Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary

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BEST PRACTICE GUIDE

For Type IB 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 According to the Regulation a variation, which is not an extension and which is not classified in the "*Commission guideline on the details of the various categories of variations*" referred to in Article 4 of the Regulation, shall by default be considered a Type IB variation. The guideline contains examples of changes that are considered Type IB variations. Furthermore, a variation published as a Type IB variation following an Article 5 recommendation shall be submitted as such. A recommendation for classification as a Type IB variation received by the CMDv shall also be submitted as such.

1.3 Type IB variations require prior approval before implementation – known as the "Tell, Wait and Do" procedure.

1.4 Type IB variations may be grouped together with other variations in a single notification. If the highest ranking variation is a Type IB variation, this will be classed as a Type IB 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 IB lead grouped variation is the same as the procedure outlined in section 4 of this document.

1.5 A marketing authorisation holder (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 worksharing initiative. Further information about work sharing is available in *Best Practice Guide for Worksharing* (CMDv/BPG/018); however, regardless of the types of variations included in the application, the timetable and principles for worksharing are the same as those used for Type II variations (see *Best Practice Guide for Type II Variations* CMDv/BPG/006).

2. Aim and Scope

2.1 This Best Practice Guide has been produced by the CMDv in order to facilitate the processing of Type IB 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 applicant's submission

package (application form and supporting documents) is considered crucial to the overall process.

~~2.2 Changes to the label and PL that do not represent changes to the harmonized label/PL such as layout of information on packs and in package leaflets, are outside the scope of this BPG. Such changes should not be submitted via the RMS but be submitted to and agreed with the Member States concerned according to their national procedures and requirements (e.g. as national C.II.6.b variations)~~

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

3.3 Commission guideline on the details of the various categories of variations.

3.4 Best Practice Guide on Grouping of Variations.

3.5 Best Practice Guide for Worksharing.

3.6 SOP for the allocation of mutual recognition/decentralised procedure application number.

3.7 Best Practice Guide for Type II Variations.

4. Type IB Notification Procedure

4.1. Pre-submission phase

4.1.1 The MAH will contact the RMS at least seven days prior to submission in order to obtain the Type IB variation procedure number.

4.1.2 In cases of doubt about the classification, the MAH, the RMS or the CMS may request the CMDv to provide a recommendation on the classification of the variation according to article 5 of Regulation (EC) No 1234/2008.

4.2. Submission phase

4.2.1 The MAH will submit simultaneously to the RMS and CMS an application containing the elements listed in Annex IV of the Regulations, presented as follows in accordance with the appropriate headings and numbering of the NTA Vol 6B format (veterinary medicinal products):

- 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:
  - a checklist of the documentation specified for the proposed change(s). This could be directly copied or printed from the Commission Guideline, if applicable.
  - or a copy of the relevant published Article 5 recommendation, if applicable.
  - or recommendation for classification received from the CMDv.
- 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 SPC, labelling or package leaflet, both the English texts and national translations should be submitted. Mock-ups or specimens should be provided according to according to guidance on the CMDv website or as discussed with the RMS on a case-by-case basis

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

4.2.3 Within seven days the RMS creates the CTS record and sends an email via the MRVE mailbox to inform the CMS about the new procedure.

4.3. Validation phase

4.3.1 The RMS and CMS will check whether the notification is correct and complete ('valid') within seven days prior to the start of the evaluation procedure. CMS should send any comments about an invalid notification to the RMS within this time frame.

4.4. Start of notification procedure (Day 0)

4.4.1 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 notification is considered valid, the RMS will also inform the CMS and MAH of the timetable and start date.

4.5. Evaluation phase (Day 0 to 30)

4.5.1 Within 30 days from the start of the notification procedure, the RMS will notify the MAH of the outcome of the procedure. If the RMS has not sent the holder its opinion within 30 days, i.e. by Day 30, the notification shall be deemed acceptable.

4.5.2 The responsibility for the evaluation of the proposed variation lies with the RMS; however, in the exceptional circumstances outlined below, the RMS should seek comments from the relevant CMS before reaching a decision. If there are objections from the CMS, they should update CTS and send their comments to the RMS within 20 calendar days from the start of the procedure. This situation may be given for the following change:

- Change in the name of the medicinal product (in a CMS)
- Change in or introduction of a DDPS (in a CMS)
- All variations under heading C.I.1-C.I.3 and C.I.6-C.I.7
- Variations under heading C.II.2 and C.II.6

Changes to the labelling and PL that do not represent changes to the harmonised labelling/PL text, such as changes to layout of information or languages included on packs and in package leaflets, are outside the scope of this BPG. Such changes should not be submitted via the RMS but be submitted to and agreed with the Member States concerned according to their national

procedures and requirements ~~(e.g. as national C.II.6.b variations)~~

4.5.3 If the notification cannot be accepted by all member states, the RMS will inform the MAH and the CMS about the grounds on which the rejection is based ('Notification with grounds') by Day 30. The clock will stop pending receipt of an amended notification by the MAH, which should be submitted to the RMS and CMS within 30 calendar days. Additionally, the MAH should send a list of the dispatch dates to the RMS, indicating the dates on which the amended notification was sent to the CMS. The RMS will re-start the procedure on receipt of the list of dispatch dates and inform the MAH accordingly. The RMS will also update CTS and send an email to the MRVE mailbox informing the CMSs of the start date (New Day 0).

MAH are reminded that if the product information is concerned by the change applied for, national translations updated in accordance with requests for amendment raised in the Notification with grounds, have to be submitted in the amended notification in order to be validated during this second 30-day period.

4.5.4 Within 30 days of receipt of the amended notification, the RMS will inform the MAH, by means of a 'Notification on a Type IB variation', of its final acceptance/rejection of the variation. If the MAH did not amend the notification within 30 days, as requested, the variation will be rejected and the CMS will be informed accordingly.

4.6. Outcome of the notification procedure

4.6.1 For grouped or worksharing variations a different outcome may apply to the different variations included in the notification, 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 Worksharing*.

4.6.2 The RMS will make the decision as to whether the notification is accepted, has to be amended, or is rejected. The following actions will be taken on or before Day 30/New Day 30.

4.6.3 Acceptance of notification: The RMS will inform the MAH and CMS that the variation is considered acceptable together with the date of acceptance. The MAH and CMS are informed of the outcome by

email via the MRVE mailbox The outcome of the procedure should be detailed in the subject of the email
The RMS should also update the CTS record. 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.

4.6.4 Mock-ups or specimens should be provided as requested by Member States.

4.6.5 Competent authorities should implement the decision nationally within six months from the end of the procedure; however, the MAH can implement the change as soon as 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.

4.6.6 Rejection of notification: The RMS will inform the MAH and the CMS that the notification has been rejected along with a short description of the reasoning for the outcome. The MAH and CMS are informed of the outcome by email. The outcome of the procedure should be detailed in the subject of the email The RMS should also update the CTS record, which should also state the reasons for rejection.

4.6.7 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 Worksharing procedures are annexed in respective Best Practice Guides.

4.6.8 All competent authorities should maintain the electronic mutual recognition databases (CTS and MR Product Index) and ensure that the information of each medicinal product is updated.

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 NOTIFICATION

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

<< *enter change applied for*>>

The notification 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 notification invalid.

Example 2

REJECTION OF NOTIFICATION

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

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

ANNEX 2

At least 7 days before submission	MAH contacts the RMS to obtain a variation procedure number and to discuss any issues that need clarification before submission.
Submission phase	• MAH submits variation to RMS and CMS and a list of dispatch dates to the RMS only • Within 7 days after receipt of the application, the list of dispatch dates and the confirmation about payment of fees, the RMS creates a CTS record and circulates an email informing the CMS about the new procedure.
Day -7 Validation phase	CMS confirms receipt of valid notification and receipt of fees, as appropriate.
Day 0	The RMS starts the procedure, completes the CTS record and circulates an email informing CMS and MAH of the procedure start date.
Until Day 20	CMS notify RMS of their objections, as applicable.
Day 30	• If the variation cannot be accepted by all member states, the RMS circulates the 'Notification with grounds' to the CMS and MAH and the clock stops. • If the variation can be accepted by all member states, the RMS circulates an acceptance notification to the CMS and MAH and the procedure ends.
Clock stop	Within 30 days of receipt of the 'Notification with grounds', the MAH submits an amended notification to the RMS and CMS and a list of dispatch dates to the RMS only.
New Day 0	The RMS restarts the clock, updates CTS and circulates an email informing the CMS & MAH the procedure has restarted.
New Day 30	If the variation can be accepted by all Member States, the RMS circulates an acceptance notification to the CMS and MAH and the procedure ends. If the variation cannot be accepted by all Member States, the RMS circulates a rejection notification to the CMS and MAH and the procedure ends. Where applicable, the MAH provides the RMS with track changes and clean versions of the SPC and/or other product literature in electronic format. The RMS checks the tracked changes and circulates these documents, together with a statement that it has endorsed the changes made, to the MAH & CMS.
Within 6 months after acceptance	The national competent authorities should implement the decision nationally.