CHAPTER 4
CMDh BEST PRACTICE GUIDE FOR THE PROCESSING OF TYPE IB MINOR VARIATIONS (NOTIFICATIONS) IN THE MUTUAL RECOGNITION PROCEDURE

1. INTRODUCTION

This Best Practice Guide was produced by the CMDh in order to facilitate the processing of Type IB Variations in the MR procedure. Guidance is given on the role of the Reference Member State (RMS) as co-ordinator of the notification process, and to reflect good practice of the Concerned Member States (CMS) in ensuring a consistent approach is maintained. This will ensure that the Type IB Variations are processed in an efficient and timely manner. Moreover, it is considered that the quality of the submission and supporting documentation, which are the responsibility of the marketing authorisation holder (MAH), are crucial to the overall process. From 4 August 2013 the same rules will apply to purely national MAs.

Variation Regulation (EC) No. 1234/2008 effective 1 January 2010 gives a general definition of variations that can be processed as Type IB Variations. According to the Regulation, a variation which is not an extension and which is not classified in the guideline referred to in Art. 4 of the Regulation, shall by default be considered a minor variation of type IB. Furthermore, a variation which is recommended as variation of type IB according to Art. 5 of the Regulation, shall be submitted as minor variation of type IB.

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 classified as a Type IB variation. Further information about the grouping of variations is available in Chapter 6 of this Best Practice Guide.

A MAH may also submit several Type IB variations to more than one of their marketing authorisations in a single application; this will be dealt with in accordance with the worksharing procedure, unless the application concerns only purely national marketing authorisations submitted to the same national competent authority, in which case the procedure will be classified as a Type IB grouped application (if the competent authority agrees to such single submission). Further information about worksharing and grouping is available in Chapter 6 and 7 of this Best Practice Guide.

In cases of doubt about the classification, the MAH may request the RMS to provide a recommendation on the classification of the variation according to Art. 5 of Regulation (EC) No. 1234/2008. Further details on the Art. 5 procedure are given in Chapter 8.
2. TYPE IB VARIATIONS

2.1 Allocation of MR variation number

Information on the allocation of the variation procedure number and the MRP variation number is presented in Chapter 1 of this Best Practice Guide.

2.2 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 Variation Regulation, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format:

- Cover letter.
- Application form, including the variation procedure number and the MRP variation number and a description of the variation(s) submitted.
- Checklist of the documentation specified for the proposed change(s) if applicable. This could be directly copied or printed from the Classification Guideline.
- If available, copy of the Art. 5 recommendation for the requested change.
- 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, both the English texts and national translations should be submitted. Mock-ups or specimens should be provided according to Chapter 7 of the NtA, or as discussed with the RMS on a case-by-case basis.

Additionally, the RMS submission should 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).

The RMS creates the CTS record within 7 days\(^1\) after receipt of the application.

For purely national MAs the variation application has to be submitted to the relevant Competent Authority of the member state concerned including the same documents.

2.3 Start of notification process

After the validation period the RMS completes the CTS record as the means of informing the CMS of the start of the notification process and the timetable. The CMS are only informed via CTS, there will be no additional mail. The MAH is informed by the RMS about the start date (Day 0).

2.4 The Evaluation Process (Day 0 to Day 30)

According to the Regulation (EC) No. 1234/2008 the timeframe for the validation and the evaluation of the change applied for is in the responsibility of the RMS.

Within 30 days from the start of the notification procedure, the RMS will notify the MAH of the outcome of the procedure. Generally, the preparation of an assessment report is not foreseen for the evaluation of type IB variations. The only exceptions are the ASMF worksharing procedures.

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\(^1\) All time lines in this document are based on calendar days, i.e. days should be read as calendar days.
If the RMS has not sent the MAH its opinion within 30 days, i.e. by Day 30, the notification shall be deemed acceptable.

However, there are some specific variations for which the RMS needs an input from the CMS for his decision. This situation may be given for the following categories of changes:

- Change in the name of the medicinal product (in a CMS);
- Change in pack size;
- All variations under heading C.I.z, C.I.1-C.I.3 and C.I.6.b-C.I.7;

In the cases of the last bullet point, changes to the C-section categories of the classification guideline, the RMS should notify the CMS within 20 days from the start of the procedure on its position regarding the change applied for. The CMS should send their comments, if any, on the RMS position and update CTS accordingly between Day 20 and Day 27 of the procedure.

If the product information is concerned by the change applied for, the national translations have to be evaluated and may be commented by the CMS until Day 27.

If the notification cannot be accepted by the RMS, taking into account the CMS comments, 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 days. Additionally, the MAH should send a list of the dispatch dates, indicating the dates on which the amended notification was sent to the CMS, to the RMS. 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 to inform the CMS.

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.

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. The CMS will be informed accordingly by updating CTS.

### 2.5 Outcome of the notification process

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

- **Approval:** The RMS will inform the MAH that the variation application is approvable, together with the date of approval. The CMS are informed of the outcome by means of the updated CTS record.
- **Refusal:** The RMS will inform the MAH and, if applicable, the CMS about the reasons leading to the refusal of the variation application. The RMS will update CTS which should also state the reasons for refusal in the annotation field of the outcome date.

Examples of suitable text for inclusion in approval or refusal notifications issued to the MAH on completion of the procedure are included in Annex 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 or withdrawn. In these cases please refer to Chapter 6 or 7 of this Best Practice Guide.
Competent authorities should implement the decision nationally within six months from the end of the procedure; however, the MAH can implement the changes prior to the marketing authorisation being updated by the national competent authority, i.e. immediately after the RMS has informed the holder that it has accepted the notification or after the notification has been deemed accepted.
ANNEX I

Sample text for inclusion in the approval or refusal notifications issued to the MAH on completion of the procedure

ACKNOWLEDGEMENT OF APPROVAL

The <<competent authority>> agrees to the request to vary the Marketing Authorisation detailed in the application. The proposed change is:

<< enter change applied for>>

The application is approved 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 application invalid.

REQUEST TO APPLICANT

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)

REFUSAL

The <<competent authority>> cannot agree to the proposed variation to the Marketing Authorisation because of the following:

<<enter reason for non-acceptance>>
## ANNEX II

### Submission
- MAH submits variation to the RMS and CMS and a list of dispatch dates to the RMS only.
- The RMS creates a CTS record.

### Day 0
The RMS starts the procedure after validation, completes the CTS record and sends an e-mail informing the MAH of the procedure start date. The CMS are only informed via CTS, there will be no additional mail.

### Until Day 20
The RMS notifies the CMS on RMS position in cases of changes to the product information acc. to the C-section categories.

### Until Day 27
CMS notify RMS of their comments in case of changes to the product information acc. to the C-section categories, product name and pack size.

### Day 30
- If the variation cannot be accepted by the RMS, taking into account the CMS comments the RMS circulates the ‘Notification with Grounds’ to the CMS and MAH and the clock stops.
- If the variation can be accepted by the RMS, taking into account the CMS comments, the RMS circulates an acceptance notification to the MAH and informs the CMS by updating CTS and the procedure ends. Where applicable, the MAH provided the RMS during the procedure highlighted and clean versions of the SmPC, labelling and/or package leaflet in electronic format, 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 CMS. All changes in the text, in comparison with the previously approved version of product information, should be marked with track-changes in the highlighted versions circulated at the end of procedure. It is recommended to upload the clean documents to CTS for transfer to the MRI index.

### 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. Where applicable, national translations updated in accordance with requests for amendment raised in the ‘Notification with Grounds’, have to be submitted in the amended notification.

### New Day 0
The RMS restarts the clock, updates CTS and sends an email informing the MAH that the procedure has restarted. The CMS are only informed via CTS, there will be no additional mail.

### Until New Day 20
The RMS notifies the CMS on RMS position in case of changes to the product information acc. to the C-section categories.

### Until New Day 27
CMS notify RMS of their comments in case of changes to the product information acc. to the C-section categories, product name and pack size.

### New Day 30
- If the variation can be accepted by the RMS, taking into account the CMS comments the RMS circulates an acceptance notification to the MAH and informs the CMS by updating CTS the procedure ends. Where applicable, the MAH provided the RMS highlighted and clean versions of the SmPC, labelling and/or package leaflet in electronic format, 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 CMS. All changes in the text, in comparison with the previously approved version of product information, should be marked with track-changes in the highlighted versions circulated at the end of procedure. It is recommended to upload the clean documents to CTS for transfer to the MRI index.
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<tr>
<th>Within 6 months after acceptance</th>
<th>Competent authorities should implement the decision nationally within six months.</th>
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- If the variation cannot be accepted by the RMS, taking into account the CMS comments, the RMS circulates a rejection notification to the CMS and MAH and the procedure ends.