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

Delegations will find attached Commission document D019622/02.

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EUROPEAN COMMISSION

Brussels, XXX
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[...] (2012) XXX draft

COMMISSION REGULATION (EU) No .../..

of XXX

amending Commission Regulation (EC) No 1234/2008 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 (EU) No .../..

of XXX

amending Commission Regulation (EC) No 1234/2008 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 EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

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 products¹, and in particular Article 27b 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 use², and in particular Article 23b(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 Agency³, and in particular Article 16(4) and Article 41(6) thereof,

Whereas:

- (1) Directive 2009/53/EC of the European Parliament and of the Council of 18 June 2009 amending Directive 2001/82/EC and Directive 2001/83/EC, as regards variations to the terms of marketing authorisations for medicinal products, requires the Commission to adopt appropriate arrangements for the examination of variations to the terms of marketing authorisations granted in accordance with Directives 2001/82/EC and 2001/83/EC not yet covered by Commission Regulation (EC) 1234/2008. It is therefore appropriate to extend the scope of Commission Regulation (EC) 1234/2008. The variations of all marketing authorisations granted in the EU in accordance with the *acquis* should be subject to the procedures laid down in Commission Regulation (EC) No 1234/2008.
- (2) The definition of variation should be clarified and updated in particular to take into consideration the provisions of Regulation (EU) No 1235/2010 of the European

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.

Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products⁴, and the provisions of Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use.⁵

- (3) For reasons of consistency and with a view to reducing the administrative burden, variations to purely national marketing authorisations should be processed in accordance with the same principles that apply to variations of marketing authorisations granted under the mutual recognition procedure and the decentralised procedure. However, the possibilities for grouping variations should be adapted to the specific characteristics of purely national marketing authorisations.
- (4) It should be possible to process variations to purely national marketing authorisations in accordance with the worksharing procedure under certain conditions. Where the use of the worksharing procedure has led to the harmonisation of a section of the summary of product characteristics, it should not be possible for the holder to later undermine the harmonisation achieved by submitting applications for variations to the section thus harmonised in some of the concerned Member States only.
- (5) Grouping of several variations in a single submission is possible in some cases. It should be clarified that, where several variations are grouped, the procedure for the handling of the variations in the group and the rules for the implementation of those variations should be those of the variation of the highest grade. In order to facilitate the acceptance of complex groupings by the relevant authorities, it should be possible to extend the assessment period.
- (6) The worksharing procedure is intended to avoid duplication of work. Accordingly, it should be possible for competent authorities to process under the same procedure variations to purely national marketing authorisations, variations to marketing authorisations granted under the mutual recognition or decentralised procedure, and variations to centralised marketing authorisations.
- (7) The procedure for the variation of human influenza vaccines should be streamlined. Competent authorities should still be able to start the assessment in the absence of clinical and stability data and take a decision if no additional information is considered necessary. However, if clinical and stability data is requested, the competent authorities should not be required to take a decision until the assessment thereof has been finalised.
- (8) For medicinal products authorised under Regulation (EC) No 726/2004, the refusal of the European Medicines Agency to accept a variation should terminate the procedure. Likewise, a Commission decision should not be required regarding variations that do not amend the terms of the decision granting the marketing authorisation.

⁴ OJ L 348, 31.12.2010, p. 1.

⁵ OJ L 348, 31.12.2010, p. 74.

- (9) The European Medicines Agency has the expertise to assess the need for urgent safety restrictions regarding medicinal products authorised under the centralised procedure. Marketing authorisation holders of medicinal products authorised under Regulation (EC) No 726/2004 should therefore inform the Agency if they consider that urgent safety measures are necessary.
- (10) A proliferation of variation procedures leading to frequent changes in the terms of the decision granting the marketing authorisation for centralised marketing authorisations has been identified. Changes that are critical for public health should be reflected in the decision granting the marketing authorisation promptly. However, other changes should be reflected in the decision granting the marketing authorisation according to timelines that ensure reasonable periodic updates of the decision granting the marketing authorisations while facilitating the identification of variations with the greatest impact on public health.
- (11) The principles governing the implementation of variations should be adjusted while keeping the principle that it should be possible for the marketing authorisation holder to implement certain variations prior to the relevant marketing authorisation being changed.
- (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

Amendments to Regulation (EC) No 1234/2008

Regulation (EC) No 1234/2008 is amended as follows:

(1) Article 1 is amended as follows:

(a) paragraph 1 is replaced by the following:

"1. This Regulation lays down provisions concerning the examination of variations to the terms of all marketing authorisations for medicinal products for human use and veterinary medicinal products granted in accordance with Regulation (EC) No 726/2004, Directive 2001/83/EC, Directive 2001/82/EC, and Council Directive 87/22/EEC⁶."

(b) the following paragraph shall be inserted after paragraph (3):

"3a. Chapter IIa shall apply only to variations to the terms of purely national marketing authorisations."

(2) Article 2 is amended as follows:

⁶ * OJ L15, 17.1.1987, p. 38.

(a) paragraph 1 is replaced by the following:

"1. 'Variation to the terms of a marketing authorisation' or 'variation' means any amendment to:

- (a) the information referred to in Articles 12(3) to 14 of Directive 2001/82 and Annex I thereto, Articles 8(3) to 11 of Directive 2001/83 and Annex I thereto, Articles 6(2) and 31(2) of Regulation (EC) No 726/2004, or Article 7 of Regulation (EC) No 1394/2007;
- (b) the terms of the decision granting the marketing authorisation for a medicinal product for human use, including the summary of the product characteristics and any conditions, obligations, or restrictions affecting the marketing authorisation, or changes to the labelling or the package leaflet connected with changes to the summary of the product characteristics;
- (c) the terms of the decision granting the marketing authorisation for a veterinary medicinal product, including the summary of the product characteristics and any conditions, obligations, or restrictions affecting the marketing authorisation, or changes to the labelling or the package leaflet."

(b) paragraph 8 is replaced by the following:

"8. 'Urgent safety restriction' means an interim change in the terms of the marketing authorisation due to new information having a bearing on the safe use of the medicinal product."

(c) the following paragraph 9 is added:

"9. 'Purely national marketing authorisation' means any marketing authorisation granted by a Member State in accordance with the acquis outside the mutual recognition or decentralised procedure and that has not been subject to a complete harmonisation following a referral procedure."

(3) Article 3 is amended as follows:

(a) paragraph 2 is replaced by the following:

"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 Article 4(1) and, where relevant, any recommendations delivered pursuant to Article 5, shall by default be considered a minor variation of type IB."

(b) in paragraph 3, point (b) is replaced by the following:

"(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 the Agency in the case of a centralised marketing authorisation,

or the competent authority in the case of a purely national marketing authorisation, concludes, following the assessment of validity of a notification in accordance with Article 9(1), Article 13b(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."

(4) Article 4 is replaced by the following:

"1. The Commission shall, after consulting the Member States and the Agency, draw up guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of this Regulation, and on the documentation to be submitted pursuant to those procedures.

2. The guidelines referred to in paragraph 1 shall be regularly updated."

(5) Article 5 is amended as follows:

(a) paragraph 1 is replaced by the following:

"1. Prior to the submission of a variation whose classification is not provided for in this Regulation, a holder may request a recommendation on the classification of the variation as follows:

- (a) to the Agency, where the variation refers to a marketing authorisation granted under Regulation (EC) No 726/2004,
- (b) to the competent authority of the Member State concerned, where the variation refers to a purely national marketing authorisation,
- (c) to the competent authority of the reference Member State, in the other cases.

The recommendation referred to in the first subparagraph shall be consistent with the guidelines referred to in Article 4(1). It shall be delivered within 45 days following receipt of the request and sent to the holder, the Agency, and the coordination group referred to in Article 31 of Directive 2001/82/EC or in Article 27 of Directive 2001/83/EC.

The 45-day period referred to in the second subparagraph may be extended by 25 days where the relevant authority deems it necessary to consult with the coordination group."

(b) the following paragraph 1a is inserted after paragraph 1:

"1a. Prior to the examination of a variation whose classification is not provided for in this Regulation, a competent authority of a Member State may request a recommendation on the classification of the variation to the coordination group.

The recommendation referred to in the first subparagraph shall be consistent with the guidelines referred to in 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."

- (6) Article 7 is replaced by the following:

"Article 7

Grouping of variations

1. Where several variations are notified or applied for, a separate notification or application in accordance with Chapters II, III, or Article 19 as appropriate 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 variation(s) of type IA to the terms of one or more 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 or 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;
 - (c) where several variations to the terms of the same marketing authorisation are submitted at the same time and the variations do not fall within one of the cases listed in Annex III, a single submission may cover all such variations provided that the competent authority of the reference Member State in consultation with the competent authorities of the Member States concerned or, in the case of a centralised marketing authorisation, the Agency agrees to such single submission.

The submission referred to in subparagraphs (b) and (c) shall be made simultaneously to all relevant authorities by means of the following:

- (i) a single notification in accordance with Articles 9 or 15 where at least one of the variations is a minor variation of type IB and the remaining variations are minor variations;
- (ii) a single application in accordance with Articles 10 or 16 where at least one of the variations is a major variation of type II and none of the variations is an extension;
- (iii) a single application in accordance with Article 19 where at least one of the variations is an extension."

- (7) In Article 9, the following paragraph 5 is added:

"5. This Article shall not apply where a type IB variation request is submitted in a grouping that includes a variation type II and does not contain an extension. In such case, the prior approval procedure in Article 10 shall apply.

This Article shall not apply where a type IB variation request is submitted in a grouping that includes an extension. In such case, the procedure in Article 19 shall apply."

(8) Article 10 is amended as follows:

(a) in paragraph 2, the second subparagraph is replaced by the following:

"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 or for grouping of variations in accordance with Article 7(2)(c)."

(b) the following paragraph 6 is added:

"6. This Article shall not apply where a type II variation request is submitted in a grouping that includes an extension. In such case, the procedure in Article 19 shall apply."

(9) Article 12 is amended as follows:

(a) paragraph 1 is replaced by the following:

"1. By way of derogation from Article 10, the procedure laid down in paragraphs 2 to 5 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."

(b) paragraphs 3, 4 and 5 are replaced by the following:

"3. The competent authority of the reference Member State shall assess the application submitted. Where deemed necessary, the competent authority of the reference Member State may request additional data to the holder in order to complete its assessment.

4. The competent authority shall prepare a decision and an assessment report within 45 days from the receipt of a valid application.

The 45-day period referred to in the first subparagraph shall be suspended from the moment when the additional data referred to in paragraph 3 is requested until the data is submitted.

5. Within 12 days from the receipt of the decision and the assessment report of the competent authority of the reference Member State, the relevant authorities shall adopt a decision accordingly and inform the competent authority of the reference Member State and the holder thereof."

(c) paragraph 6 is deleted.

(10) The following Chapter IIa is inserted after Article 13:

"CHAPTER IIa

VARIATIONS TO PURELY NATIONAL MARKETING AUTHORISATIONS

Article 13a

Notification procedure for minor variations of type IA

1. Where a minor variation of type IA is made, the holder shall submit to the competent authority 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 13e shall be taken.

Article 13b

Notification procedure for minor variations of type IB

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

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

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

Where the notification is accepted by the competent authority, the measures provided for in Article 13e shall be taken.

3. Where the competent authority 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 following the receipt of the unfavourable opinion, the holder may submit to the competent authority 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.

4. Where an amended notification has been submitted, the competent authority shall assess it within 30 days following its receipt and the measures provided for in Article 13e shall be taken.
5. This Article shall not apply where a type IB variation request is submitted in a grouping that includes a variation type II and does not contain an extension. In such case, the prior approval procedure in Article 13c shall apply.

This Article shall not apply where a type IB variation request is submitted in a grouping that includes an extension. In such case, the procedure in Article 19 shall apply.

Article 13c

‘Prior Approval’ procedure for major variations of type II

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

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

2. Within 60 days following the acknowledgement of receipt of a valid application, the competent authority shall conclude the assessment.

The competent authority 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 or for grouping of variations in accordance with Article 13d(2)(c).

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

3. Within the periods referred to in paragraph 2, the competent authority may request the holder to provide supplementary information within a time limit set by the competent authority. In this case the procedure shall be suspended until such supplementary information has been provided and the competent authority may extend the period referred to in paragraph 2.
4. Within 30 days after the conclusion of the assessment, the measures provided for in Article 13e shall be taken.
5. This Article shall not apply where a type II variation request is submitted in a grouping that includes an extension. In such case, the procedure in Article 19 shall apply.

Article 13d

Grouping of variations to purely national marketing authorisations

1. Where several variations are notified or applied for, a separate notification or application in accordance with Articles 13a, 13b, 13c, or 19 as appropriate shall be submitted to the competent authority in respect of each variation sought.
2. By way of derogation from paragraph 1 the following shall apply:
 - (a) where the same minor variation(s) of type IA to the terms of one or more marketing authorisations owned by the same holder are notified at the same time to the same competent authority, a single notification as referred to in Articles 13a may cover all such variations;
 - (b) where several variations to the terms of the same marketing authorisation are submitted at the same time to the same competent authority, a single submission may cover all such variations provided that the variations concerned fall within one of the cases listed in Annex III;
 - (c) where the same variation(s) to the terms of one or more marketing authorisations owned by the same holder are submitted at the same time to the same competent authority and they are not covered under subparagraphs (a) or (b), a single submission may cover all such variations provided that the competent authority agrees to such single submission.

The submission referred to in points (b) and (c) shall be made by means of the following:

- (i) a single notification in accordance with Article 13b where at least one of the variations is a minor variation of type IB and the remaining variations are minor variations;
- (ii) a single application in accordance with Article 13c where at least one of the variations is a major variation of type II and none of the variations is an extension;
- (iii) a single application in accordance with Article 19 where at least one of the variations is an extension.

Article 13e

Measures to close the procedures of Articles 13a to 13c

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

- (a) it shall inform the holder as to whether the variation is accepted or rejected;
- (b) where the variation is rejected, it shall inform the holder of the grounds for the rejection;

- (c) where necessary, it shall amend the decision granting the marketing authorisation in accordance with the accepted variation within the time limit laid down in paragraph 1 of Article 23.

Article 13f

Human influenza vaccines

1. By way of derogation from Article 13c, the procedure laid down in paragraphs 2 to 4 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 competent authority an application containing the elements listed in Annex IV.

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

3. The competent authority shall assess the application submitted. Where deemed necessary, the competent authority may request additional data to the holder in order to complete its assessment.
4. The competent authority shall adopt a decision within 45 days from the receipt of a valid application and shall take the measures provided for in Article 13e.

The 45-day period referred to in the first subparagraph shall be suspended from the moment when the additional data referred to in paragraph 3 is requested until the data is submitted."

- (11) Article 15 is amended as follows:

- (a) in paragraph 3, the third subparagraph is replaced by the following:

"If the holder does not amend the notification in accordance with the second subparagraph, the notification shall be deemed rejected."

- (b) the following paragraph 5 is added:

"5. This Article shall not apply where a type IB variation request is submitted in a grouping that includes a variation type II and does not contain an extension. In such case, the prior approval procedure in Article 16 shall apply.

This Article shall not apply where a type IB variation request is submitted in a grouping that includes an extension. In such case, the procedure in Article 19 shall apply."

- (12) Article 16 is amended as follows:

- (a) in paragraph 2, the second subparagraph is replaced by the following:

"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 or for grouping of variations in accordance with Article 7(2)(c)."

(b) the following paragraph 5 is added:

"5. This Article shall not apply where a type II variation request is submitted in a grouping that includes an extension. In such case, the procedure in Article 19 shall apply."

(13) Article 17 is replaced by the following:

"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 of the outcome of the assessment;
- (b) where the variation is rejected, it shall inform the holder of the grounds for the rejection;
- (c) where the outcome of the assessment is favourable and the variation affects the terms of the Commission decision granting the marketing authorisation, the Agency shall transmit to the Commission its opinion and the grounds for its opinion as well as the revised versions of the documents referred to in Article 9(4) or Article 34(4) of Regulation (EC) No 726/2004 as appropriate.

2. In the cases identified under paragraph 1(c), the Commission, having regard to the opinion from the Agency and within the time limit foreseen in Article 23(1a), shall amend where necessary the decision granting the marketing authorisation. The Community Register of Medicinal Products provided for in Article 13(1) and Article 38(1) of Regulation (EC) No 726/2004 shall be updated accordingly."

(14) Article 18 is amended as follows:

(a) paragraph 1 is replaced by the following:

"1. By way of derogation from Article 16, 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."

(b) paragraphs 3, 4, 5 and 6 are replaced by the following:

"3. The Agency shall assess the application submitted. Where deemed necessary, the Agency may request additional data to complete its assessment.

4. Within 55 days from the receipt of a valid application, the Agency shall adopt an opinion. The Agency's opinion on the application shall be transmitted to the applicant. Where the Agency's opinion is favourable, the Agency shall also transmit to the Commission its opinion and the grounds for its opinion as well as the revised versions of the documents referred in Article 9(4) of Regulation (EC) No 726/2004.

5. The 55-day period referred to in paragraph 4 shall be suspended from the moment when the additional data referred to in paragraph 3 is requested until the data is submitted.

6. Having regard to the favourable opinion of the Agency, the Commission shall amend where necessary the decision granting the marketing authorisation. The Community Register of Medicinal Products provided for in Article 13(1) of Regulation (EC) No 726/2004 shall be updated accordingly. "

(c) paragraph 7 is deleted.

(15) Article 20 is amended as follows:

(a) paragraphs 1 is replaced by the following:

"1. By way of derogation from Articles 7(1), 9, 10, 13b, 13c, 13d, 15 and 16 the holder of a marketing authorisation may choose to follow the worksharing procedure laid down in paragraphs 3 to 9 in the following cases:

- (a) for marketing authorisations referred to in Chapters II and III, where a minor variation of type IB, a major variation of type II, or a group of variations as provided for in Article 7(2) (b) or (c) that does not contain any extension relates to several marketing authorisations owned by the same holder;
- (b) for purely national marketing authorisations referred to in Chapter IIa, where a minor variation of type IB, a major variation of type II, or a group of variations as provided for in Article 13d(2) (b) or (c) that does not contain any extension relates to several marketing authorisations owned by the same holder;
- (c) for purely national marketing authorisations referred to in Chapter IIa, where a minor variation of type IB, a major variation of type II, or a group of variations as provided for in Article 13d(2) (b) or (c) that does not contain any extension relates to one marketing authorisation that is owned by the same holder in more than one Member State.

Variations covered under (a), (b), or (c) may be subject to the same worksharing procedure.

The reference authority or, in the case of purely national marketing authorisations, the competent authority may refuse to process a submission under the worksharing procedure where the same change(s) to different marketing authorisations require the submission of individual supportive data for each medicinal product concerned or a separate product-specific assessment."

(b) paragraph 2 is replaced by the following:

"2. For the purposes of this Article, 'reference authority' shall mean one of the following:

- (a) the Agency where at least one of the marketing authorisations referred to 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."

(c) in paragraph 3, the first and second subparagraphs are replaced by the following:

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

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

(d) paragraphs 4 and 5 are replaced by the following:

"4. The reference authority shall issue an opinion on a valid application as 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 or for grouping of variations in accordance with Article 7(2)(c) or Article 13d(2)(c)."

(e) paragraphs 7 and 8 are replaced by the following:

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

The Agency's opinion on the application shall be transmitted to the applicant and the Member States, together with the assessment report. Where the outcome of the assessment is favourable and the variation affects the terms of the Commission decision granting the marketing authorisation, the Agency shall also transmit to the Commission its opinion and the grounds for its opinion as well as the revised versions of the documents referred in Article 9(4) of Regulation (EC) No 726/2004.

Where the Agency issues a favourable opinion, the following shall apply:

- (a) if the opinion recommends the variation to the terms of a Commission decision granting the marketing authorisation, the Commission shall, having regard to the final opinion and within the time limits foreseen in Article 23(1a), amend the decision(s) accordingly, provided that the revised versions of the documents referred to in Article 9(4) or Article 34(4) of Regulation (EC) No 726/2004 have been received. The Community Register of Medicinal Products provided for in Article 13(1) and Article 38(1) of Regulation (EC) No 726/2004 shall be updated accordingly;
 - (b) the Member States concerned shall, within 60 days following receipt of the final opinion of the Agency, approve that final opinion, inform the Agency thereof and, where necessary, amend the marketing authorisations concerned accordingly, provided that the documents necessary for the amendment of the marketing authorisation have been transmitted to the Member States concerned.
8. Where the reference authority is the competent authority of a Member State:
- (a) it shall send its opinion 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 and inform the reference authority;
 - (c) the concerned marketing authorisations shall be amended accordingly within 30 days following the approval of the opinion, provided that the documents necessary for the amendment of the marketing authorisation have been transmitted to the Member States concerned."
- (f) the following paragraph 10 is inserted after paragraph 9:

"10. Where harmonisation of a section of the summary of product characteristics of a purely national marketing authorisation has been achieved through a worksharing procedure, any subsequent variation submission affecting the harmonised section shall be transmitted simultaneously to all Member States concerned."

- (16) In Article 21, paragraph 1 is replaced by the following:

"1. By way of derogation from Chapter I, II, IIa, and III, where a pandemic situation with respect to human influenza is duly recognised by the World Health Organisation or by the Union in the framework of Decision 2119/98/EC of the European Parliament and of the Council,⁷ 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."

- (17) In Article 22, paragraph 1 is replaced by the following:

⁷ OJ L 268, 3.10.1998, p. 1.

"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 Agency.

If the relevant authority or, in the case of a centralised marketing authorisation, the Agency has not raised objections within 24 hours following receipt of that information, the urgent safety restrictions shall be deemed accepted."

(18) Article 23 is amended as follows:

(a) paragraph 1 is replaced by the following:

"1. Amendments to the decision granting the marketing authorisation resulting from the procedures laid down in Chapters II and IIa shall be made:

- (a) in the case of major variations of type II, within two months following receipt of the information referred to in Article 11(1)(c) and Article 13e(a), provided that the documents necessary for the amendment of the marketing authorisation have been transmitted to the Member States concerned;
- (b) in the other cases, within six months following receipt of the information referred to in Article 11(1)(c) and Article 13e(a), provided that the documents necessary for the amendment of the marketing authorisation have been transmitted to the Member States concerned."

(b) the following paragraph 1a is inserted after paragraph 1:

"1a. Amendments to the decision granting the marketing authorisation resulting from the procedures laid down in Chapter III shall be made:

- (a) within two months following receipt of the information referred to in Article 17(1)(c) for the following variations:
 - (i) variations related to the addition of a new therapeutic indication or to the modification of an existing one;
 - (ii) variations related to the addition of a new contraindication;
 - (iii) variations related to a change in posology;
 - (iv) variations related to the addition of a non-food producing target species or the modification of an existing one for veterinary medicinal products;
 - (v) variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine;

(vi) variations related to changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

(vii) variations related to changes to the withdrawal period for a veterinary medicinal product;

(viii) other type II variations that are intended to implement changes to the decision granting the marketing authorisation due to a significant public health concern or significant animal health or environmental concern in the case of veterinary medicinal products.

(b) within twelve months following receipt of the information referred to in Article 17(1)(c) in the other cases.

The Agency shall determine the variations referred to in point (b)(viii) and provide reasons for such determination."

(c) paragraph 2 is replaced by the following:

"2. Where the decision granting a marketing authorisation is amended as a result of one of the procedures laid down in Chapters II, IIa, 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."

(19) The following Article 23a is inserted after article 23:

The statement indicating compliance with the agreed completed paediatric investigation plan provided for under Article 28(3) of Regulation (EC) No 1901/2006 shall be included within the technical dossier of the marketing authorisation.

The relevant authority shall provide the holder with a confirmation that the statement is included in the technical dossier within 30 days after the relevant assessment has been concluded.

(20) Article 24 is replaced by the following:

"Article 24

Implementation of variations

1. Minor variations of type IA may be implemented any time before completion of the procedures laid down in Articles 8, 13a, 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), 13e (a), and 17(1)(a).

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

(a) for variations submitted in accordance with the procedures laid down in Chapter II, 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) for variations submitted in accordance with the procedures laid down in Chapter IIa, after the relevant authority has informed the holder that it has accepted the notification pursuant to Article 13b, or after the notification is deemed accepted pursuant to Article 13b(2);
- (c) for variations submitted in accordance with the procedures laid down in Chapter III, 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);
- (d) for variations submitted in accordance with the procedure laid down in Article 20, after the reference authority has informed the holder that its opinion is favourable.

3. Major variations of type II may only be implemented in the following cases:

- (a) for variations submitted in accordance with the procedures laid down in Chapter II, 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. Where an arbitration procedure has been initiated in accordance with Article 13, the holder shall not implement the variation until the arbitration procedure has concluded that the variation is accepted.
- (b) for variations submitted in accordance with the procedures laid down in Chapter IIa, after the competent authority has informed the holder that it has accepted the variation pursuant to Article 13c.
- (c) for variations submitted in accordance with the procedures laid down in Chapter III, after the Agency has informed the holder that its opinion referred to in Article 16 is favourable, unless the variation is one referred to in Article 23(1a)(a).

Variations referred to in Article 23(2)(b) may only be implemented after the Commission has amended the decision granting the marketing authorisation and notified the holder thereof.

- (d) for variations submitted in accordance with the procedure laid down in Article 20, 30 days after the reference authority has informed the holder that its opinion is favourable, under the condition that the documents necessary for the amendment to the marketing authorisation have been provided to the Member States concerned; unless an arbitration procedure has been initiated in accordance with Article 13, or unless the procedure concerns a variation to a centralised marketing authorisation as referred to in Article 23(1a)(a).

Where an arbitration procedure has been initiated in accordance with Article 13, or where the worksharing procedure concerns a variation to a centralised marketing authorisation as referred to in Article 23(1a)(a), the holder shall not implement the variation until the arbitration procedure has concluded that the variation is accepted, or until the Commission Decision amending the decision granting the marketing authorisation has been adopted.

5. 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 and notified the holder accordingly.
6. 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 Agency.

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."

- (21) The title of Annex III is replaced by the following:

"Cases for grouping variations referred to in Article 7(2)(b) and Article 13d(2)(b)"

- (22) The following Article 24a is inserted after Article 24:

"Article 24a

Application of national provisions on variations to purely national marketing authorisations

Member States that, in accordance with Article 23b(4) of Directive 2001/83, may continue to apply their national provisions on variations to certain purely national marketing authorisations are listed in Annex VI to this Regulation."

- (23) The Annex set out in the Annex to this Regulation is added.

Article 2

Transitional arrangements

1. From [90 days following that of its publication], the following changes shall be made in Article 23(1) of Regulation (EC) No 1234/2008:
 - (a) The reference to Chapter III shall be deleted.
 - (b) Sub-paragraph (a) shall be deleted.

Article 3

Entry into force and application

1. This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.
2. It shall apply from [90 days following that of its publication].

However, points (10), (15), (18)(a) and (c), (21), (22) and (23) of Article 1 shall apply from [12 months following publication in the Official Journal of the European Union]

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

Done at Brussels,

For the Commission
On behalf of the President [...]
[Position]

ANNEX

"ANNEX VI

List of Member States referred in Article 24a

the Republic of Bulgaria,

the Federal Republic of Germany."