Annotated Version of the Draft Regulation with Detailed EMEA Comments (Date: 3 January 2007)

Cross-references to the EMEA comments (EMEA/INS/550862/2007) are included in boxed text, as well as further background for the comments made.

EMEA will be happy to further clarify/discuss these comments with the Commission in due time, and provide further input in the revision of the detailed wording of the Regulation text once the final approaches have been decided upon.

COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels,
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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

Version: 24 October 2007
Deadline for Public Consultation: 4 January 2008

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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:

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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.

6. This Regulation also applies for the examination of applications of variations to the terms of a plasma master file and of a vaccine antigen master file, as defined in Annex I of Directive 2001/83/EC. For the purpse of this regulation, in case of a VAMF, the term 'active substance' could be replaced by 'antigen'.

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

EMEA: See our comment 1.

3. Article
Definitions

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

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 toof such decision, which results from the examination of a variation submitted by the holder.

EMEA: In the CP, also extensions result in an amendment of the MA and its Annexes. Based on the definitions set-out in points 2 + 7 we understand however that extensions are considered as "variations", and are therefore covered under the above point 1. However, should the definition of extension be amended, a reference to 'extensions' should be included in point 1.

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 anyany significantnegative impact on the quality, safety or efficacy of the medicinal product concerned.

EMEA: See our comment 2. In addition, changes which would be expected to have a negative impact on Q, S or E, would normally not be approvable.

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 is expected to have a ~~has a substantial potential to have a~~ significant ~~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 major~~minor~~ variation of Type II~~B~~.

EMEA: See our comment 3 and 4.

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.

EMEA: See our comment 4. Agreement on classification of non-listed types of changes (in general, not product specific) can be obtained via discussions between MSs and EMEA as has already happened successfully in the past years. Such agreed 'interim' variations could be published via Q&A and could be used as a basis for the updating of the guideline.

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; as well as on the documentation to be submitted for such variations.

~~(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~~.

EMEA: See our comment 5.

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;

EMEA: See our comment 6. To ensure a consist and practical interpretation of "same MAH", a reference to the 1998 Commission Communication could be given here.

(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.

EMEA: See our comment 7. In addition, the relationship between related changes mentioned in the draft guideline and Annex II is unclear: e.g. variations to implement class labelling or PSUR assessment are classified as Type IA(IN) variations in the guideline, whereas they are also listed in Annex II, which, according to the above bullets, exclude combinations of Type IA variations. Please also refer to our detailed comments included in the Annex II itself.

(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.

EMEA: See our comment 8 and 13.

In addition, it should be noted that even if presented as one single application, the dossier of each individual marketing authorisation as held at EMEA or MS level will still require updating by the relevant replacement/new documents. This will have to be taken into account for the "Elements" listed in Annex III – see also our comments under that Annex.

Please also note that Article 35 of Directive 2001/83/EC states that "any application by the MAH to vary a MA which has been granted in accordance with the provisions of this chapter shall be submitted to all the MSs which have previously authorised the medicinal product concerned." This will have to be taken into account when further considering the practical implementation of the proposed grouping, Article 24 and Annex III.

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 ~~of~~offset-out in Article 32-34 ~~referred to in Article 35(2)~~ of Directive 2001/83/EC and Article ~~xxxx~~36-38~~9 (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.

EMEA: See our comment 9. Referral to EMEA should only occur after no agreement could be reached in the CMD procedure (i.e. a sequential approach as set-out in Directive 2001/83/EC and 2001/82/EC). This should also apply to requests from holders (i.e. no direct referral from MAH to EMEA, first via CMD).

More detailed procedural steps and timeframes should be set-out for the CMD procedure, as well as criteria for referral to EMEA (e.g. potential serious risk to public health).

Type IA variations should be excluded from the scope of this article.

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

17. Article
"Do and Tell" notification 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.

EMEA: It is not clear how 'forthwith' should be understood, when reading this provision together with Article 22.1, from which we understand that such variation may already be implemented 'anytime' before its required "immediate" notification.

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).

EMEA: See our comment 6 (regarding non-review).

One month to check a simple Type IA(IN) appears to be quite long compared to the current timeframes for Type IA handling.

18. Article
"Tell, Wait and Do" notification 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).~~ The Agency shall inform the holder accordingly.

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. The Agency shall inform the holder accordingly. ~~and the Agency shall close the procedure in accordance with Article 21(3).~~

EMEA: See also our comments on Article 21(3).

There seem to be overlapping and possibly duplicating steps between this article and Article 21(3). In fact, all steps as described in this point 4 provide for an effective closure of the procedure at EMEA level (as is currently the case: by the end of the timeframes mentioned in the Regulation, the EMEA informs the holder of the outcome. There is therefore no need, in our view, for a subsequent 'closing' step to be created in Article 21(3).

It is only the remaining MA-amendment steps and notification of the amended Decision which should be referred to.

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.

EMEA: See also our comment 3.

A case-by-case decision on a possible Type II upgrade, will lead to a lot of uncertainty/unpredictability and possible inconsistent decisions within the EU Regulatory system, and may lead to an increase in administrative burden and approval delays as the dossier requirements and procedural handling of a Type II variation are significantly different from Type IB variations.

E.g. in the CP, Type IB variations are only submitted to the EMEA & Rapporteur, and are finalised without CHMP involvement. A Type II variation requires submission to all CHMP members, and requires an Assessment Report to be drafted within fixed timeframes, for circulation for comments to other CHMP members. Type II variations also require the inclusion of a Quality Summary or (non-)clinical Overview in the MAH's application, as applicable, which would not have been prepared for a Type IB submission.

Therefore, EMEA proposes to delete this paragraph and re-introduce the Type II by default, together with a maximisation of pre-defined Type IA/IB variations and

possibilities for Q&A and updating of the guideline, to clarify the classification of any new non-listed variations.

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).

EMEA: As above; comment on closing.

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.

   (c) The period referred to in the first subparagraph shall be extended to 90 days in the case of variations concerning the replacement or addition of one or more new master seed viruses resulting in a new antigen or comination of antigens for a veterinary vaccine against avian influenza, foot-and-moth disease or bluetongue.

EMEA: See our comment 10.

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 11~~7~~ shall apply for the examination of variations concerning changes to the active substance for the ~~annual~~ strain update of a human influenza vaccine.

EMEA: See our comment 11.

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

EMEA: See our comment 11 + 17: such details should not be included in the Annex to the Regulation, but rather in the relevant EMEA guidelines.

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 11~~7~~.

3. ~~Within 45 days following the date referred to in paragraph 2, the Agency shall give its opinion on the valid application~~The Agency shall given an Opinion on the validation application within 60 days from the start of the procedure. This period can be reduced by the Agency as necessary.

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

~~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.~~

+ include relevant MA updating steps.

EMEA: See our comment 11.

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.

EMEA: As the above bullets only relate to Type IA/IB variations, which are notification procedures, it could be confusing to refer to “variations or notifications”, when in fact only notification procedures are to be covered by these steps.

Please note that currently the Commission does not (wish to) receive negative Type IA/IB variations. This perhaps supports again not to have this section here, but to include EMEA-closure steps within the actual Type IA/IB procedural description (as is the case in the current Regulation).

It should also be clarified what happens in the case of a negative outcome of a Type IA notification, in particular in case several Type IA are submitted as part of a single

notification (e.g. annual report). Although EMEA does not support systematic review of such annual report, in case this principle would be maintained in the Regulation, the above statement regarding "unfavourable" outcome is not clear with regard to the consequences for such a report.

(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, if necessary.

EMEA: See our general comment 12. In addition:

(a) What is "forthwith"? For Type IB, Article 18.3 already provides clear timeframes for sending of EMEA feedback to the MAH and also regarding negative outcomes – so this step (a) seems redundant. As explained in our previous comments, EMEA has always informed the MAH about the outcome of its check within the given procedural deadlines e.g. by the end of the 2 weeks for Type IA, or within 30 days for Type IB. By introducing this new section Art 21(3), it will create an additional step for notifying the MAH of the outcome of the review, with no specified timeframes ('forthwith'?).

(a) It is not explained which mechanisms will apply when the EMEA outcome is negative. For Type IB, this is clearly explained in Article 18.4; again (a) seems therefore redundant.

(c) It is not clear to us why the MA will be updated quicker after an annual report than for IN variations, for which an update seems more urgent, as IN variations affect directly the terms of the MA. For all other Type IA changes (non-IN), as these should not affect the terms of the MA, it is not clear to us why a 6-monthly MA update would be required.

For Type IB, we understand that only the 6-monthly update of the MA will apply ("where necessary" to be added, as not all Type IB variations require an update of the MA). Based on the experience with the current 6-monthly updating following Type I variations, EMEA would prefer if such MA updating could be initiated and handled mainly by the Commission, rather than by the EMEA.

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.

EMEA: See also our comment in Article 17.1

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.~~

EMEA: There seems to be an overlap with the above bullet which refers already to the acceptance of a Type IB notification. Also, paragraph 6 of Art 18 is not covered in this bullet, whereas the bullet above already covers the whole of Art 18. Therefore, the last bullet is perhaps redundant?

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.

EMEA: The text could be made clearer to indicate that the MA will be immediately amended for an extension, as for the process of a new application.

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.

EMEA: It is our understanding that it would not be necessary to agree a specific timetable for each safety related variation, as this would be practically not feasible (due to the high number of such safety-related variations). However, EMEA would pre-define standard/expected timeframes for implementation of such variations which would apply by default, unless a different timeframe is required due to the urgency of the matter, or as agreed with the Holder.)

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.

EMEA: See our general comment 13 on 'worksharing'.

Even if this could be envisaged for centralised applications, the procedural steps in 2-6 will not be appropriate for all categories listed in Annex II e.g. in the case of grouped Type IB variations, the below timeframes are too long; in the case of Annex II.1, the timeframes of an Extension procedure should be followed. Closing of such procedures, or implementation of changes that have gone through this procedure, also does not appear to be addressed in the Regulation.

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.

EMEA: See our comment 13.

Should this principle however be maintained, EMEA would like to further discuss and provide further detailed comments on the procedural handling set-out in this Article, before finalisation of the Regulation.

Please also note that Article 35 of Directive 2001/83/EC states that "any application by the MAH to vary a MA which has been granted in accordance with the provisions of this chapter shall be submitted to all the MSs which have previously authorised the medicinal product concerned."

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.

EMEA: See our comment 14.

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.

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

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.

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, […]

EMEA: Should the text foresee the possibility for amendments to be done to the Regulation via a simple procedure (if such procedure would exist or be possible), in case the practical implementation preparation would require amendments of certain technical, procedural elements of this Regulation (in case such details are retained in the text, rather than in guidelines as favoured by EMEA)?

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 one or more ~~an~~anew master seed viruses resulting in a new antigen or combination of antigens ~~by another antigen derived from an approved master seed virus in the case of~~ for a veterinary vaccine~~s~~ against avian influenza, foot-and-mouth disease or bluetongue.

EMEA: See our comment 15. Further to the insulin case, it is proposed to also provide for the possibility of an alternative manufacturing process for biologicals rather than replacement only.

(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.

ANNEX II

EMEA: See our comment 16.

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 Type IA or Type IB 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, which are of an administrative nature.

EMEA: The proposed wording is not very clear, and should probably be limited to simple changes of an administrative nature only. Any other changes (not administrative) would require the submission of data and can therefore not "solely relate to changes of the SPC …." as they automatically also lead to changes in the dossier (e.g. amended or new data). Therefore, this type of change should only be listed in the Guideline and not in this Annex.

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.

EMEA: See our comment 16. This type of change should therefore only be listed in the Guideline, but rather as a Type IB and with carefully worded conditions.

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

[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.

EMEA: See our comment 16. This type of change should therefore only be listed in the Guideline, but rather as a Type IB and with carefully worded conditions.

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

EMEA: See our comment 16. This type of change should therefore only be listed in the Guideline, but rather as a Type IB and with carefully worded conditions.

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

EMEA: See our comment 16. This type of change should therefore be listed in the Guideline as a Type II.

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.

EMEA: See our comment 16. This type of change should therefore be listed in the Guideline as a Type II.

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.

EMEA: See our comment 16. This type of change should therefore be listed in the Guideline as a Type II.

EMEA: Grouping & possible negative outcome: EMEA is of the opinion that, following assessment, in case a particular change (part of the group) would not be considered acceptable, this would not automatically result in a negative Opinion on the whole of the group. If the applicant decides to withdraw that particular change from its application, CHMP would still be able to adopt a positive opinion on the rest of the Group:

e.g. for point 5 or 6, in case a certain change in the new manufacturing process or ASMF update would not be acceptable, the applicant can either amend its variation in line with the CHMP concerns or, if not possible, withdraw that change from the group, and CHMP would adopt an opinion on the remainder of the group.

e.g. for point 1, in case an extension would also include a new indication (Type II): in case the new indication would not be acceptable, the applicant could withdraw this and CHMP would still be able to adopt a positive opinion on the Extension.

Application forms and fees would not have to be amended, as these reflect the status of the application as applied for. The assessment report would however have to describe the overall assessment process from initial application to final adoption, including the withdrawal of a certain change by the applicant. In the CP, the fee is determined at the start of the procedure in relation to the assessment work to be done.

Any subsequent withdrawal of an application (or parts of it) does not result in a (partial) reimbursement of any fee paid.

ANNEX III

EMEA: See our comment 17. We would strongly recommend not to have this Annex III to the Regulation, but to rather consider such elements to be set-out in a guideline, to be agreed with Commission, MSs and EMEA.

Due to the short timelines for consultation and the fact that the Regulation will change following this consultation, it appears a bit too early to be able to fully envisage how the new submissions will work in practice and to agree now on the detailed elements set-out in this Annex.

E.g. requirements for a Type IA(IN) submission will be different from the annual report list; requirements may differ when it concerns single or multiple products, MAHs etc ….. Grouping of variations or worksharing arrangements may require certain elements to be included in the application, which are currently difficult to envisage.

Having such practical elements part of an Annex to this Regulation does not seem to be fully necessary, may be difficult to finalise at this point in time (i.e. already foresee now in the Regulation text how the procedures will be operated in practice), and may create difficulties if amendments would be required when starting to prepare for the practical implemention of the Regulation or to reflect future, practical experience.

It may therefore be better to agree the details of this Annex as a Guideline, following discussions in fora such as NTA and CMD, with a little bit more time to fully reflect on these requirements which will impact on the practical handling of such variations. The Regulation itself could contain a very high-level statement on elements to be included (similar to what is in the current Regulation), and refer to a more detailed procedural Guideline to be developed.

Some preliminary thoughts are included below, illustrating our view that further consideration of these practical elements will be required.

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

(a) a list of the marketing authorisation(s) 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, together with the date of implementation for each variation described;

EMEA: According to Art 17.1, also Type IA(IN) must include these elements. Therefore, the above wording referring to e.g. "…made in the last 12 months" is not very clear.

(c) ~~That description shall include a~~All necessary documents, as listed in the detailed guidelines referred to in point (1) of Article 6(1) for the referred variation(s) ~~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~~;

EMEA: The description should be a separate document from the relevant documents to be provided, as these may have to replace or complement actual documents from the CTD modules of the dossier. In addition, the current guideline on Type IA/IB variations does not require documents to prove that the conditions are met. This was a policy/decision taken with the previous Regulations, and is based on a declaration of the MAH in the Variation Form. Only the supportive documents listed in the guideline are to be included in a Type I variation.

~~(c)~~(d) 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;

EMEA: Same comment as above regarding the documentation.

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

EMEA: Date of implementation could perhaps be better part of the description?

(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.

EMEA: When a Type IA(IN) will be submitted, the information regarding 'consequentiality' will be stated in the application form. Therefore, the above indent would not really be required as a separate document. When a list of Type IA will be submitted as part of the annual report, is such information really useful at that time?

~~(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].~~

EMEA: As per the current fee Regulation, a fee does not need to be paid at submission.

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

[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).

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

EMEA: Same comment as above regarding the documentation.

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

EMEA: Same comment as above regarding the documentation.

(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;

EMEA: Same comment as above regarding the consequentiality and application form.

(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 / extension 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.

EMEA: Same comment as above regarding the fee.

(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.

EMEA: Same comment as above regarding the fee.

(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.*

EMEA: See our comment 18.

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** IA$_{IN}$? If mentioned in SPC/PL?

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** IA_{IN} ? If mentioned in SPC/PL?
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** IA$_{IN}$? If mentioned in SPC/PL?
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** IA$_{IN}$? If mentioned in SPC/PL?

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**~~ IA_{IN} as this is mentioned in SPC/PL
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**~~IA$_{IN}$ As this is mentioned in SPC/PL
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]**~~ **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]**~~ **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~~IB**
b. A strength	**~~IA~~IB**
c. A pack-size(s)	**IB~~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 one or more new master seed viruses resulting in a new antigen or combination of antigens ~~derived from approved master seed viruses in the case of~~ for 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}**~~**IB**
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}**~~**IB**
NEW.10. Addition or modification of a non-food target species	**II**