COMMISSION REGULATION (EC) No 1085/2003

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 falling within the scope of Council Regulation (EEC) No 2309/93

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products [1], as amended by Commission Regulation (EC) No 649/98 [2] and in particular Articles 15(4) and 37(4) thereof,

Whereas:

(1) In the light of practical experience in the application of Commission Regulation (EC) No 542/95 of 10 March 1995 concerning the examination of variations to the terms of a marketing authorisation falling within the scope of Council Regulation (EEC) No 2309/93 [3], as amended by Regulation (EC) No 1069/98 [4], it is appropriate to simplify the procedure for varying the terms of a marketing authorisation.

(2) Due to the technical adaptation of Annex I to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code related to medicinal products for human use [5], it is appropriate to introduce in this Regulation provisions on variations related to plasma master files and vaccine antigen master files.

(3) Some of the procedures laid down in Regulation (EC) No 542/95 should therefore be adjusted but without departing from the general principles on which those procedures are based.

(4) 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 European Agency for the evaluation of medicinal products (hereinafter referred to as 'the Agency'). However, for other types of minor variations evaluation of the submitted documentation by the Agency should still be required.

(5) The various types of minor variation should be classified 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.

(6) 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 marketing authorisation for a medicinal product which has already been authorised but under a different name and with summary of product characteristics.

(7) It is appropriate to allow the Agency to reduce the evaluation period in urgent cases or to extend it in the case of a major variation entailing important changes.

(8) It is necessary to simplify the administrative procedures for minor variations regarding the updating of marketing authorisations by allowing the Commission to group these updates every six months in one single decision.

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

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(1) OJ L 214, 24. 8.1993, p. 1.
(2) OJ L 88, 24.3.1998, p. 7.
(3) OJ L 55, 11.3.1995, p. 15.
(4) OJ L 153, 27.5.1998, p. 11.
(5) OJ L 311, 28.11.2001, p. 67.

(10) Further clarification should be introduced as regards revision of the labelling, the package leaflet/insert or the summary of product characteristics; 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.

(11) For the sake of clarity, it is appropriate to replace Regulation (EC) No 542/95.

(12) 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

1. This Regulation lays down the procedure for the examination of applications for variations to the terms of a marketing authorisation granted in accordance with Regulation (EEC) No 2309/93.

2. This Regulation also applies for the examination of applications of variations to the terms of a plasma master file and of a vaccine antigen master file, as defined in Annex I of Directive 2001/83/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 extension referred to in point (a) of the first paragraph shall be evaluated in accordance with the procedures set out in Articles 6 to 10 and Articles 28 to 32 of Regulation (EEC) No 2309/93 for medicinal products for human use and veterinary medicinal products, respectively.

Article 3

Definitions

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

1. 'variation to the terms of a marketing authorisation' means an amendment to the contents of the documents referred to in Article 6(1) and (2) or Article 28(1) and (2) of Regulation (EEC) No 2309/93, such as they existed at the moment the decision on the marketing authorisation was adopted, in accordance with Article 10 or Article 32 of that Regulation or after approval of any previous variations;

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 that cannot be deemed to be a minor variation or an extension of the marketing authorisation;

4. 'urgent safety restriction' means an interim change, due to new information having a bearing on the safe use of the medicinal product, 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.

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 to the Agency a notification accompanied by

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

(b) the relevant fee provided for in Council Regulation (EC) No 297/95 [2].

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 consequential 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.

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

[2] OJ L 35, 15.2.1995, p. 1.

5. If the notification fulfils the requirements set out in paragraphs 1 to 4, the Agency shall, within 14 days following receipt of the notification, acknowledge the validity of this notification and shall inform the holder accordingly.

The Agency shall, where appropriate, disseminate the amended documents referred to in Article 3(1).

The Commission shall, where necessary and based on a proposal prepared by the Agency, update every six months the marketing authorisation which has been granted pursuant to Article 10 or Article 32 of Regulation (EEC) No 2309/93.

The updated marketing authorisation shall be notified by the Commission to the holder.

The Community Register of Medicinal Products provided for in Articles 12 and 34 of Regulation (EEC) No 2309/93 shall be updated as necessary.

Article 5

Notification procedure for minor variations type IB

1. With regard to minor variations of type IB, the holder shall submit to the Agency a notification accompanied by:

(a) all necessary documents demonstrating that the conditions laid down in Annex I for the requested variation are met, including all documents amended as a result of the application;

(b) the relevant fee provided for in Regulation (EC) No 297/95.

2. A notification shall only concern one type IB variation. Where several type IB variations are to be made to 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 application 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 Agency shall acknowledge receipt of a valid notification and shall start the procedure set out in paragraphs 6 to 10.

6. If, within 30 days of the date of the acknowledgement of receipt of a valid notification the Agency has not sent the holder its opinion provided for in paragraph 8, the variation applied for shall be deemed to have been accepted.

The Agency shall inform the holder accordingly.

The Agency shall, where appropriate, disseminate the amended documents referred to in Article 3(1).

7. The Commission shall, where necessary and based on a proposal prepared by the Agency, update every six months the marketing authorisation which has been granted pursuant to Article 10 or Article 32 of Regulation (EEC) No 2309/93.

The updated marketing authorisation shall be notified by the Commission to the holder.

The Community Register of Medicinal Products provided for in Articles 12 and 34 of Regulation (EEC) No 2309/93 shall be updated as necessary.

8. Where the Agency 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 Agency shall inform the holder accordingly.

Article 6

Approval procedure for major variations type II

1. With regard to major variations of type II, the holder shall submit to the Agency an application accompanied by:

(a) the relevant particulars and supporting documents referred to in Article 3(1);

(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) the relevant fee provided for in Regulation (EC) No 297/95.

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 also contain a reference to the other applications.

3. By way of derogation to paragraph 2, where a type II variation leads to consequential variations, a single application may cover all such consequential 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 Agency shall acknowledge receipt of a valid application and shall start the procedure set out in paragraphs 6 to 11.

6. The competent Committee of the Agency shall give its opinion within 60 days from the start of the procedure.

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

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

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

7. Within the periods laid down in paragraph 6, the competent Committee may send the holder a request for supplementary information within a time limit set by that Committee. The procedure shall be suspended until such time as the supplementary information has been provided. In this case the periods laid down in paragraph 6 may be extended for a further period to be determined by that Committee.

8. Where the competent Committee delivers an opinion, the Agency shall inform the holder and the Commission forthwith and shall send to the Commission, where appropriate, the amendments to be made to the terms of the marketing authorisation accompanied by the documents set out in Article 9(3) and 31(3) of Regulation (EEC) No 2309/93.

9. Article 9(1) and (2) or Article 31(1) and (2) of Regulation (EEC) No 2309/93 shall apply to the opinion adopted by the competent Committee.

10. The Commission shall, where necessary and based on the proposal prepared by the Agency, amend the marketing authorisation that has been granted pursuant to Article 10 or Article 32 of the Regulation (EEC) No 2309/93.

Decisions concerning variations related to safety issues shall be implemented within a time-frame as agreed between the Commission and the holder.

The amended marketing authorisation shall be notified by the Commission to the holder.

11. The Community Register of Medicinal Products provided for in Articles 12 and 34 of Regulation (EEC) No 2309/93 shall be updated as necessary.

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 6 shall apply.

2. Within 45 days following the date of the receipt of a valid application, the Agency shall give its opinion on the quality documents referred to in Module 3 of Annex I to Directive 2001/83/EC, based on an assessment report.

3. Within the period laid down in paragraph 2, the Agency may request the holder to provide supplementary information.

4. The Agency shall address forthwith its opinion to the Commission.

The Commission shall adopt a decision updating the marketing authorisation that has been granted pursuant to Article 10 of the Regulation (EEC) No 2309/93.

This decision shall be implemented on condition that the final opinion of the Agency as provided for in paragraph 5 is favourable.

The updated marketing authorisation shall be notified by the Commission to the holder.

5. The clinical data and, where appropriate, those concerning the stability of the medicinal product shall be addressed by the holder to the Agency at the latest 12 days following the end of the time limit laid down in paragraph 2.

The Agency shall evaluate these data and shall give its final opinion within 10 days of the reception of the data referred to in the first subparagraph. The Agency shall address the final opinion to the Commission and to the marketing authorisation holder within the three following days.

6. The Community Register of Medicinal Products provided for in Article 12 of Regulation (EEC) No 2309/93 shall be updated as necessary.

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 2119/98/EC of the European Parliament and of the Council [1], the Commission may exceptionally and temporarily consider the variation to the terms of the market 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 Agency thereof. If the Agency has not raised any objections within 24 hours following receipt of that information, the urgent safety restrictions shall be deemed as accepted.

The urgent safety restrictions shall be implemented within a time-frame, as agreed with the Agency.

The corresponding variation application reflecting the urgent safety restrictions shall be submitted immediately and in any case no later than 15 days after the initiation of the urgent safety restrictions to the Agency for the application of the procedures set out in Article 6.

2. Where the Commission imposes urgent safety restrictions on the holder, the holder shall be obliged to submit an application for a variation taking account of the safety restrictions imposed by the Commission.

The urgent safety restrictions shall be implemented within a time-frame, as agreed with the Agency.

For the application of the procedures set out in Article 6, the corresponding variation application reflecting the urgent safety restrictions, including appropriate documentation in support of the change, shall be submitted to the Agency immediately and in any case no later than 15 days after the initiation of the urgent safety restrictions.

The first and second subparagraphs are without prejudice to Articles 18 and 40 of Regulation (EEC) No 2309/93.

Article 10

Repeal

Regulation (EC) No 542/95 is repealed.

References made to the repealed Regulation shall be construed as references to this Regulation.

Article 11

This Regulation shall enter into force on the 20th day following its publication in the *Official Journal of the European Union*.

It shall apply from 1 October 2003. However, as regards the examination of applications of variations to the terms of plasma master files and of vaccine antigen master files, this Regulation shall apply from the date of entry into force of the Commission Directive amending Annex I of Directive 2001/83/EC.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 3 June 2003.

For the Commission

Erkki LIIKANEN

Member of the Commission

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