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COMMISSION REGULATION (EC) No 542/95

of 10 March 1995

concerning the examination of variations to the terms of a marketing authorization falling within the scope of Council Regulation (EEC) No 2309/93

(OJ L 55, 11.3.1995, p. 15)

Amended by:

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COMMISSION REGULATION (EC) No 542/95

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concerning the examination of variations to the terms of a marketing authorization falling within the scope of Council Regulation (EEC) No 2309/93

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products [1], and in particular Articles 15 (4) and 37 (4) thereof,

Whereas, appropriate provisions should be adopted for the examination of variations to the terms of a marketing authorization of medicinal products which have been authorized in accordance with Regulation (EEC) No 2309/93;

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,

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 granted in accordance with Regulation (EEC) No 2309/93.

2. This Regulation does not impede the marketing authorization holder from taking provisional urgent safety restrictions in the event (SIC! restrictions. In) of risk to public or animal health. (SIC! health, the) The holder shall forthwith inform the Agency. If the Agency has not raised any objections within 24 hours, the urgent safety restrictions may be introduced and the corresponding application for this variation shall be submitted without delay to the Agency for the application of the procedures set out in Articles 6 and 7 of this Regulation.

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3. Where the Commission imposes provisional urgent 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 Commission. This application shall be submitted without delay to the Agency for the application of the procedures set out in Articles 6 and 7 of this Regulation. This paragraph is without prejudice to Article 18 of Regulation (EEC) No 2309/93.

[1] OJ No L 214, 24. 8. 1993, p. 1.

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Article 2

For the purpose of this Regulation, the following definitions shall apply;

1. 'variation to the terms of a marketing authorization': an amendment to the contents of the documents referred to in Article 6 (1) and (2) or Article 28 (1) and (2) of Regulation (EEC) No 2309/93 such as they existed at the moment the decision on the marketing authorization has been adopted in accordance with Article 10 or Article 32 of that Regulation or after approval of any previous variations, except where a new application for a marketing authorization must be presented pursuant to Annex II to this Regulation.
2. '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 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 variation laid down in the said Annex are met.

   (b) A 'major variation' (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 the point 3 of Annex I to this Regulation, and changes to the maximum residue limit (MRL) shall not be considered as a variation in the meaning of Article 2 (1).

Notification procedure for minor variations

Article 4

1. To obtain a type I variation, the holder of the marketing authorization shall submit to the Agency an application, accompanied by documents demonstrating that the conditions laid down in Annex I to this Regulation for the requested variation are met, and all documents amended as a result of the application.

2. 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).

3. By derogation from paragraph 2, 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.

4. 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 fee provided for in the applicable Community regulation.

Article 5

1. If, within 30 days of receipt of a valid application as provided for in Article 4, the Agency has not sent the holder of the marketing authorization the notification provided for in paragraph 4, the variation applied for shall be deemed to have been accepted.

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2. The Agency shall inform the Commission within the period referred to in the preceding paragraph of the variation to be made to the terms of the marketing authorization. The Commission shall, where necessary, amend the decision taken pursuant to Article 10 or Article 32 of Regulation (EEC) No 2309/93. The decision thus amended shall take effect retroactively from the day following the end of the period referred to in paragraph 1.

3. The Community Register of Medicinal Products provided for in Articles 12 and 34 of Regulation (EEC) No 2309/93 shall be updated as necessary.

4. Where the Agency is of the opinion that the application cannot be accepted, it shall send a notification to that effect to the holder of the marketing authorization within the period referred to in paragraph 1, stating the objective grounds on which its opinion is based:

(a) within 30 days of receipt of the said notification, the marketing authorization holder may amend the application in a way which takes due account of the grounds set out in the notification. In that case the provisions of paragraphs 1, 2 and 3 shall apply to the amended application.

(b) if the marketing authorization holder does not amend the application as provided for in (a) above, this application shall be deemed to have been rejected.

Approval procedure for major variations

Article 6

1. To obtain a type II variation, the holder of the marketing authorization shall send the Agency an application 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.

2. 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).

3. By derogation from paragraph 2, 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.

4. 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 fee provided for in the applicable Community regulation.

Article 7

1. The competent Committee of the Agency shall give its opinion within 60 days following receipt of a valid application as provided for in Article 6.

2. Within that period, the competent Committee may send the marketing authorization holder a single request for information supplementary to that already supplied pursuant to Article 6. 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 Committee,

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on its own initiative or at the request of the marketing authorization holder.

Article 8

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1. Where the competent Committee delivers an opinion, the Agency shall inform the marketing authorisation holder and the Commission forthwith and shall send to the Commission the amendments to be made to the terms of the marketing authorisation accompanied by the documents set out in Article 9(3) and 31(3) of Regulation (EEC) No 2309/93.

2. Article 9(1) and (2) or Article 31(1) and (2) of Regulation (EEC) No 2309/93 shall apply to the opinion adopted by the competent Committee.

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3. The decision varying the terms of the marketing authorization shall be adopted in accordance with the procedure laid down in Article 10 or Article 32 of Regulation (EEC) No 2309/93.

4. The Community Register of Medicinal Products provided for in Articles 12 and 34 of Regulation (EEC) No 2309/93 shall be updated as necessary.

Article 9

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, 7 and 8 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 Nos 24 and 25 if the test procedure used is not a physico-chemical method for medicinal products falling within the scope of Council Directive 89/342/EEC [1], or 89/381/EEC [2], or 90/667/EEC [3]) OJ L 373, 31.12.1990, p. 26., or for medicinal products which had been considered as arising under Part A of the Annex to Regulation (EEC) No 2309/93,

— 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 Agency at the time of the approval of the variation.

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1. — *Change following modifications(s) of the manufacturing authorization(s)*

General condition: the modified manufacturing authorization 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 Nonproprietary 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 Council Directive 65/65/EEC* [4] *or Article 5a of Council Directive 81/851/EEC)* [5]

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 (SIC! 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 colorant(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.

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[1] OJ L 142, 25.5.1989, p. 14.
[2] OJ L 181, 28.6.1989, p. 44.
[3] OJ L 373, 31. 12. 1990, p. 26.
[4] OJ No 22, 9. 2. 1965, p. 369/65.
[5] OJ No L 317, 6. 11. 1981, p. 7.

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

Condition to be fulfilled: proposed flavour must be in accordance with Council Directive 88/388/EEC [1]. 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 (SIC! no) change in dissolution profile.

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

Conditions to be fulfilled: The (SIC! 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 (SIC! the) continued safety in use of the medicinal product has not been the subject of concern from pharmacovigilance, pre-clinical safety or quality data. Justification must be given.

10. *Deletion of a route of administration*

Condition to be fulfilled: The (SIC! the) continued safety in use of the medicinal product has not been the subject of concern from pharmacovigilance, pre-clinical 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 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 Pharmacopeia 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 (SIC! 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 (SIC! specifications) must be tightened or new tests and limits added.

[1] OJ L 184, 15. 7. 1988, p. 61.

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15. *Changes in manufacture of the medicinal product*

Conditions to be fulfilled: Medicinal (SIC! 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 (SIC! the) change does not affect consistency of production.

17. *Change in specification of the medicinal product*

Condition to be fulfilled: Specifications (SIC! specifications) must be tightened or new tests and limits added.

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

Conditions to be fulfilled: Specifications (SIC! 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 (SIC! specifications) must be tightened or addition of new tests and limits added.

20. *Extension of shelf life (SIC! shelf-life) as foreseen at time of authorization*

Conditions to be fulfilled: Stability (SIC! 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 *(SIC! shelf-life)* specifications are still met; the shelf life *(SIC! shelf-life)* does not exceed five years.

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20a. *Extension of the shelf life (SIC! 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 *(SIC! shelf-life)* specifications are still met.

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21. *Change in shelf life (SIC! shelf-life) after first opening*

Condition to be fulfilled: Studies (SIC! studies) must show that the agreed end of shelf life *(SIC! shelf-life)* specifications are still met.

22. *Change in shelf life (SIC! shelf-life) after reconstitution*

Condition to be fulfilled: Studies (SIC! studies) must show that the agreed end of shelf life *(SIC! shelf-life)* specifications are still met for the reconstituted product.

23. *Change in the storage conditions*

Condition to be fulfilled: Stability (SIC! 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 *(SIC! shelf-life)* specifications are still met.

24. *Change in test procedure of active substance*

Condition to be fulfilled: Results (SIC! 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 test procedures of the medicinal product*

Conditions to be fulfilled: Medicinal (SIC! 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* ►M1 [1] ◄

Conditions to be fulfilled: Change (SIC! 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 (SIC! 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 (SIC! 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 (SIC! results) of method validation show new test procedure to be at least equivalent to the former test procedure.

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30. *Change in pack size for a medicinal product*

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Conditions to be fulfilled: Specifications (SIC! 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 (SIC! The) packaging material remains the same ◄.

31. *Change in container shape*

Conditions to be fulfilled: No (SIC! 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, including addition or change of inks used for product marking*

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Condition to be fulfilled: New (SIC! 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 (SIC! no) change in dissolution profile.

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

General remarks:

— This specific variation is provided to supplement the variations already existing which can be applied in this particular context, notably the variations Nos 4, 11, 12, 18, 19 and 26.

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

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— Community legislation applicable to specific groups of products [1],

— The medicinal products containing proteinaceous component obtained through a biotechnology process fall under the scope of Part A of Regulation (EEC) No 2309/93.

— *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 physcio-chemical properties and all characteristics of the component remain the same.

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

Conditions to be fulfilled: the specifications and physico-chemical 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.

[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 European Parliament and Council Directive 94/36/EEC (OJ L 237, 10.9.1994, p. 13), food additives of Directive 88/388/EEC, extraction solvents within the meaning of Council Directive 88/344/EEC (OJ 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 biotechnology step which has been introduced in the manufacture/production shall not require to be notified (SIC! notified,) as a variation to the terms of the marketing authorisation.

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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 paragraph 4 of Regulation (EEC) No 2309/93 and cannot be granted following a variation procedure. For these changes, listed below, any new 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 of a modification of the existing marketing authorisation will have to be granted by the Community.

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):*
   - (i) addition of one or more active substance(s) including antigenic components for vaccines;
   - (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 to be administered to 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 of a maximum residue limit in accordance with Council 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.