

BEST PRACTICE GUIDE
For Type II Variations

CMDv/BPG/006

Edition 03

Edition date: 19 July 2013

Implementation date: 1 January 2010

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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, as amended by *Commission Regulation (EC) No 712/2012*.
- 1.2 The Regulation and the "*Commission guideline on the details of the various categories of variations*", referred to in Article 4 of the Regulation, set out a list of changes to be considered as Type II variations. In addition, any other change that may have a significant impact on the quality, safety or efficacy of the medicinal product must be submitted as a Type II variation. Such changes may be covered by a recommendation delivered pursuant to Article 5 of the Regulation. Also, an MAH or a National Competent Authority may request a recommendation from CMDv, or a re-classification may be requested by a National Competent Authority when validating an 'unclassified' Type IB notification.
- 1.3 Type II variations require prior approval before implementation – known as the "Prior authorisation" procedure.
- 1.4 Type II variations may be grouped together with other variations in a single application. If the highest ranking variation is a Type II variation, this will be classed as a Type II lead grouped variation. Further information about the grouping of variations is available in *Best Practice Guide of Grouping of Variations* (CMDv/BPG/016); however, the timetable and principles for a Type II lead grouped variation is the same as the procedure outlined in section 5 of this document.
- 1.5 A MAH may also submit several Type IB and/or Type II variations to one or more of their products in a single application; this will be dealt with in accordance with the work sharing initiative. Further information about work sharing is available in *Best Practice Guide for Work sharing* (CMDv/BPG/018); however, regardless of the types of variations included in the application, the timetable and principles for work sharing are the same as those used for Type II variations (see section 5 of this document).

2. Aim and Scope

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

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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 - as amended by *Commission Regulation (EC) No 712/2012*.
- 3.2 NTA - Volume 6A - Chapter 5 and Chapter 7.
- 3.3 NTA - Volume 6B.
- 3.4 Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures.
- 3.5 Best Practice Guide on Grouping of Variations.
- 3.6 Best Practice Guide for Work sharing.
- 3.7 SOP for the allocation of mutual recognition/decentralised procedure application number.
- 3.8 Best Practice Guide for "Automatic validation of applications in the Mutual Recognition Procedures.
- 3.9 SOP for disagreement in procedures Referral to CMDv (CMDv/SOP/001).

4. Timescales

- 4.1 Type II variations are normally processed according to a 60 day timescale; however, the Regulation additionally specifies a reduced (30 day) or extended (90 day) timescale.
- 4.2 The reduced timescale is intended for variations concerning safety issues.
- 4.3 The extended timescale is intended for variations concerning a change to, or addition of, the therapeutic indications including changes relating to non-food target species, replacement or addition of serotypes, strains or antigens in vaccines against Avian Influenza, Foot and Mouth disease and Bluetongue, and replacement of strains for vaccines against equine influenza.

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The competent authority of the reference Member State may extend it also to 90 days for complex grouping of variations in accordance with Article 7(2)(c), in consultation with the concerned member States.

The detailed procedural timetables for reduced, normal or extended Type II procedures are provided in Annex 2.

5. Type II Variation Procedure

5.1 Pre-submission phase

5.1.1 The MAH is encouraged to undertake prior discussions with the RMS to establish a suitable timeline. It is up to the RMS to propose a reduced timetable to the CMSs. The CMSs should accept/decline within a reasonable deadline given by the RMS. In the case where CMSs object to a reduced timetable based on reasonable grounds the RMS should propose an alternative timetable that is acceptable to all.

5.1.2 If considered necessary by both parties, the RMS and MAH may review the documentation together. In all cases the MAH should contact the RMS at least seven days prior to submission to agree a start date and timetable and to obtain the Type II variation procedure number.

5.1.3 In cases of doubt, the MAH may discuss the variation type number with the RMS.

5.2 Submission phase

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 according Directive 2009/9/EC, amending Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to medicinal products for veterinary use:

- Cover letter (including variation procedure number)
- Application form (with variation procedure number completed on page 1) including 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.
- A copy of:
 - the relevant page(s) of the Commission Guideline

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- or a copy of the relevant published Article 5 Recommendation, if applicable.
 - or recommendation for classification received from the CMDv.
- Supporting documentation as appropriate.
 - Update/Addendum to expert reports as relevant.
 - 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.

5.2.2 Additionally, the MAH should submit a list of dispatch dates to the RMS indicating the Type II 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.

5.2.3 RMS creates the CTS record and sends an e-mail via the MRVE mailbox to inform the CMSs about the new procedure.

5.3 Automatic validation

5.3.1 The check of the validity of the application will proceed as described in CMDv BPG for "Automatic validation of applications in the Mutual Recognition Procedures" and should be completed within 14 calendar days. If necessary, the CMS should send any comments about an invalid application to the RMS within this time frame.

5.4. Start of variation procedure (Day 0)

5.4.1 Following the validation period the RMS completes the CTS record and sends an email via the MRVE mailbox informing the CMS of the validation outcome. If the application is considered valid, the RMS will also inform the CMS and the MAH of the timetable and start date. The day of confirmation of receipt of a valid application is Day 0.

5.5. The Evaluation Procedure

5.5.1 Usually the normal 60 days timetable will apply; however, in specific circumstances a reduced or extended timetable may be used (refer to section 4 of this document). The possible timetables are shown in the flowcharts in Annex 2; therefore, throughout the remainder of this

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note, particular stages of the timetables are referred to as 'agreed dates'.

- 5.5.2 The RMS should ensure that the Preliminary Variation Assessment Report (PVAR) is sent to the MAH and CMSs by the agreed date. The MAH should understand that the PVAR is for information and transparency purposes only at this stage of the procedure. In exceptional cases of a delay, all CMS and the MAH should be informed.

In case of variation affecting one single CMS or several CMS but not the RMS (eg: introduction of a new Pharmacovigilance system), the RMS may request support in preparation of the PVAR from one of these CMSs.

- 5.5.3 In the PVAR the RMS should clearly indicate if it endorses the variation in its proposed form, or if it considers that the variation should be rejected or amended. If amendments are required, supplementary information can be requested from the applicant. If the application is considered to be grossly deficient it will be recommended for rejection without a request for supplementary information (RSI).
- 5.5.4 If the RMS considers the proposed changes to the SPC and/or other product literature to be unacceptable, they may propose an alternative way forward. When appropriate, the wording of the SPC and/or other product literature should be harmonised according to SPCs of other similar products approved during other MR or DC procedures, or in accordance with a Commission Decision following an Article 35 procedure. SPC changes should be focused on the points directly related to the variation application, or consequential upon it. The revision of other sections of the SPC and/or other product literature is not acceptable except for minor editorial corrections with the agreement of the RMS. The RMS will highlight such editorial changes in the PVAR.
- 5.5.5 Following receipt of the PVAR, the CMS should send their opinion about whether to accept or reject the variation to the RMS by the agreed date. The comments should be sent to the RMS via the MRVE mailbox. If a CMS sends no comments by the agreed date, the RMS will consider that the CMS endorses the PVAR of the RMS. Member States may not raise comments on matters that are unrelated to the submitted variation. If the CMS endorses a proposal of the RMS for straight acceptance or rejection, the procedure can be finalised at the end of the first phase, i.e. without the need for a clock stop as per the agreed dates.

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- 5.5.6 If the CMS does not accept the proposed variation, or the proposal of the RMS, the CMS should give the grounds for its opinion and clearly indicate what supplementary information is required from the MAH.
- 5.5.7 Additionally, the CMS may propose changes to the SPC and/or other product literature. The number of these proposals should be kept to a minimum, and the proposals should directly relate to the points subject to the variation. Other sections of the SPC and/or other product literature may be altered only in separate variation procedures. The CMS should avoid presenting extensive revision of the SPC and/or other product literature, but concentrate on giving their opinion on the proposal presented by the RMS and MAH.
- 5.5.8 If the RMS or any of the CMS do not endorse the variation proposed by the MAH, the RMS will send a request for supplementary information (RSI) to the MAH and send the CMS a copy of the request. The RMS should give a clear deadline, as per the agreed dates, to the MAH for submitting the responses to the RSI. The MAH may liaise with the RMS as necessary during the clock-stop period in case of need for clarification. The grounds for extending the clock stop period and the new deadline set should always be informed to the CMSs.
- 5.5.9 If the MAH cannot respond within a reasonable timeframe, it is recommended that the variation is withdrawn. The MAH may submit a new variation when data are available.
- 5.5.10 The applicant's response to the RSI will be sent by e-mail to the RMS, who will immediately forward it by e-mail to the CMS. The MAH will take into account Member States submission requirements as published on the CMDv website.
- 5.5.11 After receiving the supplementary information from the MAH, the RMS prepares and circulates the Final Variation Assessment Report (FVAR) and revised SPC and/or other product literature to all CMSs for comment, and to the MAH for information. The RMS should prepare the FVAR and the clock should be re-started within the agreed time frame.
- 5.5.12 In the case of disagreement between the RMS and CMS, a breakout meeting can be arranged (according to CMDv/GUI/021 – GUIDANCE Virtual CMDv product discussions). The occasion and format of the meeting should be determined by the RMS according to the CMDv breakout session protocol and communicated to the CMS, Chairman of the CMDv and the EMA. The RMS and EMA co-ordinate the

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arrangements for the breakout meeting. Reference should be made to the breakout meeting protocol for other possibilities of timing within the procedure when disagreement is foreseen.

5.5.13 CMSs should send their comments on the FVAR to the RMS by the agreed date.

5.6 Outcome of the variation procedure

5.6.1 For grouped or work sharing variations a different outcome may apply to the different variations included in the application, i.e. some changes may be accepted, whilst others may be rejected. In these cases please refer to the Best Practice Guide on Grouping of Variations, or the Best Practice Guide on Work sharing.

5.6.2 **Acceptance of variation** - In cases where the variation is accepted, the RMS will inform the MAH and CMSs that the variation is considered acceptable together with the date of acceptance. In cases where the variation results in changes to the SPC/PL/labelling the MAH should provide the RMS with the highlighted and clean versions of the SPC/PL/labelling text in electronic format. The RMS is responsible for checking the highlighted (changed) text. The RMS will circulate these documents together with a statement that it has endorsed the changes made.

5.6.3 If applicable, the MAH should send the national translations within ten calendar days of the procedure ending. Mock-ups or specimens should be provided at the end of the procedure if requested by Member States.

5.6.4 Competent authorities should implement the decision nationally within two months from the end of the procedure. However, the MAH can implement the change 30 days after the competent authority of the reference Member State has informed the holder that it has been accepted, under the condition that the necessary documentation has been provided to the Member States.

5.6.5 **Rejection:** In cases where the variation is rejected by the RMS and CMS, the RMS will inform the MAH and CMSs that the variation is considered rejected along with a description of the reasoning for the outcome. The MAH and CMS are informed of the outcome by email. The RMS will also update the CTS record, which should state the reasons for rejection.

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- 5.6.6 **Disagreement** - If there is a disagreement between the CMSs and RMS about the proposed decision by the end of the procedure, the matter should be referred to CMDv, following the procedure described in the Standard Operating Procedure For Disagreement in procedures Referral to CMDv (CMDv/SOP/001). The formal referral to CMDv should be made by the RMS, on the basis of a referral request forwarded by those objecting CMSs, which are against the opinion of the RMS. To avoid arbitration the MAH may withdraw the variation application from all CMSs and the RMS, not just those that are objecting.
- 5.6.7 Examples of suitable text for inclusion in the acceptance or rejection notifications issued to the MAH on completion of the procedure are included in Annex 1. Suitable text for the outcome of grouped variations and Work sharing procedures are annexed in respective Best Practice Guides.
- 5.6.8 All competent authorities should maintain the IT mutual recognition databases (CTS and upload the final SPC to the system) and ensure that the information of each medicinal product is updated.

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ANNEX 1

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

Example 1

ACCEPTANCE OF VARIATION

The <<*competent authority*>> accepts the Type II variation detailed in your application. The following change has been notified:

<< *enter change applied for* >>

The variation is 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 variation invalid.

Example 2

REJECTION OF VARIATION

The <<*competent authority*>> rejects your Type II variation, because of the following:

<<*enter reason for non-acceptance*>>

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ANNEX 2

Flow-charts of the Type II variation procedures:

Recommended reduced/normal/extended procedure for Type II variations			
Reduced 30 days	Normal 60 days	Extended 90 days	
Submission			<ul style="list-style-type: none"> MAH submits variation to the RMS and CMS and a list of dispatch dates to the RMS only The RMS creates a CTS record and circulates an email informing the CMS about the new procedure
Day -14 Validation phase			CMS confirms receipt of valid notification and receipt of fees, as appropriate
Day 0			Start of the procedure. The RMS notifies the timetable and start date to the MAH and CMSs
Day 15	Day 40	Day 70	RMS circulates the PVAR to the MAH and CMSs
Day 20	Day 55	Day 85	CMSs send comments on the PVAR to the RMS
Day 21	Day 59	Day 89	RMS sends the request for supplementary information to the MAH and the CMSs; clock stops
Clock off			Should not be longer than 20/120/150 days (10/60/90 days for the applicant to provide the responses, and 10/60/60 days for the RMS to prepare the FVAR)
Day 22	Day 60	Day 90	RMS circulates the FVAR to the MAH and CMSs
<i>Not appl.</i>	Day 75	Day 105	Possible break-out meeting
Day 25	Day 80	Day 110	CMSs send comments on the FVAR to the RMS

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Recommended reduced/normal/extended procedure for Type II variations			
Reduced 30 days	Normal 60 days	Extended 90 days	
Day 30	Day 90	Day 120	<p>End of the procedure.</p> <p>The RMS notifies the outcome of the procedure to the MAH and CMSs.</p> <p>Where applicable, the MAH provides the RMS with highlighted and clean versions of the SPC and/or other product literature in electronic format.</p> <p>The RMS checks the highlighted (changed) text, and circulates these documents together with a statement that it has endorsed the changes made, to the MAH and CMSs</p>

Within 10 days after approval	If applicable, the MAH sends national translations of approved SPC and/or other product literature to the national competent authorities
Within 2 months after acceptance	The national competent authorities should implement the decision nationally.