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(Acts whose publication is obligatory)

COMMISSION REGULATION (EC) No 1084/2003

of 3 June 2003

concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use ([1]), and in particular Article 35(1) thereof,

Having regard to Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products ([2]), and in particular Article 39(1) thereof,

Whereas:

(1) In the light of practical experience in the application of Commission Regulation (EC) No 541/95 of 10 March 1995 concerning the examination of variations to the terms of a marketing authorisation granted by a competent authority of a Member State ([3]), as amended by Regulation (EC) No 1146/98 ([4]), it is appropriate to simplify the procedure for varying the terms of a marketing authorisation.

(2) Some of the procedures laid down in Regulation (EC) No 541/95 should therefore be adjusted but without departing from the general principles on which those procedures are based.

(3) In consequence of the adoption of Directives 2001/82/EC and 2001/83/EC, which codified Community legislation in the field of veterinary medicinal products and medicinal products for human use respectively, references to provisions of that legislation should be updated.

(4) This Regulation should continue to apply also to the examination of applications for variation of the terms of a marketing authorisation granted under Council Directive 87/22/EEC ([5]) repealed by Directive 93/41/EEC ([6]).

(5) It is appropriate to provide for a simplified and rapid notification procedure to enable the introduction of certain minor changes, which do not affect the approved quality, safety or efficacy of the product, without prior evaluation by the reference Member State. However, for other types of minor variation evaluation of the submitted documentation by the reference Member State should still be required.

(6) In cases where the evaluation procedure is maintained the reference Member State should evaluate the file on behalf of all Member States concerned in order to avoid duplication of work.

(7) The various types of minor variation should be classified according to the conditions to be fulfilled in order to determine the procedure to follow; it is particularly necessary to give a precise definition of the type of minor variation for which no prior evaluation is needed.

(8) It is necessary to clarify the definition of an 'extension' to a marketing authorisation, although it should still be possible to submit a separate, full application for a marketing authorisation for a medicinal product which has already been authorised, but under a different name and with a different summary of product characteristics.

([1]) OJ L 311, 28.11.2001, p. 67.
([2]) OJ L 311, 28.11.2001, p. 1.
([3]) OJ L 55, 11.3.1995, p. 7.
([4]) OJ L 159, 3.6.1998, p. 31.
([5]) OJ L 15, 17.1.1987, p. 38.
([6]) OJ L 214, 24.8.1993, p. 40.

(9) It is appropriate to allow national authorities of the reference Member States to reduce the evaluation period in urgent cases or to extend it in the case of a major variation entailing important changes.

(10) The time-frame for the procedure to be followed where the competent authority imposes urgent safety restrictions should be clarified.

(11) Further clarification should be introduced as regards revision of the summary of product characteristics, labelling and package leaflet/insert; nevertheless the procedures laid down in this Regulation should not apply to changes to the labelling or to the package leaflet/insert which are not consequential to changes to the summary of product characteristics.

(12) For the sake of clarity, it is appropriate to replace Regulation (EC) No 541/95.

(13) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Medicinal Products for Human Use and the Standing Committee on Veterinary Medicinal Products,

HAS ADOPTED THIS REGULATION:

Article 1

Subject matter

This Regulation lays down the procedure for the examination of notifications of and applications for variations to the terms of a marketing authorisation of medicinal products which have been considered within the scope of application of Directive 87/22/EEC, of medicinal products having benefited from the procedures of mutual recognition set out in Articles 17, 18 and 28(4) of Directive 2001/83/EC or Articles 21, 22 and 32(4) of Directive 2001/82/EC, and medicinal products for which there has been a referral to the procedures set out in Articles 32, 33 and 34 of Directive 2001/83/EC or Articles 36, 37 and 38 of Directive 2001/82/EC.

Article 2

Scope

This Regulation shall not apply to:

(a) extensions of marketing authorisations which fulfil the conditions set out in Annex II to this Regulation;

(b) transfers of a marketing authorisation to a new holder;

(c) changes to the maximum residue limit as defined in Article 1(1)(b) of Council Regulation (EEC) No 2377/90 [1].

The extensions referred to in point (a) of the first paragraph shall be examined in accordance with the procedure referred to in Article 17 of Directive 2001/83/EC and in Article 21 of Directive 2001/82/EC.

Article 3

Definitions

For the purposes of this Regulation, the following definitions shall apply:

1. 'Variation to the terms of a marketing authorisation' means:

   (a) for medicinal products for human use: an amendment to the contents of the documents referred to in Articles 8 to 12 of Directive 2001/83/EC;

   (b) for veterinary medicinal products: an amendment to the contents of the documents referred to in Articles 12 to 15 of Directive 2001/82/EC.

2. A 'minor variation' of Type IA or Type IB means a variation listed in Annex I which fulfils the conditions set out therein.

3. A 'major variation' of Type II means a variation which cannot be deemed to be a minor variation or an extension of the marketing authorisation.

4. 'Reference Member State' means the Member State which, for a given medicinal product, has produced the assessment report which served as the basis for the procedures referred to in Article 1 or alternatively the Member State chosen in this respect by the marketing authorisation holder with a view to application of this Regulation.

5. 'Urgent safety restriction' means an interim change to the product information concerning particularly one or more of the following items in the summary of product characteristics, the indications, posology, contraindications, warnings, target species and withdrawal periods, due to new information having a bearing on the safe use of the medicinal product.

[1] OJ L 224, 18.8.1990, p. 1.

Article 4

Notification procedure for minor variations type IA

1. With regard to minor variations of type IA, the marketing authorisation holder (hereinafter referred to as the holder) shall submit simultaneously to the competent authorities of the Member States where the medicinal product has been authorised a notification accompanied by:

(a) all necessary documents including those amended as a result of the variation;

(b) a list of the Member States concerned and an indication of the reference Member State for the medicinal product under consideration;

(c) the relevant fees provided for in the applicable national rules in the Member States concerned.

2. A notification shall only concern one type IA variation. Where several type IA variations are to be made to the terms of a single marketing authorisation, a separate notification shall be submitted in respect of each type IA variation sought; each such notification shall also contain a reference to the other notifications.

3. By way of derogation from paragraph 2, where a type IA variation to the marketing authorisation leads to consequential type IA variations, a single notification may cover all such variations. The single notification shall contain a description of the relation between these consequential type IA variations.

4. Where a variation requires consequential revision of the summary of product characteristics, labelling and package leaflet/insert, this is considered as part of the variation.

5. If the notification fulfils the requirements set out in paragraphs 1 to 4, the competent authority of the reference Member State shall within 14 days following receipt of the notification acknowledge the validity of this notification and shall inform the other competent authorities concerned and the holder accordingly.

Each competent authority concerned shall, where necessary, update the marketing authorisation, which has been granted pursuant to Article 6 of Directive 2001/83/EC or Article 5 of Directive 2001/82/EC.

Article 5

Notification procedure for minor variations type IB

1. With regard to minor variations of type IB, the holder shall submit simultaneously to the competent authorities of the Member States where the medicinal product has been authorised, the notification accompanied by:

(a) all necessary documents, including those amended as a result of the variation;

(b) a list of Member States concerned and an indication of the reference Member State for the medicinal product under consideration;

(c) the relevant fees provided for in the applicable national rules in the Member States concerned.

2. A notification shall only concern one type IB variation. Where several type IB variations are to be made to the terms of a single marketing authorisation, a separate notification shall be submitted in respect of each type IB variation sought; each such notification shall also contain a reference to the other notifications.

3. By way of derogation from paragraph 2, where a type IB variation to the marketing authorisation leads to consequential type IA or type IB variations, a single type IB notification may cover all such consequential variations. The single notification shall contain a description of the relation between these consequential type I variations.

4. Where a variation requires consequential revision of the summary of product characteristics, labelling and package leaflet/insert, this is considered as part of the variation.

5. If the notification fulfils the requirements set out in paragraphs 1 to 4, the competent authority of the reference Member State shall acknowledge receipt of a valid notification and shall start the procedure set out in paragraphs 6 to 11.

6. If, within 30 days of the date of the acknowledgement of receipt of a valid notification the competent authority of the reference Member State has not sent the holder its opinion provided for in paragraph 8, the notified variation shall be deemed to have been accepted by all competent authorities of the Member States concerned.

The competent authority of the reference Member State shall inform the other competent authorities of the Member States concerned to this effect.

7. Each competent authority concerned shall, where necessary, update the marketing authorisation which has been granted pursuant to Article 6 of Directive 2001/83/EC or Article 5 of Directive 2001/82/EC.

8. Where the competent authority of the reference Member State is of the opinion that the notification cannot be accepted, it shall, within the period referred to in paragraph 6, inform the holder who has submitted the notification, stating the grounds on which its opinion is based.

9. Within 30 days of receipt of the opinion referred to in paragraph 8, the holder may amend the notification in order to take due account of the grounds set out in the opinion. In that case the provisions of paragraphs 6 and 7 shall apply to the amended notification.

10. If the holder does not amend the notification, the notification shall be deemed to have been rejected. The competent authority of the reference Member State shall forthwith inform the holder and the other competent authorities concerned accordingly.

11. Within 10 days of providing the information referred to in paragraph 10, competent authorities of the Member States concerned or the holder may refer the matter to the Agency for application of Article 35(2) of Directive 2001/83/EC or Article 39(2) of Directive 2001/82/EC.

Article 6

Approval procedure for major variations type II

1. With regard to major variations of type II, the holder shall submit simultaneously to the competent authorities of the Member States where the medicinal product has been authorised an application accompanied by:

(a) the relevant particulars and supporting documents referred to in Articles 8 to 12 of Directive 2001/83/EC or Articles 12 to 15 of Directive 2001/82/EC;

(b) the supporting data relating to the variation applied for;

(c) all documents amended as a result of the application;

(d) an addendum to or update of existing expert reports/overviews/summaries to take account of the variation applied for;

(e) a list of the Member States concerned by the application for the major variation type II and an indication of the reference Member State for the medicinal product under consideration;

(f) the relevant fees provided for in the applicable national rules in the Member States concerned.

2. An application shall only concern one type II variation. Where several type II variations are to be made to a single marketing authorisation, a separate application shall be submitted in respect of each variation sought; each such application shall contain also a reference to the other applications.

3. By way of derogation from paragraph 2, where a type II variation leads to consequential variations, a single application may cover all such variations. The single application shall contain a description of the relation between these consequential variations.

4. Where a variation requires consequential revision of the summary of product characteristics, labelling and package leaflet/insert, this is considered as part of the variation.

5. If the application fulfils the requirements set out in paragraphs 1 to 4, the competent authorities of the Member States concerned shall forthwith notify the competent authority of the reference Member States about the receipt of the valid application.

6. The competent authority of the reference Member State shall inform the other competent authorities of the Member States concerned and the holder of the date of the start of the procedure set out in paragraphs 7 to 13.

7. Within 60 days from the start of the procedure, the competent authority of the reference Member State shall prepare an assessment report and a draft decision which shall be addressed to the other competent authorities concerned.

This period may be reduced having regard to the urgency of the matter particularly for safety issues.

This period may be extended to 90 days for variations concerning changes to or addition of the therapeutic indications.

This period shall be extended to 90 days for variations concerning a change to or addition of a non-food producing target species.

8. Within the periods laid down in paragraph 7, the competent authority of the reference Member State may request the holder to provide supplementary information within a time limit set by that competent authority. The procedure shall be suspended until such time as the supplementary information has been provided. In this case the periods laid down in paragraph 7 may be extended for a further period to be determined by the competent authority of the reference Member State.

The competent authority of the reference Member State shall inform the other competent authorities concerned.

9. Within 30 days following receipt of the draft decision and the assessment report, the other competent authorities of the Member States concerned shall recognise the draft decision and inform the competent authority of the reference Member State to this effect.

The competent authority of the reference Member State shall close the procedure and shall inform the other competent authorities concerned and the holder accordingly.

10. Each competent authority concerned shall, where necessary, amend the marketing authorisation concerned which has been granted pursuant to Article 6 of Directive 2001/83/EC or Article 5 of Directive 2001/82/EC in conformity with the draft decision referred to paragraph 9.

11. Decisions concerning variations related to safety issues shall be implemented within a timeframe as agreed between the competent authority of the reference Member State and the holder in consultation with the other competent authorities of the Member States concerned.

12. If within the period laid down in paragraph 9, mutual recognition by one or more of the competent authorities of the draft decision of the competent authority of the reference Member State is not possible, the procedure referred to in Article 35(2) of Directive 2001/83/EC or Article 39(2) of Directive 2001/82/EC shall apply.

13. Within 10 days of the end of the procedure mentioned in paragraph 8 and in case where the competent authorities of the Member States concerned by the application are of the opinion that the variation cannot be accepted, the holder may refer the matter to the Agency for application of Article 35(2) of Directive 2001/83/EC or Article 39(2) of Directive 2001/82/EC.

Article 7

Human influenza vaccines

1. With regard to variations to the terms of the marketing authorisations for human influenza vaccines, the procedure set out in paragraphs 2 to 5 shall apply.

2. Within 30 days following the date of the start of the procedure, the competent authority of the reference Member State shall prepare an assessment report on the basis of the quality documents referred to in Module 3 of Annex I to Directive 2001/83/EC and a draft decision which shall be addressed to the other competent authorities concerned.

3. Within the period laid down in paragraph 2, the competent authority of the reference Member State may request the holder to provide supplementary information. It shall inform the other competent authorities of the Member States concerned.

4. Within 12 days of receipt of the draft decision and the assessment report, the other competent authorities of the Member States concerned shall recognise the draft decision and inform the competent authority of the reference Member State to this effect.

5. The clinical data and, where appropriate, data concerning the stability of the medicinal product, shall be addressed by the holder to the competent authority of the reference Member State and to the other competent authorities of the Member States concerned, at the latest 12 days following the end of the time limit laid down in paragraph 4.

The competent authority of the reference Member State shall evaluate these data and draft a final decision within 7 days of the receipt of the data. The other competent authorities concerned shall recognise the final draft decision and, within 7 days of the receipt of the draft final decision, adopt a decision in conformity with the final draft decision.

6. If, in the course of the procedure laid down in paragraphs 2 to 5, a competent authority raises a question of public health which they consider poses an obstacle to the mutual recognition of the decision to be taken, the procedure referred to in Article 35(2) of Directive 2001/83/EC shall apply.

Article 8

Pandemic situation with respect to human diseases

In case of a pandemic situation with respect to the human influenza virus, duly recognised by the World Health Organisation or by the Community in the framework of Decision No 2119/98/EC of the European Parliament and of the Council [1], competent authorities may exceptionally and temporarily consider the variation to the terms of the marketing authorisation for human influenza vaccines to be accepted after an application has been received and before the end of the procedure laid down in Article 7. Nevertheless, complete clinical safety and efficacy data can be submitted during this procedure.

In case of a pandemic situation with respect to human diseases other than the human influenza virus, the first paragraph and Article 7 may be applied *mutatis mutandis*.

Article 9

Urgent safety restrictions

1. If the holder, in the event of risk to public or animal health, takes urgent safety restrictions, he/she shall forthwith inform the competent authorities thereof. If the competent authorities have not raised any objections within 24 hours following receipt of that information, the urgent safety restrictions shall be deemed to have been accepted.

The urgent safety restriction shall be implemented within a timeframe, as agreed with the competent authorities.

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[1] OJ L 268, 3.10.1998, p. 1.