COMMISSION REGULATION (EC) No 1069/98

of 26 May 1998

amending 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

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 Evalutaion 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 following 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], appropriate adaptations should be adopted to the terms of this Regulation;

Whereas, it is appropriate to provide for a procedure to be followed in the case that the Commission imposes urgent safety restrictions;

Whereas, moreover, it is necessary to introduce some changes to the Annexes to this Regulation;

Whereas, 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

Regulation (EC) No 542/95 is hereby amended as follows:

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

'3. Where the Commission imposes provisional urgent safety restrictions on the marketing authorisation holder, the marketing authorisation holder shall be obliged to submit an application for a variation taking account of the safety restrictions imposed by the Commission. This application shall be submitted without delay to the Agency for the application of the procedures set out in Articles 6 and 7 of this Regulation. This paragraph is without prejudice to Article 18 of Regulation (EEC) No 2309/93.';

2. paragraphs 1 and 2 of Article 8 are replaced by the following:

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

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

3. in Annex I, point A is replaced by the following:

'A. By derogation, the procedure set out in Articles 6, 7 and 8 of the present Regulation shall apply:

— to the minor variations Nos 11, 12, 13, 15 and 16 as referred to below and to minor variations Nos 24 and 25 if the test procedure used is not a physico-chemical method for medicinal products falling within the scope of Council Directive 89/342/EEC (*), or 89/381/EEC (**), or 90/667/EEC (***), or for medicinal products which had been considered as arising under Part A of the Annex to Regulation (EEC) No 2309/93,

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

(*) OJ L 142, 25.5.1989, p. 14.
(**) OJ L 181, 28.6.1989, p. 44.
(***) OJ L 373, 31.12.1990, p. 26.';

(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. in Annex I, variation No 1 is replaced by the following:

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

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

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

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

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

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

— *Withdrawal of the manufacturing authorization for a site of manufacture.*';

5. in Annex I, variation No 5 is replaced by the following:

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

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

6. in Annex I, variation No 6 is replaced by the following:

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

Condition to be fulfilled: proposed flavour must be in accordance with Council Directive 88/388/EEC (*). 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.

(*) OJ L 184, 15.7.1988, p. 61.';

7. in Annex I, after variation No 10, the following variation 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 approved posology.';

8. in Annex I, after variation No 11, the following variations are 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.';

9. in Annex I, after variation No 12 the following text is added:

'Alternative condition: "... or a certificate of suitability from the European *Pharmacopeia* is provided."

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

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

10. in Annex I, after variation No 15 the following variation 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.';

11. in Annex I, after variation No 20 the following variation 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.';

12. in Annex I, after variation No 24, the following variation 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.';

13. in Annex I, the footnote to variation No 26 is amended as follows:

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

14. in Annex I, the heading of variation No 30 is replaced by the following:

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

A supplementary condition is added: 'The packaging material remains the same.';

15. in Annex I, 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.';

16. in Annex I, the heading of variation No 32 is replaced by the following:

'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*'

17. in Annex I, after variation No 33, the following variation is added:

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

General remarks:

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

— Community legislation applicable to specific groups of products (*) has to be complied with.

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

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

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

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

Conditions to be fulfilled: the specifications and physico-chemical properties and all characteristics of the component remain the same. The manufacturing method is liable to leave impurities not controlled in the pharmacopoeia monograph, these impurites 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.*

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

18. in Annex II, after the heading, the first paragraph and the following subparagraph 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 paragraph 4 of Regulation (EEC) No 2309/93 and cannot be granted following a variation procedure. For these changes, listed below, any new application has to be considered within a complete scientific evaluation procedure (as for the granting of a marketing authorisation). As the case may be, an authorisation of a modification of the existing marketing authorisation will have to be granted by the Community.

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

19. in Annex II, variation No 4, paragraph (ii) is replaced by the following:

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

(*) 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, 26 May 1998.

For the Commission

Martin BANGEMANN

Member of the Commission