as a basis for the SmPC, PIL and labelling that need to be submitted when filing a type IA/IB. This is only applicable for medicines authorised via MRP/DCP given that no variations can be submitted for medicines of which the NP has been approved but for which no MAD has been delivered yet.

Question 2.2
How should a grouping/worksharing be submitted?

Answer:
1 Grouping for 1 MA:
one module 1 with, among other things, 1 cover letter + 1 common application form for the whole group (with clear enumeration of the individual variations in the group: number from the guideline + short description for each individual variation) + one module 2, 3, 4 or 5 (according to what applies) in which all requested modifications are included.

Different groupings for 1 MA:
For each grouping, a dossier complying with the above mentioned conditions needs to be submitted.
E.g.: for product A, one wants to submit a grouping composed of variations that have an impact on the active component as well as a grouping composed of variations that have an impact on the finished product: 2 separate dossiers for which, for each group, one module 1 and 3 must be submitted (and module 2 if applicable).

1 grouping for different MA: see our e-Submission Guideline, point 3 – Nice to Know, question 6.
(http://www.fagg-afmps.be/nl/binaries/eSubmission-guidelines-V-2-2013-06-21_tcm290-226755.pdf)

Different groupings for different MA: For each grouping, a separate dossier, that complies with the description according to our e-Submission Guideline, point 3 – Nice to Know, question 6. needs to be submitted. (http://www.fagg-afmps.be/nl/binaries/eSubmission-guidelines-V-2-2013-06-21_tcm290-226755.pdf)

For annual reporting for different MA: one module 1 (and possibly module 2 or 3 if applicable) by MA.

For worksharing: see our e-Submission Guideline, point 3 – Nice to Know, question 6.
(http://www.fagg-afmps.be/nl/binaries/eSubmission-guidelines-V-2-2013-06-21_tcm290-226755.pdf)

Question 2.3
Which procedure number needs to be indicated in the application form for National groups of variations?

Answer:
a) If only one MA is concerned, the company can compose the procedure number:
e.g.: NAT/H/254/IB/xxx/G
where 254 is the Medicinal Product Number and xxx refers to the next n° in the list of the variations in the variation table. For medicines authorised via NP, the serial number of the variation is assigned when the file is uploaded in the database MeSeA. If the next chronological number is not known by the company, the FAMHP asks to use the placeholder xxx.
b) In case different MA are concerned, the company is not in position to compose the procedure number. Two possibilities occur:

- A grouping of one or more IA or administrative variations: the famhp asks to mention on top of the application form the following procedure number NAT/H/xxxx/IA/.../G. When the file is uploaded in the database MeSeA the '…' will be replaced by the correct number. For the procedure number applicable for each concerned MA the same principle described under point a) can be used to fill in the table in the application form.
- A grouping of one or more IB/II variation(s): in this case the procedure number that should be mentioned on top of the application form should be requested in advance (see question 2.4). For the procedure number applicable for each concerned MA the same principle described under point a) can be used to fill in the table in the application form

Question 2.4:
For which procedures do we have to ask in advance for a procedure number and where can we do this?

Answer:
For the following procedures the procedure number should be requested for in advance:

- one or more IB/II variation(s) for different MA authorized through national procedure(e.g.: NAT/H/xxxx/IB/125/G) (see also question 4.3)
- one or more IA-variation(s) for different MA where BE acts as RMS. (e.g.: BE/H/xxxx/IA/12/G)
- MRP 'IA-supergroup' where BE acts as 'lead'-RMS* (e.g. BE/H/xxxx/IA/20/G)
- Worksharing with Belgium as reference authority which contains only MRP products for which BE is RMS, whether or not combined with national in Belgium authorized products** (e.g.: BE/H/xxxx/WS/002)

The procedure number can be obtained by sending your request to the following e-mail address: procedurenumber@fagg-afmps.be.
Please indicate clearly in the e-mail which variations the grouping will consist of and which medicines will be included in the grouping.
The FAMHP has the intention to send you the requested procedure n° within a timeframe of 3 working days.

* For more information see CMDh BPG Chapter 6 on Grouped applications
**For more information see CMDh BPG Chapter 7 on Worksharing
(Both available on: http://www.hma.eu/96.html?&L=0)

Question 2.5
When do the national translations of the SmPC, PIL and labelling and packaging need to be submitted during a MRP and national procedure?

Answer:

	Type IA	Type IB	Type II
Submission of the translations	simultaneously with the submission of the dossier	simultaneously with the submission of the dossier	within 7 calendar days after the approval date

For Groupings and Worksharing, the rule of the highest ranked variation type that is part of the grouping or worksharing needs to be followed.

Question 2.6
How do little changes to the mock-up need to be submitted?

Answer

Type	Action towards FAMHP
Addition of a practical instruction symbol without other further modifications as regards to content (e.g.: scissors + dotted line where to cut open the packaging)	authorised via NP: --> needs to be submitted as a notification (NP: art 34§4), adapted mock-up required, payment required Authorised via DCP/MRP: --> if RMS requires notification: EU notification form (art 61.3) + adapted mock-up, payment required --> if RMS does not require notification: needs to be submitted as a notification at national level (NP: art 34§4), adapted mock-up required, payment required
Addition of a logo or other non instruction oriented symbol	--> Submission of a EU/NP notification (art 61.3/art34§4) + adapted mock-up, payment required
Modification as regards to content (=modification to the content of the QRD template – labelling part)	Modification to the labelling is not linked to a modification to the SmPC: → Submission of a notification (unless variation n° C.I.1 or n° C.1.2 is applicable), adapted labelling texts in module 1.3.1 required, adapted mock-up required, payment required - authorised via NP: Art 34§4 - Authorised via DCP/MRP: Art 61.3* * *Excepting applications for derogations, specifically for Belgium. These ones must be asked for through a national Art 34§4 notification.* Modification to the labelling is linked to a modification to the SmPC: --> Submission of a variation, adapted labelling texts in module 1.3.1 required, payment required The modified mock-up is submitted with the variation or when closing the variation

These notifications also need to be submitted to the Post MA department like for the other variations. Confirmation of receipt will be done via the automatic e-mails from MeseA.
The content of the notification dossier consists of a cover letter, application form (available on http://www.hma.eu/101.html), payment form, labelling (Word) as well as a mock-up proposal. Word documents need to be submitted out of the CTD structure in a separate folder.

When more than one strength/pharmaceutical form exists, changes to colour should be submitted through a notification as it is important to evaluate if there is enough differentiation between the different forms and strengths within the product range. Important changes in lay-out or rearrangements of the approved text should also be submitted through a notification as the readability should be evaluated.

Little modifications in colour, lay-out, rearrangement of the approved text or a combination, must not be submitted to the Agency although comments may be made within the next variation with impact on the packaging.
The fee for this type of notification is set as follows:

- Modification only affecting the label and packaging:
  see section 4 National variation e) in the overview " Registratie".
- Modification also affecting the PIL:
  see section 4 National variation d) second possibility in the overview " Registratie

You can find this overview on the Agency's website on the following link:
http://www.fagg-afmps.be/nl/items-HOME/bijdragen/

Question 2.7:
How do I need to submit a transfer of MAH? What type of variation do I need to submit? What are the fees for this type of variation?

Answer:
A transfer of MAH is an national, administrative variation, which follows the procedure of an type IA_{IN} notification: this means that the company has to notify the change immediately after the implementation of the transfer of MAH of the MA. As from the submission date, the FAMHP has 30 days for validating your application. If the application should be invalid, e.g. when the application should be incomplete, the application will be refused and the implementation should be stopped immediately.

The submission should contain the following documents and comply with the

eCTD Submission Guideline http://www.fagg-afmps.be/en/human_use/medicines/medicines/MA_procedures/esubmission/

1. cover letter
2. application form
3. fee form
4. transfer agreement signed by both parties
5. a statement that the current MAH agrees that the new MAH will be the contact person through the procedure
6. all approved documents (approved AMM and SPC/PIL/labelling)
7. Proposal of documents (like mentioned in circ. n° 542 annex 7):
    a. Draft AMM light and 4 pg (word version, not pdf)
    b. SPC FR-NL (word version, not pdf)
    c. PL FR- NL-DE (word version, not pdf)
    d. Labelling FR-NL-DE (word version, not pdf)
    e. Mock-up IN-OUT
    f. Declaration of conformity
    g. Declaration that no other changes were made

Also, the proposed MAH should have a Qualified Person for PharmacoVigilance that is recognized in Belgium and you should submit a declaration that a change in PSMF will be submitted in the near future. You can submit this under a type IA_{IN} variation number C.I.8.a : introduction of a summary of pharmacovigilance system.

For a product authorised through a MRP or DCP, the RMS should also be notified of the transfer. This should be confirmed in the cover letter.

The fee for an administrative variation is applicable.

Question 2.8:
How does a change of distributor needs to be submitted?

Answer:
A change of distributor is a national, administrative variation, which follows the procedure of a type IA with immediate notification. With a change or addition of a distributor the dossier needs to contain the following documents:
1. Cover letter;
2. Application form;
3. Form for fees
4. Document “good distribution practice”

Question 2.9:
Does the RMS need to be notified of a change of distributor?

Answer:
It is not necessary to notify the RMS.

Question 2.10:
How can a company add 2 (or more) distributors?

Answer:
If a company wishes to add 2 distributors, two administrative variations need to be submitted. Both variations may however be grouped in one dossier (see principle of grouping). This means that the fee will be calculated for two variations.

3. Questions linked to the classification of the variations

Question 3.1:
How does a PIL-user testing need to be submitted?

Answer:
For NP and MRP: variation IB n° C.I.z

Question 3.2
How can SmPC, PIL and labelling be adapted to the QRD-template/SmPC-guideline?

Answer:
This adaptation can be done together with the submission of a renewal or a type IB/II clinical variation which has impact on the Product Information.
However, when you only want to submit this adaptation – without submission of new data in support of the modifications - this can be done through NP and MRP with BE as RMS by means of a type IB n° C.I.z

Question 3.3
How should a split of common SmPC and PIL by dosage/pharmaceutical form be submitted?

Answer:
Via NP and MRP with BE as RMS: type IB n° C.I.z

Question 3.4
How should a variation for update of a complete module 3 be submitted?

Answer:
For national procedures, an update module 3 can be submitted as a type II (n° B.z). There is a specific fee for such a variation. The application form needs to clearly indicate that it concerns a complete update of module 3 and a clear overview of all changes included should be present.
This is not possible in MRP.

4. Questions linked to grouping and worksharing

Question 4.1
Is a grouping of variations possible for different MA simultaneously?

Answer:
A group with only type IA variations can be submitted for different MA simultaneously. This group of type IA variations must then be the same for each MA and all MA should belong to the same MAH.

A grouping of variations, including one or several type IB/II variations for different MA simultaneously is only possible in Worksharing, unless the concerned MA are all authorized trough the national procedure and the famhp has agreed on this grouping.

Question 4.2
What are the different grouping possibilities?

Answer:
For 1 MA:
→ grouping of different type IA variations (annual reporting)
→ grouping of a combination of IA/IB/II variations that is described in annex III of the Better Regulation or for which an agreement has been obtained from the competent authority.

For different MAs:
See question 4.1

Question 4.3
What conditions should be fulfilled for a grouping of one or more IB/II variations for different national authorized MA?

Answer:
The following conditions should be fulfilled:
- All concerned MA have the same MAH.
- Exactly the same IB/II variation or group of variations is applicable for all concerned MA.
- There is no (or very limited) need for a product specific evaluation.

When for the 'same' changes, separate sets of supportive data for each concerned product are submitted or if a separate, product specific evaluation is

necessary, then the different national authorized MA cannot be part of the same submission and separate submissions for each MA are necessary.

5. Questions concerning the approval and implementation of the variations

Question 5.1:
When must and when can a variation be implemented?

Answer:

See document on the website of the famhp
New definition of the approval date in SmPC and leaflet

Attention: this document gives you the date which should be used to calculate the date on which you can implement. The conditions (presence of the closing documents and for MRP type II the delay of 30 days) for implementation as mentioned in the Variation regulation are still applicable.

Notification art 34§4:
Date from which you may implement: date of submission + 3 months if no comments were received from the famhp or date of approval by the famhp (automatic round-up email)
Date from which you have to implement: Date from which you may implement + 6 months.

Notification art 61§3:
Date from which you may implement: date of submission + 3 months if no comments were received from the concerned member states or date of approval by the RMS (notification of approval)
Date from which you have to implement: Date from which you may implement + 6 months

Question 5.2:
What is meant by “implementation date for IA variation”?

Answer:
See Q&A of the CMDh (http://www.hma.eu/20.html): question 5.2
For each IA-variation, the implementation date should be mentioned in the application form.

Question 5.3:
When a company already implements a variation in the SmPC and PIL of the concerned product, what date of approval must then be indicated in the SmPC and PIL?

Answer:

See document on the website of the famhp:
New definition of the approval date in SmPC and leaflet

This document describes how the famhp will determine the approval date when a file will be closed administratively by the famhp and will lead to an update of the MAD.
For IA-variations you will receive very rarely an update of the MAD from the famhp. In these cases you mention the implementation date as approval date.

6. Questions related to the fee for groupings and worksharing.

Question 6.1:
How is the fee calculated for groupings or worksharings when several variations and/or different MA are concerned?

Answer:
When several variations are submitted in one grouping or worksharing, the fee is calculated by the sum of the fees for each variation. When it concerns IA and IB-variations the procedure used to obtain the initial MA defines the fee used for the calculation: if the worksharing contains MA obtained through the national procedure as well as through MR or DC procedure, then for the national authorized products the fee for national IA and IB variations will be used. For the products authorized through MR or DC procedure, the fees for MRP IA and IB variations are applicable. For those products where BE acted as RMS, the fee for MRP IA and IB variation, multiplied by two, will be counted.

Procedure type	Variation type	Product type	Fees
Grouping	1A + 1B	national	457,05 € + (152,34 € / AMM) + 457,05 € + (152,34 € / AMM) = Total fees
Grouping	1A + 1B	MR	304,72 € + (152,34 € / AMM) + 609,42 € + (152,34 € / AMM) = Total fees Multiply by 2 for products for which Be= RMS
Grouping	IA	Different MRP products BE=CMS + BE=RMS	304.72 € + (152,34 € / AMM) + 2 x[304.72 € + (152,34 € / AMM)]
Worksharing grouped	1A + 1B	National	457,05 € + (152,34 € / AMM) + 457,05 € + (152,34 € / AMM) = Total fees
Worksharing grouped	1A + 1B	MR	304,72 € + (152,34 € / AMM) + 609,42 € + (152,34 € / AMM) = Total fees Multiply by 2 for products for which Be= RMS
Worksharing grouped	1B	National + MR BE=CMS + BE=RMS	457,05 € + (152,34 € / AMM) + 609,42 € + (152,34 € / AMM) + 2x [609,42 € + (152,34 € / AMM)]

Worksharing grouped with BE as Reference Authority	1A + 1B	National only	(457,05 € + (152,34 € / AMM) + (457,05 € + (152,34 € / AMM)) = Total fees
Worksharing grouped with BE as Reference Authority	1A + 1B	MR BE=CMS only	((304,72 € + (152,34 € / AMM) + (609,42 € + (152,34 € / AMM)) = Total fees
Worksharing with BE as Reference Authority	1B	National + MR BE=CMS + BE=RMS	457,05 € + (152,34 € / AMM) + 609,42 € + (152,34 € / AMM) + 2x [609,42 € + (152,34 € / AMM)]