European Medicines Agency

London, 27 March 2009
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EMEA Procedural Advice on Recommendations on unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008

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 EMEA as well as CMD(h) and CMD(v) 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) or a competent authority of a Member State (NCA) to request CMD(h)/CMD(v) for nationally authorised products or EMEA for centrally authorised products to deliver a recommendation on classification of an unforeseen 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 two coordination groups and the EMEA is envisaged by the legislation. The recommendations shall be published once adopted.

It should be noted that such recommendations of the EMEA 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 and Veterinary 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 EMEA cannot "reclassify" a variation already listed in the annex/guideline.

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3. Submission of request

The request for a recommendation for classification from the MAH for a centrally authorised product shall be submitted to the EMEA electronically to a dedicated mailbox (art5request@emea.europa.eu). To facilitate the retrieval of the requests from EMEA, MAHs are requested to use the following standardised wording in the subject field of the email:

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

Prior to submission of the request, MAHs are encouraged to contact in advance their PTX to inform him/her about their intention to submit such a request for recommendation. The application form for Article 5 requests published on the EMEA website (http://www.emea.europa.eu/htms/human/raguidelines/intro.htm) 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. Any request, which is considered inadequately justified or covered by a variation which is already classified shall be rejected.

The EMEA will deliver a recommendation within 45 days of the receipt of the request. In order for the EMEA to have the opportunity to discuss the request in margins of the CMD(h)/CHMP or CMD(v)/CVMP monthly meetings, specific recommended submission dates as published on EMEA website should be taken into account. There will be no possibility for a clock-stop.

4. Handling of request by the EMEA PTX

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

The PTX will send the proposal for a recommendation to all CMD(h)/CMD(v) members, the representative of the relevant CXMP working party, and to the European Commission at least 2 weeks (approx. Day 21 of the EMEA procedure) before the Monday of the monthly CXMP/CMD(h,v) meetings, via the designated mailbox.

5. Member States, CXMP working parties and European Commission consultation

CMD(h) members, CMD(v) members as well as the European Commission may send comments on the EMEA proposal for a recommendation for classification to the designated mailbox copying the PTX. In addition the representative from the relevant CXMP working party may also comment on behalf of that working party. The comments should be sent at least 1 (one) week before the Monday of the monthly CXMP/CMD(h,v) meetings. If a CMD(h) or CMD(v) member or the relevant CXMP working party have a divergent view from the EMEA this should be properly justified.

[1] PTX = Product Team Leader / Product Team Member (human) or Project Manager (vet).

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

6. Discussion with the CMD Group

If divergent opinions are expressed during the above written procedure there may be a need for discussion at the CMD(h)/CMD(v) meetings.
A representative of the EMEA Variations Classification Group and/or the PTX shall attend the discussion at the CMD(h) and the CMD(v) meetings (approx. Day 35 of the procedure). No participation from the MAH is anticipated.

In cases where there remains a divergent opinion between EMEA / CMD(h) / CMD(v) the recommendation, including the arguments, shall be sent to the European Commission for information.

It should be noted that the EMEA 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 EMEA.

7. The recommendation

By Day 45, the PTX will provide the recommendation to the MAH, the Rapporteur, the CMD(h)/CMD(v) members and the European Commission.

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 EMEA.

8. Publication of recommendations

Recommendations from the EMEA shall be published on the EMEA website together with links to corresponding information on the CMD(h,v) websites. Information of a commercial confidential nature has to be deleted.

9. Annex II – classification of variations

The Commission will 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 CMD(h), CMD(v) and the EMEA.

Annex I : Process Overview
Annex II: Timetable

Annex I

Process Overview for Recommendation on unforeseen variations for centrally authorised products

	Pre-submission
	MAH gives advance notification of a forthcoming request.
	Submission of the request
Day 0	MAH sends a request to the dedicated mailbox.
Day 1	EMEA receives the classification request.
	Handling of request by the EMEA PTX
By Day 21	PTX prepares recommendation in liaison with Rapporteur and/or the EMEA Variations Classification Group, if necessary. PTX. circulates the proposed recommendation for consultation to EC, CMD(h,v) and relevant Working Party (representatives).
	Member States, CXMP working parties and European Commission consultation
By Day 28	CMD(h) , CMD(v), CXMP working parties and EC comments on the proposed recommendation to be sent to the EMEA PTX via the designated mailbox.
By Day 31	PTX compiles comments and revises the draft proposal, if needed. PTX circulates the proposal for the final recommendation.
	Discussion with the CMD Group (if needed)
By Day 35-37 (By Day 38-39 for Vet.)	If needed, discussion of the divergent position(s) at the CMD(h) or CMD (v) meeting and finalisation of EMEA recommendation.
	In cases where there remains a divergent opinion between EMEA / CMD(h) / CMD(v) the recommendation, including the arguments, shall be sent to the European Commission for information.
	Transmission of the Recommendation
By Day 45	PTX concludes the procedure and sends the final recommendation to the MAH and to the Rapporteur, CMD(h,v) and EC.
	Publication
Within 1 week after Day 45	PTX prepares the recommendation for publication (with deletion of the confidential information in consultation with the MAH). EMEA publishes the recommendation on its website.

These days are approximate deadlines and might change slightly depending on which day of CMD(h) or CMD(v) meeting, discussions will take place.

Annex II

Timetable

- For requests for medicinal products for Human use

Submission Date	EMEA Draft Recommendation by	Comments by	Discussions EMEA + CMD(h)	Final recommendation by
20/04/2009	11/05/2009	18/05/2009	26/05/2009	04/06/2009
18/05/2009	08/06/2009	15/06/2009	23/06/2009	02/07/2009
15/06/2009	06/07/2009	13/07/2009	21/07/2009	30/07/2009
N/A	**N/A**	**N/A**	**N/A**	**N/A**
17/08/2009	07/09/2009	14/09/2009	22/09/2009	01/10/2009
14/09/2009	05/10/2009	12/10/2009	20/10/2009	29/10/2009
12/10/2009	02/11/2009	09/11/2009	17/11/2009	26/11/2009
09/11/2009	30/11/2009	07/12/2009	15/12/2009	24/12/2009
14/12/2009	04/01/2010	11/01/2010	19/01/2010	28/01/2010
11/01/2010	01/02/2010	08/02/2010	16/02/2010	25/02/2010
08/02/2010	01/03/2010	08/03/2010	16/03/2010	25/03/2010
15/03/2010	05/04/2010	12/04/2010	20/04/2010	29/04/2010
12/04/2010	03/05/2010	10/05/2010	18/05/2010	27/05/2010
17/05/2010	07/06/2010	14/06/2010	22/06/2010	01/07/2010
14/06/2010	05/07/2010	12/07/2010	20/07/2010	29/07/2010
N/A	**N/A**	**N/A**	**N/A**	**N/A**
16/08/2010	06/09/2010	13/09/2010	21/09/2010	30/09/2010
13/09/2010	04/10/2010	11/10/2010	19/10/2010	28/10/2010
11/10/2010	01/11/2010	08/11/2010	16/11/2010	25/11/2010
08/11/2010	29/11/2010	06/12/2010	14/12/2010	23/12/2010
13/12/2010	03/01/2011	10/01/2011	18/01/2011	27/01/2011

- For requests for medicinal products for Veterinary use

Submission Date	EMEA Draft Recommendation by	Comments by	Discussions EMEA + CMD(v)	Final recommendation by
13/05/2009	03/06/2009	10/06/2009	18/06/2009	26/06/2009
10/06/2009	01/07/2009	08/07/2009	16/07/2009	24/07/2009
N/A	**N/A**	**N/A**	**N/A**	**N/A**
12/08/2009	02/09/2009	09/09/2009	17/09/2009	25/09/2009
09/09/2009	30/09/2009	07/10/2009	15/10/2009	23/10/2009
07/10/2009	28/10/2009	04/11/2009	12/11/2009	20/11/2009
04/11/2009	25/11/2009	02/12/2009	10/12/2009	18/12/2009
09/12/2009	30/12/2009	06/01/2010	14/01/2010	22/01/2010
06/01/2010	27/01/2010	03/02/2010	11/02/2010	19/02/2010
03/02/2010	24/02/2010	03/03/2010	11/03/2010	19/03/2010
10/03/2010	31/03/2010	07/04/2010	15/04/2010	23/04/2010
14/04/2010	05/05/2010	12/05/2010	20/05/2010	28/05/2010
12/05/2010	02/06/2010	09/06/2010	17/06/2010	25/06/2010
09/06/2010	30/06/2010	07/07/2010	15/07/2010	23/07/2010
N/A	**N/A**	**N/A**	**N/A**	**N/A**
11/08/2010	01/09/2010	08/09/2010	16/09/2010	24/09/2010
08/09/2010	29/09/2010	06/10/2010	14/10/2010	22/10/2010
06/10/2010	27/10/2010	03/11/2010	11/11/2010	19/11/2010
03/11/2010	24/11/2010	01/12/2010	09/12/2010	17/12/2010
08/12/2010	29/12/2010	05/01/2011	13/01/2011	21/01/2011