COMMISSION OF THE EUROPEAN COMMUNITIES

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Draft

COMMISSION REGULATION (EC) No …/..

of […]

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

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This document does not represent an official position of the European Commission. It is a tool to explore the views of interested parties on a preliminary proposal. The suggestions contained in this document do not prejudge the form and content of any future proposal by the European Commission.

This document is to be read together with the Public Consultation Paper 'Better Regulation of Pharmaceuticals: Towards a Simpler, Clearer and More Flexible Framework on Variations (version: 24 October 2007).

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THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

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

Having regard to Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products[2], and in particular Article XX *[39(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[3], and in particular of Article 16(4) and Article 41(6) thereof,

Whereas:

(1) (…)

HAS ADOPTED THIS REGULATION:

1 OJ L 311, 28.11.2001, p. 1. Directive as last amended by Directive 2004/27/EC (OJ L 136, 30.4.2004, p. 34).

2 OJ L 311, 28.11.2001, p. 67 Directive as last amended by Directive 2004/28/EC (OJ L 136, 30.4.2004, p. 58).

3 OJ L 136, 30.4.2004, p. 1.

CHAPTER I
General provisions

1. Article
Subject matter

This Regulation lays down provisions concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.

2. Article
Scope

1. This Regulation shall apply to amendments to the terms of marketing authorisations granted pursuant to:

   (a) Article 6 of Directive 2001/83/EC in the case of medicinal products for human use;

   (b) Article 5 of Directive 2001/82/EC in the case of veterinary medicinal products.

2. By way of derogation from paragraph 1, this Regulation shall not apply to:

   (a) transfers of a marketing authorisation to a new marketing authorisation holder (hereinafter "the holder");

   (b) changes to the maximum residue limit as defined in Article 1(1)(b) of Council Regulation (EEC) No 2377/90[4].

3. Chapter II shall only apply to variations to the terms of marketing authorisations granted in accordance with Articles 17 to 26 of Directive 2001/83/EC or Articles 21 to 30 of Directive 2001/82/EC.

4. Chapter III shall only apply to variations to the terms of marketing authorisations granted in accordance with Articles 27 to 39 of Directive 2001/83/EC or Articles 31 to 43 of Directive 2001/82/EC.

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

3. Article
Definitions

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

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

1. ‘Amendment to the terms of a marketing authorisation’ means a modification of the decision granting a marketing authorisation for a medicinal product, or of the annexes of such decision, which results from the examination of a variation submitted by the holder.

2. ‘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 8(3), 9, 10, 10a, 10b and 11 of Directive 2001/83/EC and Article 6(2) of Regulation (EC) No 726/2004 in the case of medicinal products for human use;

   (b) Articles 12(3), 13, 13a, 13b and 14 of Directive 2001/82/EC and Article 31(2) of Regulation (EC) No 726/2004 in the case of veterinary medicinal products.

   A variation may be:

   – a minor variation of Type IA, as defined in paragraph 3; or

   – a minor variation of Type IB, as defined in paragraph 5; or

   – a major variation of Type II, as defined in paragraph 6; or

   – an extension of a marketing authorisation, as defined in paragraph 7.

3. ‘Minor variation of Type IA’ means a variation which is not expected to have any negative impact on the quality, safety or efficacy of the medicinal product concerned.

4. ‘Minor variation requiring immediate notification’ means a minor variation of Type IA whose immediate reporting to the relevant authority is necessary for the continuous and permanent supervision of the medicinal product concerned.

5. ‘Minor variation of Type IB’ means a variation which is neither a minor variation of Type IA, a major variation of Type II nor an extension.

6. ‘Major variation of Type II’ means a variation, which is not an extension, and which has a substantial potential to have a negative impact on the quality, safety or efficacy of the medicinal product concerned.

7. ‘Extension of a marketing authorisation’ or ‘extension’ means a variation which is listed in Annex I and fulfils the conditions laid down therein.

8. ‘Reference Member State’ means the Member State chosen by the holder with a view to the application of this Regulation, or, in the absence of such choice, the reference Member State as referred to in Article 28 of Directive 2001/83/EC and Article 32 of Directive 2001/82/EC.

9. ‘Concerned Member State’ means a Member State whose competent authority has granted a marketing authorisation for the medicinal product in question.

10. ‘Relevant authority’ means:

(a) the competent authority of each concerned Member State; or

(b) in the case of marketing authorisations granted in accordance with Regulation (EC) No 726/2004, the Commission and the European Medicines Agency (hereinafter 'the Agency').

11. '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.

4. Article
Classification of variations

1. Any variation which is not an extension shall be classified in accordance with the detailed guidelines referred to in point (a) of Article 6(1).

2. A variation which is not an extension and whose classification is not laid down in the detailed guidelines referred to in point (a) of Article 6(1) shall be considered a minor variation of Type IB.

5. Article
Scientific recommendation on unforeseen variations

1. Prior to submission of a variation whose classification is not laid down in the detailed guidelines referred to in point (a) of Article 6(1), a holder may request the Agency to provide a scientific recommendation with a view to determining the potential impact on the quality, safety or efficacy of the referred variation on the medicinal products concerned.

The Agency shall deliver this recommendation within 60 days following receipt of the request, taking into account the guidelines referred to in point (a) of Article 6(1), Article 29(2) of Directive 2001/83/EC and Article 33(2) of Directive 2001/82/EC.

The recommendation delivered in accordance with the first subparagraph shall be sent to the holder and to the competent authorities of all Member States.

2. The Agency shall publish the recommendations delivered in accordance with paragraph 1, after deletion of all information of commercial confidential nature.

6. Article
Guidelines

1. The Commission, in consultation with Member States, the Agency and interested parties, shall draw up:

(a) detailed guidelines on the conditions for classification of variations which are not extensions;

(b) detailed guidelines on the operation of the procedures laid down in Chapters II to V 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 regularly updated, taking into account the recommendations delivered in accordance with Article 5 as well as scientific and technical progress.

7. Article
Grouping of variations

1. Where several variations are submitted, a separate procedure as laid down in Chapters II to V shall apply in respect of each variation sought.

2. By way of derogation from the first paragraph:

(a) where a variation leads to the revision of the summary of product characteristics, labelling and package leaflet or insert, this revision shall be considered as part of the same variation;

(b) where several minor variations of Type IA to the terms of one or several marketing authorisations owned by the same holder are notified simultaneously to the same relevant authority, a single notification as referred to in Article 8, 12 or 17 may cover all such variations;

(c) where a group of variations to the terms of the same marketing authorisation is submitted at once to a relevant authority and falls within one of the categories listed in Annex II, all such variations may be covered by:

– a single application as referred to in Article 23 where at least one of the referred variations is an extension;

– a single application as referred to in Articles 10, 14 and 19 where at least one of the referred variations is a major variation of Type II;

– a single notification as referred to in Articles 9, 13 and 18 where at least one of the referred variations is a minor variation of Type IB.

(d) Where a minor variation of Type IB, a major variation of Type II, an extension or a group of variations falling within one of the categories listed in Annex II relates to changes that concerns several marketing authorisations owned by the same holder, such variations may be covered by a single application as referred to in Article 24.

CHAPTER II
Variations to marketing authorisations granted by Member States without mutual recognition

8. Article
"Do and Tell" procedure for Type IA variations [Nat.]

1. Where a minor variation of Type IA is made, the holder shall submit to the relevant authority a notification including the elements listed in paragraph 1 of Annex III. This notification shall be submitted:

(a) forthwith in the case of minor variations requiring immediate notification;

(b) within twelve months following implementation of the variation in the other cases.

2. Within one month following receipt of the notification referred to in paragraph 1, the relevant authority shall close the procedure in accordance with Article 21(1).

9. Article
"Tell, Wait and Do" procedure for Type IB variations [Nat.]

1. With regard to minor variations of Type IB, the procedure laid down in paragraphs 2 to 6 shall apply.

2. The holder shall submit to the relevant authority a notification including the elements listed in paragraph 2 of Annex III.

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

3. If within 30 days following the acknowledgement of receipt of a valid notification referred to in paragraph 2 the relevant authority has not sent the holder its opinion provided for in paragraph 4, the notification shall be deemed accepted.

Where the notification is accepted, the relevant authority shall close the procedure in accordance with Article 21(1).

4. Where the relevant authority is of the opinion that the notification referred to in paragraph 2 cannot be accepted, it shall inform the holder, stating the grounds on which its opinion is based.

Within 30 days of receipt of the opinion referred to in the first subparagraph, the holder may submit to the relevant 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 and the relevant authority shall close the procedure in accordance with Article 21(1).

5. *By way of derogation from the second and third subparagraphs of paragraph 4, where the classification of the variation concerned is not laid down in the detailed guidelines referred to in point (a) of Article 6(1) and the relevant authority is of the opinion that the referred variation has a substantial potential to have a negative impact on the quality, safety or efficacy of the medicinal product concerned, the variation shall be evaluated in accordance with the procedure laid down in paragraphs 2 to 5 of Article 10.*

6. *Where an amended notification has been submitted in accordance with paragraph 4, the relevant authority shall assess it within 30 days following its receipt and close the procedure in accordance with Article 21(1).*

10. Article
"Prior Approval" procedure for Type II variations [Nat.]

1. *With regard to major variations of Type II, the procedure laid down in paragraphs 2 to 5 shall apply.*

2. *The holder shall submit to the relevant authority an application accompanied by the elements listed in paragraph 2 of Annex III.*

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

3. *The relevant authority shall evaluate the valid application referred to in paragraph 2 within 60 days following its receipt.*

   By way of derogation from the first subparagraph:

   (a) *the relevant authority may reduce the period referred to in that subparagraph, having regard to the urgency of the matter, or extend it to 90 days in the case of variations concerning a change to or addition of therapeutic indications;*

   (b) *the period referred to in the first subparagraph shall be extended to 90 days in the case of variations concerning a change to or addition of a non-food producing target species.*

4. *Within the period laid down in paragraph 3, the relevant authority may request the holder to provide supplementary information within a time limit set by that competent authority. The procedure shall be suspended until such supplementary information has been provided. In this case the period laid down in paragraph 3 may be extended for a further period to be determined by the relevant authority.*

5. *Within the period laid down in paragraph 3, the relevant authority shall, where it reaches a final opinion on the application, close the procedure in accordance with Article 21(1).*

11. Article
Human influenza vaccines [Nat.]

1. *By way of derogation from Article 10, the procedure laid down in paragraphs 2 to 5 shall apply for the examination of variations concerning changes to the active substance for the annual update of a human influenza vaccine.*

2. *The holder shall submit to the relevant authority an application accompanied by the elements listed in paragraph 3 of Annex III.*

If the application fulfils the requirements laid down in the first subparagraph, the relevant authority shall acknowledge receipt of a valid application and inform the holder of the date of the start of the procedure laid down in paragraphs 3 to 5.

3. *Within 45 days following the date referred to in paragraph 2, the relevant authority shall prepare a draft decision on the application.*

4. *Within the period laid down in paragraph 3, the relevant authority may request the holder to provide supplementary information.*

5. *Where requested, the clinical data and those concerning the stability of the medicinal product shall be submitted by the holder to the relevant authority within 12 days following the end of the period laid down in paragraph 3.*

Within 7 days following receipt of the data referred to in the first subparagraph, the relevant authority shall evaluate the data referred to in the first subparagraph, adopt a final decision and amend the marketing authorisation accordingly.

CHAPTER III
Variations to marketing authorisations granted by Member States with mutual recognition/decentralised procedure

12. Article
"Do and Tell" procedure for Type IA variations [MRP]

1. Where a minor variation of Type IA is made, the holder shall submit simultaneously to all relevant authorities a notification including the elements listed in paragraph 1 of Annex III. This notification shall be submitted:

   (a) forthwith in the case of minor variations requiring immediate notification;

   (b) within twelve months following implementation of the variation in the other cases.

2. Within one month following receipt of the elements referred to in paragraph 1, the competent authority of the reference Member State shall close the procedure in accordance with Article 21(2).

13. Article
"Tell, Wait and Do" procedure for Type IB variations [MRP]

1. With regard to minor variations of Type IB, the procedure laid down in paragraphs 2 to 6 shall apply.

2. The holder shall submit simultaneously to all relevant authorities a notification including the elements listed in paragraph 2 of Annex III.

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

3. If within 30 days following the acknowledgement of receipt of a valid notification referred to in paragraph 13, the competent authority of the reference Member State has not sent the holder its opinion provided for in paragraph 4, the notification shall be deemed accepted by all relevant authorities.

   Where the notification is accepted by the competent authority of the reference Member State, that competent authority shall close the procedure in accordance with Article 21(2).

4. Where the competent authority of the reference Member State is of the opinion that the notification referred to in paragraph 13 cannot be accepted, it shall inform the holder and the other relevant authorities, stating the grounds on which its opinion is based.

Within 30 days following the receipt of the opinion referred to in the first subparagraph, 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 competent authority of the reference Member State shall close the procedure in accordance with Article 21(2).

5. By way of derogation from the second and third subparagraphs of paragraph 4, where the classification of the variation concerned is not laid down in the detailed guidelines referred to in point (a) of Article 6(1) and the competent authority of the reference Member State is of the opinion that the referred variation has a substantial potential to have a negative impact on the quality, safety or efficacy of the medicinal product concerned, the variation shall be evaluated in accordance with the procedure laid down in paragraphs 2 to 6 of Article 14.

6. Where an amended notification has been submitted in accordance with paragraph 4, the competent authority of the reference Member State shall assess it within 30 days following its receipt and close the procedure in accordance with Article 21(2).

14. Article
"Prior Approval" procedure for Type II variations [MRP]

1. With regard to major variations of Type II, the procedure laid down in paragraphs 2 to 6 shall apply.

2. The holder shall submit simultaneously to all relevant authorities an application accompanied by the elements listed in paragraph 2 of Annex III.

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 of the date of the start of the procedure laid down in paragraphs 3 to 6.

3. Within 60 days from the date referred to in paragraph 2, the competent authority of the reference Member State shall prepare an assessment report and a draft decision on the application, which shall be addressed to the other relevant authorities.

By way of derogation from the first subparagraph:

(a) the competent authority of the reference Member State may reduce the period referred to in that subparagraph, having regard to the urgency of the matter, or extend it to 90 days in the case of variations concerning a change to or addition of therapeutic indications;

(b) the period referred to in the first subparagraph shall be extended to 90 days in the case of variations concerning a change to or addition of a non-food producing target species.

4. Within the period laid down in paragraph 3, 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 period laid down in paragraph 3 may be extended for a further period to be determined by the competent authority of the reference Member State.

5. Within 30 days following receipt of the draft decision and the assessment report referred to in paragraph 3, the relevant authorities shall recognise the draft decision and inform the competent authority of the reference Member State accordingly.

6. Where, pursuant to paragraph 5, the draft decision referred to in paragraph 3 has been recognised by all relevant authorities, the competent authority of the reference Member State shall close the procedure in accordance with Article 21(2).

15. Article
Human influenza vaccines [MRP]

1. By way of derogation from Article 14, the procedure laid down in paragraphs 2 to 6 shall apply for the examination of variations concerning changes to the active substance for the annual update of a human influenza vaccine.

2. The holder shall submit simultaneously to all relevant authorities an application accompanied by the elements listed in paragraph 3 of Annex III.

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 of the date of the start of the procedure laid down in paragraphs 3 to 6.

3. Within 30 days following the date referred to in paragraph 2, the competent authority of the reference Member State shall prepare an assessment report and a draft decision on the application, which shall be addressed to the other relevant authorities.

4. Within the period laid down 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 of receipt of the draft decision and the assessment report referred to in paragraph 3, the relevant authorities shall recognise the draft decision and inform the competent authority of the reference Member State to this effect.

6. Where requested by the competent authority of the reference Member State, the clinical data and those concerning the stability of the medicinal product shall be

submitted by the holder to all relevant authorities within 12 days following the end of the period laid down 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 7 days following receipt of the data. The other relevant authorities shall recognise that final decision and, within 7 days following its receipt, adopt a decision accordingly.

16. Article
Coordination group and arbitration [MRP]

1. Where, during the course of the procedures laid down in Articles 12 to 15, a relevant authority is not in agreement with the opinion or the draft decision of the competent authority of the reference Member State, it shall bring the matter:

   (a) to the coordination group laid down in Article 27 of Directive 2001/83/EC in the case of medicinal products for human use;

   (b) to the coordination group laid down in Article 31 of Directive 2001/82/EC in the case of veterinary medicinal products.

   Within the coordination group, all Member States shall use their best endeavour to reach agreement on the action to be taken.

2. The procedure referred to in Article 35(2) of Directive 2001/83/EC and Article 39 (2) of Directive 2001/82/EC shall apply in the following cases:

   (a) upon request from the holder, where in disagreement with the final outcome of a procedure laid down in Article 13 or Article 14 and within 10 days following receipt of the information referred to in point (a) of Article 21(2);

   (b) upon request from a relevant authority, where in disagreement with the final outcome of a procedure laid down in Article 13 and within 10 days following receipt of the information referred to in point (a) of Article 21(2);

   (c) where recognition of a draft decision in accordance with paragraph 5 of Article 14 and paragraphs 5 and 6 of Article 15 by a relevant authority is not possible, for reasons of public or animal health.

CHAPTER IV
Variations to marketing authorisations granted in accordance with Regulation (EC) No 726/2004

17. Article
"Do and Tell" procedure for Type IA variations [Centr.]

1. Where a minor variation of Type IA is made, the holder shall submit to the Agency a notification including the elements listed in paragraph 1 of Annex III. This notification shall be submitted:

   (a) forthwith in the case of minor variations requiring immediate notification;

   (b) within twelve months following implementation of the variation in the other cases.

2. Within one month following receipt of the elements referred to in paragraph 1, the procedure shall be closed in accordance with Article 21(3).

18. Article
"Tell, Wait and Do" procedure for Type IB variations [Centr.]

1. With regard to minor variations of Type IB, the procedure laid down in paragraphs 2 to 6 shall apply.

2. The holder shall submit to the Agency a notification including the elements listed in paragraph 2 of Annex III.

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

3. If within 30 days following the acknowledgement of receipt of a valid notification referred to in paragraph 2 the Agency has not sent the holder its opinion provided for in paragraph 4, that opinion shall be deemed favourable.

   Where the opinion of the Agency on the notification is favourable, the Agency shall close the procedure in accordance with Article 21(3).

4. Where the Agency is of the opinion that the notification referred to in paragraph 2 cannot be accepted, it shall inform the holder, stating the grounds on which its opinion is based.

   Within 30 days of receipt of the opinion referred to in paragraph 4, 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 that paragraph, the notification shall be deemed rejected and the Agency shall close the procedure in accordance with Article 21(3).

5. By way of derogation from the second and third subparagraphs of paragraph 4, where the classification of the variation concerned is not laid down in the detailed guidelines referred to in point (a) of Article 6(1) and the Agency or the Commission is of the opinion that the referred variation has a substantial potential to have a negative impact on the quality, safety or efficacy of the medicinal product concerned, the variation shall be evaluated in accordance with the procedure laid down in paragraphs 2 to 6 of Article 19.

6. Where an amended notification has been submitted in accordance with paragraph 4, the Agency shall assess it within 30 days following its receipt and close the procedure in accordance with Article 21(3).

19. Article
"Prior Approval" procedure for Type II variations [Centr.]

1. With regard to major variations of Type II, the procedure laid down in paragraphs 2 to 6 shall apply.

2. The holder shall submit to the Agency an application accompanied by the elements listed in paragraph 2 of Annex III.

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

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

   By way of derogation from the first subparagraph:

   (a) the Agency may reduce the period referred to in that subparagraph, having regard to the urgency of the matter, or extend it to 90 days in the case of variations concerning a change to or addition of therapeutic indications;

   (b) the period referred to in the first subparagraph shall be extended to 90 days in the case of variations concerning a change to or addition of a non-food producing target species.

4. Within the period laid down in paragraph 3, the Agency may send the holder a request for supplementary information within a certain time limit set by that the Agency. The procedure shall be suspended until such time as the supplementary information has been provided. In this case the period laid down in paragraph 3 may be extended for a further period to be determined by the Agency.

5. Articles 9(1), 9(2), 9(3), 34(1), 34(2) and 34(3) of Regulation (EC) No 726/2004 shall apply to the opinion referred to in paragraph 3.

6. Where the opinion referred to in paragraph 3 is favourable, the Agency shall send to the Commission a proposal for amendments to be made to the terms of the marketing authorisation, accompanied by the documents referred to in Article 9(4) and 34(4) of Regulation (EEC) No. 726/2004.

Where necessary and based on the proposal referred to in the first subparagraph, the Commission shall amend the marketing authorisation and update the Community Register of Medicinal Products provided for in Articles 13(1) and 38(1) of Regulation (EC) No 726/2004 accordingly.

20. Article
Human influenza vaccines [Centr.]

1. By way of derogation from Article 19, the procedure laid down in paragraphs 2 to 7 shall apply for the examination of variations concerning changes to the active substance for the annual update of a human influenza vaccine.

2. The holder shall submit to the Agency an application accompanied by the elements listed in paragraph 3 of Annex III.

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 of the date of the start of the procedure laid down in paragraphs 3 to 7.

3. Within 45 days following the date referred to in paragraph 2, the Agency shall give its opinion on the valid application.

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

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

The Commission shall, where necessary and based on the opinion referred to in the first subparagraph, adopt a decision amending the marketing authorisation and inform the holder accordingly.

This decision shall be implemented by the holder under the condition that the final opinion of the Agency as provided for in paragraph 6 is favourable.

6. Where requested, the clinical data and those concerning the stability of the medicinal product shall be submitted by the holder to the Agency within 12 days following the end of the period laid down 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 reception of the data. The Agency shall address its final opinion to the Commission and to the holder within the 3 following days.

7. Where necessary and based on the final opinion of the Agency referred to in paragraph 6, the Commission shall amend the marketing authorisation and update the

Community Register of Medicinal Products provided for in Articles 13(1) of Regulation (EC) No 726/2004 accordingly.

CHAPTER V

SECTION 1
CLOSURE OF PROCEDURES AND IMPLEMENTATION

21. Article
Closure of procedures

1. Where reference is made to this paragraph, the following provisions shall apply:

(a) The relevant authority shall forthwith provide the holder with the following information:

– whether the variation or notification is accepted or rejected;

– where the variation or notification is rejected, the grounds on which that rejection is based;

– whether the variation or notification requires any amendment to the terms of the marketing authorisation.

(b) Where necessary, the relevant authority shall amend the marketing authorisation in accordance with the accepted variation or notification:

– within two months after sending the information referred to in point (a) in the case of minor variations of Type IA which do not require immediate notification;

– within 6 months after sending the information referred to in point (a) in the other cases.

2. Where reference is made to this paragraph, the following provisions shall apply:

(a) The competent authority of the reference Member State shall forthwith provide the holder and the other relevant authorities with the following information:

– whether the variation or notification is accepted or rejected;

– where the variation or notification is rejected, the grounds on which that rejection is based;

– whether the variation or notification requires any amendment to the terms of the marketing authorisation.

(b) Without prejudice to Article 16, each relevant authority shall, where necessary, amend the marketing authorisation in accordance with the accepted variation or notification:

– within two months following receipt of the information referred to in point (a) in the case of minor variations of Type IA which do not require immediate notification;

– within 6 months following receipt of the information referred to in point (a) in the other cases.

3. Where reference is made to this paragraph, the following provisions shall apply:

(a) The Agency shall forthwith provide the holder and the Commission with the following information:

– whether the opinion of the Agency on the variation or notification is favourable or unfavourable;

– where the opinion of the Agency on the variation or notification is unfavourable, the grounds on which that opinion is based;

– whether the variation or notification requires any amendment to the terms of the marketing authorisation.

(b) The Commission shall, where necessary and based on a proposal from the Agency, amend the marketing authorisation and update the Community Register of Medicinal Products provided for in Articles 13(1) and 38(1) of Regulation (EC) No 726/2004 accordingly.

(c) The amendment of the marketing authorisation referred to in point (b) shall be made:

– within two months following receipt of the information referred to in point (a) in the case of minor variations of Type IA which do not require immediate notification;

– within 6 months following receipt of the information referred to in point (a) in the other cases.

4. Where a marketing authorisation is amended as a result of one of the procedures laid down in Chapters II to IV, the amended marketing authorisation shall be notified to the holder by the relevant authority.

22. Article
Implementation by economic operators

1. A minor variation of Type IA may be implemented anytime before completion of the procedures laid down in Articles 8, 12 and 17.

2. Minor variations of Type IB and major variations of Type II may only be implemented:

– once the relevant authority has accepted the notification or variation pursuant to Article 9 or Article 10 and informed the holder accordingly; or

– once the competent authority of the reference Member State has accepted the notification or variation pursuant to Article 13 or Article 14 and informed the holder accordingly; or

– once the Agency has informed the holder that its opinion referred to in Article 18 or Article 19 is favourable; or

– in the case of minor variations of Type IB, once the corresponding notification is deemed accepted pursuant to paragraph 3 of Articles 9, 13 or 18.

3. An extension may only be implemented once the relevant authority has amended the marketing authorisation in accordance with the approved extension and notified the holder accordingly.

4. Urgent safety restrictions and variations which are related to safety issues shall be implemented within a timeframe agreed by the holder and the relevant authority.

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 Articles 27 to 39 of Directive 2001/83/EC or Articles 31 to 43 of Directive 2001/82/EC shall be implemented within a timeframe agreed by the holder and the competent authority of the reference Member State, in consultation with the other relevant authorities.

SECTION 2
SPECIAL PROCEDURES

23. Article
Extensions of marketing authorisations

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

24. Article
Worksharing procedure

1. Where a minor variation of Type IB, a major variation of Type II, an extension or a group of variations falling within one of the categories listed in Annex II relates to changes that concerns several marketing authorisations, the holder of such authorisations may follow the procedure laid down in paragraphs 2 to 6.

2. The holder shall submit to the Agency an application accompanied by the elements listed in points (a) to (g)(1) of paragraph 2 of Annex III.

In the application referred to in the first subparagraph, the holder shall specify:

(a) whether the concerned marketing authorisations all relate to the same medicinal product; or

(b) whether the concerned marketing authorisations relate to different medicinal products.

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

3. The Agency shall issue an opinion on the valid application referred to in paragraph 2 within:

(a) 60 days following receipt of the valid application in the case of minor variations of Type IB or major variations of Type II;

(b) 210 days following receipt of the valid application in the case of extensions.

4. By way of derogation from point (a) of paragraph 3:

(a) the Agency may reduce the period referred to in that point, having regard to the urgency of the matter, or extend it to 90 days in the case of variations concerning a change to or addition of therapeutic indications;

(b) the period referred to in point (a) of paragraph 3 shall be extended to 90 days in the case of variations concerning a change to or addition of a non-food producing target species.

5. Within the period laid down in paragraph 3, the Agency may send the holder a request for supplementary information within a certain time limit set by that the Agency. The procedure shall be suspended until such time as the supplementary information has been provided.

Where supplementary information is requested in accordance with the first subparagraph, the period laid down in points (a) of paragraph 3 may be extended for a further period to be determined by the Agency.

6. Where it reaches a final opinion on the application referred to in paragraph 2, the Agency shall send it to the holder and to all relevant authorities, together with a list of all the marketing authorisations concerned.

7. Upon request from the Agency, concerned Member States shall provide any information related to the marketing authorisations affected by the variation, which is deemed relevant by the Agency for the purpose of:

– verifying the validity of the application referred to in paragraph 2;

– issuing the opinion referred to in paragraph 3.

25. Article
Pandemic situation with respect to human influenza

1. By way of derogation from Articles 11, 15, 20 and 23, 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[5], the relevant authorities 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 timeframe decided by the relevant authority. Continuation of the concerned marketing authorisation shall be linked to the submission and assessment of these data.

26. Article
Urgent safety restrictions

1. Where, in the event of a risk to public or animal health, the holder takes urgent safety restrictions on its own initiative, it shall forthwith inform all relevant authorities.

   If no relevant authority has raised objections within 24 hours following receipt of the information referred to in the first subparagraph, the referred urgent safety restrictions shall be deemed accepted.

2. The holder shall take urgent safety restrictions where requested by a relevant authority.

3. Where an urgent safety restriction is taken, the holder shall submit the corresponding variation within 15 days following the initiation of that restriction.

CHAPTER VI
Final provisions

27. Article
Continuous monitoring

At any time, the relevant authority may request the holder to submit information related to the implementation of a given variation, including minor variations of Type IA. The holder shall supply this information without delay.

28. Article
Reporting

Within 5 years of entry into force of this Regulation, the Commission shall publish a report on its application. This report shall include information on the number of procedures carried out in accordance with this Regulation and an analysis of the administrative burden entailed by these procedures.

For the purposes of the first paragraph, the Member States shall communicate to the Commission the necessary information related to the application of Chapters II, III and V.

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5 OJ L 268, 3.10.1998, p. 1.

29. Article
Pending applications

This Regulation shall not apply to valid notifications or applications for variations, which are pending at the time of application of this Regulation.

30. Article
Repeal

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

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

31. Article
Entry into force

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

It shall apply from [*when the co-decision part applies*]

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

Done at Brussels, […]

For the Commission
[…]
Member of the Commission

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 necessary for the annual update of a human influenza vaccine submitted in accordance with Articles 11, 15 or 20;

   – replacement of an antigen by another antigen derived from an approved master seed virus in the case of veterinary vaccines against avian influenza, foot-and-mouth disease or bluetongue.

   (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[1].

3. Other changes specific to veterinary medicinal products to be administered to food-producing animals: change or addition of target species.

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[1] For parenteral administration, it is necessary to distinguish between intraarterial, 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.

ANNEX II

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 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.

7. 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.

8. All variations in the group are consequential to a given urgent safety restriction and submitted in accordance with paragraph 3 of Article 26.

9. All variations in the group relate to the implementation of a given class labelling.

10. All variations in the group are consequential to the assessment of a given periodic safety update report.

11. All variations in the group are consequential to a given post-authorisation study conducted under the supervision of the holder.

12. All variations in the group are consequential to a specific obligation carried out pursuant to Article 14(7) of Regulation (EC) No 726/2004.

13. All variations in the group are consequential to a specific procedure or condition carried out pursuant to Article 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 III

1. Elements referred to in Articles 8, 12 and 17:

   (a) a list of the marketing authorisations affected by the notification;

   (b) where the notification does not only relate to minor variations requiring immediate notification, a description, per marketing authorisation affected, of all minor variations of Type IA made in the last twelve months to the terms of the concerned marketing authorisation and which have not been already notified. That description shall include all necessary documents demonstrating that the conditions laid down in the detailed guidelines referred to in point (a) of Article 6(1) for the referred variations are met;

   (c) where the notification only relates to minor variations requiring immediate notification, a description, per marketing authorisation affected, of the minor variation(s) requiring immediate notification. That description shall include all necessary documents demonstrating that the conditions laid down in the detailed guidelines referred to in point (a) of Article 6(1) for the referred variation(s) are met;

   (d) the date of implementation for each variation described;

   (e) 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.

   (f) where the marketing authorisation(s) affected by the notification has been granted in accordance with Regulation (EC) No 726/2004, the relevant fee provided for in Council Regulation (EC) No 297/95[2].

   (g) where the marketing authorisation(s) affected by the notification has been granted by several competent authorities of the Member States:

      (1) a list of those Member States with an indication of the reference Member State if applicable;

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

2. Elements referred to in Articles 9, 10, 13, 14, 18, 19 and 24:

   (a) a list of the marketing authorisations affected by the notification or application;

   (b) all necessary documents demonstrating that the conditions laid down in the detailed guidelines referred to in point (a) of Article 6(1) for the requested variation(s) are met, including all relevant data, particulars and documents

[2] OJ L 35, 15.2.1995, p. 1. Regulation as last amended by Regulation (EC) No 1905/2005 (OJ L 304, 23.11.2005, p. 1).

referred to in Articles 8 to 12 of Directive 2001/83/EC or Articles 12 to 15 of Directive 2001/82/EC;

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

(d) where the variation(s) lead(s) to or is the consequence of other variations to the terms of the same marketing authorisation, a description of the relation between these variations;

(e) in the case of major variations of Type II and extensions, an addendum to or update of existing expert reports/overviews/summaries to take account of the variation applied for.

(f) where the marketing authorisation(s) for the concerned medicinal product has been granted in accordance with Regulation (EC) No 726/2004, or where the application is submitted pursuant to Article 24, the relevant fee provided for in Council Regulation (EC) No 297/95.

(g) where the marketing authorisation(s) affected by the notification or application has been granted by one or several competent authorities of the Member States:

(1) a list of those Member States with an indication of the reference Member State if applicable;

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

3. Elements referred to in Articles 11, 15 and 20:

(a) the administrative information and quality data referred to in Sections 1 and 3, Part I of Annex I to Directive 2001/83/EC;

(b) where the marketing authorisation(s) affected by the application has been granted in accordance with Regulation (EC) No 726/2004, the relevant fee provided for in Council Regulation (EC) No 297/95.

(c) where the marketing authorisation(s) affected by the application has been granted by several competent authorities of the Member States:

(1) a list of those Member States with an indication of the reference Member State if applicable;

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

DRAFT DETAILED GUIDELINE REFERRED TO IN ARTICLE 6(1)(a): CONDITIONS FOR CLASSIFICATION OF VARIATIONS

Note: *This draft guideline is of scientific and technical nature. Finalisation of the guideline requires gathering of all available expertise in the various fields concerned. The draft provided in the frame of this public consultation is therefore preliminary only and not definitive. It is only intended to be used as a starting point for technical discussions with Member States, the EMEA and interested parties. These discussions will take place not only during this public consultation phase, but also afterwards, in parallel with the regulatory procedure for the adoption of the legal proposal reviewing the Variations Regulations.*

Introduction

IA means a minor variation of Type IA;

IA_{IN} means a minor variation of Type IA requiring immediate notification;

IB: means a minor variation of Type IB;

II: means a major variation of Type II.

Extensions are outside the scope of this detailed guideline.

The conditions necessary for a given variation are outlined for each subcategory and listed below each variation. Changes compared to the current Variations Regulations are highlighted in ~~strikethrough~~ and *italic*.

A variation which falls within variation subcategory NEW.1 and another variation subcategory shall be considered to be of subcategory NEW.1.

A variation which is classified in this guideline but which does not fulfil all the necessary conditions laid down in the relevant subcategory shall be considered to be of Type II.

Classification

Title of variation/conditions to be fulfilled	**Type**
1. Change in the name and/or address of the marketing authorisation holder	~~**IA**~~ IA_{IN}
Conditions: The marketing authorisation holder shall remain the same legal entity.	
2. Change in the name of the medicinal product	~~**IA**~~ IA_{IN}
Conditions: No confusion with the names of existing medicinal products or with the International Non-proprietary Name (INN). The check by the relevant authority on the acceptability of the new name by the concerned Member States is finalised and positive.	
3. Change in the name of the active substance	~~**IA**~~ IA_{IN}

Conditions: The active substance shall remain the same.		
4. Change in the name and/or address of a manufacturer of the active substance where no Ph.Eur. Certificate of Suitability is available		~~**IA**~~ IA_{IN}
Conditions: The manufacturing site shall remain the same.		
5. Change in the name and/or address of a manufacturer of the finished product		~~**IA**~~ IA_{IN}
Conditions: The manufacturing site shall remain the same.		
6. Change in ATC Code		
a. Medicinal products for human use		~~**IA**~~ IA_{IN}
Conditions: Change following granting of or amendment to ATC Code by WHO.		
b. Veterinary medicinal products		~~**IA**~~ IA_{IN}
Conditions: Change following granting of or amendment to ATC Vet Code.		
7. Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product		
a. Secondary packaging for all types of pharmaceutical forms	Conditions: 1,2 (see below)	~~**IA**~~ IA_{IN}
b. Primary packaging site		
1. Solid pharmaceutical forms, e.g. tablets and capsules	Conditions: 1,2,3,5	~~**IA**~~ IA_{IN}
2. Semi-solid ~~or liquid~~ pharmaceutical forms	Conditions: 1,2,3,5	~~**IB**~~ IA_{IN}
3. Liquid pharmaceutical forms (*e.g.* suspensions, emulsions)	Conditions : 1,2,3,4,5	**IB**
c. All other manufacturing operations except batch release	Conditions : 1,2,4,5	**IB**

Conditions: 1. Satisfactory inspection in the last 3 years by an inspection service of one of the Member States of the EEA or of a country where an operational Good Manufacturing Practice (GMP) mutual recognition agreement (MRA) exists between the country concerned and the EU. 2. Site appropriately authorised (to manufacture the pharmaceutical form or product concerned). 3. Product concerned is not a sterile product. 4. Validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches. 5. Product concerned is not a biological medicinal product.		
8. Change in batch release arrangements and quality control testing of the finished product		
a. Replacement or addition of a site where batch control/testing takes place	Conditions: 2, 3, 4 (see below)	**IA**
	Conditions: 2, 4 (see below)	***IB***
b. Replacement or addition of a manufacturer responsible for batch release		
1. Not including batch control/ testing	Conditions: 1, 2	~~**IA**~~ IA_{IN}
2. Including batch control/testing	Conditions: 1, 2, 3, 4	~~**IA**~~ IA_{IN}
	Conditions: 1, 2, 4	***IB***
Conditions: 1. The manufacturer responsible for batch release must be located within the EEA. 2. The site is appropriately authorised. 3. The product is not a biological medicinal product. 4. Method transfer from the old to the new site or new test laboratory has been successfully completed.		
9. 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)		**IA**
~~Conditions: None~~		
10. Minor change in the manufacturing process of the active substance		**IB**

Conditions: 1. No change in qualitative and quantitative impurity profile or in physico-chemical properties. 2. The product concerned is not a biological medicinal product ~~active substance is not of biological origin~~. 3. The synthetic route remains the same, i.e. intermediates remain the same. In the case of herbal medicinal products, the geographical source, production of the herbal substance and the manufacturing route remain the same.		
11. Change in batch size of active substance or intermediate		
a. Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation	Conditions: 1,2,3,4 (see below)	**IA**
b. Downscaling	Conditions: 1,2,3,4,5	**IA**
c. More than 10-fold compared to the original batch size approved at the grant of the marketing authorisation	Conditions: 1,2,3,4	**IB**
Conditions: 1. Any changes to the manufacturing methods are only those necessitated by scale-up, e.g. use of different sized equipment. 2. Test results of at least two batches according to the specifications should be available for the proposed batch size. 3. The product concerned is not a biological medicinal product.~~active substance is not a biological substance~~. 4. The change does not affect the reproducibility of the process. 5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.		
12. Change in the specification of an active substance or a starting material/intermediate/reagent used in the manufacturing process of the active substance		
a. Tightening of specification limits	Conditions: 1,2,3 (see below)	**IA**
	Conditions: 2,3	**IB**
b. Addition of a new test parameter to the specification of		
1. An active substance	Conditions: 2,4~~,5~~	**IA ~~[IB]~~**
2. A starting material/intermediate/ reagent used in the manufacturing process of the active substance	Conditions: 2,4	**IA ~~[IB]~~**

Conditions: 1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a Type II variation procedure). 2. The change should not be the result of unexpected events arising during manufacture. 3. Any change should be within the range of currently approved limits. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. ~~5. The active substance is not a biological substance.~~		
13. Change in test procedure for active substance or starting material, intermediate, or reagent used in the manufacturing process of the active substance		
a. Minor change to an approved test procedure	Conditions: 1,2,3~~,5~~ (see below)	**IA**
b. Other changes to a test procedure, including replacement or addition of a test procedure	Conditions: 2,3,4,5	**IB**
Conditions: 1. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method); no new impurities are detected. 2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines 3. Results of method validation show new test procedure to be at least equivalent to the former procedure. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. ~~5. The active substance, starting material, intermediate or reagent is not a biological substance.~~		
14. Change in the manufacturer of the active substance or starting material/reagent/intermediate in the manufacturing process of the active substance where no Ph. Eur. Certificate of Suitability is available		
a. Change in site of the already approved manufacturer (replacement or addition)	Conditions: 1,2,4 (see below)	**IB**
b. New manufacturer (replacement or addition)	Conditions: 1,2,3,4	**IB**

Conditions: 1. The specifications (including in-process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved. 2. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.* 3. The current or new active substance manufacturer does not use a Drug Master File. 4. The change does not concern a biological medicinal product ~~containing a biological active substance~~.		
15. Submission of a new or updated Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance		
a. From a manufacturer currently approved	Conditions: 1,2,4 (see below)	**IA**
b. From a new manufacturer (replacement or addition)		
1. Sterile substance	Conditions: 1,2,3,4	**IA ~~[IB]~~**
2. Other substances	Conditions: 1,2,3,4	**IA**
c. Substance in veterinary medicinal product for use in animal species susceptible to TSE	Conditions: 1,2,3,4	**IA ~~[IB]~~**
Conditions: 1. The finished product release and end of shelf life specifications remain the same. 2. Unchanged additional (to Ph. Eur) specifications for impurities and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable. 3. The active substance will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability, or if data to support a retest period is not provided. 4. The manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.		
16. Submission of a new or updated TSE Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance for a currently approved manufacturer and currently approved manufacturing process		

a. Substance in veterinary medicinal product for use in animal species susceptible to TSE	Conditions: None	**IA ~~[IB]~~**
b. Other substances	Conditions: None	**IA**
17. Change in :		
a. The re-test period of the active substance	Conditions: 1,2~~,3~~ (see below)	**IB**
b. The storage conditions for the active substance	Conditions: 1,2	**IB**
Conditions: 1. Stability studies have been done according to the currently approved protocol. The studies must show that the agreed relevant specifications are still met. 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. ~~3. The active substance is not a biological substance.~~		
18. Replacement of an excipient with a comparable excipient		
a. The replacement leads to a change in the Summary of Product Characteristics	*Conditions: 1, 2, 3, 4, 5 (see below)*	**IB**
b. The replacement does not lead to a change in the Summary of Product Characteristics	*Conditions: 1,2, 3, 4, 5*	***IA***

Conditions: 1. Same functional characteristics of the excipient. 2. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one (no significant differences regarding comparability cf Note for Guidance on Bioavailability and Bioequivalence, Annex II; the principles contained in this note for guidance for medicinal products for human use should still be taken into account for veterinary medicinal products, if relevant). For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one. 3. Any new excipient does not include the use of materials of human or animal origin for which assessment is required of viral safety data. For excipients in a veterinary medicinal product for use in animal species susceptible to TSE, a risk assessment has been carried out by the competent authority. 4. The product concerned is not a biological medicinal product. ~~It does not concern a medicinal product containing a biological active substance~~. 5. Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalised. Data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).		
19. Change in specification of an excipient		
a. Tightening of specification limits	Conditions: 1,2,3 (see below)	**IA**
	Conditions: 2,3	**IB**
b. Addition of a new test parameter to the specification	Conditions: 2,~~4,5~~	**IA ~~[IB]~~**
Conditions: 1. The change is not a consequence of any commitment from previous assessments (e.g. made during the procedure for the marketing authorisation application or a Type II variation procedure). 2. The change should not be the result of unexpected events arising during manufacture. 3. Any change should be within the range of currently approved limits. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. ~~5. The change does not concern adjuvant for vaccines or excipient of biological origin.~~		
20. Change in test procedure for an excipient		
a. Minor change to an approved test procedure	Conditions: 1,2,3,5 (see below)	**IA**

b. Minor change to an approved test procedure for a biological excipient	Conditions: 1,2,3	**IA ~~[IB]~~**
c. Other changes to a test procedure, including replacement of an approved test procedure by a new test procedure	Conditions: 2,3,4~~,5~~	**IB**
Conditions: 1. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method); no new impurities are detected. 2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines. 3. Results of method validation show new test procedure to be at least equivalent to the former procedure. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. ~~5. The substance is not a biological excipient.~~		
21. Submission of a new or updated Ph. Eur. Certificate of Suitability for an excipient		
a. From a manufacturer currently approved	Conditions: 1,2,3 (see below)	**IA**
b. From a new manufacturer (replacement or addition)		
1. Sterile substance	Conditions: 1,2,3	**IA ~~[IB]~~**
2. Other substances	Conditions: 1,2,3	**IA**
c. Substance in veterinary medicinal product for use in animal species susceptible to TSE	Conditions: 1,2,3	**IA ~~[IB]~~**
Conditions: 1. The finished product release and end of shelf life specifications remain the same. 2. Unchanged additional (to Ph. Eur) specifications for product specific requirements (e.g. particle size profiles, polymorphic form), if applicable. 3. The manufacturing process of the excipient does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.		
22. Submission of a new or updated TSE Ph. Eur. Certificate of Suitability for an excipient		
a. From a manufacturer currently approved or a new manufacturer (replacement or addition)	Conditions: None	**IA**

b. Excipient in veterinary medicinal product for use in animal species susceptible to TSE	Conditions: None	**IA ~~[IB]~~**
23. Change in source of an excipient or reagent from a TSE risk to a vegetable or synthetic material		
a. Excipient or reagent used in manufacture of biological active substance or manufacture of a finished product containing biological active substance	Conditions: (see below)	**IB**
b. Other cases	Conditions: (see below)	**IA**
Conditions: Excipient and finished product release and end of shelf life specifications remain the same.		
24. Change in synthesis or recovery of a non-pharmacopoeial excipent (when described in the dossier)		**IA ~~[IB]~~**
Conditions: 1. Specifications are not adversely affected; no change in qualitative and quantitative impurity profile or in physico-chemical properties. 2. The excipient is not a biological substance.		
25. Change to comply with Ph. Eur. or with the national pharmacopoeia of a Member State		
a. Change of specification(s) of a former non-European pharmacopoeial substance to comply with Ph. Eur. or with the national pharmacopoeia of a Member State		
1. Active substance	Conditions: 1,2 (see below)	**IA ~~[IB]~~**
2. Excipient	Conditions: 1,2	**IA ~~[IB]~~**
b. Change to comply with an update of the relevant monograph of the Ph. Eur or national pharmacopoeia of a Member State		
1. Active substance	Conditions: 1,2	**IA**
2. Excipient	Conditions: 1,2	**IA**
Conditions: 1. The change is made exclusively to comply with the pharmacopoeia. 2. Unchanged specifications (additional to the pharmacopoeia) for product specific properties (e.g. particle size profiles, polymorphic form), if applicable.		

26. Change in the specifications of the immediate packaging of the finished product		
a. Tightening of specification limits	Conditions: 1,2,3,(see below)	**IA**
	Conditions: 2,3	**IB**
b. Addition of a new test parameter	Conditions: 2,4	**IA ~~[IB]~~**
Conditions: 1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a Type II variation procedure). 2. The change should not be the result of unexpected events arising during manufacture. 3. Any change should be within the range of currently approved limits. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.		
27. Change to a test procedure of the immediate packaging of the finished product		
a. Minor change to an approved test procedure	Conditions: 1,2,3 (see below)	**IA**
b. Other changes to a test procedure, including replacement or addition of a test procedure	Conditions: 2,3,4	**IB**
Conditions: 1. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method). 2. Appropriate (re-)validation studies were performed in accordance with relevant guidelines 3. Results of method validation show new test procedure to be at least equivalent to the former procedure. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.		
28. Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used))		**IA**
Conditions: The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the finished product.		

29. Change in the qualitative and/or quantitative composition of the immediate packaging material		
a. Semi-solid and liquid pharmaceutical forms	Conditions: 1,2,3,4 (see below)	**IB**
b. All other pharmaceutical forms	Conditions, 1,2,3,4	~~**IA**~~ IA_{IN}
	Conditions, 1,3,4	~~**IB**~~ IA_{IN}
Conditions: 1. The product concerned is not a biological or sterile medicinal product. 2. The change only concerns the same packaging type and material (e.g. blister to blister). 3. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties. 4. Relevant stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).		
30. Change (replacement, addition or deletion) in supplier of packaging components or devices (when mentioned in the dossier), spacer devices for metered dose inhalers are excluded.		
a. Deletion of a supplier	Conditions: 1 (see below)	**IA**
b. Replacement or addition of a supplier	Conditions: 1,2,3,4	**IA** ~~**[IB]**~~
Conditions: 1. No deletion of packaging component or device. 2. The qualitative and quantitative composition of the packaging components/device remains the same. 3. The specifications and quality control method are at least equivalent. 4. The sterilisation method and conditions remain the same, if applicable.		
31. Change to in-process tests or limits applied during the manufacture of the product		
a. Tightening of in-process limits	Conditions: 1,2,3 (see below)	**IA**
	Conditions: 2,3	**IB**
b. Addition of new tests and limits	Conditions: 2,4	**IA** ~~**[IB]**~~

Conditions: 1. The change is not a consequence of any commitment from previous assessments (e.g. made during the procedure for the marketing authorisation application or a Type II variation procedure). 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 3. Any change should be within the range of the currently approved limits. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.		
32. Change in batch size of the finished product		
a. Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation	Conditions: 1,2,3,4,5 (see below)	**IA**
b. Downscaling down to 10-fold	Conditions: 1,2,3,4,5,6	**IA**
c. Other situations	Conditions: 1,2,3,4,5,6,7	**IB**
Conditions: 1. The change does not affect the reproducibility and/or consistency of the product. 2. The change relates only to standard immediate release oral pharmaceutical forms and to non-sterile liquid forms. 3. Any changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch-size, e.g. use of different sized equipment. 4. Validation scheme is available or validation of the manufacture has been successfully carried out according to the current protocol with at least three batches at the proposed new batch size in accordance with the relevant guidelines. 5. The product concerned is not a biological medicinal product. ~~It does not concern a medicinal product containing a biological active substance~~. 6. The change should not be a result of unexpected events arisen during manufacture or because of stability concerns. 7. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batches and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).		
33. Minor change in the manufacture of the finished product		**IA ~~[IB]~~**

Conditions: 1. The overall manufacturing principle remains the same. 2. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy. 3. The product concerned is not a biological medicinal product ~~does not contain a biological active substance~~. 4. In case of a change in the sterilisation process, the change is to a standard pharmacopoeial cycle only. 5. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batches and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).		
34. Change in the colouring system or the flavouring system currently used in the finished product		
a. Reduction or deletion of one or more components of the		
1. Colouring system	Conditions: 1,2,3,4,7 (see below)	**IA**
2. Flavouring system	Conditions: 1,2,3,4,7	**IA**
b. Increase, addition or replacement of one or more components of		
1. Colouring system	Conditions: 1,2,3,4,5,6,7	**IB**
2. Flavouring system	Conditions: 1,2,3,4,5,6,7	**IB**

Conditions: 1. No change in functional characteristics of the pharmaceutical form e.g. disintegration time, dissolution profile. 2. Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the finished product formulation. 3. The finished product specification has only been updated in respect of appearance/odour/taste and if relevant, deletion or addition of an identification test. ~~4.~~ Stability studies (long-term and accelerated) in accordance with relevant guidelines have been started with at least two pilot scale or industrial batches and at least three months satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalised. Data shall be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). In addition, where relevant, photostability testing should be performed. 5. Any new components must comply with the relevant Directives (e.g. Directive 78/25/EEC as amended for colourants and Directive 88/388/EEC for flavours). 6. Any new component does not include the use of materials of human or animal origin fir which assessment is required of viral safety data or compliance with the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.* 7. Biological veterinary medicinal products for oral use for which the colouring or flavouring agent is important for the uptake by the target animal species are excluded.		
35. Change in coating weight of tablets or change in weight of capsule shells		
a. Immediate release oral pharmaceutical forms	Conditions: 1,3,4 (see below)	**IA**
b. Gastro-resistant, modified or prolonged release pharmaceutical forms	Conditions: 1,2,3,4	**IB**
Conditions: 1. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one. For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one. 2. The coating is not a critical factor for the release mechanism. 3. The finished product specification has only been updated in respect of weight and dimensions, if applicable. 4. Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalised. Data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).		

36. Change in shape or dimensions of the container or closure		
a. Sterile pharmaceutical forms and biological medicinal products	Conditions: 1,2,3 (see below)	**IB**
b. Other pharmaceutical forms	Conditions: 1,2,3	**IA**
Conditions: 1. No change in qualitative or quantitative composition of the container. 2. The change does not concern a fundamental part of the packaging material, which affect the delivery, use, safety or stability of the finished product. 3. In case of a change in the head space or a change in the surface/volume ratio, stability studies in accordance with the relevant guidelines have been started with at least two pilot scale (three for biological medicinal products) or industrial scale batches and at least three months (six months for biological medicinal products) stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).		
37. Change in the specification of the finished product		
a. Tightening of specification limits	Conditions: 1,2,3 (See below)	**IA**
	Conditions: 2,3	**IB**
b. Addition of a new test parameter	Conditions: 2,~~4,5~~	**IA ~~[IB]~~**
Conditions: 1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a Type II variation procedure). 2. The change should not be the result of unexpected events arising during manufacture. 3. Any change should be within the range of currently approved limits. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. ~~5. The test procedure does not apply to a biological active substance or biological excipient in the medicinal product.~~		
38. Change in test procedure of the finished product		
a. Minor change to an approved test procedure	Conditions: 1,2,3,4,5 (see below)	**IA**
b. Minor change to an approved test procedure for biological active substance or biological excipent	Conditions: 1,2,3,4	**IA ~~[IB]~~**

c. Other changes to a test procedure, including replacement or addition of a test procedure	Conditions: 2,3,4~~,5~~	**IB**
Conditions: 1. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method). 2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines. 3. Results of method validation show new test procedure to be at least equivalent to the former procedure. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. ~~5. The test procedure does not apply to a biological active substance or biological excipient in the medicinal product.~~		
39. Change or addition of imprints, bossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marking		**IA**
Conditions: 1. Finished product release and end of shelf life specifications have not been changed (except for appearance). 2. Any new ink must comply with the relevant pharmaceutical legislation.		
40. Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean mass		
a. Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets	Conditions: 1,2 (see below)	**IB**
b. All other tablets, capsules, suppositories and pessaries	Conditions: 1,2	**IA**
Conditions: 1. The dissolution profile of the reformulated product is comparable to the old one. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the new product compared to the old one. 2. Release and end of shelf life specifications of the product have not been changed (except for dimensions).		
41. Change in pack size of the finished product		
a. Change in the number of units (e.g. tablets, ampoules, etc.) in a pack		
1. Change within the range of the currently approved pack sizes	Conditions: 1,2 (see below)	**IA**

2. Change outside the range of the currently approved pack sizes	Conditions: 1,2	**IA_{IN} ~~[IB]~~**
b. Change in the fill-weight/fill volume of non-parenteral multi-dose products	Conditions: 1,2	**IA_{IN} ~~[IB]~~**
Conditions: 1. New pack size should be consistent with the posology and treatment duration as approved in the Summary of Product Characteristics. 2. The primary packaging material remains the same.		
42. Change in :		
a. The shelf-life of the finished product		
1. As packaged for sale	Conditions: 1,2,3 (see below)	**IB**
2. After first opening	Conditions: 1,2	**IB**
3. After dilution or reconstitution	Conditions: 1,2	**IB**
b. The storage conditions of the finished product or the diluted/reconstituted product	Conditions: 1,2~~,4~~	**IB**
Conditions: 1. Stability studies have been done according to the currently approved protocol. The studies must show that the agreed relevant specifications are still met. 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 3. The shelf life does not exceed five years. ~~4. The product is not a biological medicinal product.~~		
43. Addition, replacement or deletion of a measuring or administration device not being an integrated part of the primary packaging (spacer devices for metered dose inhalers are excluded)		
a. Medicinal products for human use		
1. Addition or replacement	Conditions: 1,2 (see below)	**IA**
2. Deletion	Conditions: 3	**IB**
b. Veterinary medicinal products	Conditions: 1,2	**IB**

Conditions: 1. The proposed measuring device must accurately deliver the required dose for the product concerned in line with the approved posology and the results of such studies should be available. 2. The new device is compatible with the medicinal product. 3. The medicinal product can still be accurately delivered.		
44. Change in specification of a measuring device or administration device for veterinary medicinal products		
a. Tightening of specification limits	Conditions: 1,2,3 (see below)	**IA**
	Conditions: 2,3	**IB**
b. Addition of a new test parameter	Conditions: 2,4	**IB**
Conditions: 1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a Type II variation procedure). 2. The change should not be the result of unexpected events arising during manufacture. 3. Any change should be within the range of currently approved limits. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.		
45. Change in test procedure of a measuring or administration device for veterinary medicinal products		
a. Minor change to an approved test procedure	Conditions: 1,2,3 (see below)	**IA**
b. Other changes to a test procedure, including replacement of approved test procedure by new test procedure	Conditions: 2,3,4	**IB**
Conditions: 1. The new or updated procedure is demonstrated to be at least equivalent to the former test procedure. 2. Appropriate (re-)validation studies have been performed in accordance with the relevant guidelines. 3. Results of method validation show new test procedure to be at least equivalent to the former procedure. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.		

46. Change in the summary of product characteristics, *labelling and package leaflet/insert of a generic medicinal product* ~~an essentially similar product~~ following a Commission Decision for a referral for an original medicinal product in accordance with Article 30 of Directive 2001/83/EC or Article 34 of Directive 2001/82/EC	**IA_{IN} ~~[IB]~~**
Conditions: 1. The proposed summary of product characteristics, labelling or package leaflet/insert is identical for the concerned sections to that annexed to the Commission Decision on the referral procedure for the original product. 2. The application is submitted within 90 days after the publication of the Commission Decision.	
47. Change in the summary of product characteristics, labelling and package leaflet/insert as a consequence of a final opinion in the context of a referral procedure in accordance with Articles 31 and 32 of Directive 2001/83/EC or Articles 35 and 36 of Directive 2001/82/EC	**IA_{IN} ~~[IB]~~**
Conditions: The variation only concerns the introduction of changes to the summary of product characteristics, labelling and package leaflet/insert in order to take account of a scientific opinion delivered in the context of a referral in accordance with Articles 31 and 32 of Directive 2001/83/EC or Articles 35 and 36 of Directive 2001/82/EC.	
48. Deletion of:	
a. A pharmaceutical form	**IA**
b. A strength	**IA**
c. A pack-size(s)	**IA**
Conditions: The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.	

[New variations conditions]

NEW.1. Submission of a variation which has already been evaluated in accordance with Article 24		
a. The variation has been evaluated pursuant to point (a) of Article 24(2)	Conditions: 1 (see below)	**IA_{IN}**
b. The variation has been evaluated pursuant to point (b) of Article 24(2)	Conditions: 1,2 (see below)	**IA_{IN}**
	Conditions: 1,3 (see below)	**IB**

Conditions: 1. The opinion issued by the Agency pursuant to Article 24 on the concerned variation is positive. 2. Prior to evaluation by the Agency pursuant to Article 24, the variation was considered as a minor variation of Type IB. 3. Prior to evaluation by the Agency pursuant to Article 24, the variation was considered as a major variation of Type II or an extension.	
NEW.2. Inclusion of a new, updated or amended Plasma Master File or Vaccine Antigen Master File in the marketing authorisation dossier	
a. First-time inclusion of a new Plasma Master File or Vaccine Antigen Master File	**IB**
b. Inclusion of an updated/amended Plasma Master File or Vaccine Antigen Master File	**IA_{IN}**
Conditions: The new, updated or amended Plasma Master File or Vaccine Antigen Master File has been granted a certificate of compliance with Community legislation in accordance with Annex I to Directive 2001/83/EC.	
NEW.3. Replacement or addition of a new master seed virus for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue.	**II**
NEW.4. Replacement or addition of a new antigen or combination of antigens derived from approved master seed viruses in the case of a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue.	**II**
NEW.5. Inclusion of a new design space.	**II**
Conditions: The submitted design space has been developed in compliance with the Note for guidance on pharmaceutical development of the Agency *[ICH Q8]*	
NEW.6. Modification of an approved new design space.	**II**
Conditions: The modified design space has been developed in compliance with the Note for guidance on pharmaceutical development of the Agency *[ICH Q8]*	
NEW.7. Administrative change in the summary of product characteristics, labelling and package leaflet/insert	**IA_{IN}**
Conditions: The change is of purely administrative nature and does not require to be substantiated by any sort of scientific data.	

NEW.8. Change in the summary of product characteristics, labelling and package leaflet/insert following an urgent safety restriction, class labelling, or a periodic safety update report	**IA_{IN}**
Conditions: The change is purely a consequence of the urgent safety restriction, class labelling or periodic safety update report and does not require to be substantiated by any new, additional scientific data.	
NEW.9. Addition, modification or deletion of a therapeutic indication	
a. Addition of a new therapeutic indication or modification of an approved one	**II**
b. Deletion of a therapeutic indication	**IA_{IN}**