

CMDv/BPG/016

BEST PRACTICE GUIDE
for
Grouping of Variations

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1. INTRODUCTION

- 1.1 This Best Practice Guide is the consequence of the implementation of *Commission Regulation (EC) No 1234/2008* effective from 1 January 2010.
- 1.2 Article 7 of the Regulation states that a separate notification or application should be submitted in respect of each change applied for, i.e. one application per change.
- 1.3 However, there are two possible exemptions to this rule as outlined below:
- 1) A number of Type IA or Type IA_{IN} changes to the terms of one or several marketing authorisations, held by the same marketing authorisation holder (MAH) to the same relevant authority, may be applied for under cover of a single notification, e.g.
 - One change to several MAs
 - Several identical changes to several MAs
 - Several changes to one MA
 - 2) A number of changes to the terms of the same marketing authorisation may be applied for at the same time under cover of a single application. At least one of the changes must be a Type IB, II or an Extension. The changes concerned must also fall within one of the cases listed in Annex III of the Regulation, or, if they do not fall within one of the cases listed, all member states involved agree to progress the variation as a 'group'.
- 1.4 Therefore, Article 7 in connection with Annex III of the Variation Regulation allows the combination of several changes into one single application.
- 1.5 In the sense of the variation regulation a grouped application for one marketing authorisation (MA) means one application for all strengths and pharmaceutical forms of one product.

2. AIM AND SCOPE

This Best Practice Guide has been introduced by the CMDv in order to facilitate the processing of grouped variations in the Mutual Recognition (MR) procedure. Guidance is given on the role of the Reference Member State (RMS), the Concerned Member State(s) (CMS) and the applicant to ensure that a consistent, timely and efficient procedural approach is maintained. It is noted that the quality of the MAH's submission package (application form and supporting documents) is considered crucial to the overall process.

3. REFERENCES AND RELATED DOCUMENTS

- 3.1 Regulation 1234/2008 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State.
- 3.2 NTA - Volume 6A - Chapter 5 (not yet relevant).

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- 3.3 Commission guideline on the details of the various categories of variations.
- 3.4 CMDv BPG004 Type IA Variations
- 3.5 CMDv BPG005 Type IB Variations
- 3.6 CMDv BPG006 Type II Variations
- 3.7 SOP for the allocation of mutual recognition /decentralised procedure application numbers.
- 3.8 CMDv/GUI/003 Guidance for Management of e-mail use during procedures and standardisation of subheadings

4. PROCEDURE

4.1 Application type and timelines

4.1.1 The timetable and procedures adopted for a grouped variation is dependent on the highest ranking variation in the group; therefore, submissions should be made according to the following rules:

- Where all changes are minor variations of Type IA and/or Type IA_{IN} a single notification according to Article 8 of the Variation Regulation should be submitted, which will be referred to as a Type IA lead grouped variation. Please refer to the *CMDv Best Practice Guide for Type IA variations*.
- Where the highest ranking variation is a Type IB change, a single notification according to Article 9 of the Variation Regulation should be submitted, which will be referred to as a Type IB lead grouped variation. Please refer to the *CMDv Best Practice Guide for Type IB variations*.
- Where the highest ranking variation is a Type II change, a single application according to Article 10 of the Variation Regulation should be submitted, which will be referred to as a Type II lead grouped variation. Please refer to the *CMDv best Practice Guide for Type II variations*.
- Where the highest ranking variation is an Extension, a single application according to Article 19 of the Variation Regulation should be submitted, which will be referred to as an Extension lead grouped variation.

4.1.2 A grouped variation is handled in the same way as the respective application type for a single variation of the highest rank, e.g. a Type II lead grouped variation will follow the same timetable and procedures outlined in the *CMDv Best Practice Guide on Type II variations*. For further details about timetables and procedures please refer to the respective CMDv Best Practice Guides.

4.1.3 According to Article 19 an Extension lead grouped variation will be handled according to the timeline of a new application procedure. An Extension may only be included as part of a group variation if the change introduced by the Extension is retained as part of the original MA, and not authorised as an MA in its own right.

4.1.4 A grouped variation will be submitted as one single application with one procedure number and only one CTS record.

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4.1.5 The MAH will submit simultaneously to the RMS and CMS an application containing the elements listed in Annex IV of the Regulation. Additionally, the MAH should submit a list of dispatch dates to the RMS indicating the variation procedure number, the dates on which the applications were sent to the RMS and the CMS, and confirmation that the relevant fees have been paid as required by each national competent authority.

4.2 Variation numbering

4.2.1 The numbering of the variation should also follow the rule of the 'highest ranking variation'.

4.2.1.1 The variation should be named CC/V/nnnn/IA/vvvv/G in case the highest variation in the grouped application is Type IA and concerns one marketing authorisation.

4.2.1.2 The variation should be named CC/V/xxxx/IA/vvvv/G in case the highest variation in the grouped application is Type IA and concerns more than one marketing authorisation. XXXX is literally meant.

4.2.1.3 The variation should be named CC/V/nnnn/IB/vvvv/G in case the highest variation in the grouped application is Type IB.

4.2.1.4 The variation should be named CC/V/nnnn/II/vvvv/G in case the highest variation in the grouped application is Type II.

4.2.1.5 In case one of the variations in the grouped application is an Extension a new speciality number will be created. Furthermore, this new speciality and all other licences concerned in the grouped application will receive the number CC/V/nnnn/X/vvvv/G.

Where:

CC	=	two letter country code of the RMS
V	=	Veterinary Domain
nnnn	=	product counter (if 1 MA) / xxxx (if >1 MA)
IA, IB, II, X	=	procedure qualifier
vvvv	=	chronological number - if 1 MA: next available sequential variation counter - If >1 MA: sequential variation grouping counter (for Type IA only)
g	=	Grouping qualifier (G)

4.3 Outcome of procedures

4.3.1 In order to avoid an unnecessary reassessment of already evaluated and agreed changes, an 'all or nothing' approach will not be adopted for grouped variations, i.e. a different outcome may be reached for different parts of the application; some changes may be accepted whilst other changes may be rejected.

4.3.2 The MAH may withdraw changes from a grouped application when it becomes obvious that the change(s) is likely to be rejected.

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- 4.3.3 At the end of the procedure the RMS will inform the MAH and CMS of the outcome(s) of the application by e-mail. In cases where some or all changes are rejected, the RMS should provide a description of the reasoning for the outcome. The notification to the MAH and CMS should also include details of any changes that were withdrawn during the procedure.
- 4.3.4 The RMS will also update the CTS record, which should state the reasons for rejection, if applicable by downloading the notification to the MAH and CMS into CTS.
- 4.3.5 For the purpose of CTS, it should be noted that a grouped variation will be considered approved if all changes are accepted. In case only some changes are accepted it will be considered partially accepted; however, it will be considered refused if all changes are rejected, or if some are rejected and some are withdrawn. If all changes are withdrawn, the application will be considered withdrawn.
- 4.3.6 The procedure for the submission of a revised SPC and product literature, in cases where these documents were affected by the variation(s), is the same as the one outlined in the separate *Best Practice Guides on Type IA, Type IB and Type II variations*. This also applies to the procedure for implementing the decision(s) nationally.
- 4.3.7 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.

4.4 Referrals

- 4.4.1 If, in case of one or more Type II variations or Extensions within a group, there is no agreement between the member states about whether they should be accepted or rejected the procedure will, in cases of potential serious risk concerns to human or animal health or to the environment, be referred to the CMDv.
- 4.4.2 The party in disagreement shall give a detailed statement of the reasons for its position to all Member States concerned and to the MAH.
- 4.4.3 The RMS collects the reasoning and refers the matter to CMDv if the variation in question has not been withdrawn by the MAH before the finalisation of the variation procedure.
- 4.4.4 In case single Type II changes are referred to the CMDv the whole group of changes will not be accepted until the referral is finalised. However, the CMDv discussion will only deal with the single change in question, not with the whole group.
- 4.4.5 In individual cases, where single changes are very urgent and completely independent from the referred change, the marketing authorisation holder may request to implement these changes in advance before approval of the whole group with his RMS. The RMS has to take a decision on this request.
- 4.4.6 Procedures may only be referred to the CMDv by the RMS and not by the MAH.

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ANNEX 1

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 changes detailed in your application. The following changes have been notified:

<< enter changes 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 changes were withdrawn from this application during the procedure]

Example 2

ACCEPTANCE/REJECTION OF THE GROUPED VARIATION

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

<< enter changes 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 changes for the reasons given below:

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

Example 3

REJECTION OF THE GROUPED VARIATION

The <<competent authority>> rejects all the changes 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]