Chapter 2 - Procedure for automatic validation of Mutual Recognition Procedures for Variations

Completion of CTS records by all Member States is essential for the operation of the procedure (see Best Practice Guide for MRP and DCP). Especially positive validation and Clock Starts should be communicated via CTS only in order to avoid unnecessary emails.

1. Introduction

This procedure has been introduced by the CMDh in order to facilitate the initiation of variation procedures according to Regulation (EC) No. 1234/2008 effective 1 January 2010.

Procedures for the allocation of the MR variation procedure number and the submission of the variation apply to all categories of variations. It should be noted that in cases where the CMS have not received the variation application or the fee has not been paid at the time of submission or in accordance with national competent authority requirements, the application will be deemed invalid and the procedure stopped.

2. Allocation of MR variation procedure number

The MAH will be responsible for identifying and assigning their own procedure number according to guidance given in Chapter 1. In case of doubt, the RMS or Reference Authority should be contacted.

3. Submission phase

The MAH submits the variation and supporting documentation simultaneously to the RMS and CMS. Only the RMS should additionally receive the list of despatch dates (all dates of despatch to the CMS and a statement that the relevant national fees have been paid as required by national competent authorities). This may be sent after the notification/variation submission. Sample text for inclusion in the list of despatch dates is shown in Annex 1.

4. Start of variation process

The process for acknowledging or as appropriate starting the notification or variation is summarised in the flow charts in Annex II.
4.1. Type IA Notifications

Within 5 calendar days of receipt of the Notification (Type IA and IAIN) and list of despatch dates, the RMS completes the CTS record including for transparency a description of the proposed change(s). This may be done by ticking all single changes from the provided list in CTS or by using the free text field. In case of the latter, the application form has to be uploaded to CTS, preferably as a word file. This informs CMS of the start of the notification process i.e. Day 0 as well as of details concerning the changes applied for. Day 0 should be backdated as necessary to coincide with the actual date of receipt of the notification. The CMS are only informed via CTS, there will be no additional email.

CMS should not comment on the validity of the notification in respect of content. CMS may only inform the RMS and the applicant in case of non-receipt or non-payment of fees. This should be done by indicating the invalid field on CTS, adding a comment in the annotation field and additionally informing the RMS and the applicant by email. The RMS will take the appropriate action should they be informed of any irregularity.

4.2. Type IB Notifications

Within 7 calendar days of receipt of the variation application, supporting documentation – taking into account any listed examples in the Commission Guideline -, and if applicable a copy of the Article 5 Recommendation, and the list of despatch dates, the RMS creates the CTS record, including a text description of the proposed change, as a means of informing CMS about the submission.

CMS should not comment on the validity of the variation in respect of content but may indicate on CTS and by email to the applicant within 7 calendar days of the CTS record in case the application is invalid due to non-receipt or non-payment of fees. The CMS should then inform the RMS on the validity of the application within 7 calendar days of receipt of the possible missing information/fee by the applicant.

The RMS will not start the clock until the CMS confirms to the RMS that issues have been resolved and the application is valid. However, the same rules apply for starting the procedure as in the Procedural Advice on Validation of MR/Repeat-Use/DC Procedures, https://www.hma.eu/91.html.

If the RMS receives no invalid notification from CMS within the 7 calendar day period, the RMS completes the CTS record as a means of informing CMS of the start of the variation process (Day 0). The CMS are only informed via CTS, there will be no additional email.

The RMS additionally informs the MAH. CMS should not subsequently inform the RMS that the application is not valid.

When the proposed variation is not considered as a minor variation of Type IB following the Commission Classification Guideline or has not be classified as a minor variation of type IB in a recommendation pursuant article 5 of the variation regulation the RMS should confirm within these 7 calendar days whether the proposed change can be considered a minor variation of Type IB, and acceptable as a Type IB notification, or whether it is of the opinion that the proposed change has the potential to have a significant impact on the quality, safety or efficacy of the medicinal product and is not acceptable as a Type IB notification or whether there is a need to consult with CMS on the classification of the proposed change.

When the RMS is of the opinion that the proposed change has the potential to have a significant impact on the quality, safety or efficacy of the medicinal product, the RMS will inform the CMS immediately by email through the MRVE-mailbox mentioning “upgrade” in the email subject in addition to procedure number and product name. In these situations, the validation period can be extended by an additional 7 calendar days to give the RMS and CMS time to discuss this. If the CMS disagree with the RMS, the
RMS shall take the final decision on the classification of the proposed variation having taken into account the comments received:

- If it is decided by the RMS that a Type IB notification is still appropriate, the RMS completes the CTS record as a means of informing CMS of the start of the variation process (Day 0). The RMS additionally informs the MAH. CMS should not subsequently inform the RMS that the application is not valid.

- If it is decided by the RMS that the proposed change has the potential to have a significant impact on the quality, safety or efficacy of the medicinal product and that a Type IB notification procedure is not appropriate, the RMS will inform the MAH accordingly, supporting this decision on scientific reasons. The MAH will be requested to revise and supplement the variation application so that the requirements for a Type II variation application are met. The RMS will indicate the upgrade of the variation application to a Type II variation in CTS.

After receiving a request from the RMS to upgrade the proposed variation, the MAH has 21 calendar days to update the application form for a Type II variation, pay the corresponding fee and to submit any supplementary documentation. Once the variation is resubmitted as a Type II variation, the normal timeline for a Type II variation application applies after the procedure has been started by the RMS.

4.3. Type II Variations

The RMS enters the procedure into CTS, including a text description of the proposed change, immediately after receiving the variation application as a means of informing the CMS of the variation at an early stage. On receipt of the list of despatch dates the RMS circulates to the CMS by e-mail the proposed procedure start date and variation timetable. The procedure start date is normally set at 14 calendar days from receipt of the list of despatch dates to allow CMS to comment on the validity of the application or the proposed timetable.

After receiving a request from the CMS to validate the variation application, the MAH has 21 calendar days to update the application form for a Type II variation, pay the corresponding fee and to submit any supplementary documentation. Once the variation is resubmitted as a Type II variation, the normal timeline for a Type II variation application applies after the procedure has been started by the RMS.

The CMS should inform the RMS within the 14 calendar day period of acceptance of a valid application by indicating on CTS. Positive validation should only be indicated in CTS, not via email. Invalidation issues should be communicated by email to the RMS and the applicant. If no comments are received during the 14 day validation period, the RMS notifies the MAH and CMS of the procedure start date. This is Day 0. The CMS are only informed via CTS, there will be no additional email. If a CMS has previously informed the RMS that the application is not valid, the clock will not be started until that CMS confirms to the RMS that the issues have been resolved and the application is valid. The CMS has a duty to update the status of the CTS record accordingly.

Variations listed in part 1 of Annex V of the Regulation are automatically subject to the extended timetable of 90 days. However, if the RMS is of the opinion that a proposed grouping of variations, in accordance with Article 7(2)(c) of the Regulation, is complex and should also be the subject of the extended timetable, the RMS will decide this without consultation with the CMS.

The RMS completes the CTS record as a means of informing CMS of the start of the variation process (Day 0) and confirmation of the extended timetable. The RMS additionally informs the MAH.

4.4. Grouped applications

Grouped applications are handled according to the highest variation type being part of the application and specifying the procedure type as described under 4.1-4.3.
4.5. *Worksharing procedure*

Worksharing applications are handled according to the procedure as described under 4.3 with the reference authority taking the responsibilities of the RMS.
ANNEX I

Sample information for inclusion in the MAH's list of despatch dates

Mutual Recognition Procedure Variation Number

(e.g. UK/H/0123/001/II/002)

<table>
<thead>
<tr>
<th>Name of competent authority/agency for despatch*</th>
<th>Date of submission</th>
<th>Date of payment of fees, as appropriate</th>
<th>MA Holder</th>
</tr>
</thead>
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* Note: Address for delivery of the notification/variation to the concerned member states is referenced in Notice to Applicants, Volume IIA, Chapter 7
ANNEX II

Flowchart for automatic validation: Starting the notification or variation procedure

Type IA Notification

MAH assigns MR notification number

MAH submits notification simultaneously to RMS and CMS

MAH submits list of despatch dates to RMS

RMS creates and completes CTS record within 5 calendar days

Start of notification process Day 0

CTS record should be backdated to date of receipt
**Type IB Notification**

MAH assigns MR notification number

MAH submits notification simultaneously to RMS and CMS

MAH submits list of despatch dates to RMS

RMS creates CTS record immediately upon receipt

Start of the validation phase (7 calendar days) – The validation period can be extended by an extra 7 calendar days to deal with ‘unforeseen’ IB variation

RMS takes decision on classification (as type IB or type II) and validity of the application

CMS may comment on possible upgrade to type II

RMS confirms type IB

RMS waits for feedback from CMS

CMS have no comments or comments that do not prevent the RMS to start the procedure

Application to be resubmitted as type II variation

Valid submission (to be recorded in CTS)

Procedure starting date Day 0

CMS report within 7 days from the CTS record on issues preventing the RMS to start the procedure according to Chapter 2, 4.2.

Invalid submission (to be recorded in CTS)

Suspension of automatic validation process – MAH requested to provide missing information/fee

MAH submits missing information/fee to CMS

CMS informs RMS of validity of submission within 7 calendar days of receipt of appl. response

RMS confirms validity
**Type II Variation**

- MAH assigns MR notification number
- MAH submits notification simultaneously to RMS and CMS
  - RMS creates CTS record
    - CMS informed of submission
- MAH submits list of despatch dates to RMS
- RMS circulates proposed procedure start date and variation timetable
- 14 calendar days allowed for CMS comment on submission/timetable

**Timetable**

- CMS send comments to RMS concerning:
  - non receipt
  - non payment of fee
  - objection to timetable
  - validity of content

- RMS/CMS Agree timetable

**Validity**

- MAH requested to submit missing information/fee

- CMS informs RMS of valid submission within 7 calendar days of receipt

- CMS : acceptance (or no comment)

- Procedure start date
  - Day 0

- MAH submits missing information/fee to CMS