CHAPTER 8
CMDh BEST PRACTICE GUIDE ON
CMDh RECOMMENDATIONS ON UNFORESEEN VARIATIONS

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1. INTRODUCTION

Article 3, paragraph 1 of Commission Regulation (EC) No 1234/2008 (variation Regulation) refers to Annex II where a classification of minor variations, type IA and major variations, type II, is laid down. The classification of extensions of a marketing authorisation is laid down in a list in Annex I. Article 4 of the variation Regulation confers on the Commission the obligation to establish guidelines on the details of the various categories of variations (classification guideline). These guidelines shall be regularly updated, taking into account inter alia the recommendations of the CMDh and CMDv or, in the case of centralised marketing authorisations, the EMA.

Article 5 of the variation Regulation provides the basis for a marketing authorisation holder (MAH) to request the Reference Member State (RMS), EMA (in case of centralised marketing authorisations) or a national competent authority of a Member State (NCA) (in case of purely national marketing authorisations) to deliver a recommendation on classification of an unforeseen variation before submission of the variation. This recommendation shall be consistent with the Commission guidelines and be delivered to the MAH, EMA, CMDh and CMDv within 45 days following the receipt of the request.

Article 5 of the variation Regulation also provides the basis for a NCA to request the CMDh or CMDv to deliver a recommendation on classification of an unforeseen variation before examination of the variation. This recommendation shall be consistent with the Commission guidelines and be delivered to the MAH, EMA and all NCAs within 45 days following the receipt of the request.

Cooperation between the two coordination groups and the EMA is envisaged by the legislation. The recommendations will be published once adopted.

It should be noted that the recommendation of the CMDh is not a (pre-) assessment of the future variation application but a recommendation of the classification of a variation. The recommendation relate to the situation described in the request.

2. SCOPE

This guidance covers medicinal products for human use that have been authorised through the mutual recognition, decentralised or purely national procedures. The request shall apply only to variations whose classification is not provided for in the a.m. annexes (unforeseen variations). The CMDh cannot “reclassify” a variation already listed in the annexes/guidelines.
3. SUBMISSION AND VALIDATION OF REQUEST FROM MAH

A request for a recommendation of a classification from a MAH shall be submitted to the relevant authority prior to submission of the variation. To facilitate the retrieval of the requests MAHs are requested to use the following standardised wording in the subject field of the email:

<MRP> - <Product name>-Art. 5 variation classification request.

The application form for Article 5 requests published on the CMDh website (http://www.hma.eu/265.html) should be used. It is important that the request includes a detailed description of the product and a detailed description of the proposed variation of the terms of the authorisation, as the time available to request additional information is very limited. The request should include information detailing whether a similar variation has been previously submitted to a NCA and if so how it was classified and in accordance with which guidance. The request should in addition include a justification of why the variation is considered to be unclassified according to the variation Regulation.

It is the responsibility of the relevant authority to validate the request with respect to the classification guideline.

Invalid request: If the relevant authority considers the variation to fall under the scope of a foreseen variation, if a recommendation has already been issued or if the variation should clearly be classified as type IB by default according to the classification guideline, the authority will deem the request invalid and inform the MAH thereof.

Valid request: If the relevant authority considers the variation to be unclassified, it is recommended that the request is forwarded to the coordination group for discussion in order to avoid any discrepancies in recommendations. This should be done at the latest within 25 days following receipt of the request in order to have no less than 45 days left for the CMDh phase. The timetables for Article 5 recommendations as published by the CMDh (http://www.hma.eu/293.html) have to be considered and the requests have to be forwarded by the relevant authority in advance of the next start date.

4. SUBMISSION OF REQUEST TO CMDh FROM NCA

A request for a recommendation of a classification from a NCA shall be submitted to the CMDh secretariat electronically (H-CMDhSecretariat@ema.europa.eu) prior to examination of a variation or following a valid request from a MAH. The NCA request should comply with the submission details described under section 3 above.

The CMDh is obliged to deliver a recommendation within 45 days of the receipt of the request. In order for the CMDh to have the opportunity to discuss the request at one of their monthly meetings specific submission dates should be adhered to.

5. HANDLING OF REQUEST AND COOPERATION WITH CMDv AND EMA

The NCA that received the request from a MAH or that triggered the Article 5 procedure will be the Rapporteur.
The CMDh secretariat shall without delay send the request to all CMDh members, the secretariat of CMDv and the contact point at EMA, for information. The mailbox devoted to the procedure should be used.

The procedure will be started according to the timetables published on the CMDh website (http://www.hma.eu/293.html). The Rapporteur may choose to apply a shorter timetable. However, sufficient time (at least 1 week) should be given between the circulation of the rapporteur’s proposal for classification and the discussion of the recommendation in the CMDh meeting in order to allow CMDh members, CMDv members and EMA to comment.

Where the CMDh secretariat receives notification of a request submitted to CMDv or EMA, they will circulate details of that request to CMDh members. The CMDh Rapporteur will be the same MS that has received the request by the MAH. The Rapporteur should circulate a short statement to the following mailboxes: list-h-cmd@eudra.org; list-v-cmd@eudra.org on whether the request is applicable to variations handled by the CMDh or not. In case the variation is applicable to CMDh, CMDh members will provide comments to the Rapporteur, who in turn would coordinate and forward a CMDh response to the CMDv secretariat or EMA contact point as appropriate. The CMDh response must be sent to the CMDv secretariat no later than Monday the week before the CMDv meeting where the Article 5 recommendation will be discussed. Comments to a request submitted to EMA must be sent no later than day 28 after receipt of the Article 5 request.

6. THE RAPPORTEUR

The Rapporteur shall propose a recommendation for a classification with an appropriate justification. The proposed recommendation will reflect the consideration of the facts presented to it in the request from the MAH or the NCA, but must be consistent with the Commission guidelines on categories of variations.

The proposed recommendation should include a proposal for the information to be published, for discussion at the CMDh/CMDv meeting.

The proposal for a recommendation for a classification should be sent to the following mailboxes; list-h-cmd@eudra.org; list-v-cmd@eudra.org at least 2 weeks before the Monday of the monthly CMDh meeting.

7. MEMBER STATES AND CHMP WORKING PARTIES COMMENTS

All CMDh members, CMDv members and the EMA may send comments on the Rapporteur’s proposal for a recommendation for a classification. In addition one representative from a relevant CHMP working party may also comment through the designated mailbox on behalf of that working party. The comments should be sent at least 1 (one) week before the Monday of the monthly CMDh meeting. If a CMDh or CMDv member, EMA or the relevant CHMP working party have a divergent view from the Rapporteur this should be properly justified.

If no divergent opinions are expressed during the above written procedure there may be no need for discussion at the CMDh meeting.

8. DISCUSSION AT CMDh MEETING

The EMA, members of CMDv and European Commission shall be invited to the discussion at CMDh. National experts may attend in the same manner as for referral procedures. No participation from the MAH is anticipated.
In case of divergent opinions among members of the CMDh the voting procedure in the Rules of Procedure shall apply (http://www.hma.eu/205.html).

In cases where there remains a divergent opinion between CMDv/CMDh/EMA, the recommendation, including the arguments, shall be sent to the European Commission for information.

It should be noted that CMDh is not empowered to issue a decision but to deliver a recommendation according to Article 5 of the variation Regulation. However it is anticipated that the MAH will accept and follow the recommendation of the CMDh.

After the CMDh discussion, the Rapporteur updates the recommendation to reflect the outcome of the discussion and sends the final agreed CMDh recommendation including the information for publication to the following mailboxes: list-h-cmd@eudra.org; list-v-cmd@eudra.org at day 44/45.

9. THE RECOMMENDATION

In case the Article 5 request has been submitted to a NCA by a MAH, the NCA will communicate the outcome of the CMDh procedure to the MAH by day 45.

The recommendation should include the conditions applicable for the recommended classification of the variation but not the required documentation.

There is no possibility to appeal a recommendation issued by the CMDh.

10. PUBLICATION OF RECOMMENDATIONS

Recommendations from CMDh shall be published on the CMDh website together with links to corresponding information on the CMDv and EMA websites. It should also be mentioned in the monthly CMDh press release, to ensure ease of accessibility. Information of a commercial confidential nature has to be deleted.

11. ANNEX II – CLASSIFICATION OF VARIATIONS

It is the responsibility of the Commission to initiate regular updates of the guideline referred to in Article 4 point (a) and Annex II of the variation Regulation taking into account the recommendations adopted by the CMDh, CMDv and EMA.
### ANNEX

**Flow chart for Recommendations on unforeseen variations**

<table>
<thead>
<tr>
<th>Day -25</th>
<th>MAH sends a request to NCA electronically.</th>
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<tr>
<td>Between day -25 and day 0</td>
<td>NCA (= the Rapporteur) performs validation of request and, if valid, forwards it to the CMDh. If not valid, the request will be refused and the applicant informed accordingly. The Rapporteur circulates the valid request to the CMDh secretariat (<a href="mailto:H-CMDhSecretariat@ema.europa.eu">H-CMDhSecretariat@ema.europa.eu</a>)</td>
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| Day 0 | CMDh secretariat circulates the request together with the appropriate timetable to:  
  - the Rapporteur  
  - CMDh members via the designated mailbox  
  - CMDv  
  - EMA contact point |
| Day 25 | The Rapporteur makes a proposal for the classification of the variation. The Rapporteur circulates this proposal to the following mailboxes:  
  - list-h-cmd@eudra.org  
  - list-v-cmd@eudra.org |
| Day 32 | The Rapporteur receives the comments from:  
  - CMDh members  
  - CMDv (if applicable)  
  - EMA contact point |
| Day 38/39 | Discussion at the CMDh plenary meeting. Final position on the recommendation. |
| Day 44/45 | The Rapporteur circulates the updated final recommendation via the following mailboxes:  
  - list-h-cmd@eudra.org  
  - list-v-cmd@eudra.org  
In cases where there remains a divergent opinion between CMDv / CMDh / EMA the CMDh secretariat sends the recommendation including the arguments to the European Commission for information. |
| Day 45 | The NCA (Rapporteur) communicates the outcome to the MAH. |
| | The recommendation is published on the CMDh website. |