COMMISSION REGULATION (EC) No 1085/2003

of 3 June 2003

concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93

(Text with EEA relevance)

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 authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products [1], as amended by Commission Regulation (EC) No 649/98 [2] and in particular Articles 15(4) and 37(4) thereof,

Whereas:

(1) In the light of practical experience in the application of Commission Regulation (EC) No 542/95 of 10 March 1995 concerning the examination of variations to the terms of a marketing authorisation falling within the scope of Council Regulation (EEC) No 2309/93 [3], as amended by Regulation (EC) No 1069/98 [4], it is appropriate to simplify the procedure for varying the terms of a marketing authorisation.

(2) Due to the technical adaptation of Annex I to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code related to medicinal products for human use [5], it is appropriate to introduce in this Regulation provisions on variations related to plasma master files and vaccine antigen master files.

(3) Some of the procedures laid down in Regulation (EC) No 542/95 should therefore be adjusted but without departing from the general principles on which those procedures are based.

(4) It is appropriate to provide for a simplified and rapid notification procedure to enable the introduction of certain minor changes, which do not affect the approved quality, safety or efficacy of the product, without prior evaluation by the European Agency for the evaluation of medicinal products (hereinafter referred to as 'the Agency'). However, for other types of minor variations evaluation of the submitted documentation by the Agency should still be required.

(5) The various types of minor variation should be classified in order to determine the procedure to follow; it is particularly necessary to give a precise definition of the type of minor variation for which no prior evaluation is needed.

(6) It is necessary to clarify the definition of an 'extension' to a marketing authorisation, although it should still be possible to submit a separate, full application for marketing authorisation for a medicinal product which has already been authorised but under a different name and with summary of product characteristics.

(7) It is appropriate to allow the Agency to reduce the evaluation period in urgent cases or to extend it in the case of a major variation entailing important changes.

(8) It is necessary to simplify the administrative procedures for minor variations regarding the updating of marketing authorisations by allowing the Commission to group these updates every six months in one single decision.

(9) The time-frame for the procedure to be followed where the Commission imposes urgent safety restrictions should be clarified.

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(1) OJ L 214, 24. 8.1993, p. 1.
(2) OJ L 88, 24.3.1998, p. 7.
(3) OJ L 55, 11.3.1995, p. 15.
(4) OJ L 153, 27.5.1998, p. 11.
(5) OJ L 311, 28.11.2001, p. 67.

(10) Further clarification should be introduced as regards revision of the labelling, the package leaflet/insert or the summary of product characteristics; nevertheless the procedures laid down in this Regulation should not apply to changes to the labelling or to the package leaflet/insert which are not consequential to changes to the summary of product characteristics.

(11) For the sake of clarity, it is appropriate to replace Regulation (EC) No 542/95.

(12) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Medicinal products for Human Use and the Standing Committee on Veterinary Medicinal Products,

HAS ADOPTED THIS REGULATION:

Article 1

Subject matter

1. This Regulation lays down the procedure for the examination of applications for variations to the terms of a marketing authorisation granted in accordance with Regulation (EEC) No 2309/93.

2. 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.

Article 2

Scope

This Regulation shall not apply to:

(a) extensions of marketing authorisations which fulfil the conditions set out in Annex II to this Regulation;

(b) transfers of a marketing authorisation to a new holder;

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

The extension referred to in point (a) of the first paragraph shall be evaluated in accordance with the procedures set out in Articles 6 to 10 and Articles 28 to 32 of Regulation (EEC) No 2309/93 for medicinal products for human use and veterinary medicinal products, respectively.

Article 3

Definitions

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

1. 'variation to the terms of a marketing authorisation' means 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 authorisation was adopted, in accordance with Article 10 or Article 32 of that Regulation or after approval of any previous variations;

2. a 'minor variation' of type IA or type IB means a variation listed in Annex I which fulfils the conditions set out therein;

3. a 'major variation' of type II means a variation that cannot be deemed to be a minor variation or an extension of the marketing authorisation;

4. 'urgent safety restriction' means an interim change, due to new information having a bearing on the safe use of the medicinal product, to the product information concerning particularly one or more of the following items in the summary of product characteristics: the indications, posology, contraindications, warnings, target species and withdrawal periods.

Article 4

Notification procedure for minor variations type IA

1. With regard to minor variations of type IA, the marketing authorisation holder (hereinafter referred to as 'the holder') shall submit to the Agency a notification accompanied by

(a) all necessary documents including those amended as a result of the variation;

(b) the relevant fee provided for in Council Regulation (EC) No 297/95 [2].

2. A notification shall only concern one type IA variation. Where several type IA variations are to be made to the terms of a single marketing authorisation, a separate notification shall be submitted in respect of each type IA variation sought; each such notification shall also contain a reference to the other notifications.

3. By way of derogation from paragraph 2, where a type IA variation to the marketing authorisation leads to consequential type IA variations, a single notification may cover all such consequential variations. The single notification shall contain a description of the relation between these consequential type IA variations.

4. Where a variation requires consequential revision of the summary of product characteristics, labelling and package leaflet/insert, this is considered as part of the variation.

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

[2] OJ L 35, 15.2.1995, p. 1.

5. If the notification fulfils the requirements set out in paragraphs 1 to 4, the Agency shall, within 14 days following receipt of the notification, acknowledge the validity of this notification and shall inform the holder accordingly.

The Agency shall, where appropriate, disseminate the amended documents referred to in Article 3(1).

The Commission shall, where necessary and based on a proposal prepared by the Agency, update every six months the marketing authorisation which has been granted pursuant to Article 10 or Article 32 of Regulation (EEC) No 2309/93.

The updated marketing authorisation shall be notified by the Commission to the holder.

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 5

Notification procedure for minor variations type IB

1. With regard to minor variations of type IB, the holder shall submit to the Agency a notification accompanied by:

(a) all necessary documents demonstrating that the conditions laid down in Annex I for the requested variation are met, including all documents amended as a result of the application;

(b) the relevant fee provided for in Regulation (EC) No 297/95.

2. A notification shall only concern one type IB variation. Where several type IB variations are to be made to a single marketing authorisation, a separate notification shall be submitted in respect of each type IB variation sought; each such notification shall also contain a reference to the other notifications.

3. By way of derogation from paragraph 2, where a type IB variation to the marketing authorisation leads to consequential type IA or type IB variations, a single type IB notification may cover all such consequential variations. The single application shall contain a description of the relation between these consequential type I variations.

4. Where a variation requires consequential revision of the summary of product characteristics, labelling and package leaflet/insert, this is considered as part of the variation.

5. If the notification fulfils the requirements set out in paragraphs 1 to 4, the Agency shall acknowledge receipt of a valid notification and shall start the procedure set out in paragraphs 6 to 10.

6. If, within 30 days of the date of the acknowledgement of receipt of a valid notification the Agency has not sent the holder its opinion provided for in paragraph 8, the variation applied for shall be deemed to have been accepted.

The Agency shall inform the holder accordingly.

The Agency shall, where appropriate, disseminate the amended documents referred to in Article 3(1).

7. The Commission shall, where necessary and based on a proposal prepared by the Agency, update every six months the marketing authorisation which has been granted pursuant to Article 10 or Article 32 of Regulation (EEC) No 2309/93.

The updated marketing authorisation shall be notified by the Commission to the holder.

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

8. Where the Agency is of the opinion that the notification cannot be accepted, it shall, within the period referred to in paragraph 6, inform the holder who has submitted the notification, stating the grounds on which its opinion is based.

9. Within 30 days of receipt of the opinion referred to in paragraph 8, the holder may amend the notification in order to take due account of the grounds set out in the opinion. In that case the provisions of paragraphs 6 and 7 shall apply to the amended notification.

10. If the holder does not amend the notification, the notification shall be deemed to have been rejected. The Agency shall inform the holder accordingly.

Article 6

Approval procedure for major variations type II

1. With regard to major variations of type II, the holder shall submit to the Agency an application accompanied by:

(a) the relevant particulars and supporting documents referred to in Article 3(1);

(b) the supporting data relating to the variation applied for;

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

(d) an addendum to or update of existing expert reports/overviews/summaries to take account of the variation applied for;

(e) the relevant fee provided for in Regulation (EC) No 297/95.

2. An application shall only concern one type II variation. Where several type II variations are to be made to a single marketing authorisation, a separate application shall be submitted in respect of each variation sought; each such application shall also contain a reference to the other applications.

3. By way of derogation to paragraph 2, where a type II variation leads to consequential variations, a single application may cover all such consequential variations. The single application shall contain a description of the relation between these consequential variations.

4. Where a variation requires consequential revision of the summary of product characteristics, labelling and package leaflet/insert, this is considered as part of the variation.

5. If the application fulfils the requirements set out in paragraphs 1 to 4, the Agency shall acknowledge receipt of a valid application and shall start the procedure set out in paragraphs 6 to 11.

6. The competent Committee of the Agency shall give its opinion within 60 days from the start of the procedure.

This period can be reduced having regard to the urgency of the matter, particularly for safety issues.

This period can be extended to 90 days for variations concerning changes to or addition of the therapeutic indications.

This period will be extended to 90 days for variations concerning a change to or addition of a non-food-producing target species.

7. Within the periods laid down in paragraph 6, the competent Committee may send the holder a request for supplementary information within a time limit set by that Committee. The procedure shall be suspended until such time as the supplementary information has been provided. In this case the periods laid down in paragraph 6 may be extended for a further period to be determined by that Committee.

8. Where the competent Committee delivers an opinion, the Agency shall inform the holder and the Commission forthwith and shall send to the Commission, where appropriate, 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.

9. 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.

10. The Commission shall, where necessary and based on the proposal prepared by the Agency, amend the marketing authorisation that has been granted pursuant to Article 10 or Article 32 of the Regulation (EEC) No 2309/93.

Decisions concerning variations related to safety issues shall be implemented within a time-frame as agreed between the Commission and the holder.

The amended marketing authorisation shall be notified by the Commission to the holder.

11. 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 7

Human influenza vaccines

1. With regard to variations to the terms of the marketing authorisations for human influenza vaccines, the procedure set out in paragraphs 2 to 6 shall apply.

2. Within 45 days following the date of the receipt of a valid application, the Agency shall give its opinion on the quality documents referred to in Module 3 of Annex I to Directive 2001/83/EC, based on an assessment report.

3. Within the period laid down in paragraph 2, the Agency may request the holder to provide supplementary information.

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

The Commission shall adopt a decision updating the marketing authorisation that has been granted pursuant to Article 10 of the Regulation (EEC) No 2309/93.

This decision shall be implemented on condition that the final opinion of the Agency as provided for in paragraph 5 is favourable.

The updated marketing authorisation shall be notified by the Commission to the holder.

5. The clinical data and, where appropriate, those concerning the stability of the medicinal product shall be addressed by the holder to the Agency at the latest 12 days following the end of the time limit laid down in paragraph 2.

The Agency shall evaluate these data and shall give its final opinion within 10 days of the reception of the data referred to in the first subparagraph. The Agency shall address the final opinion to the Commission and to the marketing authorisation holder within the three following days.

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

Article 8

Pandemic situation with respect to human diseases

In case of a pandemic situation with respect to the human influenza virus, 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 [1], the Commission may exceptionally and temporarily consider the variation to the terms of the market authorisation for human influenza vaccines to be accepted after an application has been received and before the end of the procedure laid down in Article 7. Nevertheless, complete clinical safety and efficacy data can be submitted during this procedure.

In case of a pandemic situation with respect to human diseases other than the human influenza virus, the first paragraph and Article 7 may be applied *mutatis mutandis*.

Article 9

Urgent safety restrictions

1. If the holder in the event of risk to public or animal health takes urgent safety restrictions, he/she shall forthwith inform the Agency thereof. If the Agency has not raised any objections within 24 hours following receipt of that information, the urgent safety restrictions shall be deemed as accepted.

The urgent safety restrictions shall be implemented within a time-frame, as agreed with the Agency.

The corresponding variation application reflecting the urgent safety restrictions shall be submitted immediately and in any case no later than 15 days after the initiation of the urgent safety restrictions to the Agency for the application of the procedures set out in Article 6.

2. Where the Commission imposes urgent safety restrictions on the holder, the holder shall be obliged to submit an application for a variation taking account of the safety restrictions imposed by the Commission.

The urgent safety restrictions shall be implemented within a time-frame, as agreed with the Agency.

For the application of the procedures set out in Article 6, the corresponding variation application reflecting the urgent safety restrictions, including appropriate documentation in support of the change, shall be submitted to the Agency immediately and in any case no later than 15 days after the initiation of the urgent safety restrictions.

The first and second subparagraphs are without prejudice to Articles 18 and 40 of Regulation (EEC) No 2309/93.

Article 10

Repeal

Regulation (EC) No 542/95 is repealed.

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

Article 11

This Regulation shall enter into force on the 20th day following its publication in the *Official Journal of the European Union*.

It shall apply from 1 October 2003. However, as regards the examination of applications of variations to the terms of plasma master files and of vaccine antigen master files, this Regulation shall apply from the date of entry into force of the Commission Directive amending Annex I of Directive 2001/83/EC.

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

Done at Brussels, 3 June 2003.

For the Commission

Erkki LIIKANEN

Member of the Commission

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

ANNEX I

LIST AND CONDITIONS FOR MINOR VARIATIONS (TYPES IA AND IB) TO A MARKETING AUTHORISATION AS REFERRED TO IN ARTICLES 3 TO 5

Introductory statements

The titles of the variations are numbered and subcategories depicted by letters and numbers in smaller font. The conditions necessary for a given variation to follow either a type IA or a type IB procedure are outlined for each subcategory and listed below each variation.

To cover any other changes, it is necessary to submit applications for any consequential or parallel variations, which may be linked to the change applied for, at the same time and to clearly describe the relation between these variations.

For notifications including a certificate of suitability from the European pharmacopoeia and when the variation concerns the dossier submitted for the certificate, the documentation required for this change is to be submitted to the European Directorate for the Quality of Medicines (EDQM). If the certificate is revised following evaluation of this change, any marketing authorisation concerned must be updated. In many cases this can be done through a type IA notification.

A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and for which a combination of physico-chemical-biological testing and the production process and its control is needed for its characterisation and the determination of its quality.

As a result, the following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma as defined in Article 1(4) and (10) of Directive 2001/83/EC, respectively; immunological veterinary medicinal products as defined in Article 1(7) of Directive 2001/82/EC; medicinal products falling within the scope of Part A of the Annex to Regulation (EEC) No 2309/93; advanced therapy medicinal products as defined in Part IV of Annex I to Directive 2001/83/EC.

A change in the manufacturing process of a non-proteinaceous component due to a subsequent introduction of a biotechnology step can be made in accordance with the provisions of variations type I No 15 or No 21, as appropriate. This specific variation is without prejudice to other variations listed in this Annex which can be applied in this particular context. Introduction of a proteinaceous component obtained through a biotechnology process listed in Part A of the Annex to Council Regulation (EEC) No 2309/93 in a medicinal product fall within the scope of said Regulation. Community legislation applicable to specific groups of products [1] shall be complied with.

There is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that compliance with the updated monograph is implemented within six months of its publication and reference is made to the 'current edition' in the dossier of an authorised medicinal product.

For the purposes of this document, 'test procedure' has the same meaning as 'analytical procedure' and 'limits' have the same meaning as 'acceptance criteria'.

The Commission, in consultation with Member States, the Agency and interested parties, will draw up and publish detailed guidance on the documentation to be submitted.

[1] Food and food ingredients compliant with Regulation (EC) No 258/97 of the European Parliament and 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 manufacturing/production are not required to be notified as a variation to the terms of the marketing authorisation.

	Title of variation/conditions to be fulfilled		Type
1.	Change in the name and/or address of the marketing authorisation holder		IA
	Conditions: The marketing authorisation holder shall remain the same legal entity.		
2.	Change in the name of the medicinal product		IB
	Conditions: 1. No confusion with the names of existing medicinal products or with the international non-proprietary name (INN). 2. The check by the EMEA on the acceptability of the new name by the Member States should be finalised before the variation application is submitted. 3. The change does not concern the addition of a name.		
3.	Change in the name of the active substance		IA
	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 European Pharmacopoeia certificate of suitability is available		IA
	Conditions: The manufacturing site shall remain the same.		
5.	Change in the name and/or address of a manufacturer of the finished product		IA
	Conditions: The manufacturing site shall remain the same.		
6.	Change in ATC Code		
	(a) Medicinal products for human use		IA
	Conditions: Change following granting of or amendment to ATC Code by WHO.		
	(b) Veterinary medicinal products		IA
	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
	(b) Primary packaging site		
	1. Solid pharmaceutical forms, e.g. tablets and capsules	Conditions: 1, 2, 3, 5	IA
	2. Semi-solid or liquid pharmaceutical forms	Conditions: 1, 2, 3, 5	IB
	3. Liquid pharmaceutical forms (suspensions, emulsions)	Conditions: 1, 2, 3, 4, 5	IB
	(c) All other manufacturing operations except batch release	Conditions: 1, 2, 4, 5	IB

Title of variation/conditions to be fulfilled		Type
Conditions: 1. Satisfactory inspection in the last three 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
(b) Replacement or addition of a manufacturer responsible for batch release		
1. Not including batch control/testing	Conditions: 1, 2	IA
2. Including batch control/testing	Conditions: 1, 2, 3, 4	IA
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 and 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 active substance is not a biological substance. 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.		

Title of variation/conditions to be fulfilled		Type
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 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	IB
2. a starting material/intermediate/ reagent used in the manufacturing process of the active substance	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. 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

Title of variation/conditions to be fulfilled		Type
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 European Pharmacopoeia 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 medicinal product containing a biological active substance.		
15. Submission of a new or updated European Pharmacopoeia 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	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	IB
Conditions: 1. The finished product release and end of shelf life specifications remain the same. 2. Unchanged additional (to European Pharmacopoeia) 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 European Pharmacopoeia 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.		

Title of variation/conditions to be fulfilled		Type
16. Submission of a new or updated TSE European Pharmacopoeia 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	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		IB
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 Bio-availability and Bio-equivalence, 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. 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	IB

Title of variation/conditions to be fulfilled		Type
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 a biological excipient.		
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	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 European Pharmacopoeia 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	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	IB
Conditions: 1. The finished product release and end of shelf-life specifications remain the same. 2. Unchanged additional (to European Pharmacopoeia) 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.		

Title of variation/conditions to be fulfilled		Type
22. Submission of a new or updated TSE European Pharmacopoeia 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	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 excipient (when described in the dossier)		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 European Pharmacopoeia or with the national pharmacopoeia of a Member State		
(a) Change of specification(s) of a former non-European pharmacopoeial substance to comply with European Pharmacopoeia or with the national pharmacopoeia of a Member State		
1. Active substance	Conditions: 1, 2 (see below)	IB
2. Excipient	Conditions: 1, 2	IB
(b) Change to comply with an update of the relevant monograph of the European Pharmacopoeia 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.		

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

Title of variation/conditions to be fulfilled		Type
Conditions: 1. The product concerned is not a biological or sterile 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	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	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

Title of variation/conditions to be fulfilled		Type
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. 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 batch 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		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 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 batch 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.		

Title of variation/conditions to be fulfilled		Type
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, photo-stability testing should be performed. 5. Any new components must comply with the relevant Directives (e.g. Council Directive 78/25/EEC (OJ L 229, 15.8.1978, p. 63) as amended for colorants and Directive 88/388/EEC for flavours). 6. Any new component does not include the use of materials of human or animal origin fir which assessment is required of viral safety data or compliance with the current Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products. 7. Biological veterinary medicinal products for oral use for which the colouring or flavouring agent is important for the uptake by the target animal species are excluded.		
35. Change in coating weight of tablets or change in weight of capsule shells		
(a) Immediate release oral pharmaceutical forms	Conditions: 1, 3, 4 (see below)	IA
(b) Gastro-resistant, modified or prolonged release pharmaceutical forms	Conditions: 1, 2, 3, 4	IB
Conditions: 1. The dissolution profile of the new product, determined on a minimum of two pilot scale batches, is comparable to the old one. For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one. 2. The coating is not a critical factor for the release mechanism. 3. The finished product specification has only been updated in respect of weight and dimensions, if applicable. 4. Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least three months' satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalised. Data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).		
36. Change in shape or dimensions of the container or closure		
(a) Sterile pharmaceutical forms and biological medicinal products	Conditions: 1, 2, 3 (see below)	IB
(b) Other pharmaceutical forms	Conditions: 1, 2, 3	IA
Conditions: 1. No change in qualitative or quantitative composition of the container. 2. The change does not concern a fundamental part of the packaging material, which affect the delivery, use, safety or stability of the finished product. 3. In case of a change in the head space or a change in the surface/volume ratio, stability studies in accordance with the relevant guidelines have been started with at least two pilot scale (three for biological medicinal products) or industrial scale batches and at least three months' (six months for biological medicinal products) stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).		

Title of variation/conditions to be fulfilled		Type
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	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 excipient	Conditions: 1, 2, 3, 4	IB
(c) Other changes to a test procedure, including replacement or addition of a test procedure	Conditions: 2, 3, 4, 5	IB
Conditions: 1. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method). 2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines. 3. Results of method validation show new test procedure to be at least equivalent to the former procedure. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. 5. The test procedure does not apply to a biological active substance or biological excipient in the medicinal product.		
39. Change or addition of imprints, bossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marking		IA
Conditions: 1. Finished product release and end of shelf-life specifications have not been changed (except for appearance). 2. Any new ink must comply with the relevant pharmaceutical legislation.		

Title of variation/conditions to be fulfilled		Type
40. Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean mass		
(a) Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets	Conditions: 1, 2 (see below)	IB
(b) All other tablets, capsules, suppositories and pessaries	Conditions: 1, 2	IA
Conditions: 1. The dissolution profile of the reformulated product is comparable to the old one. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the new product compared to the old one. 2. Release and end of shelf-life specifications of the product have not been changed (except for dimensions).		
41. Change in pack size of the finished product		
(a) Change in the number of units (e.g. tablets, ampoules, etc.) in a pack		
1. Change within the range of the currently approved pack sizes	Conditions: 1, 2 (see below)	IA
2. Change outside the range of the currently approved pack sizes	Conditions: 1, 2	IB
(b) Change in the fill weight/fill volume of non-parenteral multi-dose products	Conditions: 1, 2	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.		

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

Title of variation/conditions to be fulfilled	Type
46. 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	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.	
47. Deletion of:	
(a) a pharmaceutical form	IA
(b) a strength	IA
(c) a pack size(s)	IA
Conditions: The remaining product presentations(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.	

ANNEX II

CHANGES TO A MARKETING AUTHORISATION LEADING TO AN EXTENSION APPLICATION AS REFERRED TO IN ARTICLE 2

These changes, listed below, will be regarded as an 'extension' application as referred to in Article 2.

An extension to or a modification of the existing marketing authorisation will have to be granted by the Community.

The name of the medicinal product will be the same for the 'extension' as it is for the existing marketing authorisation of the medicinal product.

The Commission, in consultation with Member States, the Agency and interested parties, will draw up and publish detailed guidance on the documentation to be submitted.

Changes requiring an extension application

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

   (i) replacement of the active substance(s) by a different salt/ester complex/derivative (with the same therapeutic moiety) where the efficacy/safety characteristics are not significantly different,

   (ii) 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,

   (iii) replacement of a biological substance or product of biotechnology with one of a slightly different molecular structure. Modification of the vector used to produce the antigen/source material, including a new master cell bank from a different source where the efficacy/safety characteristics are not significantly different,

   (iv) a new ligand or coupling mechanism for a radio-pharmaceutical,

   (v) 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:*

   (i) change of bio-availability;

   (ii) change of pharmaco-kinetics e.g. change in rate of release,

   (iii) change or addition of a new strength/potency,

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

   (v) change or addition of a new route of administration [1].

3. *Other changes specific to veterinary medicinal products to be administered to food-producing animals:*

   Change or addition of target species.

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