

COMMISSION REGULATION (EC) No 1146/98

of 2 June 1998

amending Regulation (EC) No 541/95 concerning the examination of variations in the terms of a marketing authorisation granted by a competent authority of a Member State

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

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

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

Whereas, following practical experience in the application of Commission Regulation (EC) No 541/95⁽⁵⁾ appropriate provisions should be made to the terms of this Regulation;

Whereas it is appropriate to provide for a procedure to be followed in the case where national competent authority imposes urgent safety restrictions;

Whereas, moreover, it is necessary to simplify the notification procedure for minor variations and to introduce some changes to the annexes to this Regulation;

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

HAS ADOPTED THIS REGULATION:

Article 1

Regulation (EC) No 541/95 is amended as follows:

1. In Article 1 the following paragraph 3 is added:

‘3. Where national competent authorities impose urgent provisional safety restrictions on the marketing

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

2. In Article 4, paragraph 2 is replaced by the following text:

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

3. After Article 7, Article 7a and Article 7b are added:

‘Article 7a

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

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

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

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

⁽¹⁾ OJ L 147, 9. 6. 1975, p. 13.

⁽²⁾ OJ L 214, 24. 8. 1993, p. 22.

⁽³⁾ OJ L 317, 6. 11. 1981, p. 1.

⁽⁴⁾ OJ L 214, 24. 8. 1993, p. 31.

⁽⁵⁾ OJ L 55, 11. 3. 1995, p. 7.

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

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

5. If, in the course of the procedure foreseen in the present Article, a competent authority raises a question of public health which they consider poses an obstacle to the mutual recognition of the decision to be taken, reference shall be made without delay to the provisions of Article 15, last paragraph, of Directive 75/319/EEC.

Article 7b

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

4. In Annex I:

— The text of point A is replaced by the following text:

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

- to the minor variations Nos 11, 12, 13, 15 and 16 as referred to below and to minor variations 24 and 25 if the test procedure used is not a physicochemical method for medicinal products falling within the scope of Council Directives 89/342/EEC ⁽¹⁾, or 89/381/EEC ⁽²⁾, or 90/677/EEC ⁽³⁾, or for medicinal products which had been considered as arising under List A of Directive 87/22/EEC,
- to any minor variation when a specific inspection of a manufacturing site needs to be carried out'.

— The text of variation No 1 is replaced by the following text:

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

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

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

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

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

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

— withdrawal of the manufacturing authorisation for a site of manufacture'.

— The text of variation No 5 is replaced by the following text:

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

Condition to be fulfilled: Same functional characteristics, no change in dissolution profile for solid dosage forms. Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the formulation'.

— The text of variation No 6 is replaced by the following text:

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

Condition to be fulfilled: proposed flavour must be in accordance with Directive 88/388/EEC. Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the formulation'.

— After variation No 10 the following text is added:

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

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

— After variation No 11 the following text is added:

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

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

- 11b. *Change in supplier of an intermediate compound used in the manufacture of the active substance*
- Condition to be fulfilled: the specifications, synthetic route and quality control procedures are the same as those already approved’.
- After variation No 12 the following text is added:
- ‘Alternative condition: “... or a certificate of suitability from the European Pharmacopoeia is provided”.
- 12a. *Change in specification of starting material or intermediate used in the manufacture of the active substance*
- Condition to be fulfilled: specification must be tightened or addition of new test and limits’.
- After variation No 15 the following text is added:
- ‘15a. *Change in in-process controls applied during the manufacture of the product*
- Condition to be fulfilled: specification must be tightened or addition of new test and limits’.
- After variation No 20 the following text is added:
- ‘20a. *Extension of the shelf life or retest period of the active substance*
- Condition to be fulfilled: stability studies have been done to the protocol which was approved at the time of the issue of the marketing authorisation; the studies must show that the agreed end of shelf life specifications are still met’.
- After variation No 24 the following text is added:
- ‘24a. *Change in test procedure for a starting material or intermediate used in the manufacture of the active substance*
- Condition to be fulfilled: results of method validation show new test procedure to be at least equivalent to the former procedure. Specification not adversely affected’.
- The footnote of variation No 26 is changed as follows:
- ‘In cases where the marketing authorisation holder refers to the current edition of the pharmacopoeia, no variation application is required provided the
- change is introduced within six months of adoption of the revised monograph’.
- The heading of variation No 30 is replaced by the following text:
- ‘30. *Change in pack size for a medicinal product*
- A supplementary condition is added: ‘The packaging material remains the same’.
- A new condition is added to variation No 31:
- ‘The change does not concern a fundamental component of the packaging material which affects the delivery or use of the product’.
- The heading of variation No 32 is replaced by the following text:
- ‘32. *Change of imprints, bossing or other markings (except scoring) on tablets or printing on capsules, including addition or change of inks used for product marking*’.
- After variation No 33 variation No 34 is added:
- ‘34. *Change in the manufacturing process of a non proteinaceous component due to the subsequent introduction of a biotechnology step*
- General remarks:
- This specific variation is without prejudice to other variations in this Annex which can be applied in this particular context.
- Community legislation applicable to specific groups of products (*) has to be complied with.
- The medicinal products containing a proteinaceous component obtained through a biotechnology process fall within the scope of part A of Council Regulation (EEC) No 2309/93 (**).
- *Change in the manufacturing process for components compliant with a European Pharmacopoeia monograph and verified by means of a certificate of suitability from the European Pharmacopoeia*
- Conditions to be fulfilled: the specifications and physicochemical properties and all characteristics of the component remain the same.
- *Change in the manufacturing process for components requesting a new impurities test procedure*

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

(^o) Food and food ingredients compliant with Regulation (EC) No 258/97 of the European Parliament and of the Council (OJ L 43, 14.2.1997, p. 1), colours for use in foodstuffs within the scope of Council Directive 94/36/EEC (OJ L 237, 10.9.1994, p. 13), food additives within the scope of Council Directive 88/388/EEC (OJ L 184, 15.7.1988, p. 61), extraction solvents within the meaning of Council Directive 88/344/EEC (OJ L 157, 24.6.1988, p. 28) as last amended by Directive 92/115/EEC (OJ L 409, 31.12.1992, p. 31) and foods or food ingredients derived from a biotechnology step which has been introduced in the manufacture/production are not required to be notified as a variation to the terms of the marketing authorisation.

(^{aa}) OJ L 214, 24.8.1993, p. 1.

5. In Annex II:

- After the heading, the text of the first paragraph and the following subheading are replaced as follows:

‘Certain changes to a marketing authorisation have to be considered to fundamentally alter the terms of this authorisation and therefore cannot be considered as a variation in the meaning of Article 15 of Directive 75/319/EEC or in the meaning of

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

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

- The text of variation No 1, paragraph (i) is replaced by the following text:

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

- The text of variation No 4, paragraph (ii) is replaced by the following text:

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

(^o) OJ L 224, 18.8.1990, p. 1.’

Article 2

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

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

Done at Brussels, 2 June 1998.

For the Commission

Martin BANGEMANN

Member of the Commission