CHAPTER 5
CMDh BEST PRACTICE GUIDE FOR THE HANDLING OF TYPE II VARIATIONS IN THE MUTUAL RECOGNITION PROCEDURE

1. INTRODUCTION

The Best Practice Guide has been introduced by the CMDh to facilitate the processing of type II variation applications according to Regulation (EC) No.1234/2008 effective 1 January 2010. It aims to provide guidance on the role of the Reference Member State (RMS) as co-ordinator of the procedure, and to reflect good practice of the Concerned Member States (CMS) in handling of type II variations.

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.

Type II variations require prior approval before implementation.

Type II variations may be grouped together with other variations in a single application if it concerns a single MA. If the highest ranking variation is a Type II variation, this will be classified as a Type II 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 II variations to more than one of their marketing authorisations in a single application; this will be dealt with in accordance with the worksharing procedure. Further information about worksharing is available in Chapter 7 of this Best Practice Guide.

2. TIMESCALES

Variations are normally processed according to a 60-day time scale, however the Regulation additionally specifies a reduced or extended (90-day) time scale for Type II variations. The reduced time (recommended 30-days) in the Regulation is intended for variations concerning safety issues. The RMS and MAH should decide when the expedited procedure is appropriate bearing in mind that a 24-hour urgent safety restriction procedure is available (see http://www.hma.eu/uploads/media/safety.pdf). The 90-day process is intended for variations concerning changes to, or addition of, the therapeutic indications and also for complex groupings submitted under paragraph (2)(c) of Article 7 of the Regulation. The detailed procedural timetables for 30-, 60- and 90-day type II procedures are given in the flowcharts at the end of this document.

1 All time lines in this document are based on calendar days, i.e. days should be read as calendar days.
It should be noted that these reflect overall time scales of 30, 90 and 120 days for completion of the procedures (excluding clock-off times).

Flow-charts of the Type II variation procedures are provided in Annex II.

3. ALLOCATION OF VARIATION PROCEDURE 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. In case of doubt, the RMS or Reference Authority should be contacted.

4. SUBMISSION PHASE

The MAH submits 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 of the EU-CTD format:

- Cover letter (including variation procedure number).
- Application form, including the variation procedure number and 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 published Article 5 Recommendation, if applicable.
  - The recommendation for classification received from the CMDh, if applicable.
- 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.
  - For variations that affect the SmPC, labelling or package leaflet, only the draft English texts 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.

RMS creates the CTS record to inform the CMSs about the new procedure.

5. AUTOMATIC VALIDATION

The automatic validation procedure is described in Chapter 2 of this Best Practice Guide.

6. START OF VARIATION PROCEDURE (Day 0)

Following the validation period the RMS completes the CTS record to inform the CMS on the start of the procedure. The RMS will also inform the MAH of the start date (Day 0).

7. EVALUATION
Generally the 60 days timetable will apply. In special cases the competent authority, in the role of the RMS, should agree with the Marketing Authorisation Holder (MAH) on the timetable of the procedure and aim to synchronise the possible parallel or sequential variation procedures so that overlapping of procedures is avoided, where practical. The 60 and 90-day time frames are maximum time lines thus allowing flexibility for shorter procedures in particular situations. In such exceptional circumstances the MAH should contact the RMS as soon as possible. It is up to the RMS to propose an accelerated time table (e.g. 30-day procedure) to the CMS, which is then part of the automatic validation procedure of this variation. Nevertheless CMS may object to a shortened procedure, in which case the RMS should propose the acceptable timetable. For straightforward changes to the indication the 60-day time frame should be the rule, however the period can be extended to 90 days for variations concerning changes to or addition of therapeutic indication requiring more comprehensive assessment or for complex groupings in accordance with Article 7(2)(c) of the Regulation. The agreed timetable is included in CTS.

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 the variation concerns the introduction of new DDPS in one or more CMS (following a transfer of MAH in the CMS provided that there was already a DDPS approved for the medicinal product concerned) the RMS may request support in preparation of the PVAR from this CMS.

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 MAH. If the application is considered to be grossly deficient it will be recommended for rejection without a request for supplementary information (RSI).

If the RMS considers the proposed changes to the SmPC, labelling or package leaflet to be unacceptable, they may propose an alternative way forward. When appropriate, the wording of the SmPC, labelling or package leaflet should be harmonised according to SmPCs of other similar products approved during other MR or DC procedures, or in accordance with a Commission Decision following an Article 30 procedure. SmPC changes should be focused on the points directly related to the variation application, or consequential upon it. The revision of other sections of the SmPC, labelling or package leaflet is not acceptable except for minor editorial corrections with the agreement of the RMS. The RMS will highlight such editorial changes in the PVAR.

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. CMSs 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.

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.

Additionally, the CMS may propose changes to the SmPC, labelling or package leaflet. 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 SmPC, labelling or package leaflet may be altered only in separate variation procedures. The CMS should avoid presenting extensive revision
of the SmPC and/or other product literature, but concentrate on giving their opinion on the proposal presented by the RMS and MAH.

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 communicated to the CMSs.

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.

After receiving the supplementary information from the MAH, the RMS prepares and circulates the Final Variation Assessment Report (FVAR) and revised SmPC, labelling or package leaflet 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.

In the case of disagreement between the RMS and CMS, a breakout session can be arranged (e.g. by Vitero). The CMDh Best Practice Guide on Break-Out Sessions is followed.

CMSs should send their comments on the FVAR to the RMS by the agreed date. CMS are reminded that generally all comments should be addressed on the PVAR in order to avoid new issues arising in the second phase of the procedure. In general, CMS comments in the second phase should be restricted to those cases when comments on the PVAR have not been adequately addressed in the response or when the response to initial questions raises PSRPH concerns.

Applicants are reminded that the response documents should only contain responses on questions raised by member states. Additional information outside the scope of the variation should be avoided. Generally, significant responses in order to resolve major objections and PSRPH should only be submitted during the clock stop period and cannot be considered after circulation of the FVAR. In case of remaining major objections and PSRPH of the RMS in the FVAR applicants should consider withdrawal of the variation and resubmission of a new variation application with an amended dossier. Responses on minor issues submitted very late during the second procedure phase cannot necessarily be assessed in the remaining time or considered in the final RMS’ position.

8. OUTCOME

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 SmPC/PL/labelling the MAH should provide the RMS with the highlighted and clean versions of the SmPC/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.

If applicable, the MAH should send the national translations within five days of the procedure ending.

These translations may be implemented within 30 days after submission unless any comments of the respective competent authorities have been received.

Competent authorities should implement the decision nationally within two months from the end of the procedure.
**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.

**Disagreement** - If one of the CMS can not approve the variation on the basis of a Potential Serious Risk to Public Health (PSRPH), the matter should be referred to CMDh, following the procedure described in the Standard Operating Procedure for Disagreement in procedures Referral to CMDh. The formal referral to CMDh should be made by the RMS, on the basis of a referral request forwarded by those objecting CMSs which raised a PSRPH. To avoid arbitration the MAH may withdraw the variation application from all CMSs and the RMS, not just those that are objecting.

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.

For grouped or worksharing 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 Chapters 6 and 7 of this Best Practice Guide.
ANNEX I

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

\textit{<<enter change applied for>>}

REQUEST TO APPLICANT

\textit{In case of changes to the product information}

Applicants are reminded to submit the national translations taking into consideration the recommendations of the Best Practice on the submission of high quality national translations no later than 5 days after the procedure is closed.

\textit{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)"

Example 2

REJECTION OF VARIATION

The \textit{<<competent authority>>} rejects your Type II variation, because of the following:

\textit{<<enter reason for non-acceptance>>}
ANNEX II

Flow-charts of the type II variation procedures:

Recommended reduced (30-day) procedure for type II variations

Day 0  Start of the procedure, RMS notifies the timetable to the CMS's by CTS and to the MAH by email
Day 15 RMS circulates the PVAR to the CMS's and to the MAH
Day 20 CMS’s send the possible comments on the PVAR to the RMS
Day 21 RMS sends the request for supplementary information to the MAH and the CMS's, clock stop
Clock off period Should not be longer than 10 + 10 days (10 days for the MAH to provide the responses and 10 days for the RMS to prepare the FVAR)
Day 22 RMS circulates the FVAR to the CMS's and to the MAH
Day 25 CMS's send the possible comments on the FVAR to the RMS
Day 30 End of the procedure, the RMS notifies the completion of the procedure and, when applicable, circulates both highlighted and clean versions of the endorsed, finalised SmPC/PL/labelling to the CMS's and the MAH

60-day procedure for type II variations

Day 0  Start of the procedure, RMS notifies the timetable to the CMS's by CTS and to the MAH by email
Day 40 RMS circulates the PVAR to the CMS’s and to the MAH
Day 55 CMS's send the possible comments on the PVAR to the RMS
Day 59 RMS sends the request for supplementary information to the MAH and the CMS's, clock stop
Clock off period Should not be longer than 60 + 60 days (60 days for the MAH to provide the responses and 60 days for the RMS to prepare the FVAR)
Day 60 RMS circulates the FVAR to the CMS's and to the MAH
Day 75 The possible break-out meeting
Day 80 CMS's send the possible comments on the FVAR to the RMS
Day 90 End of the procedure, the RMS notifies the completion of the procedure and, when applicable, circulates both highlighted and clean versions of the endorsed, finalised SmPC/PL/labelling to the CMS's and the MAH
### 90-day procedure for type II variations

<table>
<thead>
<tr>
<th>Day</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Start of the procedure, RMS notifies the timetable to the CMS's by CTS and to the MAH by email</td>
</tr>
<tr>
<td>70</td>
<td>RMS circulates the PVAR to the CMS's and to the MAH</td>
</tr>
<tr>
<td>85</td>
<td>CMS's send the possible comments on the PVAR to the RMS</td>
</tr>
<tr>
<td>89</td>
<td>RMS sends the request for supplementary information to the MAH and the CMS's, clock stop</td>
</tr>
<tr>
<td></td>
<td>Clock off period</td>
</tr>
<tr>
<td>90</td>
<td>Should not be longer than 90 + 60 days (90 days for the MAH to provide the responses and 60 days for the RMS to prepare the FVAR)</td>
</tr>
<tr>
<td>90</td>
<td>Re-start of the procedure. RMS circulates the FVAR to the CMSs and to the MAH</td>
</tr>
<tr>
<td>105</td>
<td>The possible break-out meeting</td>
</tr>
<tr>
<td>110</td>
<td>CMS's send the possible comments on the FVAR to the RMS</td>
</tr>
<tr>
<td>120</td>
<td>End of the procedure, the RMS notifies the completion of the procedure and, when applicable, circulates both highlighted and clean versions of the endorsed, finalised SmPC/PL/labelling to the CMS's and the MAH</td>
</tr>
</tbody>
</table>