II

(Acts whose publication is not obligatory)

COUNCIL

COUNCIL DIRECTIVE

of 26 October 1983

amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products

(83/570/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,

Having regard to the opinion of the European Parliament (1),

Having regard to the opinion of the Economic and Social Committee (2),

Whereas the Directives on the approximation of the laws relating to proprietary medicinal products must be adapted to scientific progress and take account of the experience obtained since their adoption;

Whereas Article 15 (2) of Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (3) provides that the Commission shall submit to the Council a proposal containing appropriate measures leading towards the abolition of any remaining barriers to the free movement of proprietary medicinal products, not later than four years after the entry into force of the abovementioned Directive;

Whereas it is necessary from the point of view of public health and the free movement of medicinal products for the competent authorities to have at their disposal all useful information on authorized proprietary products, based in particular on summaries, adopted in the other Member States, of the characteristics of products;

Whereas it is necessary to specify certain provisions relating to physicochemical, biological or microbiological tests on proprietary medicinal products and to introduce the principle of bio-availability and mutagenesis tests in order to safeguard public health;

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(1) OJ No C 287, 9. 11. 1981, p. 127.
(2) OJ No C 189, 30. 7. 1981, p. 39.
(3) OJ No L 147, 9. 6. 1975, p. 13.

Whereas the approximation of laws brought about in this connection must enable a proprietary product, manufactured and marketed in one Member State on the basis of harmonized provisions, to be allowed into another Member State, taking into due consideration the initial authorization, save in exceptional cases submitted for an opinion to the Committee for Proprietary Medicinal Products set up by Directive 75/319/EEC,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (1) is hereby amended as follows:

1. The second paragraph of Article 4 is amended as follows:

   (a) in point 6, 'if less than three years' is deleted;

   (b) in point 8 (a) of the English version, 'a List of published references' is replaced by 'a bibliography';

   (c) point 9 is replaced by the following:

   '9. A summary, in accordance with Article 4a, of the product characteristics, one or more specimens or mock-ups of the sales presentation of the proprietary product, together with a package leaflet where one is to be enclosed.'

2. The following Article 4a is inserted:

   'Article 4a

   The summary of the product characteristics referred to in point 9 of the second paragraph of Article 4 shall contain the following information:

   1. Name of the proprietary product.

   2. Qualitative and quantitative composition in terms of the active ingredients and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product; the international non-proprietary names recommended by the World Health Organization shall be used, where such names exist, or failing this, the usual common name or chemical description.

   3. Pharmaceutical form.

   4. Pharmacological properties and, in so far as this information is useful for therapeutic purposes, pharmacokinetic particulars.

   5. Clinical particulars:

      5.1. therapeutic indications,
      5.2. contra-indications,
      5.3. undesirable effects (frequency and seriousness),
      5.4. special precautions for use,
      5.5. use during pregnancy and lactation,
      5.6. interaction with other medicaments and other forms of interaction,
      5.7. posology and method of administration for adults and, where necessary, for children,

(1) OJ No 22, 9. 2. 1965, p. 369/65.

5.8. overdose (symptoms, emergency procedures, antidotes)
5.9. special warnings,
5.10. effects on ability to drive and to use machines.

6. Pharmaceutical particulars:

6.1. incompatibilities (major),
6.2. shelf life, when necessary after reconstitution of the product or when the container is opened for the first time,
6.3. special precautions for storage,
6.4. nature and contents of container,
6.5. name or style and permanent address or registered place of business of the holder of the marketing authorization.'

3. The following Article 4b is inserted:

'*Article 4b*

When the marketing authorization referred to in Article 3 is issued, the person responsible for placing that product on the market shall be informed, by the competent authorities of the Member State concerned, of the summary of the product characteristics as approved by them. The competent authorities shall take all necessary measures to ensure that the information given in the summary is in conformity with that accepted when the marketing authorization is issued or subsequently.'

4. The following Article 9a is inserted:

'*Article 9a*

After an authorization has been issued, the person responsible for placing the product on the market must, in respect of the control methods provided for in Article 4 (7), take account of technical and scientific progress and introduce any changes that may be required to enable the proprietary medicinal product to be checked by means of generally accepted scientific methods. These changes must be accepted by the competent authorities of the Member State concerned.'

5. Article 10 is amended as follows:

'*Article 10*

An authorization shall be valid for five years and be renewable for five-year periods on application by the holder at least three months before expiry.'

6. The second paragraph of Article 11 shall be amended as follows:

'An authorization shall also be suspended or revoked where the particulars supporting the application as provided for in Articles 4 and 4a are incorrect or have not been amended in accordance with Article 9a, or when the controls referred to in Article 8 of this Directive or in Article 27 of Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (1) have not been carried out.

(1) OJ No L 147, 9. 6. 1975, p. 13.'

7. in the first paragraph of Article 13, points 1, 2 and 7 are amended as follows:

'1. Name of the proprietary products, which may be a brand name or a common name accompanied by a trade mark or the name of the manufacturer, or a scientific name accompanied by a trade mark or the name of the manufacturer.

Where the special name of a medicinal product containing only one active ingredient is a brand name, this name must be followed in legible characters by the international non-proprietary name recommended by the World Health Organization, where such name exists, or, where no such name exists, by the usual common name.

2. A statement of the active ingredients expressed qualitatively and quantitatively per dosage unit or according to the form of administration for a particular volume or weight, using the international non-proprietary names recommended by the World Health Organization, where such names exist, or, where no such names exist, the usual common names.'

'7. Expiry date in plain language.'

Article 2

The Annex to Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (1) is hereby amended as follows:

1. In part 1 (C) 1, the seventh paragraph is replaced by the following:

'The routine tests carried out on each batch of starting materials must be as stated in the application for marketing authorization. If tests other than those mentioned in the pharmacopoeia are used, proof must be supplied that the starting materials meet the quality requirements of that pharmacopoeia.'

The following is added to the eighth paragraph:

'The competent authorities shall inform the authorities responsible for the pharmacopoeia in question.'

2. In part 1 (C) the following paragraph 3 is added:

'3. **Physico-chemical characteristics liable to affect bio-availability**

The following items of information concerning active ingredients, whether or not listed in the pharmacopoeias, shall be provided as part of the general description of the active principles if the bio-availability of the medicinal product depends on them:

— crystalline form and solubility coefficients,

— particle size, where appropriate after pulverization,

— state of hydration,

— oil/water coefficient of partition (1).

The first three indents are not applicable to substances used solely in solution.

(1) The competent authorities may also request the pK and pH values if they think this information is essential.'

3. In part 1 (E) the following is inserted as first paragraph:

'For the control of the finished product, a batch of a proprietary medicinal product comprises all the units of a pharmaceutical form which are made from the

(1) OJ No L 147, 9. 6. 1975, p. 1.

same initial mass of material and have undergone a single series of manufacturing operations or a single sterilization operation or, in the case of a continuous production process, all the units manufactured in a given period of time.'

4. The following fourth paragraph is added to part 1 (E) (1):

'Furthermore, solid pharmaceutical forms having to be administered orally shall be subjected to *in vitro* studies on the liberation and dissolution rate of the active ingredient or ingredients; these studies shall also be carried out where administration is by another means if the competent authorities of the Member State concerned consider this necessary. The conditions of the test, the apparatus employed and the standards shall be described in precise detail as long as they are not given in the European Pharmacopoeia or the national pharmacopoeia of the Member States; the same shall apply in cases where the methods prescribed by such pharmacopoeias are not applicable.'

5. In part 1 (E) (2) the following new paragraphs are inserted between the second and third paragraphs:

'Unless there is appropriate justification, the maximum acceptable deviation in the active-ingredient content of the finished product shall not exceed ± 5 % at the time of manufacture.

On the basis of the stability tests, the manufacturer must propose and justify maximum acceptable deviations in the active-ingredient content of the finished product up to the end of the proposed shelf-life.'

6. In part 1 (E) (3), the third paragraph is replaced by the following:

'An upper limit test shall be obligatory in respect of preserving agents and any other excipient constituent liable to affect adversely physiological functions; an upper and lower limit test shall be obligatory in respect of the excipient if it is liable to affect the bio-availability of an active substance, unless bio-availability is guaranteed by other appropriate tests.'

7. In part 1 (E) (5), the first paragraph is replaced by the following:

'If general monographs on pharmaceutical forms appear in the European Pharmacopoeia or, failing this, in the national pharmacopoeias of the Member States, finished products must meet the requirements contained therein. If not, the finished-product specifications should include the following tests as appropriate for the formulation.'

In addition, the ninth, 12th, 13th and 15th paragraphs are amended as follows:

Injectable preparations: '10 ml' is replaced by '15 ml'.

'Ointments, creams, etc.: colour and consistency; particle size of the active ingredients; weight and acceptable margin of variation; nature of container; microbiological control tests, if necessary.'

'Suspensions: colour, sedimentation rate; where settlement occurs, the ease with which suspensions can be restored.'

'Suppositories and pessaries: colour; particle size of the active ingredients; weight and acceptable variations in unit weight; melting temperature or disintegration time, with the methods used to determine these.'

8. In chapter I of part 2, the following section Da is inserted between titles D and E:

'Da. MUTAGENIC POTENTIAL

The purpose of the study of mutagenic potential is to reveal the changes which a substance may cause in the genetic material of individuals or cells and which have the effect of making successors permanently and hereditarily different from their predecessors. This study is obligatory for any new substance.

The number and types of results and the criteria for their evaluation shall depend on the state of scientific knowledge at the time when the application is lodged.'

9. In chapter I of part 2, section E is replaced by:

'E. CARCINOGENIC POTENTIAL

Tests to reveal carcinogenic effects shall normally be required:

1. in respect of substances having a close chemical analogy with known carcinogenic or cocarcinogenic compounds;

2. in respect of substances which have given rise to suspicious changes during the long term toxicological tests;

3. in respect of substances which have given rise to suspicious results in the mutagenic-potential tests or in other short-term carcinogenicity tests.

Such tests may also be required in respect of substances to be included in proprietary medicinal products likely to be administered regularly over a prolonged period of a patient's life.

The state of scientific knowledge at the time when the application is lodged shall be taken into account when determining the details of the tests.'

10. In chapter I (G) of part 2, the following new paragraph is inserted between the fourth and fifth paragraphs:

'For medicinal products which must be subjected to a bio-availability assessment, the data must include changes in the results as a function of time and, more generally, indicate the bio-availability of the product or of its metabolities.'

11. Chapter II of part 3 is amended as follows:

— the title is replaced by:

'A. PHARMACOLOGICAL PARTICULARS (Clinical pharmacology and bio-availability)'

— the following paragraph is added:

'5. The assessment of bio-availability must be undertaken in all cases where it is essential in the interests of patients, e.g. where the therapeutic safety index number is low or where the previous tests have revealed anomalies which may be related to variable absorption, or if this process is necessary for the proprietary products referred to in Article 4 (8) of Directive 65/65/EEC.'

Article 3

Chapter III of Directive 75/319/EEC is hereby replaced by the following:

'CHAPTER III

Committee for Proprietary Medicinal Products

Article 8

1. In order to facilitate the adoption of a common position by the Member States with regard to decisions on the issuing of marketing authorizations and to promote thereby the free movement of proprietary medicinal products, a Committee for Proprietary Medicinal Products, hereinafter referred to as "the Committee", is hereby set up. The Committee shal consist of representatives of the Member States and of the Commission.

2. The Committee's task shall be to examine, at the request of a Member State or the Commission and in accordance with Articles 9 to 14, questions concerning the application of Articles 5, 11 or 20 of Directive 65/65/EEC.

3. The Committee shall draw up its own rules of procedure.

Article 9

1. In order to make it easier to obtain a marketing authorization in at least two other Member States taking into due consideration an authorization issued in one Member State in accordance with Article 3 of Directive 65/65/EEC, the holder of the latter authorization may submit an application to the competent authorities of the Member States concerned together with the information and documents referred to in Articles 4, 4a and 4b of Directive 65/65/EEC. He shall testify to its identity with the dossier accepted by the first Member State, specifying any additions it may contain, and shall certify that all the dossiers filed as part of this procedure are identical.

2. The holder of the marketing authorization shall notify the Committee of this application, inform it of the Member States concerned and send it a copy of his authorization. He shall also inform the Member State which granted him the initial authorization and notify it of any additions to the original dossier; that State may require the applicant to provide it with all the particulars and documents necessary to enable it to check the identity of the dossiers filed with the dossier on which took its decision.

3. The holder of the marketing authorization shall notify the dates on which the dossiers were sent to the Member States concerned. As soon as the Committee has noted that all the Member States concerned are in possession of the dossier, it shall forthwith inform all the Member States and the applicant of the date on which the last Member State concerned received the dossier. The Member State(s) concerned shall either grant the authorization valid for their markets within a period of 120 days of the aforementioned date, taking into due consideration the authorization issued within the meaning of paragraph 1, or put forward a reasoned objection.

Article 10

1. Where a Member State considers that it is unable to grant a marketing authorization, it shall forward to the Committee and to the person responsible for placing

the proprietary medicinal product on the market its reasoned objection in accordance with Article 5 of Directive 65/65/EEC, within the time limits stipulated in Article 9 (3).

2. Upon the expiry of this period, the matter shall be referred to the Committee and the procedure referred to in Article 14 shall be applied.

3. On receipt of the reasoned objection referred to in paragraph 1, the person responsible for placing the product on the market shall immediately send the Committee a copy of the particulars and documents enumerated in Article 9 (1).

Article 11

If several applications submitted in accordance with Articles 4 and 4a of directive 65/65/EEC have been made for a marketing authorization for a particular proprietary medicinal product, and one or more Member States have granted an authorization while one or more of the other Member States have refused it, one of the Member States concerned or the Commission may refer the matter to the Committee for application of the procedure referred to in Article 14 of this Directive.

The same shall apply where one or more Member States have suspended or revoked a marketing authorization while one or more other Member States have not done so.

In both cases, the person responsible for placing the proprietary medicinal product on the market shall be informed of any decision of the Committee to apply the procedure laid down in Article 14.

Article 12

The competent authorities of Member States may, in specific cases where the interests of the Community are involved, refer the matter to the Committee before reaching a decision on a request for a marketing authorization or on the suspension or revocation of an authorization.

Article 13

1. The competent authorities shall draw up an assessment report and comments on the dossier as regards the results of the analytical and toxico-pharmacological tests on, and clinical trials of, any proprietary products containing a new active substance which are the subject of a request for a marketing authorization in the Member States concerned for the first time.

2. As soon as the notification referred to in Article 9 is received, the competent authorities shall immediately communicate to the Member States concerned any assessment report accompanied by a summary of the dossier relating to a particular proprietary product. This report shall also be communicated to the Committee where a matter is referred to the Committee pursuant to Article 10.

The assessment report shall also be forwarded to the other Member States concerned and to the Committee as soon as a matter is referred to the Committee under the procedure laid down in Article 11. Any assessment report so forwarded shall remain confidential.

The competent authorities shall bring the assessment report up to date as soon as it is in possession of information which is of importance for the evaluation of the balance between effectiveness and risk.

Article 14

1. When reference is made to the procedure described in this Article, the Committee shall consider the matter concerned and issue a reasoned opinion within 60 days of the date on which the matter was referred to it.

In the cases referred to in Article 10 the person responsible for placing the product on the market may, at his request, explain himself orally or in writing before the Committee issues its opinion. The Committee may extend the time limit referred to in the preceding paragraph to give the applicant time to explain himself orally or in writing.

In the case referred to in Article 11, the person responsible for placing the product on the market may be asked to explain himself orally or in writing.

2. The Committee's opinion shall concern the grounds for the objection provided for in Article 10 (1) and the grounds on which the marketing authorization has been refused, suspended or withdrawn in the cases described in Article 11.

The Committee shall immediately inform the Member State(s) concerned and the person responsible for placing the product on the market of its opinion or of those of its members in the case of divergent opinions.

3. The Member State(s) concerned shall decide what action to take on the Committee's opinion within 60 days of receipt of the information referred to in paragraph 2. They shall immediately inform the Committee of their decision.

Article 15

1. The Commission shall report to the Council every two years on the operation of the procedure laid down in this chapter and its effects on the development of intra-Community trade.

2. In the light of experience, the Commission shall, not later than four years after the entry into force of this Directive, submit to the Council a proposal containing appropriate measures leading towards the abolition of any remaining barriers to the free movement of proprietary medicinal products.

3. The Councli shall decide on the Commission proposal no later than one year after its submission.'

Article 4

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive within 24 months of its notification (1). They shall forthwith inform the Commission thereof.

Requests for marketing authorizations lodged after expiry of the time limit referred to in the first paragraph must comply with the provisions of this Directive.

(1) This Directive was notified to the Member States on 31 October 1983.

Articles 1 and 2 of this Directive, where relevant, shall be progressively extended to existing proprietary medicinal products by the end of the period stipulated in Article 39 (2) of Directive 75/319/EEC.

Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

Article 5

This Directive is addressed to the Member States.

Done at Luxembourg, 26 October 1983.

For the Council
The President
G. MORAITIS