(9) It is appropriate to allow national authorities of the reference Member States to reduce the evaluation period in urgent cases or to extend it in the case of a major variation entailing important changes.

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

(11) Further clarification should be introduced as regards revision of the summary of product characteristics, labelling and package leaflet/insert; 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.

(12) For the sake of clarity, it is appropriate to replace Regulation (EC) No 541/95.

(13) 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

This Regulation lays down the procedure for the examination of notifications of and applications for variations to the terms of a marketing authorisation of medicinal products which have been considered within the scope of application of Directive 87/22/EEC, of medicinal products having benefited from the procedures of mutual recognition set out in Articles 17, 18 and 28(4) of Directive 2001/83/EC or Articles 21, 22 and 32(4) of Directive 2001/82/EC, and medicinal products for which there has been a referral to the procedures set out in Articles 32, 33 and 34 of Directive 2001/83/EC or Articles 36, 37 and 38 of Directive 2001/82/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 extensions referred to in point (a) of the first paragraph shall be examined in accordance with the procedure referred to in Article 17 of Directive 2001/83/EC and in Article 21 of Directive 2001/82/EC.

Article 3

Definitions

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

1. 'Variation to the terms of a marketing authorisation' means:

   (a) for medicinal products for human use: an amendment to the contents of the documents referred to in Articles 8 to 12 of Directive 2001/83/EC;

   (b) for veterinary medicinal products: an amendment to the contents of the documents referred to in Articles 12 to 15 of Directive 2001/82/EC.

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 which cannot be deemed to be a minor variation or an extension of the marketing authorisation.

4. 'Reference Member State' means the Member State which, for a given medicinal product, has produced the assessment report which served as the basis for the procedures referred to in Article 1 or alternatively the Member State chosen in this respect by the marketing authorisation holder with a view to application of this Regulation.

5. 'Urgent safety restriction' means an interim change 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, due to new information having a bearing on the safe use of the medicinal product.

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

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 simultaneously to the competent authorities of the Member States where the medicinal product has been authorised a notification accompanied by:

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

(b) a list of the Member States concerned and an indication of the reference Member State for the medicinal product under consideration;

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

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 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.

5. If the notification fulfils the requirements set out in paragraphs 1 to 4, the competent authority of the reference Member State shall within 14 days following receipt of the notification acknowledge the validity of this notification and shall inform the other competent authorities concerned and the holder accordingly.

Each competent authority concerned shall, where necessary, update the marketing authorisation, which has been granted pursuant to Article 6 of Directive 2001/83/EC or Article 5 of Directive 2001/82/EC.

Article 5

Notification procedure for minor variations type IB

1. With regard to minor variations of type IB, the holder shall submit simultaneously to the competent authorities of the Member States where the medicinal product has been authorised, the notification accompanied by:

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

(b) a list of Member States concerned and an indication of the reference Member State for the medicinal product under consideration;

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

2. A notification shall only concern one type IB variation. Where several type IB variations are to be made to the terms of 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 notification 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 competent authority of the reference Member State shall acknowledge receipt of a valid notification and shall start the procedure set out in paragraphs 6 to 11.

6. If, within 30 days of the date of the acknowledgement of receipt of a valid notification the competent authority of the reference Member State has not sent the holder its opinion provided for in paragraph 8, the notified variation shall be deemed to have been accepted by all competent authorities of the Member States concerned.

The competent authority of the reference Member State shall inform the other competent authorities of the Member States concerned to this effect.

7. Each competent authority concerned shall, where necessary, update the marketing authorisation which has been granted pursuant to Article 6 of Directive 2001/83/EC or Article 5 of Directive 2001/82/EC.

8. Where the competent authority of the reference Member State 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 competent authority of the reference Member State shall forthwith inform the holder and the other competent authorities concerned accordingly.

11. Within 10 days of providing the information referred to in paragraph 10, competent authorities of the Member States concerned or the holder may refer the matter to the Agency for application of Article 35(2) of Directive 2001/83/EC or Article 39(2) of Directive 2001/82/EC.

Article 6

Approval procedure for major variations type II

1. With regard to major variations of type II, the holder shall submit simultaneously to the competent authorities of the Member States where the medicinal product has been authorised an application accompanied by:

(a) the relevant particulars and supporting documents referred to in Articles 8 to 12 of Directive 2001/83/EC or Articles 12 to 15 of Directive 2001/82/EC;

(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) a list of the Member States concerned by the application for the major variation type II and an indication of the reference Member State for the medicinal product under consideration;

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

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 contain also a reference to the other applications.

3. By way of derogation from paragraph 2, where a type II variation leads to consequential variations, a single application may cover all such 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 competent authorities of the Member States concerned shall forthwith notify the competent authority of the reference Member States about the receipt of the valid application.

6. The competent authority of the reference Member State shall inform the other competent authorities of the Member States concerned and the holder of the date of the start of the procedure set out in paragraphs 7 to 13.

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

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

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

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

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

The competent authority of the reference Member State shall inform the other competent authorities concerned.

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

The competent authority of the reference Member State shall close the procedure and shall inform the other competent authorities concerned and the holder accordingly.

10. Each competent authority concerned shall, where necessary, amend the marketing authorisation concerned which has been granted pursuant to Article 6 of Directive 2001/83/EC or Article 5 of Directive 2001/82/EC in conformity with the draft decision referred to paragraph 9.

11. Decisions concerning variations related to safety issues shall be implemented within a timeframe as agreed between the competent authority of the reference Member State and the holder in consultation with the other competent authorities of the Member States concerned.

12. If within the period laid down in paragraph 9, mutual recognition by one or more of the competent authorities of the draft decision of the competent authority of the reference Member State is not possible, the procedure referred to in Article 35(2) of Directive 2001/83/EC or Article 39(2) of Directive 2001/82/EC shall apply.

13. Within 10 days of the end of the procedure mentioned in paragraph 8 and in case where the competent authorities of the Member States concerned by the application are of the opinion that the variation cannot be accepted, the holder may refer the matter to the Agency for application of Article 35(2) of Directive 2001/83/EC or Article 39(2) of Directive 2001/82/EC.

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 5 shall apply.

2. Within 30 days following the date of the start of the procedure, the competent authority of the reference Member State shall prepare an assessment report on the basis of the quality documents referred to in Module 3 of Annex I to Directive 2001/83/EC and a draft decision which shall be addressed to the other competent authorities concerned.

3. Within the period laid down in paragraph 2, the competent authority of the reference Member State may request the holder to provide supplementary information. It shall inform the other competent authorities of the Member States concerned.

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

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

The competent authority of the reference Member State shall evaluate these data and draft a final decision within 7 days of the receipt of the data. The other competent authorities concerned shall recognise the final draft decision and, within 7 days of the receipt of the draft final decision, adopt a decision in conformity with the final draft decision.

6. If, in the course of the procedure laid down in paragraphs 2 to 5, a competent authority raises a question of public health which they consider poses an obstacle to the mutual recognition of the decision to be taken, the procedure referred to in Article 35(2) of Directive 2001/83/EC shall apply.

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 No 2119/98/EC of the European Parliament and of the Council [1], competent authorities may exceptionally and temporarily consider the variation to the terms of the marketing 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 competent authorities thereof. If the competent authorities have not raised any objections within 24 hours following receipt of that information, the urgent safety restrictions shall be deemed to have been accepted.

The urgent safety restriction shall be implemented within a timeframe, as agreed with the competent authorities.

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

The corresponding variation application reflecting the urgent safety restriction shall be submitted immediately and in any case not later than 15 days after the initiation of the urgent safety restriction, to the competent authorities for the application of the procedures set out in Article 6.

2. Where competent authorities impose 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 competent authorities.

The urgent safety restriction shall be implemented within a timeframe, as agreed with the competent authorities.

The corresponding variation application reflecting the urgent safety restriction, including appropriate documentation in support of the change, shall be submitted immediately and in any case not later than 15 days after the initiation of the urgent safety restriction, to the competent authorities concerned for the application of the procedures set out in Article 6.

This paragraph is without prejudice to Article 36 of Directive 2001/83/EC and Article 40 of Directive 2001/82/EC.

Article 10

Repeal

Regulation (EC) No 541/95 is repealed.

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

Article 11

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

It shall apply from 1 October 2003.

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

ANNEX I

LIST AND CONDITIONS FOR MINOR VARIATIONS (TYPE 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 Articles 1(4) and 1(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 Council Regulation (EEC) No 2309/93 [1]; 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 [2] 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 updated monograph is implemented within 6 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.

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[1] OJ L 214, 24.8.1993, p. 1.

[2] 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/EC (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 into 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: No confusion with the names of existing medicinal products or with the international non-proprietary name (INN).		
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, 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, see Note for Guidance on bioavailability and bioequivalence, Annex II; the principles contained in this note for guidance for medicinal products for human use should still be taken into account for veterinary medicinal products, if relevant). For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one. 3. Any new excipient does not include the use of materials of human or animal origin for which assessment is required of viral safety data. For excipients in a veterinary medicinal product for use in animal species susceptible to TSE, a risk assessment has been carried out by the competent authority. 4. 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 excipent (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 batches and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).		
33. Minor change in the manufacture of the finished product		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 batches and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).		
34. Change in the colouring system or the flavouring system currently used in the finished product		
(a) Reduction or deletion of one or more components of the		
1. Colouring system	Conditions: 1, 2, 3, 4, 7 (see below)	IA
2. Flavouring system	Conditions: 1, 2, 3, 4, 7	IA
(b) Increase, addition or replacement of one or more components of		
1. Colouring system	Conditions: 1, 2, 3, 4, 5, 6, 7	IB
2. Flavouring system	Conditions: 1, 2, 3, 4, 5, 6, 7	IB
Conditions: 1. No change in functional characteristics of the pharmaceutical form e.g. disintegration time, dissolution profile. 2. Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the finished product formulation. 3. The finished product specification has only been updated in respect of appearance/odour/taste and if relevant, deletion or addition of an identification test.		

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, photostability 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 colourants and Directive 88/388/EEC for flavours). 6. Any new component does not include the use of materials of human or animal origin fir which assessment is required of viral safety data or compliance with the current Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products. 7. Biological veterinary medicinal products for oral use for which the colouring or flavouring agent is important for the uptake by the target animal species are excluded.		
35. Change in coating weight of tablets or change in weight of capsule shells		
(a) Immediate release oral pharmaceutical forms	Conditions: 1, 3, 4 (see below)	IA
(b) Gastro-resistant, modified or prolonged release pharmaceutical forms	Conditions: 1, 2, 3, 4	IB
Conditions: 1. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one. For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one. 2. The coating is not a critical factor for the release mechanism. 3. The finished product specification has only been updated in respect of weight and dimensions, if applicable. 4. Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalised. Data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).		
36. Change in shape or dimensions of the container or closure		
(a) Sterile pharmaceutical forms and biological medicinal products	Conditions: 1, 2, 3 (see below)	IB
(b) Other pharmaceutical forms	Conditions: 1, 2, 3	IA
Conditions: 1. No change in qualitative or quantitative composition of the container. 2. The change does not concern a fundamental part of the packaging material, which affects 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 excipent	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 of an essentially similar product following a Commission Decision for a referral for an original medicinal product in accordance with Article 30 of Directive 2001/83/EC or Article 34 of Directive 2001/82/EC	IB
Conditions: 1. The proposed summary of product characteristics is identical for the concerned sections to that annexed to the Commission Decision on the referral procedure for the original product. 2. The application is submitted within 90 days after the publication of the Commission Decision.	

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 competent authorities.

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 radiopharmaceutical;

   (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 bioavailability;

   (ii) change of pharmacokinetics 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 intra-arterial, 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.