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Chapter 6 - CMDh Best Practice Guide for the processing of grouped applications in the Mutual Recognition Procedure

1. Introduction

Article 7 of Commission Regulation (EU) No 1234/2008 of 24 November 2008 (Variation Regulation) as amended by Commission Regulation (EU) 712/2012 points out that in case that several variations are notified or applied for, separate notifications or applications for each variation sought should be submitted.

However, there are 3 possible exemptions of this rule stated in the Regulation:

1. In case the same holder applies for several identical variations of type IA and/or Type IAIN to the terms of one or several marketing authorisations to the same authority, these may be submitted as one single notification, as pointed out in Article 8 of the Variation Regulation, e. g.
 - One variation to several MAs
 - Several identical variations to several MAs
 - Several variations to one MA
 2. In case the same holder applies for several identical variations of type IA to the terms of one or several marketing authorisations to the same authority, these may be submitted as one single notification in the form of a so-called Annual Report within a maximum of 12 months after implementation of the first change applied for, as pointed out in Article 8 of the Variation Regulation.
 3. Annex III of the Regulation refers to several cases where it is possible to group several variations of type IA, IAIN, IB, II or extension applications to the terms of the same marketing authorisation at the same time into one single application. This is covered under Article 7(2)(b) of the Regulation. Furthermore, in case several single variations are not listed in Annex III of the variation regulation, under Article 7(2)(c) the RMS in consultation with the CMS may agree to group these single variations to one procedure. In order to facilitate the planning of grouped
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applications the CMDh has published a list of “Examples for acceptable and not acceptable groupings for MRP/DCP products” (<https://www.hma.eu/96.html>)

Therefore, Article 7 in connection with Annex III of the Variation Regulation allows the combination of several variations into one single application.

One MAH could have more marketing authorisations with different RMSs for which the same type IA variation or the same set of type IA variations needs to be submitted. If the MAH wishes to submit these as grouped applications, i.e. as a group containing more than one MA, it is also possible to combine marketing authorisations of more than one RMS in one grouped application. However, there are special rules concerning this procedure mentioned below that have to be considered **before** submission of such an application. This procedure is restricted to purely administrative changes and other variations of type IA/IAIN that do not contain any product specific information. Furthermore, the flowchart in Annex II of this chapter has to be considered.

For the purpose of handling a grouped application, the following definition of a marketing authorisation is used: all strengths and pharmaceutical forms of a certain product. For MRP/DCP products this would imply that all products belonging to e.g. AT/H/1234/001-n will be considered to belong to the same marketing authorisation.

Concerning purely national MAs the same rules apply as for MRP/DCP as listed above with the following differences:

1. Grouped applications are only possible within one single member state. It is not possible to combine purely national MAs from different member states within one single application. In those cases a worksharing procedure would apply (see also Chapter 7 of this guidance document)
2. One or several variations to several purely national MAs which are licenced in only one member state may be submitted as one grouped application, independent from the procedure type. However, the variations have to be identical for all products concerned. These procedures are handled according to the national rules of the relevant competent authority.

2. Application

The type of variation as well as the timetable of the grouped application is dependent on the “highest” type of the single variations. Submissions should therefore be made according to the following rules:

- A single notification of type IA according to Articles 8 of the Variation Regulation should be submitted in form of a so called Annual Report where all variations are minor variations of type IA. Type IAIN notifications may also be added to the annual reporting if this is submitted immediately and not only 12 months after the first variation applied for has been implemented.
- A single notification of type IB according to Articles 9 of the Variation Regulation should be submitted where at least one of the variations is a minor variation of type IB and all variations are minor variations.
- A single application of type II according to Articles 10 of the Variation Regulation should be submitted where at least one of the variations is a major variation of type II and none of the variations is an extension.
- A single application for an extension application according to Article 19 of the Variation Regulation should be submitted where at least one of the variations is an extension. Though it is possible to submit an extension application together with other variations for the basic licences acc. to Annex

III it is strongly recommended not to use this construct as the variations for the basic licences might be severely delayed by the longer timetable of the extension application.

- A grouped procedure will be submitted as one single application with one variation procedure number and only one CTS record. This variation procedure number has to be introduced on the first page of the application form. The MRP variation numbers are not to be listed on the cover letter or the first page of application form in the field 'Variation procedure number(s). MRP variation numbers should only be listed in the table 'Products concerned by this application' in the application form but not in the cover letter (see also Chapter 1).
- In case of purely national MAs the variation procedure number has to be allocated according the national rules of the relevant competent authority, no CTS record will be created.

In case an applicant intends to submit a grouped application with variations of type IA or IAIN or a grouped variation of type IA/IAIN for a group of products with different RMS he has to contact the RMS chosen as "Lead-"RMS for this grouped application and to request his acceptance to act as this. If the chosen RMS accepts to act as "Lead-"RMS he informs the applicant and issues a variation procedure number according to the principles as laid down in Chapter 1 with his own initials in the country code. The Lead-RMS then sends an email to all member states concerned in the grouped application via the MRVE-mailbox to inform them about the intended submission including the proposed variations, the acceptance of the "Lead-"RMS and the variation procedure number. The heading of these emails should contain the wording "IA-supergroup". Member states may comment, if necessary, within one week on this announcement. If member states, which are RMS in one of these procedures, cannot agree they have to inform the "Lead-"RMS accordingly stating their reasons for their refusal. The "Lead-"RMS as well as the applicant have to consider these reasons and must not integrate these procedures in the grouped application. The applicant has to send separate applications per RMS in all cases where the RMS does not accept to participate as concerned member state in a "Lead-"RMS-procedure. Purely national MAs are excluded from this possibility, they can only be grouped within one member state.

3. Variation numbering

Information on the allocation of the variation procedure number is presented in Chapter 1 of this Best Practice Guide. For grouped type IA variations in which >1 MA is included, the variation procedure number has to be requested from the RMS or Reference Authority of relevant Competent Authority before submission. The MAH will insert the variation procedure number on the application form and in the cover letter. MRP variation numbers should only be listed in the table 'Products concerned by this application' in the application form but not in the cover letter (see also Chapter 1).

4. Validation of the application

The MAH will submit simultaneously to the RMS and CMS an application containing the elements listed in Annex IV of the Regulation, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format.

- Cover letter (including variation procedure number).
- Application form, including the variation procedure number and the MRP variation number and the details of the MA(s) concerned. Where a variation is the consequence of another variation, a description of the relation between these variations should be provided in the appropriate section of the application form. In case an extension application is part of the grouped application the

application form for a new application has to be submitted with the additional variation application form introducing the variations applied for as annex.

- **A copy of:**
 - the relevant published Article 5 recommendation, if applicable.
 - a recommendation for classification received from the CMDh, if applicable.
- Supporting documentation as appropriate:
 - For variations requested by a national competent authority, e.g. following assessment of Follow Up Measures (FUMs), Specific Obligations (SOs) and Periodic Safety Update Reports (PSURs), or class labelling, a copy of the request should be annexed to the cover letter.
 - For variations that affect the SmPC, labelling or package leaflet, mock-ups or specimens should be provided according to the CMDh “Mock-ups, Specimens and Samples for variations and renewals (<http://www.hma.eu/96.html>), or as discussed with the RMS on a case-by-case basis. In case a type IA or type IB variation is the highest variation in the group, both the English texts and the national translations for SmPC, labelling or package leaflet should be submitted.

Additionally, the RMS submission would include the list of dispatch dates (all the dates of dispatch to the CMS) and declaration that the relevant national fees have been paid at time of submission. No dispatch list is required in case of purely national MAs.

In case of a grouped application of type IA variations for procedures with more than one RMS the applicant has to add the following information to his submitted documentation:

- List of concerned marketing authorisations.
- Explanation as to why all concerned marketing authorisations are considered to belong to the same holder¹.
- Description of the variation.
- Preferred “Lead-RMS” authority.
- In case the preferred “Lead-RMS” authority has not granted a marketing authorisation for all concerned marketing authorisations, the MAH should explain this choice
- Planned submission date.

The table on page 3 of the application form has to contain all the correct sequential MRP variation procedure numbers for each RMS procedure. If the product information is concerned the applicant has to assure that all national translations have been sent to the member states concerned and confirm this to the “Lead-”RMS. The “Lead-”RMS is responsible for the validation of the procedure. All procedures concerned will be entered into CTS under the respective procedure number. (The sequential numbering of the MRP variation number will be automatically issued by the CTS system. It is in the responsibility of the “Lead-”RMS to check if this number is consistent with the number in the table on page 3 of the application form.) Member states concerned may comment, if national translations of the product information have not been received or are not acceptable via email to the “Lead-”RMS and the applicant. The “Lead-”RMS has to refuse the procedures in those cases. The “Lead-”RMS is responsible for the evaluation and finalisation of the procedure.

¹ as per Commission Communication 98/C 229/03

5. Handling and timelines of grouped applications

The highest variation type of the grouped application and where relevant complexity determines the rules and timelines of the grouped variations. The grouped application is handled in the same way as the respective application type for a single variation of the highest type. The principle of Type IA notification applies also when the Type IA variation is part of a grouped application. The Type IA variation may be implemented before submission of the grouping. In case a Type IA variation is dependent on the outcome of other variations in a grouped application this variation may be submitted with an implementation date in the future and the variation will be implemented as soon as the complete grouped application is approved.

According to Article 19 a grouped variation in which the highest type is an extension application will be handled according to the timeline of a new application procedure.

6. Finalisation of Procedures

Grouped applications are finalised according to the same procedure as single variations of the same procedure type. In order to avoid an unnecessary reassessment of already evaluated and agreed variations, the outcome will concern the single variations applied for and not the grouped application as a whole.

It should also be possible for the MAH to withdraw single variations from the grouped application when it becomes obvious that these are regarded as non-approvable.

In case all single variations are regarded as approvable, the RMS will circulate an approval letter for the grouped application to the MAH. The CMS will be informed via CTS.

In case single variations are not approvable or withdrawn by the MAH, a combined letter will be circulated by the RMS stating the refused or withdrawn single variations including reasons leading to the refusal as well as listing all approved variations of the grouped application. This letter will be addressed to the MAH by email and introduced as data file into CTS for information of the CMS.

If all single variations are refused a refusal letter for the whole grouped application stating reasons for the refusal of every single variation will be circulated by the RMS to the MAH. CMS will be informed via CTS. The refusal letter will not be introduced as data file into CTS.

The outcome of the grouped variation is to be introduced in CTS by the RMS:

- The procedure will be introduced as **approved** in case all single variations are regarded as approvable.
- The procedure will be introduced as partially **approvable** in case single variations are refused or withdrawn. In this case detailed information about approved and refused or withdrawn variations will be given in the letter to the MAH which will be saved in the CTS data file.
- In case the whole group has to be refused / withdrawn the grouped procedure is introduced as **refused / withdrawn** in the CTS system.

The procedure for the submission and approval of a revised SmPC, labelling or package leaflet, in cases where these documents were affected by the variation(s), is the same as the one outlined in Chapters 3, 4 and 5 of this Best Practice Guide. This also applies to the procedure for implementing the decision(s) nationally.

In case of grouped applications of Type IA for products with more than one RMS the outcome, "valid, invalid or partially approved" will be introduced in CTS. Reasons for (partial) invalidation have to be

mentioned in the outcome letter and this has to be uploaded in CTS. The applicant and all other member states being the RMS in one of the procedures concerned will be informed about the outcome via email (member states to MRVE-Mailbox).

Examples of suitable text for inclusion in the acceptance, acceptance/rejection or rejection notifications issued to the MAH on completion of the procedure are included in Annex 1.

7. Referrals

If in case of one or more type II variations or extensions within a group there is a CMS that cannot approve the application on the basis of a potential serious risk to public health, the RMS will refer the procedure to the CMDh, unless the application is withdrawn by the MAH before the finalisation of the procedure.

The Member State in disagreement shall give a detailed statement of the reasons for its position to all Member States concerned and to the MAH. The RMS collects the reasoning and refers the whole matter to CMDh.

Generally, in case single type II variations are referred to the CMDh the whole group of variations will not be approved until the referral is finalised. However, the CMDh discussion will only deal with the single variations in question, not with the whole group. In individual cases, where single variations are very urgent and completely independent from the referred variation, the MAH may request to implement these variations in advance before approval of the whole group with his RMS. The RMS has to take a decision on this request.

Procedures may only be referred to the CMDh by the RMS and not by the marketing authorisation holder. Grouped applications for purely national procedures which are only within one member state will not be referred to the CMDh as the relevant Competent Authority has to decide on approval or refusal within the single national market.

Annex I

Sample text for inclusion in the acceptance, acceptance/rejection or rejection notifications issued to the MAH on completion of the procedure

Example 1

Acceptance of the grouped variation

The <<competent authority>> accepts all the variations detailed in your application. The following variations have been notified:

<< enter variations applied for >>

The variations are considered acceptable on the basis that the application has been submitted simultaneously to all Concerned Member States and the relevant fees have been paid as required by national competent authorities. Failure to comply with this provision may subsequently deem the variations invalid.

[Please note the following variations were withdrawn from this application during the procedure]

Request to applicant

In case of changes to the product information

Applicants are reminded to submit the national translations taking into consideration the recommendations of the Best Practice on the submission of high quality national translations no later than 5 days² after the procedure is closed.

In case of approval new or update RMP

The applicant is requested to send the list of safety concerns included in the approved RMP to CMDh secretariat, e-mail address: H-CMDhSecretariat@ema.europa.eu by using the form published by CMDh (<http://www.hma.eu/464.html>)”

Example 2

Acceptance/rejection of the grouped variation

The <<competent authority>> accepts some of the variations detailed in your application including the following:

<< enter variations applied for >>

The above variations are considered acceptable on the basis that the application has been submitted simultaneously to all Concerned Member States and the relevant fees have been paid as required by national competent authorities. Failure to comply with this provision may subsequently deem the variations invalid.

However, the <<competent authority>> rejects the following variations for the reasons given below:

² All time lines in this document are based on calendar days, i.e. days should be read as calendar days.

[Please note the following variations were withdrawn from this application during the procedure]

Request to applicant

In case of changes to the product information

Applicants are reminded to submit the national translations taking into consideration the recommendations of the Best Practice on the submission of high quality national translations no later than 5 days after the procedure is closed.

In case of approval new or update RMP

The applicant is requested to send the list of safety concerns included in the approved RMP to CMDh secretariat, e-mail address: H-CMDhSecretariat@ema.europa.eu by using the form published by CMDh (<http://www.hma.eu/464.html>)”

Example 3

Rejection of the grouped variation

The <<competent authority>> rejects all the variations detailed in your application for the following reasons:

<<enter reason for non-acceptance>>

[Please note the following changes were withdrawn from this application during the procedure].

Annex II

Flowchart for submission of Type IA-“Supergroups” with more than one RMS

Pre-Submission phase - Day 14	The applicant contacts the RMS chosen as “Lead”-RMS and informs him about the planned grouped application including the proposed variations and the concerned MRP procedure numbers.
Pre-Submission phase – Day 7	The “Lead”-RMS issues the variation procedure number and sends an email to the applicant and all member states concerned via the MRVE-mailbox with the heading “IA-supergroup”. Member states, which are RMS in one of the procedures concerned, may comment within one week if they refuse to participate in the procedure stating their reasons. The applicant has to consider that before submitting the documentation.
Submission phase	To the RMS and CMS the MAH submits the application accompanied by supporting documentation as appropriate. The MAH submits list of dispatch dates to the RMS.
Day 0	The RMS starts the procedure and completes the CTS record. The CMS are only informed via CTS, there will be no additional email.
Until Day 30	The RMS checks if the notification can be accepted. The CMS only checks if the notification has been received, if the fee has been paid as appropriate and his own national translations are correct.
Day 30	The RMS will inform the MAH on behalf of the CMSs of the outcome of the variation notification. CMS are informed accordingly via the updated CTS record. The RMS checks the highlighted (changed) text, and circulates a statement that it has endorsed the changes made, to the MAH and CMSs. The applicant and those member states being the RMS in one of the procedures concerned will be informed about the outcome via email (member states to the MRVE-mailbox).
Within 6 months after acceptance	Competent authorities should implement the decision nationally within six months.