

Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (Text with EEA relevance)

COMMISSION REGULATION (EC) No 1234/2008

of 24 November 2008

concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

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<sup>(1)</sup>, and in particular Article 39(1) thereof,

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<sup>(2)</sup>, and in particular Article 35(1) thereof,

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency<sup>(3)</sup>, and in particular of Article 16(4) and Article 41(6) thereof,

Whereas:

- (1) The Community legal framework regarding variations to the terms of marketing authorisations is laid down in 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<sup>(4)</sup> and 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<sup>(5)</sup>. In the light of practical experience in the application of those two Regulations, it is appropriate to proceed to their review in order to establish a simpler, clearer and more flexible legal framework, while guaranteeing the same level of public and animal health protection.
- (2) The procedures laid down in Regulations (EC) No 1084/2003 and (EC) No 1085/2003 should therefore be adjusted, without departing from the general principles on which those procedures are based. For reasons of proportionality, homeopathic and traditional herbal medicinal products which have not been granted a marketing authorisation but

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are subject to a simplified registration procedure should remain excluded from the scope of the Regulation.

- (3) Variations to medicinal products can be classified in different categories, depending on the level of risk to public or animal health and the impact on the quality, safety and efficacy of the medicinal product concerned. Definitions for each of those categories should therefore be laid down. In order to bring further predictability, guidelines on the details of the various categories of variations should be established and regularly updated in the light of scientific and technical progress, taking in particular account of developments regarding international harmonisation. The European Medicines Agency (hereinafter the Agency) and the Member States should also be empowered to give recommendations on the classification of unforeseen variations.
- (4) It should be clarified that certain changes which have the highest potential impact on the quality, safety or efficacy of medicinal products require a complete scientific assessment, in the same way as for the evaluation of new marketing authorisation applications.
- (5) In order to further reduce the overall number of variations procedures and to enable competent authorities to focus on those variations that have a genuine impact on quality, safety or efficacy, an annual reporting system should be introduced for certain minor variations. Such variations should not require any prior approval and should be notified within 12 months following implementation. However, other types of minor variations whose immediate reporting is necessary for the continuous supervision of the medicinal product concerned should not be subject to the annual reporting system.
- (6) Each variation should require a separate submission. Grouping of variations should nevertheless be allowed in certain cases, in order to facilitate the review of the variations and reduce the administrative burden. Grouping of variations to the terms of several marketing authorisations from the same marketing authorisation holder should be allowed only insofar as all concerned marketing authorisations are affected by the exact same group of variations.
- (7) In order to avoid duplication of work in the evaluation of variations to the terms of several marketing authorisations, a worksharing procedure should be established under which one authority, chosen amongst the competent authorities of the Member States and the Agency, should examine the variation on behalf of the other concerned authorities.
- (8) Provisions should be established reflecting those laid down in Directive 2001/82/EC and Directive 2001/83/EC as regards the role of the coordination groups established under Article 31 of Directive 2001/82/EC and Article 27 of Directive 2001/83/EC, to increase cooperation between Member States and allow for the settlement of disagreements in the evaluation of certain variations.
- (9) This Regulation should clarify when the holder of a marketing authorisation is allowed to implement a given variation as such clarification is essential for economic operators.

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- (10) A transitional period should be established in order to give all interested parties, in particular Member States authorities and the industry, time to adapt to the new legal framework.
- (11) The measures provided for in this Regulation are in accordance with the opinions of the Standing Committee on Medicinal Products for Human Use and the Standing Committee on Veterinary Medicinal Products,

HAS ADOPTED THIS REGULATION:

## CHAPTER I

### GENERAL PROVISIONS

#### *Article 1*

##### **Subject matter and scope**

1 This Regulation lays down provisions concerning the examination of variations to the terms of the following marketing authorisations for medicinal products for human use and veterinary medicinal products:

- a authorisations granted in accordance with Council Directive 87/22/EEC<sup>(6)</sup>, Articles 32 and 33 of Directive 2001/82/EC, Articles 28 and 29 of Directive 2001/83/EC and Regulation (EC) No 726/2004;
- b authorisations granted following a referral, as provided for in Articles 36, 37 and 38 of Directive 2001/82/EC or Articles 32, 33 and 34 of Directive 2001/83/EC, which has led to complete harmonisation.

2 This Regulation shall not apply to transfers of a marketing authorisation from one marketing authorisation holder (hereinafter holder) to another.

3 Chapter II shall apply only to variations to the terms of marketing authorisations granted in accordance with Directive 87/22/EEC, Chapter 4 of Directive 2001/82/EC or Chapter 4 of Directive 2001/83/EC.

4 Chapter III shall apply only to variations to the terms of marketing authorisations granted in accordance with Regulation (EC) No 726/2004 (hereinafter centralised marketing authorisations).

#### *Article 2*

##### **Definitions**

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

1. 'Variation to the terms of a marketing authorisation' or 'variation' means an amendment to the contents of the particulars and documents referred to in:
  - (a) Articles 12(3), 13, 13a, 13b, 13c, 13d and 14 of Directive 2001/82/EC and Annex I thereto, and Article 31(2) of Regulation (EC) No 726/2004 in the case of veterinary medicinal products;

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- (b) Articles 8(3), 9, 10, 10a, 10b, 10c and 11 of Directive 2001/83/EC and Annex I thereto, Article 6(2) of Regulation (EC) No 726/2004, point (a) of Article 7(1) and Article 34(1) of Regulation (EC) No 1901/2006 of the European Parliament and of the Council<sup>(7)</sup> and Articles 7 and 14(1) of Regulation (EC) No 1394/2007 of the European Parliament and of the Council<sup>(8)</sup> in the case of medicinal products for human use;
2. ‘Minor variation of type IA’ means a variation which has only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned;
  3. ‘Major variation of type II’ means a variation which is not an extension and which may have a significant impact on the quality, safety or efficacy of the medicinal product concerned;
  4. ‘Extension of a marketing authorisation’ or ‘extension’ means a variation which is listed in Annex I and fulfils the conditions laid down therein;
  5. ‘Minor variation of type IB’ means a variation which is neither a minor variation of type IA nor a major variation of type II nor an extension;
  6. ‘Member State concerned’ means a Member State whose competent authority has granted a marketing authorisation for the medicinal product in question;
  7. ‘Relevant authority’ means:
    - (a) the competent authority of each Member State concerned;
    - (b) in the case of centralised marketing authorisations, the Agency;
  8. ‘Urgent safety restriction’ means an interim change to the product information due to new information having a bearing on the safe use of the medicinal product, concerning in particular one or more of the following items in the summary of product characteristics: therapeutic indications, posology, contra-indications, warnings, target species and withdrawal periods.

### *Article 3*

#### **Classification of variations**

- 1 In relation to any variation which is not an extension the classification laid down in Annex II shall apply.
- 2 A variation which is not an extension and whose classification is undetermined after application of the rules provided for in this Regulation, taking into account the guidelines referred to in point (a) of Article 4(1) and, where relevant, any recommendations delivered pursuant to Article 5, shall by default be considered a minor variation of type IB.
- 3 By way of derogation from paragraph 2, a variation which is not an extension and whose classification is undetermined after application of the rules provided for in this Regulation shall be considered a major variation of type II in the following cases:
  - a upon request from the holder when submitting the variation;
  - b where the competent authority of the reference Member State as referred to in Article 32 of Directive 2001/82/EC and Article 28 of Directive 2001/83/EC (hereinafter the reference Member State), in consultation with the other Member States concerned or, in the case of a centralised marketing authorisation, the Agency concludes, following

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the assessment of validity of a notification in accordance with Article 9(1) or Article 15(1) and taking into account the recommendations delivered pursuant to Article 5, that the variation may have a significant impact on the quality, safety or efficacy of the medicinal product concerned.

#### *Article 4*

### **Guidelines**

1 The Commission shall, after consulting the Member States, the Agency and interested parties, draw up:

- a guidelines on the details of the various categories of variations;
- b guidelines on the operation of the procedures laid down in Chapters II, III and IV of this Regulation as well as on the documentation to be submitted pursuant to these procedures.

2 Guidelines referred to in point (a) of paragraph 1 shall be drawn up by the date referred to in the second subparagraph of Article 28 and shall be regularly updated, taking into account the recommendations delivered in accordance with Article 5 as well as scientific and technical progress.

#### *Article 5*

### **Recommendation on unforeseen variations**

1 Prior to submission or examination of a variation whose classification is not provided for in this Regulation, a holder or a competent authority of a Member State may request the coordination group referred to in Article 31 of Directive 2001/82/EC or in Article 27 of Directive 2001/83/EC (hereinafter the coordination group) or, in the case of a variation to the terms of a centralised marketing authorisation, the Agency to provide a recommendation on the classification of the variation.

The recommendation referred to in the first subparagraph shall be consistent with the guidelines referred to in point (a) of Article 4(1). It shall be delivered within 45 days following receipt of the request and sent to the holder, the Agency and the competent authorities of all Member States.

2 The Agency and the two coordination groups referred to in paragraph 1 shall cooperate to ensure the coherence of the recommendations delivered in accordance with that paragraph and publish those recommendations after deletion of all information of commercial confidential nature.

#### *Article 6*

### **Variations leading to the revision of product information**

Where a variation leads to the revision of the summary of product characteristics, labelling or package leaflet, this revision shall be considered as part of that variation.

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## Article 7

### Grouping of variations

1 Where several variations are notified or applied for, a separate notification or application as laid down in Chapters II, III and IV shall be submitted in respect of each variation sought.

2 By way of derogation from paragraph 1, the following shall apply:

- a where the same minor variations of type IA to the terms of one or several marketing authorisations owned by the same holder are notified at the same time to the same relevant authority, a single notification as referred to in Articles 8 and 14 may cover all such variations;
- b where several variations to the terms of the same marketing authorisation are submitted at the same time, a single submission may cover all such variations provided that the variations concerned fall within one of the cases listed in Annex III or, if they do not fall within one of those cases, provided that the competent authority of the reference Member State in consultation with the other Member States concerned or, in the case of a centralised marketing authorisation, the Agency agrees to subject those variations to the same procedure.

The submission referred to in point (b) of the first subparagraph shall be made by means of the following:

- a single notification as referred to in Articles 9 and 15 where at least one of the variations is a minor variation of type IB and all variations are minor variations;
- a single application as referred to in Articles 10 and 16 where at least one of the variations is a major variation of type II and none of the variations is an extension;
- a single application as referred to in Article 19 where at least one of the variations is an extension.

## CHAPTER II

### VARIATIONS TO MARKETING AUTHORISATIONS GRANTED IN ACCORDANCE WITH DIRECTIVE 87/22/EEC, CHAPTER 4 OF DIRECTIVE 2001/82/EC OR CHAPTER 4 OF DIRECTIVE 2001/83/EC

## Article 8

### Notification procedure for minor variations of type IA

1 Where a minor variation of type IA is made, the holder shall submit simultaneously to all relevant authorities a notification containing the elements listed in Annex IV. This notification shall be submitted within 12 months following the implementation of the variation.

However, the notification shall be submitted immediately after the implementation of the variation in the case of minor variations requiring immediate notification for the continuous supervision of the medicinal product concerned.

2 Within 30 days following receipt of the notification, the measures provided for in Article 11 shall be taken.

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## Article 9

### **Notification procedure for minor variations of type IB**

1 The holder shall submit simultaneously to all relevant authorities a notification containing the elements listed in Annex IV.

If the notification fulfils the requirement laid down in the first subparagraph, the competent authority of the reference Member State shall, after consulting the other Member States concerned, acknowledge receipt of a valid notification.

2 If within 30 days following the acknowledgement of receipt of a valid notification, the competent authority of the reference Member State has not sent the holder an unfavourable opinion, the notification shall be deemed accepted by all relevant authorities.

Where the notification is accepted by the competent authority of the reference Member State, the measures provided for in Article 11 shall be taken.

3 Where the competent authority of the reference Member State is of the opinion that the notification cannot be accepted, it shall inform the holder and the other relevant authorities, stating the grounds on which its unfavourable opinion is based.

Within 30 days following the receipt of the unfavourable opinion, the holder may submit to all relevant authorities an amended notification in order to take due account of the grounds laid down in that opinion.

If the holder does not amend the notification in accordance with the second subparagraph, the notification shall be deemed rejected by all relevant authorities and the measures provided for in Article 11 shall be taken.

4 Where an amended notification has been submitted, the competent authority of the reference Member State shall assess it within 30 days following its receipt and the measures provided for in Article 11 shall be taken.

## Article 10

### **‘Prior Approval’ procedure for major variations of type II**

1 The holder shall submit simultaneously to all relevant authorities an application containing the elements listed in Annex IV.

If the application fulfils the requirements laid down in the first subparagraph, the competent authority of the reference Member State shall acknowledge receipt of a valid application and inform the holder and the other relevant authorities that the procedure starts from the date of such acknowledgement.

2 Within 60 days following the acknowledgement of receipt of a valid application, the competent authority of the reference Member State shall prepare an assessment report and a decision on the application, which shall be communicated to the other relevant authorities.

The competent authority of the reference Member State may reduce the period referred to in the first subparagraph, having regard to the urgency of the matter, or extend it to 90 days for variations listed in Part 1 of Annex V.

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The period referred to in the first subparagraph shall be 90 days for variations listed in Part 2 of Annex V.

3 Within the period referred to in paragraph 2, 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. In this case:

- a the competent authority of the reference Member State shall inform the other competent authorities concerned of its request for supplementary information;
- b the procedure shall be suspended until such supplementary information has been provided;
- c the competent authority of the reference Member State may extend the period referred to in paragraph 2.

4 Without prejudice to Article 13 and within 30 days following receipt of the decision and of the assessment report referred to in paragraph 2, the relevant authorities shall recognise the decision and inform the competent authority of the reference Member State accordingly.

If, within the period referred to in the first subparagraph, a relevant authority has not expressed its disagreement in accordance with Article 13, the decision shall be deemed recognised by that relevant authority.

5 Where the decision referred to in paragraph 2 has been recognised by all relevant authorities in accordance with paragraph 4, the measures provided for in Article 11 shall be taken.

#### *Article 11*

### **Measures to close the procedures of Articles 8 to 10**

1 Where reference is made to this Article, the competent authority of the reference Member State shall take the following measures:

- a it shall inform the holder and the other relevant authorities as to whether the variation is accepted or rejected;
- b where the variation is rejected, it shall inform the holder and the other relevant authorities of the grounds for the rejection;
- c it shall inform the holder and the other relevant authorities as to whether the variation requires any amendment to the decision granting the marketing authorisation.

2 Where reference is made to this Article, each relevant authority shall, where necessary and within the time limit laid down in paragraph 1 of Article 23, amend the decision granting the marketing authorisation in accordance with the accepted variation.

#### *Article 12*

### **Human influenza vaccines**

1 By way of derogation from Article 10, the procedure laid down in paragraphs 2 to 6 shall apply to the examination of variations concerning changes to the active substance for the purposes of the annual update of a human influenza vaccine.

2 The holder shall submit simultaneously to all relevant authorities an application containing the elements listed in Annex IV.



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If the application fulfils the requirements laid down in the first subparagraph, the competent authority of the reference Member State shall acknowledge receipt of a valid application and inform the holder and the other relevant authorities that the procedure starts from the date of such acknowledgement.

3 Within 30 days following the acknowledgement of receipt of a valid application, the competent authority of the reference Member State shall prepare an assessment report and a decision on the application, which shall be communicated to the other relevant authorities.

4 Within the period referred to in paragraph 3, the competent authority of the reference Member State may request the holder to provide supplementary information. It shall inform the other relevant authorities accordingly.

5 Within 12 days from the date of receipt of the decision and of the assessment report referred to in paragraph 3, the relevant authorities shall recognise the decision and inform the competent authority of the reference Member State accordingly.

6 Where requested by the competent authority of the reference Member State, the clinical data and data concerning the stability of the medicinal product shall be submitted by the holder to all relevant authorities within 12 days from the expiry of the period referred to in paragraph 5.

The competent authority of the reference Member State shall evaluate the data referred to in the first subparagraph and draft a final decision within seven days following receipt of the data. The other relevant authorities shall, within seven days following its receipt, recognise that final decision and adopt a decision in accordance with the final decision.

### *Article 13*

#### **Coordination group and arbitration**

1 Where recognition of a decision in accordance with Article 10(4) or approval of an opinion in accordance with point (b) of Article 20(8) is not possible on grounds of a potential serious risk to public health in the case of medicinal products for human use or, in the case of veterinary medicinal products, on grounds of a potential serious risk to human or animal health or to the environment, a relevant authority shall request that the matter of disagreement be forthwith referred to the coordination group.

The party in disagreement shall give a detailed statement of the reasons for its position to all Member States concerned and to the applicant.

2 Article 33(3), (4) and (5) of Directive 2001/82/EC or Article 29(3), (4) and (5) of Directive 2001/83/EC shall apply to the matter of disagreement referred to in paragraph 1.

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## CHAPTER III

### VARIATIONS TO CENTRALISED MARKETING AUTHORISATIONS

#### *Article 14*

##### **Notification procedure for minor variations of type IA**

1 Where a minor variation of type IA is made, the holder shall submit to the Agency a notification containing the elements listed in Annex IV. This notification shall be submitted within 12 months following implementation of the variation.

However, the notification shall be submitted immediately after the implementation of the variation in the case of minor variations requiring immediate notification for the continuous supervision of the medicinal product concerned.

2 Within 30 days following receipt of the notification, the measures provided for in Article 17 shall be taken.

#### *Article 15*

##### **Notification procedure for minor variations of type IB**

1 The holder shall submit to the Agency a notification containing the elements listed in Annex IV.

If the notification fulfils the requirement laid down in the first subparagraph, the Agency shall acknowledge receipt of a valid notification.

2 If within 30 days following the acknowledgement of receipt of a valid notification the Agency has not sent the holder an unfavourable opinion, its opinion shall be deemed favourable.

Where the opinion of the Agency on the notification is favourable, the measures provided for in Article 17 shall be taken.

3 Where the Agency is of the opinion that the notification cannot be accepted, it shall inform the holder, stating the grounds on which its unfavourable opinion is based.

Within 30 days of receipt of the unfavourable opinion, the holder may submit to the Agency an amended notification in order to take due account of the grounds laid down in that opinion.

If the holder does not amend the notification in accordance with the second subparagraph, the notification shall be deemed rejected and the measures provided for in Article 17 shall be taken.

4 Where an amended notification has been submitted, the Agency shall assess it within 30 days following its receipt and the measures provided for in Article 17 shall be taken.

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## Article 16

### **‘Prior Approval’ procedure for major variations of type II**

1 The holder shall submit to the Agency an application containing the elements listed in Annex IV.

If the application fulfils the requirements laid down in the first subparagraph, the Agency shall acknowledge receipt of a valid application.

2 The Agency shall issue an opinion on the valid application referred to in paragraph 1 within 60 days following its receipt.

The Agency may reduce the period referred to in the first subparagraph, having regard to the urgency of the matter, or extend it to 90 days for variations listed in Part 1 of Annex V.

The period referred to in the first subparagraph shall be 90 days for variations listed in Part 2 of Annex V.

3 Within the period referred to in paragraph 2, the Agency may request the holder to provide supplementary information within a time limit set by the Agency. The procedure shall be suspended until such time as the supplementary information has been provided. In this case the Agency may extend the period referred to in paragraph 2.

4 Article 9(1) and (2) and Article 34(1) and (2) of Regulation (EC) No 726/2004 shall apply to the opinion on the valid application.

Within 15 days from the adoption of the final opinion on the valid application, the measures provided for in Article 17 shall be taken.

## Article 17

### **Measures to close the procedures of Articles 14 to 16**

1 Where reference is made to this Article, the Agency shall take the following measures:

- a it shall inform the holder and the Commission as to whether its opinion on the variation is favourable or unfavourable;
- b where its opinion on the variation is unfavourable, it shall inform the holder and the Commission of the grounds for that opinion;
- c it shall inform the holder and the Commission as to whether the variation requires any amendment to the decision granting the marketing authorisation.

2 Where reference is made to this Article, the Commission shall, where necessary, based on a proposal from the Agency and within the time limit laid down in paragraph 1 of Article 23, amend the decision granting the marketing authorisation and update the Community Register of Medicinal Products provided for in Article 13(1) and Article 38(1) of Regulation (EC) No 726/2004 accordingly.

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## Article 18

### Human influenza vaccines

1 By way of derogation from Article 16, the procedure laid down in paragraphs 2 to 7 shall apply to the examination of variations concerning changes to the active substance for the purposes of the annual update of a human influenza vaccine.

2 The holder shall submit to the Agency an application containing the elements listed in Annex IV.

If the application fulfils the requirements laid down in the first subparagraph, the Agency shall acknowledge receipt of a valid application and inform the holder that the procedure starts from the date of such acknowledgement.

3 Within 45 days following the acknowledgement of receipt of a valid application, the Agency shall give its opinion on the application.

4 Within the period referred to in paragraph 3, the Agency may request the holder to provide supplementary information.

5 The Agency shall submit forthwith its opinion to the Commission.

The Commission shall, where necessary and on the basis of that opinion, adopt a decision on the variation to the terms of the marketing authorisation and inform the holder accordingly.

6 Where requested, the holder shall submit the clinical data and the data concerning the stability of the medicinal product to the Agency within 12 days from the expiry of the period referred to in paragraph 3.

The Agency shall evaluate the data referred to in the first subparagraph and shall give its final opinion within 10 days following receipt of the data. The Agency shall communicate its final opinion to the Commission and to the holder within three days from the date of issue of its final opinion.

7 Where necessary and based on the final opinion of the Agency, the Commission shall amend the decision granting the marketing authorisation and update the Community Register of Medicinal Products provided for in Article 13(1) of Regulation (EC) No 726/2004 accordingly.

## CHAPTER IV

### SECTION 1

#### Special procedures

## Article 19

### Extensions of marketing authorisations

1 An application for an extension of a marketing authorisation shall be evaluated in accordance with the same procedure as for the initial marketing authorisation to which it relates.

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2 An extension shall either be granted a marketing authorisation in accordance with the same procedure as for the granting of the initial marketing authorisation to which it relates or be included in that marketing authorisation.

## Article 20

### Worksharing procedure

1 By way of derogation from Article 7(1) and Articles 9, 10, 15 and 16, where a minor variation of type IB, a major variation of type II or a group of variations in the cases of point (b) of Article 7(2) which does not contain any extension relates to several marketing authorisations owned by the same holder, the holder of such authorisations may follow the procedure laid down in paragraphs 3 to 9 of this Article.

2 For the purposes of paragraphs 3 to 9, 'reference authority' shall mean one of the following:

- a the Agency where at least one of the marketing authorisations referred to in paragraph 1 is a centralised marketing authorisation;
- b the competent authority of a Member State concerned chosen by the coordination group, taking into account a recommendation of the holder, in the other cases.

3 The holder shall submit to all relevant authorities an application containing the elements listed in Annex IV, with an indication of the recommended reference authority.

If the application fulfils the requirements laid down in the first subparagraph, the coordination group shall chose a reference authority and that reference authority shall acknowledge receipt of a valid application.

Where the chosen reference authority is the competent authority of a Member State which has not granted a marketing authorisation for all the medicinal products affected by the application, the coordination group may request another relevant authority to assist the reference authority in the evaluation of that application.

4 The reference authority shall issue an opinion on the valid application referred to in paragraph 3 within one of the following periods:

- a a period of 60 days following acknowledgement of receipt of a valid application in the case of minor variations of type IB or major variations of type II;
- b a period of 90 days following acknowledgement of receipt of a valid application in the case of variations listed in Part 2 of Annex V.

5 The reference authority may reduce the period referred to in point (a) of paragraph 4, having regard to the urgency of the matter, or extend it to 90 days for variations listed in Part 1 of Annex V.

6 Within the period referred to in paragraph 4, the reference authority may request the holder to provide supplementary information within a time limit set by the reference authority. In this case:

- a the reference authority shall inform the other relevant authorities of its request for supplementary information;
- b the procedure shall be suspended until such supplementary information has been provided;
- c the reference authority may extend the period referred to in point (a) of paragraph 4.

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7 Where the reference authority is the Agency, Article 9(1), (2) and (3) and Article 34(1), (2) and (3) of Regulation (EC) No 726/2004 shall apply to the opinion on a valid application referred to in paragraph 4.

Where the opinion on a valid application is favourable:

- a the Commission shall, within 30 days following receipt of the final opinion and on the basis of a proposal from the Agency, amend where necessary the concerned centralised marketing authorisations and update the Community Register of Medicinal Products provided for in Article 13(1) and Article 38(1) of Regulation (EC) No 726/2004 accordingly;
- b the Member States concerned shall, within 30 days following receipt of the final opinion of the Agency, approve that final opinion, inform the Agency thereof and amend where necessary the concerned marketing authorisations accordingly, unless a referral procedure in accordance with Article 35 of Directive 2001/82/EC or Article 31 of Directive 2001/83/EC is initiated within 30 days following receipt of the final opinion.

8 Where the reference authority is the competent authority of a Member State:

- a it shall send its opinion on the valid application to the holder and to all relevant authorities;
- b without prejudice to Article 13 and within 30 days following receipt of the opinion, the relevant authorities shall approve that opinion, inform the reference authority and amend the concerned marketing authorisations accordingly.

9 Upon request from the reference authority, the Member States concerned shall provide information related to the marketing authorisations affected by the variation for the purpose of verifying the validity of the application and of issuing the opinion on the valid application.

#### *Article 21*

### **Pandemic situation with respect to human influenza**

1 By way of derogation from Articles 12, 18 and 19, where a pandemic situation with respect to human influenza is 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<sup>(9)</sup>, the relevant authorities or, in the case of centralised marketing authorisations, the Commission may exceptionally and temporarily accept a variation to the terms of a marketing authorisation for a human influenza vaccine, where certain non-clinical or clinical data are missing.

2 Where a variation is accepted pursuant to paragraph 1, the holder shall submit the missing non-clinical and clinical data within a time limit set by the relevant authority.

#### *Article 22*

### **Urgent safety restrictions**

1 Where, in the event of a risk to public health in the case of medicinal products for human use or, in the case of veterinary medicinal products, in the event of a risk to human or animal health or to the environment, the holder takes urgent safety restrictions on its own initiative, it shall forthwith inform all relevant authorities and, in the case of a centralised marketing authorisation, the Commission.

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If no relevant authority or, in the case of a centralised marketing authorisation, the Commission has raised objections within 24 hours following receipt of that information, the urgent safety restrictions shall be deemed accepted.

2 In the event of a risk to public health in the case of medicinal products for human use or, in the case of veterinary medicinal products, in the event of a risk to human or animal health or to the environment, relevant authorities or, in the case of centralised marketing authorisations, the Commission may impose urgent safety restrictions on the holder.

3 Where an urgent safety restriction is taken by the holder or imposed by a relevant authority or the Commission, the holder shall submit the corresponding application for variation within 15 days following the initiation of that restriction.

## SECTION 2

### **Amendments to the decision granting the marketing authorisation and implementation**

#### *Article 23*

#### **Amendments to the decision granting the marketing authorisation**

1 The amendment to the decision granting the marketing authorisation resulting from the procedures laid down in Chapters II and III shall be made:

- a within 30 days following receipt of the information referred to in Article 11(1)(c) and Article 17(1)(c), where the concerned variation leads to a six-month extension of the period referred to in Article 13(1) and (2) of Council Regulation (EEC) No 1768/92<sup>(10)</sup>, in accordance with Article 36 of Regulation (EC) No 1901/2006;
- b within two months following receipt of the information referred to in Article 11(1)(c) and Article 17(1)(c), in the case of major variations of type II and minor variations of type IA which do not require immediate notification for the continuous supervision of the medicinal product concerned;
- c within six months following receipt of the information referred to in Article 11(1)(c) and Article 17(1)(c), in the other cases.

2 Where the decision granting a marketing authorisation is amended as a result of one of the procedures laid down in Chapters II, III and IV, the relevant authority or, in the case of centralised marketing authorisations, the Commission shall notify the amended decision without delay to the holder.

#### *Article 24*

#### **Implementation of variations**

1 A minor variation of type IA may be implemented any time before completion of the procedures laid down in Articles 8 and 14.

Where a notification concerning one or several minor variations of type IA is rejected, the holder shall cease to apply the concerned variation(s) immediately after receipt of the information referred to in Articles 11(1)(a) and 17(1)(a).

2 Minor variations of type IB may only be implemented in the following cases:

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- a after the competent authority of the reference Member State has informed the holder that it has accepted the notification pursuant to Article 9, or after the notification is deemed accepted pursuant to Article 9(2);
  - b after the Agency has informed the holder that its opinion referred to in Article 15 is favourable, or after that opinion is deemed favourable pursuant to Article 15(2);
  - c after the reference authority referred to in Article 20 has informed the holder that its opinion is favourable.
- 3 Major variations of type II may only be implemented in the following cases:
- a 30 days after the competent authority of the reference Member State has informed the holder that it has accepted the variation pursuant to Article 10, under the condition that the documents necessary for the amendment to the marketing authorisation have been provided to the Member States concerned;
  - b after the Commission has amended the decision granting the marketing authorisation in accordance with the accepted variation and notified the holder accordingly;
  - c 30 days after the reference authority referred to in Article 20 has informed the holder that its final opinion is favourable, unless an arbitration procedure in accordance with Article 13 or a referral procedure in accordance with Article 35 of Directive 2001/82/EC or Article 31 of Directive 2001/83/EC has been initiated.
- 4 An extension may only be implemented after the relevant authority or, in the case of extensions to a centralised marketing authorisation, the Commission has amended the decision granting the marketing authorisation in accordance with the approved extension and notified the holder accordingly.
- 5 Urgent safety restrictions and variations which are related to safety issues shall be implemented within a time frame agreed by the holder and the relevant authority and, in the case of a centralised marketing authorisation, the Commission.

By way of derogation from the first subparagraph, urgent safety restrictions and variations related to safety issues which concern marketing authorisations granted in accordance with Chapter 4 of Directive 2001/82/EC or Chapter 4 of Directive 2001/83/EC shall be implemented within a time frame agreed by the holder and the competent authority of the reference Member State, in consultation with the other relevant authorities.

## CHAPTER V

### FINAL PROVISIONS

#### *Article 25*

#### **Continuous monitoring**

Where requested by a relevant authority, the holder shall supply without delay any information related to the implementation of a given variation.



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## Article 26

### Review

By two years from the date referred to in the second subparagraph of Article 28, the Commission services shall assess the application of this Regulation as regards the classification of variations, with a view to proposing any necessary amendments to adapt Annexes I, II and V to take account of scientific and technical progress.

## Article 27

### Repeal and transitional provision

1 Regulations (EC) No 1084/2003 and (EC) No 1085/2003 are hereby repealed.

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

2 By way of derogation from paragraph 1, Regulations (EC) Nos 1084/2003 and 1085/2003 shall continue to apply to valid notifications or applications for variations which are pending at the date referred to in the second subparagraph of Article 28.

## Article 28

### Entry into force

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 January 2010.

By way of derogation from the second subparagraph, the recommendations on unforeseen variations provided for in Article 5 may be requested, delivered and published from the date of entry into force referred to in the first subparagraph.

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

Done at Brussels, 24 November 2008.

*For the Commission*  
Günter VERHEUGEN  
*Vice-President*

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## ANNEX I

### Extensions of marketing authorisations

1. Changes to the active substance(s):
  - (a) replacement of a chemical active substance by a different salt/ester complex/derivative, with the same therapeutic moiety, where the efficacy/safety characteristics are not significantly different;
  - (b) replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer), where the efficacy/safety characteristics are not significantly different;
  - (c) replacement of a biological active substance with one of a slightly different molecular structure where the efficacy/safety characteristics are not significantly different, with the exception of:
    - changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;
    - replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue;
    - replacement of a strain for a veterinary vaccine against equine influenza;
  - (d) modification of the vector used to produce the antigen or the source material, including a new master cell bank from a different source, where the efficacy/safety characteristics are not significantly different;
  - (e) a new ligand or coupling mechanism for a radiopharmaceutical, where the efficacy/safety characteristics are not significantly different;
  - (f) change to the extraction solvent or the ratio of herbal drug to herbal drug preparation where the efficacy/safety characteristics are not significantly different.
2. Changes to strength, pharmaceutical form and route of administration:
  - (a) change of bioavailability;
  - (b) change of pharmacokinetics e.g. change in rate of release;
  - (c) change or addition of a new strength/potency;
  - (d) change or addition of a new pharmaceutical form;
  - (e) change or addition of a new route of administration<sup>(11)</sup>.
3. Other changes specific to veterinary medicinal products to be administered to food-producing animals: change or addition of target species.

## ANNEX II

### Classification of variations

1. The following variations shall be classified as minor variations of type IA:

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- (a) variations of purely administrative nature that are related to the identity and contact details of:
    - the holder;
    - the manufacturer or supplier of any starting material, reagent, intermediate, active substance used in the manufacturing process or finished product;
  - (b) variations related to the deletion of any manufacturing site, including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place;
  - (c) variations related to minor changes to an approved physico-chemical test procedure, where the updated procedure is demonstrated to be at least equivalent to the former test procedure, appropriate validation studies have been performed and the results show that the updated test procedure is at least equivalent to the former;
  - (d) variations related to changes made to the specifications of the active substance or of an excipient in order to comply with an update of the relevant monograph of the European Pharmacopoeia or of the national pharmacopoeia of a Member State, where the change is made exclusively to comply with the pharmacopoeia and the specifications for product specific properties are unchanged;
  - (e) variations related to changes in the packaging material not in contact with the finished product, which do not affect the delivery, use, safety or stability of the medicinal product;
  - (f) variations related to the tightening of specification limits, where the change is not a consequence of any commitment from previous assessment to review specification limits and does not result from unexpected events arising during manufacture.
2. The following variations shall be classified as major variations of type II:
- (a) variations related to the addition of a new therapeutic indication or to the modification of an existing one;
  - (b) variations related to significant modifications of the summary of product characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance findings;
  - (c) variations related to changes outside the range of approved specifications, limits or acceptance criteria;
  - (d) variations related to substantial changes to the manufacturing process, formulation, specifications or impurity profile of the active substance or finished medicinal product which may have a significant impact on the quality, safety or efficacy of the medicinal product;
  - (e) variations related to modifications in the manufacturing process or sites of the active substance for a biological medicinal product;
  - (f) variations related to the introduction of a new design space or the extension of an approved one, where the design space has been developed in accordance with the relevant European and international scientific guidelines;
  - (g) variations concerning a change to or addition of a non-food producing target species;

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- (h) variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue;
- (i) variations concerning the replacement of a strain for a veterinary vaccine against equine influenza;
- (j) variations related to changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;
- (k) variations related to changes to the withdrawal period for a veterinary medicinal product.

### ANNEX III

#### Cases for grouping variations referred to in Article 7(2)(b)

1. One of the variations in the group is an extension of the marketing authorisation.
2. One of the variations in the group is a major variation of type II; all other variations in the group are variations which are consequential to this major variation of type II.
3. One of the variations in the group is a minor variation of type IB; all other variations in the group are minor variations which are consequential to this minor variation of type IB.
4. All variations in the group relate solely to changes of administrative nature to the summary of product characteristics, labelling and package leaflet or insert.
5. All variations in the group are changes to an Active Substance Master File, Vaccine Antigen Master File or Plasma Master File.
6. All variations in the group relate to a project intended to improve the manufacturing process and the quality of the medicinal product concerned or its active substance(s).
7. All variations in the group are changes affecting the quality of a human pandemic influenza vaccine.
8. All variations in the group are changes to the pharmacovigilance system referred to in points (ia) and (n) of Article 8(3) of Directive 2001/83/EC or points (k) and (o) of Article 12(3) of Directive 2001/82/EC.
9. All variations in the group are consequential to a given urgent safety restriction and submitted in accordance with Article 22.
10. All variations in the group relate to the implementation of a given class labelling.
11. All variations in the group are consequential to the assessment of a given periodic safety update report.
12. All variations in the group are consequential to a given post-authorisation study conducted under the supervision of the holder.
13. All variations in the group are consequential to a specific obligation carried out pursuant to Article 14(7) of Regulation (EC) No 726/2004.

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14. All variations in the group are consequential to a specific procedure or condition carried out pursuant to Articles 14(8) or 39(7) of Regulation (EC) No 726/2004, Article 22 of Directive 2001/83/EC or Article 26(3) of Directive 2001/82/EC.

## ANNEX IV

### Elements to be submitted

1. A list of all the marketing authorisations affected by the notification or application.
2. A description of all the variations submitted, including:
  - (a) in the case of minor variations of type IA, the date of implementation for each variation described;
  - (b) in the case of minor variations of type IA which do not require immediate notification, a description of all minor variations of type IA made in the last 12 months to the terms of the concerned marketing authorisation(s) and which have not been already notified.
3. All necessary documents as listed in the guidelines referred to in point (b) of Article 4(1).
4. Where a variation leads to or is the consequence of other variations to the terms of the same marketing authorisation, a description of the relation between these variations.
5. In the case of variations to centralised marketing authorisations, the relevant fee provided for in Council Regulation (EC) No 297/95<sup>(12)</sup>.
6. In the case of variations to marketing authorisations granted by the competent authorities of Member States:
  - (a) a list of those Member States with an indication of the reference Member State if applicable;
  - (b) the relevant fees provided for in the applicable national rules in the Member States concerned.

## ANNEX V

### PART 1

Variations concerning a change to or addition of therapeutic indications.

### PART 2

1. Variations concerning a change to or addition of a non-food producing target species.
2. Variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue.

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3. Variations concerning the replacement of a strain for a veterinary vaccine against equine influenza.

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- (1) OJ L 311, 28.11.2001, p. 1.
- (2) OJ L 311, 28.11.2001, p. 67.
- (3) OJ L 136, 30.4.2004, p. 1.
- (4) OJ L 159, 27.6.2003, p. 1.
- (5) OJ L 159, 27.6.2003, p. 24.
- (6) OJ L 15, 17.1.1987, p. 38.
- (7) OJ L 378, 27.12.2006, p. 1.
- (8) OJ L 324, 10.12.2007, p. 121.
- (9) OJ L 268, 3.10.1998, p. 1.
- (10) OJ L 182, 2.7.1992, p. 1.
- (11) For parenteral administration, it is necessary to distinguish between intra-arterial, intravenous, intramuscular, subcutaneous and other routes. For administration to poultry, respiratory, oral and ocular (nebulisation) routes used for vaccination are considered to be equivalent routes of administration.
- (12) OJ L 35, 15.2.1995, p. 1.

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