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COMMISSION REGULATION (EC) No 541/95

of 10 March 1995

concerning the examination of variations to the terms of a marketing authorization granted by a competent authority of a Member State

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COMMISSION REGULATION (EC) No 541/95

of 10 March 1995

concerning the examination of variations to the terms of a marketing authorization granted by a competent authority of a Member State

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Directive 75/319/EEC of 20 May 1975, on the approximation of provisions laid down by law, regulations or administrative action relating to medicinal products [1], as last amended by Council Directive 93/39/EEC [2] of 14 June 1993, and in particular Article 15 thereof,

Having regard to Council Directive 81/851/EEC of 28 September 1981, on the approximation of legislation of the Member States relating to veterinary medicinal products [3], as last amended by Council Directive 93/40/EEC [4], and in particular Article 23 thereof,

Whereas, appropriate provisions should be adopted for the examination of variations to the terms of a marketing authorization of medicinal products which have benefited from the procedures of mutual recognition foreseen in Articles 7 and 7a of Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products [5], as last amended by Directive 93/39/EEC, in Article 9 (4) of Council Directive 75/319/EEC or in Articles 8, 8a and 17 (4) of Council Directive 81/851/EEC, and medicinal products for which there has been a referral to the procedures foreseen by Articles 13 and 14 of Directive 75/319/EEC or Articles 21 and 22 of Directive 81/851/EEC;

Whereas, these provisions should also apply to the examination of applications to vary the terms of a marketing authorization which had been considered within the scope of application of Council Directive 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high technology medicinal products, particularly those derived from biotechnology [6];

Whereas, it is appropriate to include a notification system or administrative procedures concerning minor variations for which it is necessary to precisely define minor variations;

Whereas, moreover, it is necessary to distinguish from amongst those variations which do not qualify as minor variations, those which must be considered to so fundamentally alter the marketing authorization, particularly from the point of view of the quality, safety or efficacy of a medicinal product, that a new application for a marketing authorization would be required;

Whereas, the provisions of this Regulation are in accordance with the opinion of the Standing Committee on Medicinal Products for Human use and the Standing Committee on Veterinary Medicinal Products,

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[1] OJ No L 147, 9. 6. 1975, p. 13.
[2] OJ No L 214, 24. 8. 1993, p. 22.
[3] OJ No L 317, 6. 11. 1981, p. 1.
[4] OJ No L 214, 24. 8. 1993, p. 31.
[5] OJ No 22, 9. 2. 1965, p. 369/65.
[6] OJ No L 15, 17. 1. 1987, p. 38.

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HAS ADOPTED THIS REGULATION:

Scope and definitions

Article 1

1. This Regulation lays down the procedure for the examination of applications for variations to the terms of a marketing authorization of medicinal products which have been considered within the scope of application of Directive 87/22/EEC, of medicinal products having benefited from the procedures of mutual recognition foreseen in Articles 7 and 7a of Directive 65/65/EEC, Article 9 (4) of Directive 75/319/EEC or Articles 8, 8a and 17 (4) of Directive 81/851/EEC, and medicinal products for which there has been a referral to the procedures foreseen by Articles 13 and 14 of Directive 75/319/EEC or Articles 21 and 22 of Directive 81/851/EEC.

2. This Regulation does not impede the marketing authorization holder(s) from taking provisional urgent safety restrictions in the event of risk to public or animal health. The holder(s) shall forthwith inform the national competent authorities. If the competent authorities have not raised any objections within 24 hours, the urgent safety restrictions may be introduced and the applications for this variation shall be submitted to the national competent authorities for the application of the procedures set out in Articles 6 and 7 of this Regulation.

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3. Where national competent authorities impose urgent provisional safety restrictions on the marketing authorisation holder, the marketing authorisation holder shall be obliged to submit an application for a variation taking account of the safety restrictions imposed by the national authorities. This application shall be submitted without delay to the national competent authorities concerned for the application of the procedures set out in Articles 6 and 7 of this Regulation. This paragraph is without prejudice to Article 15a of Directive 75/319/EEC and Article 23a of Directive 81/851/EEC.

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Article 2

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

1. Variation to the terms of a marketing authorization:
   - — for medicinal products for human use: an amendment to the contents of the documents referred to in Articles 4 and 4a of Directive 65/65/EEC, in the Annex of Directive 75/318/EEC and in Article 2 of Directive 75/319/EEC, such as they existed at the moment of the decision on the marketing authorization or after approval of any previous variations; except where a new application for a marketing authorization must be presented pursuant to Annex II of this Regulation;
   - — for veterinary medicinal products: an amendment to the contents of the documents referred to in Articles 5, 5a and 7 of Directive 81/851/EEC such as they existed at the moment of the decision on the marketing authorization or after approval of any previous variation; except where a new application for a marketing authorization must be presented pursuant to Annex II of this Regulation.
2. Reference Member State: the Member State which, for a given medicinal product, has produced the assessment report which served as the basis for the Community procedures foreseen in Article 1 of this Regulation or alternatively the Member State chosen in this respect by the authorization holder with a view to application of this Regulation.
3. Urgent safety restriction: an interim change to product information by the marketing authorization holder restricting the indication(s), and/or dosage, and/or target species of the medicinal product; or

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adding a contra-indication, and/or warning due to new information having a bearing on the safe use of the product.

Article 3

1. (a) A 'minor variation' (type I) means a variation as defined in Article 2 and listed in Annex I to this Regulation, provided the conditions for such variations laid down in the said Annex are met.

(b) A 'major variation' (or type II) means a variation as defined in Article 2 which cannot be deemed to be a type I variation within the meaning of the preceding paragraph.

2. For the purposes of this Regulation, transfer of marketing authorization to a new holder, except for the situations covered by point 3 of Annex I to this Regulation shall not be considered as a variation in the meaning of Article 2 (1).

Notification procedure for minor variations

Article 4

1. (a) To obtain a type I variation, an identical application shall be submitted simultaneously to the national competent authorities of the different Member States where the medicinal product has been authorized; it shall be accompanied by documents demonstrating that the conditions laid down in Annex I of this Regulation for the requested variation have been met and all documents amended as a result of the application.

(b) The abovementioned documents shall include the list of Member States concerned by the application for the variation and shall identify the reference Member State for the medicinal product under consideration.

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2. The reference Member State shall forthwith inform all other concerned Member States about the date of the start of the procedure. The reference Member State shall also inform the marketing authorisation holder(s) about the date of the start of the procedure.

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3. An application within the meaning of paragraph 1 shall not concern more than one variation in the marketing authorization. Where several variations are to be made to a single marketing authorization, an application shall be submitted within the meaning of paragraph 1 in respect of each variation sought; each such application shall contain a reference to the other application(s).

4. By derogation to paragraph 3, where a variation in the marketing authorization entails one or more further changes, a single application may cover all such consequential variations. The single application shall describe the relation between the main variation and its consequential variations.

5. To be valid, an application within the meaning of paragraph 1 shall be consistent with the provisions of this Article and accompanied by the relevant fees provided for this purpose by the applicable national regulations.

Article 5

1. If, within 30 days of the date of the start of the procedure, the national competent authority of the reference Member State has not sent to the marketing authorization holder, who submitted the application, the notification provided for in paragraph 2 of this Article, the variation requested is deemed accepted by all Member States which have received the application.

2. Where one of the national competent authorities concerned cannot accept the request for the variation, that authority shall send objective grounds for non-acceptance to the reference Member State within a

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period of 20 days following the date of the start of the procedure. The reference Member State shall send, before the end of the period foreseen in paragraph 1, a notification with grounds to the marketing authorization holder who has submitted the application;

(a) within 30 days of receipt of the said notification, the marketing authorization holder may amend on one occasion only the application in order to take due account of the grounds set out in the notification. In that case the provisions of this present Article apply to the amended application and all applications foreseen by Article 4 are deemed to have been modified in the same sense;

(b) if the marketing authorization holder does not amend the application as provided for in (a) above, all applications are deemed to have been rejected. The national competent authority of the reference Member State shall forthwith notify the refusal to the marketing authorization holder and to the other concerned national competent authorities.

3. Within 10 days of the end of the procedure mentioned in paragraph 2 of this Article, and in cases of divergent positions among the national competent authorities of the concerned Member States leading to a refusal, the marketing authorization holder may refer the matter to the Agency for application of Article 15, last paragraph, of Directive 75/319/EEC or Article 23, last paragraph, of Directive 81/851/EEC.

Approval procedure for major variations

Article 6

1. (a) To obtain a type II variation, an identical application shall be submitted simultaneously to the national competent authorities of the different Member States where the medicinal product has been authorized. It shall be accompanied by the relevant particulars and supporting documents referred to in Article 2 (1) of this Regulation.

The application must also be accompanied by:

— the supporting data relating to the variation applied for,

— all documents amended as a result of the application,

— an Addendum to or updating of existing expert report(s) to take account of the variation applied for;

(b) The abovementioned documents shall include the list of Member States concerned by the application for the variation and shall identify the reference Member State for the medicinal product under consideration.

2. The Member States concerned shall forthwith notify the reference Member States about the receipt of the application. The reference Member State shall inform the Member States concerned and the marketing authorization holder(s) about the date of the start of the procedure.

3. An application within the meaning of paragraph 1 shall not concern more than one variation in the marketing authorization. Where several variations are to be made to a single marketing authorization, an application shall be submitted within the meaning of paragraph 1 in respect of each variation sought; each such application shall contain a reference to the other application(s).

4. By derogation to paragraph 3, where a variation in the marketing authorization entails one or more further changes, a single application may cover all such consequential variations. The single application shall describe the relation between the main variation and its consequential variations.

5. To be valid an application within the meaning of paragraph 1 shall be consistent with the provisions of this Article and accompanied by the relevant fees provided for this purpose by the applicable national regulations.

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Article 7

1. Within 60 days following the date of the start of the procedure, the national competent authority of the reference Member State shall prepare an assessment report and a draft decision which shall be addressed to the other national competent authorities concerned.

2. Within that period, the competent authority of the reference Member State may send the marketing authorization holder a single request for information supplementary to that already supplied pursuant to Article 6. It shall inform the other competent authorities concerned. In this case the period shall be extended by a further 60 days. This period may be extended for a period to be determined by the competent authority on its own initiative or upon request of the marketing authorization holder.

3. Within 30 days following receipt of the draft decision and the assessment report, the other national competent authorities concerned shall accept this draft decision and inform the national competent authority of the reference Member State to this effect.

4. Each national competent authority concerned by the application for the variation shall adopt a decision in conformity with the draft decision foreseen in the preceding paragraph. The national decisions shall take effect on the day agreed after discussion between the national competent authority of the reference Member State and the marketing authorization holder in consultation with the other national competent authorities concerned.

5. If within the period foreseen in paragraph 3, mutual recognition by one or more national competent authorities of the draft decision of the national competent authority of the reference Member State is not possible, reference shall be made to the provisions of Article 15, last paragraph, of Directive 75/319/EEC or Article 23, last paragraph, of Directive 81/851/EEC.

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Article 7a

Because of the specificities inherent in the manufacturing of human influenza vaccines, the following dispositions are applicable:

1. Within 30 days following the date of the start of the procedure, the national competent authorities of the reference Member State shall prepare an assessment report on a pharmaceutical dossier and a draft decision which shall be addressed to the other national competent authorities concerned.

2. Within that period, the competent authority of the reference Member State may send the marketing authorisation holder a single request for information in addition to that already supplied pursuant to Article 6. It shall inform the other competent authorities concerned.

3. Within 12 days of receipt of the draft decision and the assessment report, the other competent national authorities concerned shall accept this draft decision and inform the competent national authority of the reference Member State to this effect.

4. The clinical data and, where appropriate, those concerning the stability of the medicinal product shall be addressed by the applicant to the competent authorities of the reference Member State and to those of the other Member States concerned at the latest 12 days following the end of the time limit laid down in paragraph 3.

   The reference Member State shall evaluate these data and draft a final decision within seven days of the reception of the data mentioned in the first subparagraph. Each of the other national competent authorities shall accept this draft decision and adopt a decision in conformity with this project within the seven following days.

5. If, in the course of the procedure foreseen in the present Article, a competent authority raises a question of public health which they consider poses an obstacle to the mutual recognition of the decision

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to be taken, reference shall be made without delay to the provisions of Article 15, last paragraph, of Directive 75/319/EEC.

Article 7b

Notwithstanding Article 7a, in case of a pandemic situation duly recognised by the World Health Organisation, competent national authorities may exceptionally and temporarily consider the variation to be accepted after a complete application has been lodged and before the end of the procedure foreseen in Article 7a.

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Article 8

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

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

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ANNEX I

MINOR VARIATIONS (TYPE I) TO A MARKETING AUTHORIZATION AS REFERRED TO IN ARTICLE 3 (1)

Introductory statements

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A. By derogation, the procedure set out in Articles 6 and 7 of the present Regulation shall apply:

— to the minor variations Nos 11, 12, 13, 15 and 16 as referred to below and to minor variations 24 and 25 if the test procedure used is not a physicochemical method for medicinal products falling within the scope of Council Directives 89/342/EEC [1], or 89/381/EEC [2], or 90/677/EEC [3], or for medicinal products which had been considered as arising under List A of Directive 87/22/EEC,

— to any minor variation when a specific inspection of a manufacturing site needs to be carried out.

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B. Where a variation requires consequential updating of the product information (summary of product characteristics, labelling, package and/or leaflet), this is considered part of the variation and the time period for implementing the consequential update must be agreed with the competent authority at the time of the approval of the variation.

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1. *Change following modification(s) to the manufacturing authorisation(s)*

General condition: the modified manufacturing authorisation must be submitted to the competent authority.

— Change in the name of a manufacturer of the medicinal product

Condition to be fulfilled: the manufacturing site shall remain the same.

— Change of the manufacturing site(s) for part or all of the manufacturing process of the medicinal product

Condition to be fulfilled: no change either in the manufacturing process or in the specifications, including test methods.

— withdrawal of the manufacturing authorization for a site of manufacture.

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2. *Change in the name of the medicinal product (either invented name or common name)*

Condition to be fulfilled: confusion with names of other existing medicinal products or INN (International Non-proprietary Name) name must be avoided; when the name is a common name, the change has to be made in the following order: from common name to pharmacopoeial name or to INN.

3. *Change in the name and/or address of the marketing authorization holder (see Article 4a of Directive 65/65/EEC or Article 5a of Directive 81/851/EEC)*

Condition to be fulfilled: the marketing authorization holder shall remain the same person.

4. *Replacement of an excipient with a comparable excipient (excluding adjuvants for vaccines and biologically derived excipients)*

Condition to be fulfilled: Same functional characteristics, no change in dissolution profile for solid dosage forms.

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5. *Change in the colouring system of the product (addition, deletion or replacement of colourant(s))*

Condition to be fulfilled: Same functional characteristics, no change in dissolution profile for solid dosage forms. 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 formulation.

6. *Change in the flavouring system of the product (addition, deletion or replacement of flavour(s))*

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[1] OJ No L 142, 25. 5. 1989, p. 14.
[2] OJ No L 181, 28. 6. 1989, p. 44.
[3] OJ No L 373, 31. 12. 1990, s. 26.

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Condition to be fulfilled: proposed flavour must be in accordance with Directive 88/388/EEC. 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 formulation.

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7. *Change in coating weight of tablets or change in weight of capsule shells*

Condition to be fulfilled: No change in dissolution profile.

8. *Change in the qualitative composition of immediate packaging material*

Conditions to be fulfilled: The proposed packaging material must be at least equivalent to the approved material on relevant properties, and the change does not relate to sterile products.

9. *Deletion of an indication*

Conditions to be fulfilled: The continued safety in use of the medicinal product has not been the subject of concern from pharmacovigilance, preclinical safety or quality data. Justification must be given.

10. *Deletion of a route of administration*

Condition to be fulfilled: The continued safety in use of the medicinal product has not been the subject of concern from pharmacovigilance, preclinical safety or quality data. Justification must be given.

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10a. *Addition or replacement of measuring device for oral liquid dosage forms and other dosage forms*

Condition to be fulfilled: the size and, where applicable, the accuracy of the proposed measuring device must be compatible with the approved posology.

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11. *Change in the manufacturer(s) of active substance*

Condition to be fulfilled: the specifications, synthetic route and quality control procedures are the same as those already approved or a European Pharmacopoeia Certificate of suitability covering the active substance is submitted.

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11a. *Change in the name of a manufacturer of the active substance*

Condition to be fulfilled: the manufacturer of the active substance shall remain the same.

11b. *Change in supplier of an intermediate compound used in the manufacture of the active substance*

Condition to be fulfilled: the specifications, synthetic route and quality control procedures are the same as those already approved.

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12. *Minor change of manufacturing process of the active substance*

Condition to be fulfilled: Specifications are not adversely affected; no change in the physical properties, no new impurities or change in level of impurities which would require further qualifications in safety studies.

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Alternative condition: "… or a certificate of suitability from the European Pharmacopoeia is provided.

12a. *Change in specification of starting material or intermediate used in the manufacture of the active substance*

Condition to be fulfilled: specification must be tightened or addition of new test and limits.

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13. *Batch size of active substance*

Condition to be fulfilled: Batch data must show that the change does not affect consistency of production, or physical properties.

14. *Change in specifications of active substance*

Condition to be fulfilled: Specifications must be tightened or addition of new tests and limits.

15. *Minor changes in manufacture of the medicinal product*

Conditions to be fulfilled: Medicinal product specifications are not adversely affected; the new process must lead to an identical product regarding all aspects of quality, safety and efficacy.

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15a. *Change in in-process controls applied during the manufacture of the product*

Condition to be fulfilled: specification must be tightened or addition of new test and limits.

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16. *Change in the batch size of finished product*

Condition to be fulfilled: the change does not affect consistency of production.

17. *Change in specification of the medicinal product*

Condition to be fulfilled: Specifications must be tightened or addition of new tests and limits.

18. *Synthesis or recovery of non-Pharmacopoeial excipients which had been described in the original dossier*

Conditions to be fulfilled: Specifications are not adversely affected, no new impurities or change in level of impurities which would require further qualification in safety studies, no change in physico-chemical properties.

19. *Change in specification of excipients in the medicinal product (excluding adjuvants for vaccines)*

Condition to be fulfilled: Specifications must be tightened or addition of new tests and limits.

20. *Extension of shelf life as foreseen at time of authorization*

Conditions to be fulfilled: Stability studies have been done to the protocol which was approved at the time of the issue of the marketing authorization; the studies must show that the agreed end of shelf life specifications are still met; the shelf life does not exceed five years.

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20a. *Extension of the shelf life or retest period of the active substance*

Condition to be fulfilled: stability studies have been done to the protocol which was approved at the time of the issue of the marketing authorisation; the studies must show that the agreed end of shelf life specifications are still met.

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21. *Change in shelf life after first opening*

Condition to be fulfilled: Studies must show that the agreed end of shelf life specifications are still met.

22. *Change in shelf life after reconstitution*

Condition to be fulfilled: Studies must show that the agreed end of shelf life specifications are still met for the reconstituted product.

23. *Change in the storage conditions*

Condition to be fulfilled: Stability studies have been done to the protocol which was approved at the time of issue of the marketing authorization. The studies must show that the agreed end of shelf life specifications are still met.

24. *Change in test procedure of active substance*

Condition to be fulfilled: Results of method validation show new test procedure to be at least equivalent to the former procedure.

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24a. *Change in test procedure for a starting material or intermediate used in the manufacture of the active substance*

Condition to be fulfilled: results of method validation show new test procedure to be at least equivalent to the former procedure. Specification not adversely affected.

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25. *Change in the test procedures of the medicinal product*

Conditions to be fulfilled: Medicinal product specifications are not adversely affected; results of method validation show new test procedure to be at least equivalent to the former procedure.

26. *Changes to comply with supplements to pharmacopoeias* [1]

[1] ►M1 In cases where the marketing authorisation holder refers to the current edition of the pharmacopoeia, no variation application is required provided the change is introduced within six months of adoption of the revised monograph. ◄

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Conditions to be fulfilled: change is made exclusively to implement the new provisions of the supplement.

27. *Change in test procedures of non-pharmacopoeial excipients*

Condition to be fulfilled: Results of method validation show new test procedure to be at least equivalent to the former test procedure.

28. *Change in test procedure of immediate packaging*

Condition to be fulfilled: Results of method of validation show new test procedure to be at least equivalent to the former test procedure.

29. *Change in test procedure of administration device*

Condition to be fulfilled: Results of method validation show new test procedure to be at least equivalent to the former test procedure.

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Change in pack size for a medicinal product

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Conditions to be fulfilled: Specifications of the medicinal product are not affected, the new size is consistent with the dosage regimen and duration of use as approved in the summary of product characteristics; the change does not relate to parenteral preparations. ►M1 The packaging material remains the same ◄.

31. *Change in container shape*

Conditions to be fulfilled: No change in the quality and in the stability of the product in the container, no change in the container-product interactions.

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The change does not concern a fundamental component of the packaging material which affects the delivery or use of the product.

32. *Change of imprints, bossing or other markings (except scoring) on tablets or printing on capsules,*

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Condition to be fulfilled: New markings do not cause confusion with other tablets or capsules.

33. *Change of dimensions of tablets, capsules, suppositories or pessaries without change of quantitative composition and mean mass*

Condition to be fulfilled: No change in dissolution profile.

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34. *Change in the manufacturing process of a non proteinaceous component due to the subsequent introduction of a biotechnology step*

General remarks:

This specific variation is without prejudice to other variations in this Annex which can be applied in this particular context.

Community legislation applicable to specific groups of products [1] has to be complied with.

The medicinal products containing a proteinaceous component obtained through a biotechnology process fall within the scope of part A of Council Regulation (EEC) No 2309/93 [2].

— *Change in the manufacturing process for components compliant with a European Pharmacopoeia monograph and verified by means of a certificate of suitability from the European Pharmacopoeia*

Conditions to be fulfilled: the specifications and physicochemical properties and all characteristics of the component remain the same.

— *Change in the manufacturing process for components requesting a new impurities test procedure*

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(1) Food and food ingredients compliant with Regulation (EC) No 258/97 of the European Parliament and of the Council (OJ L 43, 14. 2. 1997, p. 1), colours for use in foodstuffs within the scope of Council Directive 94/36/EEC (OJ L 237, 10. 9. 1994, p. 13), food additives within the scope of Council Directive 88/388/EEC (OJ L 184, 15. 7. 1988, p. 61), extraction solvents within the meaning of Council Directive 88/344/EEC (OJ L 157, 24. 6. 1988, p. 28) as last amended by Directive 92/115/EEC (OJ L 409, 31. 12. 1992, p. 31) and foods or food ingredients derived from a biotechnology step which has been introduced in the manufacture/production are not required to be notified as a variation to the terms of the marketing authorisation.

(2) OJ L 214, 24. 8. 1993, p. 1.

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Conditions to be fulfilled: the specifications and physicochemical properties and all characteristics of the component remain the same. The manufacturing method is liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities must be declared and a suitable test procedure must be described. This supplementary test must be specified in a certificate of suitability from the European Pharmacopoeia.

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ANNEX II

Changes to a marketing authorization leading to a new application as referred to in Article 2

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Certain changes to a marketing authorisation have to be considered to fundamentally alter the terms of this authorisation and therefore cannot be considered as a variation in the meaning of Article 15 of Directive 75/319/EEC or in the meaning of Article 23 of Directive 81/851/EEC and cannot be granted following variation procedures foreseen in Articles 4 to 7 of this Regulation. For these changes, listed below, any application has to be considered within a complete scientific evaluation procedure (as for the granting of a marketing authorisation). As the case may be, an authorisation or a modification to the existing marketing authorisation will have to be issued by the competent national authorities.

This Annex is without prejudice to the provisions of Article 4 of Directive 65/65/EEC and Article 5 of Directive 81/851/EEC.

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1. *Changes to the active substance(s):*

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(i) addition of one or more active substance(s) including antigenic components for vaccines, without prejudice to Articles 7a and 7b concerning human influenza

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(ii) deletion of one or more active substance(s) including antigenic components for vaccines;

(iii) quantitative change to the active substance(s);

(iv) replacement of the active substance(s) by a different salt/ester complex/derivative (with the same therapeutic moiety);

(v) replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer);

(vi) replacement of a biological substance or product of biotechnology with one of a different molecular structure; modification of the vector used to produce the antigen/source material, including a master cell bank from a different source;

(vii) a new ligand or coupling mechanism for a radiopharmaceutical.

2. *Changes to the therapeutic indications* [1]:

(i) addition of an indication in a different therapeutic area, either treatment, diagnosis or prophylaxis;

(ii) change of the indication to a different therapeutic area, either treatment, diagnosis or prophylaxis.

3. *Changes to strength, pharmaceutical form and route of administration* [2]:

(i) change of bioavailability;

(ii) change of pharmacokinetics e.g. change in rate of release;

(iii) addition of a new strength;

(iv) change or addition of a new pharmaceutical form;

(v) addition of a new route of administration.

4. *Other changes specific to veterinary medicinal products used in food-producing animals:*

(i) addition or change of target species;

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(ii) shortening of the withdrawal period of a veterinary medicinal product if the change is not linked to the establishment or a modification to a maximum residue limit in accordance with Regulation (EEC) No 2377/90 [3].

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[1] Therapeutic area is defined as the third level of the Anatomical Therapeutic Chemical (A.T.C./A.T.C. Vet) code.

[2] For parenteral administration, it is necessary to distinguish between intraarterial, intravenous, intramuscular, subcutaneous, and other routes. For administration to poultry, respiratory, oral, ocular (nebulization) routes used for vaccination are considered to be the equivalent routes of administration.

[3] OJ L 224, 18. 8. 1990, p. 1.