COUNCIL DIRECTIVE

of 22 December 1986

amending Directive 75/318/EEC on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products

(87/19/EEC)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100 thereof,

Having regard to the proposal from the Commission (1),

Having regard to the opinion of the European Parliament (2),

Having regard to the opinion of the Economic and Social Committee (3),

Whereas the testing of proprietary medicinal products must regularly be adapted to scientific and technical progress in order to ensure optimum protection of public health in the Community;

Whereas, in order to achieve such optimum protection of health, the resources allocated to pharmaceutical research must not be squandered on obsolete or repetitive tests resulting from divergences between the Member States in assessing the state of the art in science and technology;

Whereas, for ethical reasons, it is necessary to replace existing methods as soon as scientific and technical advances so allow by methods involving as few laboratory animals as possible;

Whereas, it is therefore necessary to introduce a rapid procedure for adapting to technical progress the requirements regarding the testing of proprietary medicinal products listed in the Annex to Directive 75/318/EEC (4), as amended by Directive 83/570/EEC (5), whilst ensuring close cooperation between the Commission and the Member States within a 'Committee for the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Proprietary Medical Products Sector';

Whereas the requirements relating to the testing of medicinal products must also be capable of rapid revision by the same procedure, having regard to the evolution of test methods and of good laboratory practices recognized by the Community or in international trade in proprietary medicinal products,

(1) OJ No C 293, 5. 11. 1984, p. 4.
(2) OJ No C 36, 17. 2. 1986, p. 152.
(3) OJ No C 160, 1. 7. 1985, p. 18.
(4) OJ No L 147, 9. 6. 1975, p. 1.
(5) OJ No L 332, 28. 11. 1983, p. 1.

HAS ADOPTED THIS DECISION:

Article 1

Directive 75/318/EEC is hereby amended as follows:

1. The following Articles 2a, 2b and 2c shall be inserted:

'Article 2a

Any changes which are necessary in order to adapt the Annex to take account of technical progress shall be adopted in accordance with the procedure laid down in Article 2c.

If appropriate, the Commission shall propose to the Council that the procedure in Article 2c be reviewed in connection with the detailed rules set for the exercise of the powers of implementation granted to the Commission.

Article 2b

1. A Committee on the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Proprietary Medicinal Products Sector, hereinafter called "the Committee", is hereby set up; it shall consist of representatives of the Member States with a representative of the Commission as chairman.

2. The Committee shall adopt its own rules of procedure.

Article 2c

1. Where the procedure laid down in this Article is to be followed, matters shall be referred to the Committee by the chairman either on his own initiative or at the request of the representative of a Member State.

2. The representative of the Commission shall submit to the Committee a draft of the measures to be adopted. The Committee shall deliver its opinion on the draft within a time limit set by the chairman, having regard to the urgency of the matter. It shall act by a qualified majority, the votes of the Member States being weighted as provided in Article 148 (2) of the Treaty. The chairman shall not vote.

3. (a) The Commission shall adopt the measures envisaged where they are in accordance with the opinion of the Committee.

(b) Where the measures envisaged are not in accordance with the opinion of the Committee, or if no opinion is adopted, the Commission shall without delay propose to the Council the measures to be adopted. The Council shall act by a qualified majority.

(c) If, within three months of the proposal being submitted to it, the Council has not acted, the proposed measures shall be adopted by the Commission.' ;

2. Part 1 of the Annex, 'Physico-Chemical, Biological or Microbiological Tests of Proprietary Medicinal Products', shall be amended as follows :

(a) In (A), the following section shall be inserted :

'4. An explanation should be provided with regard to the choice of composition, constituents and container, supported by scientific data on development pharmaceutics. The overage, with justification thereof, should be stated.' ;

(b) In (B) the following fifth indent shall be inserted :

'— experimental studies validating the manufacturing process, where a non-standard method of manufacture is used or where it is critical for the product.' ;

(c) In (C) (2), subparagraph (b) shall be replaced by the following :

'(b) the description of the substance, set down in a form similar to that used in a descriptive item in the European Pharmacopoeia, shall be accompanied by any necessary explanatory evidence, especially concerning the molecular structure where appropriate ; it must be accompanied by an appropriate description of the method of synthetic preparation. Where substances can only be described by their method of preparation, the description should be sufficiently detailed to characterize a substance which is constant both in its composition and in its effects ;'

3. Part 2 of the Annex, 'Toxicological and Pharmacological Tests', is hereby amended as follows :

(a) The following paragraph shall be inserted after the introductory paragraph :

'Member States shall ensure that the safety tests are executed in conformity with the principles of good laboratory practice recognized by Community law in the field of tests on dangerous substances, or in the absence thereof, with those recommended by the Organization for Economic Cooperation and Development.' ;

(b) In Chapter 1 (B), the text of paragraph 1 shall be replaced by the following :

'1. **Single dose toxicity**

An acute test infers a qualitative and quantitative study of the toxic reactions which may result from a single administration of the active substance or substances contained in the proprietary medicinal product, in the proportions and physico-chemical state in which they are present in the actual product.

The acute toxicity test must be carried out in two or more mammalian species of known strain unless a single species can be justified. At least two different routes of administration shall normally be used, one being identical with or similar to that proposed for use in human beings and the other ensuring systemic absorption of the substance.

This study will cover the signs observed, including local reactions. The period during which the test animals are observed shall be fixed by the investigator as being adequate to reveal tissue or organ damage or recovery, usually for a period of 14 days but not less than seven days, but without exposing the animals to prolonged suffering. Animals dying during the observation period should be subject to autopsy as also should all animals surviving to the end of the observation period. Histopathological examinations should be considered on any organ showing macroscopic changes at autopsy. The maximum amount of information should be obtained from the animals used in the study. The single dose toxicity tests should be conducted in such a way that signs of acute toxicity are revealed and the mode of death assessed as far as reasonably possible. In suitable species a quantitative evaluation of the approximate lethal dose and information on the dose effect relationship should be obtained, but a high level of precision is not required.

These studies may give some indication of the likely effects of acute overdosage in man and may be useful for the design of toxicity studies requiring repeated dosing on the suitable animal species.

In the case of active substances in combination, the study must be carried out in such a way as to check whether or not there is enhancement of toxicity or if novel toxic effects occur.'

Article 2

Member States shall take the measures necessary in order to comply with this Directive no later than 1 July 1987. They shall forthwith inform the Commission thereof.

Article 3

This Directive is addressed to the Member States.

Done at Brussels, 22 December 1986.

For the Council

The President

G. SHAW