EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Division

EMA Procedural Advice on Recommendations on unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008

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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. These guidelines shall be regularly updated, taking into account inter alia the recommendations of the EMA as well as CMDh in the case of nationally authorised products through the mutual recognition/decentralised procedure.

Article 5 of the Variation Regulation provides the basis for a marketing authorisation holder (MAH) to request EMA (in case of centralised marketing authorisations), the Reference Member State (RMS) (in case of Mutual Recognition or Decentralised 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 the submission of the variation. This recommendation shall be consistent with the Commission guideline and be delivered within 45 days following the receipt of the request. Cooperation between the CMDh and the EMA is envisaged by the legislation. The 45 days may be extended by an additional 25 days where the EMA deems it necessary to consult with the CMDh. The recommendations shall be published once adopted.

It should be noted that such recommendations of the EMA cannot be considered a pre-assessment of the future variation application as they concern the classification of that variation only. In addition, it should be noted that the recommendation relates to the situation described in the specific request.

2. Scope

This guidance covers medicinal products for Human use that have been authorised through the centralised procedure. The request shall apply only to variations whose classification is not provided for in the a.m. annex or guideline (i.e. unforeseen variations). The EMA cannot "reclassify" a variation already listed in the annex/guideline.

3. Submission of request

The request for a recommendation for classification from the MAH for a centrally authorised product shall be submitted to the EMA as a ticket via the EMA Service Desk, selecting the tab "Business Services", category "Human Regulatory". The subcategory to be selected is "Post-authorisation - Human", followed by the sub-option: "Article 5 procedure request". To facilitate the retrieval of the requests from EMA, MAHs are requested to use the following standardised wording in the title of the ticket:

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

The application form for Article 5 requests published on the EMA website (Article 5 procedure: Regulatory and procedural guidance | European Medicines Agency (europa.eu)) should be used. It is

important that the request includes a detailed description of the product and a detailed description of the proposed variation to the terms of the marketing authorisation, as the time available to request additional information, should this be necessary, is very limited. The request should include a justification of why the variation is considered to be unclassified in the variation guideline, together with a proposed classification.

If the EMA 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 a type IB by default according to the classification guideline, the EMA will inform the MAH.

If the EMA considers the variation to be unclassified, the request will be shared with the CMDh 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. A joint EMA/CMDh recommendation will be delivered to the MAH. There will be no possibility for a clock-stop.

Prior to submission of the request, MAHs are encouraged to inform us in advance about their intention to submit such a request for recommendation by raising a ticket via EMA Service Desk, selecting the tab "Business Services", category "Human Regulatory". The subcategory to be selected is "Post-authorisation - Human", followed by the sub-option: "Article 5 procedure request".

If you do not have an EMA Account, you may create one via the EMA Account Management portal. For further information or guidance about how to create an EMA Account reference the guidance "Create an EMA Account".

4. Handling of request by the EMA PM

Upon receipt of the request, the PM[1] in consultation with the Rapporteur, if necessary, and the EMA Variations Classification Group (CLAG) will propose a recommendation for classification with an appropriate justification. The proposed recommendation will reflect the consideration of the facts presented in the request from the MAH, but must be consistent with the Commission guideline on categorisation of variations.

If the EMA 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 a type IB by default according to the classification guideline, the EMA will inform the MAH.

If the variation is considered unclassified, the PM will send the proposal for a recommendation to all CMDh members and the representative of the relevant CHMP working party (if deemed necessary) at least 2 weeks before the Monday of the monthly CHMP/CMDh meetings.

5. Member States and CHMP working parties consultation

The Agency and CMDh shall cooperate to ensure the coherence of the recommendations. CMDh members may send comments on the EMA proposal for a recommendation for classification. In addition, the representative from the relevant CHMP working party may also comment on behalf of that working party. The comments should be sent at least one week before the Monday of the monthly

[1] PM = Procedure Manager.

CHMP/CMDh meetings. If a CMDh member or the relevant CHMP working party have a divergent view from the EMA, 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.

6. Discussion with the CMDh Group

If divergent opinions are expressed during the above written procedure, there may be a need for discussion at the CMDh meeting.

A representative of the EMA CLAG and/or the PM shall attend the discussion at the CMDh meeting. No participation from the MAH is anticipated.

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

It should be noted that the EMA 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 EMA.

7. The recommendation

By Day 45, the PM will provide the recommendation to the MAH and the CMDh members. The 45 days may be extended by an additional 25 days where the EMA deems it necessary to consult with the CMDh.

The recommendation may 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 EMA.

8. Publication of recommendations

Recommendations from the EMA will be published together with the CMDh recommendations on the CMDh website (Heads of Medicines Agencies: Art 5 recommendations (hma.eu)). This link is also included on the EMA website. Information of a commercial confidential nature are deleted prior to publication.

Annex I: Process Overview

Annex I

Process overview for recommendation on unforeseen variations for centrally authorised products

	Pre-submission
	MAH gives advance notification of a forthcoming request by raising a ticket via EMA Service Desk, selecting the tab "Business Services", category "Human Regulatory". The subcategory to be selected is "Post-authorisation - Human", followed by the sub-option: "Article 5 procedure request".
	Submission of the request
	MAH raises a ticket via the EMA Service Desk, selecting the tab "Business Services", category "Human Regulatory". The subcategory to be selected is "Post-authorisation - Human", followed by the sub-option: "Article 5 procedure request".
	Handling of request by the EMA PM
	PM prepares recommendation in liaison with Rapporteur, if necessary, and the EMA Variations Classification Group. If the variation is considered unclassified, PM circulates the proposed recommendation for consultation to CMDh and to the relevant CHMP Working Party representatives (if deemed necessary). If not, PM informs the MAH.
	Member States and CHMP working parties consultation
	CMDh and CHMP working parties comments on the proposed recommendation to be sent to the EMA PM.
	PM compiles comments and revises the draft proposal, if needed. PM circulates the proposal for the final recommendation.
	Discussion with the CMDh Group (if needed)
	If needed, discussion of the divergent position(s) at the CMDh meeting and finalisation of EMA recommendation.
	In cases where there remains a divergent opinion between EMA / CMDh, the recommendation, including the arguments, shall be sent to the European Commission for information.
	Transmission of the Recommendation
	PM concludes the procedure and sends the final recommendation to the MAH and to the CMDh.
	Publication
Within 1 week after adoption of the recommendation	CMDh update the Recommendation for classification of unforeseen variations according to article 5 of Commission Regulation (EC) 1234/2008 on its website.