

DIRECTIVE 65/65/EEC

Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products

(OJ L No 22 of 9. 2. 1965, p. 369)

(As amended by Directives 66/454/EEC, 75/319/EEC, 83/570/EEC, 87/21/EEC, 89/341/EEC, 89/342/EEC, 89/343/EEC, 92/27/EEC, 92/73/EEC et 93/39/EEC)

THE COUNCIL OF THE EUROPEAN ECONOMIC COMMUNITY,

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 primary purpose of any rules concerning the production and distribution of medicinal products must be to safeguard public health;

Whereas, however, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community;

Whereas trade in medicinal products within the Community is hindered by disparities between certain national provisions, in particular between provisions relating to medicinal products (excluding substances or combinations of substances which are foods, animal feedingstuffs or toilet preparations); and whereas such disparities, directly affect the establishment and functioning of the common market;

Whereas such hindrances must accordingly be removed; and whereas this entails approximation of the relevant provisions;

Whereas, however, such approximation can only be achieved progressively; and whereas priority must be given to eliminating the disparities liable to have the greatest effect on the functioning of the common market;

HAS ADOPTED THIS DIRECTIVE:

(1) OJ No 84 of 4. 6. 1963, p. 1531/63.

(2) OJ No 158 of 16. 10. 1964, p. 2503/64.

CHAPTER I

Definitions and scope

Article 1

For the purposes of this Directive, the following shall have the meanings hereby assigned to them:

1. *Proprietary medicinal product*: any ready-prepared medicinal product placed on the market under a special name and in a special pack.
2. *Medicinal product*: any substance or combination of substances presented for treating or preventing disease in human beings or animals.
Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product.
3. *Substance*: Any matter irrespective of origin which may be:
 - human, e.g.
human blood and human blood products;
 - animal, e.g.
micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products, etc.;
 - vegetable, e.g.
micro-organisms, plants, parts of plants, vegetable secretions, extracts, etc.;
 - chemical, e.g.
elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis.
4. *Magistral formula*: any medicinal product prepared in a pharmacy in accordance with a prescription for an individual patient.
5. *Officinal formula*: any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question.

Article 2

1. Chapters II to V shall apply to proprietary medicinal products for human use intended to be placed on the market in Member States.
2. Where a Member State authorizes the placing on the market of industrially produced medicinal products which do not comply with the definition of a proprietary medicinal product, it shall also apply Chapters II to V to them.
3. Chapters II to V shall not apply to:
 - medicinal products prepared on the basis of a magistral or official formula,
 - medicinal products intended for research and development trials,
 - intermediate products intended for further processing by an authorized manufacturer.

4. A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from Chapters II to V medicinal products supplied in response to a *bona fide* unsolicited order, formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients on his direct personal responsibility.

CHAPTER II

Authorization to place medicinal products on the market

Article 3

No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive or an authorization has been granted in accordance with Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products ⁽¹⁾.

The provisions of this Directive shall not affect the powers of the Member States' authorities either as regards the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes, on the basis of health, economic and social conditions.

Article 4

In order to obtain an authorisation to place a medicinal product on the market as provided for in Article 3, the person responsible for placing that product on the market shall make application to the competent authority of the Member State concerned.

The person responsible for placing medicinal products on the market shall be established in the Community. In respect of medicinal products authorized on the date of implementation of this Directive, the Member State shall if necessary apply this provision at the time of the five-yearly renewal of the marketing authorization provided for in Article 10.

The application shall be accompanied by the following particulars and documents:

1. Name or corporate name and permanent address of the person responsible for placing the proprietary product on the market and, where applicable, of the manufacturer.
2. Name of the proprietary product (brand name, or common name together with a trade mark or name of the manufacturer, or scientific name together with a trade mark or name of the manufacturer).
3. Qualitative and quantitative particulars, of all the constituents of the proprietary product in usual terminology, but excluding empirical chemical formulae, with mention of the international non-proprietary name recommended by the World Health Organisation where such name exists.
4. Brief description of the method of preparation.

⁽¹⁾ OJ No L 214 of 24. 8. 1993, p. 1.

5. Therapeutic indications, contra-indications and side-effects.
6. Posology, pharmaceutical form, method and route of administration and expected shelf life.
If applicable, reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of any potential risks presented by the medicinal product for the environment.
7. Description of the control methods employed by the manufacturer (qualitative and quantitative analysis of the constituents and of the finished product, special tests, e.g. sterility tests, tests for the presence of pyrogenic substances, the presence of heavy metals, stability tests, biological and toxicity tests, controls carried out at an intermediate stage of the manufacturing process).
8. Results of:
 - physico-chemical, biological or microbiological tests,
 - pharmacological and toxicological tests,
 - clinical trials.

However, and without prejudice to the law relating to the protection of industrial and commercial property:

- a) The applicant shall not be required to provide the results of pharmacological and toxicological tests or the results of clinical trials if he can demonstrate:
 - i) either that the medicinal product is essentially similar to a product authorized in the country concerned by the application and that the person responsible for the marketing of the original proprietary medicinal product has consented to the pharmacological, toxicological or clinical references contained in the file on the original medicinal product being used for the purpose of examining the application in question;
 - ii) or by detailed references to published scientific literature presented in accordance with the second paragraph of Article 1 of Directive 75/318/EEC that the constituent or constituents of the medicinal product have a well established medicinal use, with recognized efficacy and an acceptable level of safety;
 - iii) or that the medicinal product is essentially similar to a product which has been authorized within the Community, in accordance with Community provisions in force, for not less than six years and is marketed in the Member State for which the application is made; this period shall be extended to 10 years in the case of high-technology medicinal products within the meaning of Part A in the Annex to Directive 87/22/EEC ⁽¹⁾ or of a medicinal product within the meaning of Part B in the Annex to that Directive for which the procedure laid down in Article 2 thereof has been followed; furthermore, a Member State may also extend this period to 10 years by a single Decision covering all the products marketed on its territory where it considers this necessary in the interest of public health. Member States are at liberty not to apply the abovementioned six-year period beyond the date of expiry of a patent protecting the original product.

⁽¹⁾ The annex to Directive 87/22/EEC is replaced by the annex to Regulation (EEC) No 2309/93.

However, where the medicinal product is intended for a different therapeutic use from that of the other medicinal products marketed or is to be administered by different routes or in different doses, the results of appropriate pharmacological and toxicological tests and/or of appropriate clinical trials must be provided.

- b) In the case of new medicinal products containing known constituents not hitherto used in combination for therapeutic purposes, the results of pharmacological and toxicological tests and of clinical trials relating to that combination must be provided, but it shall not be necessary to provide references relating to each individual constituent.
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.
10. A document showing that the manufacturer is authorised in his own country to produce proprietary products.
11. Copies of any authorization obtained in another Member State or in a third country to place the relevant medicinal product on the market, together with a list of those Member States in which an application for authorization submitted in accordance with this Directive is under examination. Copies of the summary of the product characteristics proposed by the applicant in accordance with Article 4a or approved by the competent authorities of the Member State in accordance with Article 4b. Copies of the package leaflet proposed in accordance with Article 6 of Directive 92/27/EEC or approved by the competent authorities of the Member State in accordance with Article 10 of the same Directive. Details of any decision to refuse authorization, whether in the Community or in a third country, and the reasons for such decision.

This information shall be updated on a regular basis.

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,
 - 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,
 - 6.6 special precautions for disposal of unused products or waste materials derived from such products, if appropriate.
7. Full details of internal radiation dosimetry.
8. Additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready to use pharmaceutical will conform with its specifications.

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 it. 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. The competent authorities shall forward to the European Agency for the Evaluation of Medicinal Products a copy of the authorization together with the summary of the product characteristics referred to in Article 4a.

Furthermore, the competent authorities shall draw up an assessment report and comments on the dossier as regards the results of the analytical and pharmacotoxicological tests and the clinical trials of the medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is of importance for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

Article 5

The authorisation provided for in Article 3 shall be refused if, after verification of the particulars and documents listed in Article 4, it proves that the medicinal product is harmful in the normal conditions of use, or that its therapeutic efficacy is lacking or is insufficiently substantiated by the applicant, or that its qualitative and quantitative composition is not as declared.

Authorisation shall likewise be refused if the particulars and documents submitted in support of the application do not comply with Article 4.

Article 6

This Directive shall not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products as contraceptives or abortifacients. The Member States shall communicate the national legislation concerned to the Commission.

Article 7

1. Member states shall take all appropriate measures to ensure that the procedure for granting an authorization to place a medicinal product on the market is completed within 210 days of the submission of a valid application.

2. Where a Member State notes that an application for authorization submitted after 1 January 1995 is already under active examination in another Member State in respect of that medicinal product, the Member State concerned may decide to suspend the detailed examination of the application in order to await the assessment report prepared by the other Member State in accordance with Article 4b.

The Member State concerned shall inform the other Member State and the applicant of its decision to suspend detailed examination of the application in question. As soon as it has completed the examination of the application and reached a decision, the other Member State shall forward a copy of its assessment report to the Member State concerned.

Within 90 days of the receipt of the assessment report, the Member State concerned shall either recognize the decision of the other Member State and the summary of the product characteristics as approved by it, or, if it considers that there are grounds for supposing that the authorization of the medicinal product concerned may present a risk to public health ⁽¹⁾, it shall apply the procedures set out in Articles 10 to 14 of Directive 75/319/EEC.

Article 7a

With effect from 1 January 1998, where a Member State is informed in accordance with point 11 of the second paragraph of Article 4 that another Member State has authorized a medicinal product which is the subject of an application for authorization in the Member State concerned, that Member State shall forthwith request the authorities of the Member State which has granted the authorization to forward to it the assessment report referred to in the second paragraph of Article 4b.

⁽¹⁾ The expression 'risk to public health' refers to the quality, safety and efficacy of the medicinal product.

Within 90 days of the receipt of the assessment report, the Member State concerned shall either recognize the decision of the first Member State and the summary of the product characteristics as approved by it or, if it considers that there are grounds for supposing that the authorization of the medicinal product concerned may present a risk to public health ⁽¹⁾, it shall apply the procedures set out in Articles 10 to 14 of Directive 75/319/EEC.

Article 8

Member States shall take all appropriate measures to ensure that the holder of an authorisation furnishes proof that the controls have been carried out on the finished product in accordance with the methods described by the applicant pursuant to item 7 of the second paragraph of Article 4.

Article 9

Authorisation shall not affect the civil and criminal liability of the manufacturer and, where applicable, of the person responsible for placing the medicinal product on the market.

Article 9a

After an authorization has been issued, the person responsible for placing the product on the market must, in respect of the methods of preparation and control provided for in points 4 and 7 of the second paragraph of Article 4, take account of technical and scientific progress and introduce any changes that may be required to enable that medicinal product to be manufactured and checked by means of generally accepted scientific methods. These changes shall be subject to the approval of the competent authority of the Member State concerned.

Article 10

1. Authorization shall be valid for five years and shall be renewable for five-year periods, on application by the holder at least three months before the expiry date and after consideration by the competent authority of a dossier containing in particular details of the data on pharmacovigilance and other information relevant to the monitoring of the medicinal product.

2. In exceptional circumstances, and following consultation with the applicant, an authorization may be granted subject to certain specific obligations, including:

- the carrying out of further studies following the granting of authorization,
- the notification of adverse reactions to the medicinal product.

These exceptional decisions may be adopted only for objective and verifiable reasons and shall be based on one of the causes referred to in Part 4 (G) of the Annex to Directive 75/318/EEC.

⁽¹⁾ The expression 'risk to public health' refers to the quality, safety and efficacy of the medicinal product.

CHAPTER III

Suspension and revocation of authorisation to market medicinal products

Article 11

The competent authorities of the Member States shall suspend or revoke an authorisation to place a medicinal product on the market where that product proves to be harmful in the normal conditions of use, or where its therapeutic efficacy is lacking, or where its qualitative and quantitative composition is not as declared. Therapeutic efficacy is lacking when it is established that therapeutic results cannot be obtained with the medicinal product.

An authorisation 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 medicinal products ⁽¹⁾ have not been carried out.

Article 12

All decisions taken pursuant to Articles 5, 6 or 11 shall state in detail the reasons on which they are based. A decision shall be notified to the party concerned, who shall at the same time be informed of the remedies available to him under the laws in force and of the time limit allowed for the exercise of such remedies.

Authorisations to place a medicinal product on the market and decisions to revoke authorisations shall be published by each Member State in the appropriate official publication.

CHAPTER IV

Labelling of medicinal products

Articles 13 – 20

These articles are repealed by Directive 92/27/EEC.

CHAPTER V

General and final provisions

Article 21

An authorisation to market a medicinal product shall not be refused, suspended or revoked except on the grounds set out in this Directive.

⁽¹⁾ OJ No L147 of 9. 6. 1975, p. 13.

Article 22

Member States shall put into force the measures needed in order to comply with this Directive within eighteen months of its notification and shall inform the Commission forthwith.

Article 23

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

Article 24

Within the time limits and under the conditions laid down in Article 39 (2) and (3) of second Directive 75/319/EEC, the rules laid down in this Directive shall be applied progressively to proprietary medicinal products covered by an authorization to place on the market by virtue of previous provisions

Article 25

This Directive is addressed to the Member States.

Done at Brussels, 26 January 1965.

For the council

The President

M. COUVE DE MURVILLE