DIRECTIVE 75/319/EEC

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

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

(As amended by Directives 83/570/CEE (OJ No L 332 of 28. 11. 1983, p. 1), 89/341/CEE (OJ No L 142 of 25. 5. 1989, p. 11), 89/342/CEE (OJ No L 142 of 25. 5. 1989, p. 14), 89/343/CEE (OJ No L 142 of 25. 5. 1989, p. 16), 89/381/CEE (OJ No L 181 of 28. 6. 1989, p. 44), 92/027/CEE (OJ No L 113 of 30. 4. 1992, p. 8) and 93/39/CEE (OJ No L 214 of 24. 8. 1993, p. 22))

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 approximation begun by Council Directive 65/65/EEC ([3]) of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products should be continued and the implementation of the principles laid down in that Directive should be ensured;

Whereas in order to reduce the disparities which remain, rules should be laid down on the control of medicinal products and the duties incumbent upon the Member States' competent authorities should be specified with a view to ensuring compliance with legal requirements;

Whereas, in order to progress towards free movement of medicinal products, the issue of authorizations to place one and the same medicinal product on the market in two or more Member States should be facilitated;

Whereas, for this purpose, a Committee for Proprietary Medicinal Products should be set up, consisting of representatives of the Member States and of the Commission, responsible for giving an opinion as to whether a particular medicinal product complies with the requirements set out in Directive 65/65/EEC;

Whereas this Directive represents merely one step towards achievement of the objective of the free movement of medicinal products; whereas, therefore, further measures with a view to abolishing any remaining barriers to the free movement of medicinal products will be necessary in the light of experience gained, particularly in the abovementioned Committee;

([1]) OJ No 96 of 2. 6. 1965, p. 1677/65.

([2]) OJ No 107 of 19. 6.1 965, p. 1825/65.

([3]) OJ No 22 of 9. 2. 1965, p. 369/65.

Whereas in order to facilitate the movement of medicinal products and to prevent the controls carried out in one Member State from being repeated in another, minimum requirements should be laid down for manufacture and imports coming from third countries and for the grant of the authorization relating thereto;

Whereas it should be ensured that, in the Member States, the supervision and control of the manufacture of medicinal products is carried out by a person who fulfils minimum conditions of qualification;

Whereas, moreover, the provisions of this Directive and that of Directive 65/65/EEC which relate to medicinal products, although appropriate, are inadequate for vaccines, toxins and serums, medicinal products based on human blood or blood constituents, medicinal products based on radio-active isotopes and homeopathic medicinal products; whereas the application thereof should consequently not be imposed at the present time in respect of such medicinal products;
Whereas certain rules in this Directive entail amendments to various provisions of Directive 65/65/EEC,

HAS ADOPTED THIS DIRECTIVE:

CHAPTER 1

Application for authorization to place medicinal products on the market

Article 1

Member States shall take all appropriate measures to ensure that the documents and particulars listed in points 7 and 8 of Article 4, second paragraph, of Directive 65/65/EEC are drawn up by experts with the necessary technical or professional qualifications before they are submitted to the competent authorities. These documents and particulars shall be signed by the experts.

Article 2

The duties of the experts according to their respective qualifications shall be:

a) to perform tasks falling within their respective disciplines (analysis, pharmacology and similar experimental sciences, clinical trials) and to describe objectively the results obtained (qualitatively and quantitatively);

b) to describe their observations in accordance with Council Directive 75/318/EEC ([1]) of 20 May 1975, on the approximation of the laws of the Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products, and to state, in particular:

   — in the case of the analyst, whether the product is consistent with the declared composition, giving any substantiation of the control methods employed by the manufacturer;

   — in the case of the pharmacologist or the specialist with similar experimental competence, the toxicity of the product and the pharmacological properties observed;

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

— in the case of the clinician, whether he has been able to ascertain effects on persons treated with the product which correspond to the particulars given by the applicant in accordance with Article 4 of Directive 65/65/EEC, whether the patient tolerates the product well, the posology the clinician advises and any contra-indications and side-effects;

c) where applicable, to state the grounds for using the published references mentioned in point 8 a) and b) of Article 4, second paragraph, of Directive 65/65/EEC under the conditions set out in Directive 75/318/EEC.

Detailed reports by the experts shall form part of the particulars accompanying the application which the applicant submits to the competent authorities.

Article 3

In the event of Article 2 of this Directive not being complied with, Article 5, second paragraph, of Directive 65/65/EEC shall apply.

CHAPTER II

Examination of the application for authorization to place medicinal products on the market

Article 4

In order to examine the application submitted in accordance with Article 4 of Directive 65/65/EEC, the competent authorities of the Member States:

a) must verify whether the particulars submitted in support of the application comply with the said Article 4 and examine whether the conditions for issuing an authorization to place medicinal products on the market (marketing authorization) are complied with;

b) may submit the medicinal product, its starting materials and, if need be, its intermediate products or other constituent materials for testing by a State laboratory or by a laboratory designated for that purpose in order to ensure that the control methods employed by the manufacturer and described in the particulars accompanying the application in accordance with the second subparagraph of point 7 of Article 4 of Directive 65/65/EEC are satisfactory.

c) may, where appropriate, require the applicant to supplement the particulars accompanying the application in respect of the items listed in the second paragraph of Article 4 of Directive 65/65/EEC. Where the competent authorities avail themselves of this option, the time limits laid down in Article 7 of the said Directive shall be suspended until such time as the supplementary information required has been provided. Likewise, these time limits shall be suspended for the time allowed the applicant, where appropriate, for giving oral or written explanation.

Article 5

Member States shall take all appropriate measures to ensure that:

a) the competent authorities verify that manufacturers and importers of products coming from third countries are able to carry our manufacture in compliance with the particulars supplied pursuant to point 4 of Article 4, second paragraph, of Directive 65/65/EEC and/or to carry out controls according to the methods described in the particulars accompanying the application in accordance with point 7 of Article 4, second paragraph, of that Directive;

b) the competent authorities may allow manufacturers and importers of products coming from third countries, in exceptional and justifiable cases, to have certain stages of manufacture and/or certain of the controls referred to in (a) carried out by third parties; in such cases, the verifications by the competent authorities shall also be made in the establishment designated.

Articles 6 – 7

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

CHAPTER III

Committee for Proprietary Medicinal Products

Article 8

1. In order to facilitate the adoption of common decisions by Member States on the authorization of medicinal products for human use on the basis of the scientific criteria of quality, safety and efficacy, and to achieve thereby the free movement of medicinal products within the Community, a Committee for Proprietary Medicinal Products, hereinafter referred to as the 'the Committee', is hereby set up. The Committee shall be part of the European Agency for the Evaluation of Medicinal Products established by Council 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]), hereinafter referred to as 'the Agency'.

2. In addition to the other responsibilities conferred upon it by Community law, the Committee shall examine any question relating to the granting, variation, suspension or withdrawal of marketing authorization for a medicinal product which is submitted to it in accordance with this Directive.

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

([1]) OJ No L 214 of 24. 8. 1993, p. 1.

Article 9

1. In order to obtain the recognition according to the procedures laid down in this Chapter in one or more of the Member States of an authorization issued by a Member State in accordance with Article 3 of Directive 65/65/EEC, the holder of the authorization shall submit an application to the competent authorities of the Member State or Member States concerned, together with the information and particulars referred to in Articles 4, 4a and 4b of Directive 65/65/EEC. He shall testify that the dossier is identical to that accepted by the first Member State, or shall identify any additions or amendments it may contain. In the latter case, he shall certify that the summary of the product characteristics proposed by him in accordance with Article 4a of Directive 65/65/EEC is identical to that accepted by the first Member State in accordance with Article 4b of Directive 65/65/EEC. Moreover he shall certify that all the dossiers filed as part of the 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 of the dates of submission of the application and send it a copy of the authorization granted by the first Member State. He shall also send the Committee copies of any such authorization which may have been granted by the other Member States in respect of the medicinal product concerned, and shall indicate whether any application for authorization is currently under consideration in any Member State.

3. Except in cases referred to in Article 7a of Directive 65/65/EEC, before submitting the application, the holder of the authorization shall inform the Member State which granted the authorization on which the application is based that an application is to be made in accordance with this Directive and shall notify it of any additions to the original dossier; that Member State may require the applicant to provide it with all the particulars and documents necessary to enable it to check that the dossiers filed are identical.

In addition the holder of the authorization shall request the Member State which granted the initial authorization to prepare an assessment report in respect of the medicinal product concerned, or, if necessary, to update any existing assessment report. That Member State shall prepare the assessment report, or update it, within 90 days of the receipt of the request.

At the same time as the application is submitted in accordance with paragraph 1 the Member State which granted the initial authorization shall forward the assessment report to the Member State or Member States concerned by the application.

4. Save in the exceptional case provided for in Article 10 (1), each Member State shall recognize the marketing authorization granted by the first Member State within 90 days of receipt of the application and the assessment report. It shall inform the Member State which granted the initial authorization, the other Member States concerned by the application, the Committee, and the person responsible for placing the medicinal product on the market.

Article 10

1. Notwithstanding Article 9(4), where a Member State 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 forthwith inform the applicant, the Member State which granted the initial authorization, any other Member States concerned by the application and the Committee. The Member State shall state its reasons in detail and shall indicate what action may be necessary to correct any defect in the application.

2. All the Member States concerned shall use their best endeavours to reach agreement on the action to be taken in respect of the application. They shall provide the applicant with the opportunity to make his point of view known orally or in writing. However, if the Member States have not reached agreement within the time limit referred to in Article 9 (4) they shall forthwith refer the matter to the Committee for the application of the procedure laid down in Article 13.

3. Within the time limit referred to in paragraph 2, the Member States concerned shall provide the Committee with a detailed statement of the matters on which they have been unable to reach agreement and the reasons for their disagreement. The applicant shall be provided with a copy of this information.

4. As soon as he is informed that the matter has been referred to the Committee, the applicant shall forthwith forward to the Committee a copy of the information and particulars referred to 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 marketing authorization for a particular medicinal product, and Member States have adopted divergent decisions concerning the authorization of the medicinal product or its suspension or withdrawal from the market, a Member State, or the Commission, or the person responsible for placing the medicinal product on the market may refer the matter to the Committee for application of the procedure laid down in Article 13.

The Member State concerned, the person responsible for placing the medicinal product on the market or the Commission shall clearly identify the question which is referred to the Committee for consideration and, where appropriate, shall inform the aforementioned person thereof.

The Member States and the person responsible for placing the medicinal product on the market shall forward to the Committee all available information relating to the matter in question.

Article 12

The Member States or the Commission or the applicant or holder of the marketing authorization may, in specific cases where the interests of the Community are involved, refer the matter to the Committee for the application of the procedure laid down in Article 13 before reaching a decision on a request for a marketing authorization or on the suspension or withdrawal of an authorization, or on any other variation to the terms of a marketing authorization which appears necessary, in particular to take account of the information collected in accordance with Chapter Va.

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

The Member State concerned or the Commission shall clearly identify the question which is referred to the Committee for consideration and shall inform the person responsible for placing the medicinal product on the market.

The Member States and the aforementioned person shall forward to the Committee all available information relating to the matter in question.

Article 13

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 90 days of the date on which the matter was referred to it.

However, in cases submitted to the Committee in accordance with Articles 11 and 12, this period may be extended by 90 days.

In case of urgency, on a proposal from its Chairman, the Committee may agree to impose a shorter deadline.

2. In order to consider the matter, the Committee may appoint one of its members to act as rapporteur. The Committee may also appoint individual experts to advise it on specific questions. When appointing experts, the Committee shall define their tasks and specify the time limit for the completion of these tasks.

3. In the cases referred to in Articles 10 and 11, before issuing its opinion, the Committee shall provide the person responsible for placing the medicinal product on the market with an opportunity to present written or oral explanations.

In the case referred to in Article 12, the person responsible for placing the medicinal product on the market may be asked to explain himself orally or in writing.

If it considers it appropriate, the Committee may invite any other person to provide information relating to the matter before it.

The Committee may suspend the time limit referred to in paragraph 1 in order to allow the person responsible for placing the medicinal product on the market to prepare explanations.

4. Where the opinion of the Committee is that:

— the application does not satisfy the criteria for authorization, or

— the summary of the product characteristics proposed by the applicant in accordance with Article 4a of Directive 65/65/EEC should be amended, or

— the authorization should be granted subject to conditions, with regard to conditions considered essential for the safe and effective use of the medicinal product including pharmacovigilance, or

— a marketing authorization should be suspended, varied or withdrawn,

the Agency shall forthwith inform the person responsible for placing the medicinal product on the market. Within 15 days of the receipt of the opinion, the aforementioned person may notify the Agency in writing of his intention to appeal. In that case, he shall forward the detailed grounds for appeal to the Agency within 60 days of receipt of the opinion. Within 60 days of receipt of the grounds for appeal, the Committee shall consider whether its opinion should be revised, and the conclusions reached on the appeal shall be annexed to the assessment report referred to in paragraph 5.

5. Within 30 days of its adoption, the Agency shall forward the final opinion of the Committee to the Member States, the Commission and the person responsible for placing the medicinal product on the market together with a report describing the assessment of the medicinal product and stating the reasons for its conclusions.

In the event of an opinion in favour of granting or maintaining an authorization to place the medicinal product concerned on the market, the following documents shall be annexed to the opinion:

a) a draft summary of the product characteristics, as referred to in Article 4a of Directive 65/65/EEC;

b) any conditions affecting the authorization within the meaning of paragraph 4.

Article 14

1. Within 30 days of the receipt of the opinion, the Commission shall prepare a draft of the decision to be taken in respect of the application, taking into account Community law.

In the event of a draft decision which envisages the granting of marketing authorization, the documents referred to in Article 13 (5) a) and b) shall be annexed.

Where, exceptionally, the draft decision is not in accordance with the opinion of the Agency, the Commission shall also annex a detailed explanation of the reasons for the differences.

The draft decision shall be forwarded to the Member States and the applicant.

2. A final decision on the application shall be adopted in accordance with the procedure laid down in Article 37b.

3. The rules of procedure of the Committee referred to in Article 37b shall be adjusted to take account of the tasks incumbent upon it in accordance with this Directive.

These adjustments shall involve the following:

— except in cases referred to in the third subparagraph of paragraph 1, the opinion of the Standing Committee shall be obtained in writing,

— each Member State is allowed at least 28 days to forward written observations on the draft decision to the Commission,

— each Member State is able to require in writing that the draft decision be discussed by the Standing Committee, giving its reasons in detail.

Where, in the opinion of the Commission, the written observations of a Member State raise important new questions of a scientific or technical nature which have not been addressed in the opinion of the Agency, the Chairman shall suspend the procedure and refer the application back to the Agency for further consideration.

The provisions necessary for the implementation of this paragraph shall be adopted by the Commission in accordance with the procedure laid down in Article 37a.

4. A decision adopted in accordance with this Article shall be addressed to the Member States concerned by the matter and to the person responsible for placing the medicinal product on the market. The Member States shall either grant or withdraw marketing authorization, or vary the terms of a marketing authorization as necessary to comply with the decision within 30 days of its notification. They shall inform the Commission and the Committee thereof.

5. The procedure referred to in Articles 8 to 14 shall not apply in the cases provided for in Article 9 (2) of Council Directive 92/73/EEC of 22 September 1992 widening the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of the laws of the Member States on medicinal products and laying down additional provisions on homeopathic medicinal products ([1]).

Article 15

Any application by the person responsible for placing the medicinal product on the market to vary a marketing authorization which has been granted in accordance with the provisions of this Chapter shall be submitted to all the Member States which have previously authorized the medicinal product concerned.

The Commission shall, in consultation with the Agency, adopt appropriate arrangements for the examination of variations to the terms of a marketing authorization.

These arrangements shall include a notification system or administration procedures concerning minor variations and define precisely the concept of 'a minor variation'.

These arrangements shall be adopted by the Commission in the form of an implementing Regulation in accordance with the procedure laid down in Article 37a.

The procedure laid down in Articles 13 and 14 shall apply by analogy to variations made to marketing authorizations for products subject to the Commission's arbitration.

Article 15a

1. Where a Member State considers that the variation of the terms of a marketing authorization which has been granted in accordance with the provisions of this Chapter or its suspension or withdrawal is necessary for the protection of public health, the Member State concerned shall forthwith refer the matter to the Committee for the application of the procedures laid down in Articles 13 and 14.

2. Without prejudice to the provisions of Article 12, in exceptional cases, where urgent action is essential to protect public health, until a definitive decision is adopted a Member State may suspend the marketing and the use of the medicinal product concerned on its territory. It shall inform the Commission and the other Member States no later than the following working day of the reasons for its action.

Article 15b

Articles 15 and 15a shall apply by analogy to medicinal products authorized by Member States following an opinion of the Committee given in accordance with Article 4 of Directive 87/22/EEC before 1 January 1995.

Article 15c

1. The Agency shall publish an annual report on the operation of the procedures laid down in this chapter and shall forward that report to the European Parliament and the Council for information.

([1]) OJ No L 297 of 13. 10. 1992, p. 8.

2. By 1 January 2001, the Commission shall publish a detailed review of the operation of the procedures laid down in this chapter and shall propose any amendments which may be necessary to improve these procedures.

The Council shall decide, under the conditions provided for in the Treaty, on the Commission proposal within one year of its submission.

CHAPTER IV

Manufacture and imports coming from third countries

Article 16

1. Member States shall take all appropriate measures to ensure that the manufacture of medicinal products is subject to the holding of an authorization. This manufacturing authorization shall be required notwithstanding that the medicinal products manufactured are intended for export.

2. The authorization referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation.

However, such authorization shall not be required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorized in the Member States to carry out such processes.

3. Authorization referred to in paragraph 1 shall also be required for imports coming from third countries into a Member State; this Chapter and Article 29 shall have corresponding application to such imports as they have to manufacture.

Article 17

In order to obtain the authorization referred to in Article 16, the applicant must meet at least the following requirements:

a) specify the medicinal products and pharmaceutical forms which are to be manufactured or imported and also the place where they are to be manufactured and/or controlled;

b) have at his disposal, for the manufacture or import of the above, suitable and sufficient premises, technical equipment and control facilities complying with the legal requirements which the Member State concerned lays down as regards both manufacture and control and the storage of products, in accordance with Article 5 a);

c) have at his disposal the services of at least one qualified person within the meaning of Article 21.

The applicant must provide particulars in support of the above in his application.

Article 18

1. The competent authority of the Member State shall issue the authorization referred to in Article 16 only after having made sure of the accuracy of the particulars supplied pursuant to Article 17, by means of an inquiry carried out by its agents.

2. In order to ensure that the requirements referred to in Article 17 are complied with, authorization may be made conditional on the carrying out of certain obligations imposed either when authorization is granted or at a later date.

3. The authorization shall apply only to the premises specified in the application and to the medicinal products and pharmaceutical forms specified in that same application.

Article 19

The holder of an authorization referred to in Article 16 shall at least be obliged:

a) to have at his disposal the services of staff who comply with the legal requirements existing in the Member State concerned both as regards manufacture and controls;

b) to dispose of the authorized proprietary medicinal products only in accordance with the legislation of the Member States concerned;

c) to give prior notice to the competent authority of any changes he may wish to make to any of the particulars supplied pursuant to Article 17; the competent authority shall in any event be immediately informed if the qualified person referred to in Article 21 is replaced unexpectedly;

d) to allow the agents of the competent authority of the Member State concerned access to his premises at any time;

e) to enable the qualified person referred to in Article 21 to carry out his duties, for example by placing at his disposal all the necessary facilities;

f) to comply with the principles and guidelines of good manufacturing practice for medicinal products as laid down by Community law.

Article 19a

The principles and guidelines of good manufacturing practices for medicinal products referred to in Article 19 f) shall be adopted in the form of a directive addressed to the Member States, in accordance with the procedure laid down in Article 37a of Directive 75/319/EEC. Detailed guidelines in line with those principles will be published by the Commission and revised as necessary to take account of technical and scientific progress.

Article 20

1. The Member States shall take all appropriate measures to ensure that the time taken for the procedure for granting the authorization referred to in Article 16 does not exceed 90 days from the day on which the competent authority receives the application.

2. If the holder of the authorization requests a change in any of the particulars referred to in Article 17 a) and b), the time taken for the procedure relating to this request shall not exceed 30 days. In exceptional cases this period of time may be extended to 90 days.

3. Member States may require from the applicant further information concerning the particulars supplied pursuant to Article 17 and concerning the qualified person referred to in Article 21; where the competent authority concerned exercises this right, application of the time limits referred to in paragraphs 1 and 2 shall be suspended until the additional data required have been supplied.

Article 21

1. Member States shall take all appropriate measures to ensure that the holder of the authorization referred to in Article 16 has permanently and continuously at his disposal the services of at least one qualified person, in accordance with the conditions laid down in Article 23, responsible in particular for carrying out the duties specified in Article 22.

2. If he personally fulfils the conditions laid down in Article 23, the holder of the authorization may himself assume the responsibility referred to in paragraph 1.

Article 22

1. Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 21, without prejudice to his relationship with the holder of the authorization referred to in Article 16, is responsible, in the context of the procedures referred to in Article 25, for securing:

a) in the case of medicinal products manufactured within the Member States concerned that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorization;

b) in the case of medicinal products coming from third countries, that each production batch has undergone in the importing country a full qualitative analysis, a quantitative analysis of at least all the active constituents and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorization.

The batches of products which have undergone such controls in a Member State shall be exempt from the above controls if they are imported into another Member State, accompanied by the control reports signed by the qualified person.

In the case of medicinal products imported from a third country, where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the Community and to ensure that the controls referred to under b) have been carried out in the exporting country, the qualified person may be relieved of responsibility for carrying out those controls.

2. In all cases and particularly where the medicinal products are released for sale the qualified person must certify in a register or equivalent document provided for that purpose that each production batch satisfies the provisions of this Article; the said register or equivalent document must be kept up to date as operations are carried out and must remain at the disposal of the agents of the competent authority for the period specified in the provisions of the Member State concerned and in any event for at least five years.

Article 23

Member States shall ensure that the qualified person referred to in Article 21 fulfils the following minimum conditions of qualification:

a) Possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course of study, or a course recognized as equivalent by the Member State concerned, extending over a period of at least four years of theoretical and practical study in one of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology. However:

— the minimum duration of the university course may be three and a half years where the course is followed by a period of theoretical and practical training of a minimum duration of one year and including a training period of at least six months in a pharmacy open to the public, corroborated by an examination at university level;

— where two university courses or two courses recognized by the State as equivalent co-exist in a Member State and where one of these extends over four years and the other over three years, the three-year course leading to a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course or its recognized equivalent shall be considered to fulfil the condition of duration referred to in a) in so far as the diplomas, certificates or other evidence of formal qualifications awarded on completion of both courses are recognized as equivalent by the State in question.

The course shall include theoretical and practical study bearing upon at least the following basic subjects:

— Applied physics

— General and inorganic chemistry

— Organic chemistry

— Analytical chemistry

— Pharmaceutical chemistry, including analysis of medicinal products

— General and applied biochemistry (medical)

— Physiology

— Microbiology

— Pharmacology

— Pharmaceutical technology

— Toxicology

— Pharmacognosy (medical aspects) (study of the composition and effects of the active principles of natural substances of plant and animal origin).

Studies in these subjects should be so balanced as to enable the person concerned to fulfil the obligations specified in Article 22.

In so far as certain diplomas, certificates or other evidence of formal qualifications mentioned in a) do not fulfil the criteria laid down above, the competent authority of the Member State shall ensure that the person concerned provides evidence of adequate knowledge of the subjects involved.

b) Practical experience for at least two years, in one or more undertakings which are authorized to manufacture medicinal products, in the activities of qualitative analysis of medicinal products, of quantitative analysis of active substances and of the testing and checking necessary to ensure the quality of medicinal products.

The duration of practical experience may be reduced by one year where a university course lasts for at least five years and by a year and a half where the course lasts for at least six years.

Article 24

1. A person engaging in the activities of the person referred to in Article 21 in a Member State at the time when this Directive is brought into force in that State but without complying with the provisions of Article 23 shall be eligible to continue to engage in those activities in the State concerned.

2. The holder of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course – or a course recognized as equivalent by the Member State concerned – in a scientific discipline allowing him to engage in the activities of the person referred to in Article 21 in accordance with the laws of that State may – if he began his course prior to the notification of this Directive – be considered as qualified to carry out in that State the duties of the person referred to in Article 21 provided that he has previously engaged in the following activities for at least two years before the end of the tenth year following notification of this directive in one or more undertakings authorized pursuant to Article 16: production supervision and/or qualitative analysis, quantitative analysis of active substances, and the necessary testing and checking under the direct authority of the person referred to in Article 21 to ensure the quality of the proprietary medicinal products.

If the person concerned has acquired the practical experience referred to in the first subparagraph more than 10 years prior to the notification of this Directive, a further one year's practical experience in accordance with the conditions referred to in the first subparagraph will be required to be completed immediately before he engages in such activities.

3. A person who, at the time when this Directive is brought into force, is engaged in direct collaboration with a person referred to in Article 21 in production supervision activities and/or in qualitative and quantitative analysis of active substances and the testing and checking necessary to ensure the quality of medicinal products may, for a period of five years after this Directive has been brought into force, be considered as qualified to take up in that State the duties of the person referred to in Article 21 provided that that Member State ensures that the person shows evidence of adequate theoretical and practical knowledge and has engaged in the activities mentioned for at least five years.

Article 25

Member States shall ensure that the duties of qualified persons referred to in Article 21 are fulfilled, either by means of appropriate administrative measures or by making such persons subject to a professional code of conduct.

Member States may provide for the temporary suspension of such a person upon the commencement of administrative or disciplinary procedures against him for failure to fulfil his obligations.

CHAPTER V

Supervision and sanctions

Article 26

The competent authority of the Member State concerned shall ensure, by means of repeated inspections, that the legal requirements governing medicinal products are complied with.

After every inspection as referred to in the first subparagraph, the officials representing the competent authority shall report on whether the manufacturer complies with the principles and guidelines of good manufacturing practice laid down by Community law. The content of such reports shall be communicated to the manufacturer who has to undergo the inspection.

Such inspections shall be carried out by officials representing the competent authority who must be empowered to:

a) inspect manufacturing or commercial establishments and any laboratories entrusted by the holder of the authorization referred to in Article 16 with the task of carrying out checks pursuant to Article 5 b);

b) take samples;

c) examine any documents relating to the object of the inspection, subject to the provisions in force in the Member States at the time of notification of this Directive and which place restrictions on these powers with regard to the descriptions of the method of preparation.

Article 27

Member States shall take all appropriate measures to ensure that the person responsible for marketing a medicinal product and, where appropriate, the holder of the authorization referred to in Article 16, furnish proof of the controls carried out on the finished product and/or the ingredients and of the controls carried out at an intermediate stage of the manufacturing process, in accordance with the methods laid down for the purposes of the marketing authorization.

Article 28

1. Notwithstanding the measures provided for in Article 11 of Directive 65/65/EEC, Member States shall take all appropriate measures to ensure that the supply of the medicinal product shall be prohibited and the medicinal product withdrawn from the market if:

a) the medicinal product proves to be harmful under normal conditions of use;

b) it is lacking in therapeutic efficacy;

c) its qualitative and quantitative composition is not as declared;

d) the controls on the finished product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the authorization referred to in Article 16 has not been fulfilled.

2. The competent authority may limit the prohibition to supply the product, or its withdrawal from the market, to those batches which are the subject of dispute.

Article 28a

At the request of the manufacturer, the exporter or the authorities of an importing third country, Member States shall certify that a manufacturer of medicinal products is in possession of the authorization referred to in Article 16 (1). When issuing such certificates they shall comply with the following conditions:

1. Member States shall have regard to the prevailing administrative arrangements of the World Health Organization.
2. For medicinal products intended for export which are already authorized on their territory, they shall supply the summary of the product characteristics as approved in accordance with Article 4b of Directive 65/65/EEC.
3. When the manufacturer is not in possession of a marketing authorization he shall provide the authorities responsible for establishing the certificate referred to above with a declaration explaining why no marketing authorization is available.

Article 29

1. The competent authority of a Member State shall suspend or revoke the authorization referred to in Article 16 for a category of preparations or all preparations where any one of the requirements laid down in Article 17 is no longer met.

2. In addition to the measures specified in Article 28, the competent authority of a Member State may suspend manufacture or imports of medicinal products coming from third countries, or suspend or revoke the authorization referred to in Article 16 for a category of preparations or all preparations where Articles 18, 19, 22 and 27 are not complied with.

CHAPTER Va

Pharmacovigilance

Article 29a

In order to ensure the adoption of appropriate regulatory decisions concerning the medicinal products authorized within the Community, having regard to information obtained about adverse reactions to medicinal products under normal conditions of use, the Member States shall establish a pharmacovigilance system. This system shall be used to collect information useful in the surveillance of medicinal products, with particular reference to adverse reactions in human beings, and to evaluate such information scientifically.

Such information shall be collated with data on consumption of medicinal products.

This system shall also collate information on frequently observed misuse and serious abuse of medicinal products.

Article 29b

For the purpose of this Directive, the following definitions shall apply:

— adverse reaction means a reaction which is harmful and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function,

— serious adverse reaction means an adverse reaction which is fatal, life-threatening, disabling, incapacitating, or which results in or prolongs hospitalization,

— unexpected adverse reaction means an adverse reaction which is not mentioned in the summary of product characteristics,

— serious unexpected adverse reaction means an adverse reaction which is both serious and unexpected.

Article 29c

The person responsible for placing the medicinal product on the market shall have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance.

That qualified person shall be responsible for the following:

a) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the company, and to medical representatives, is collected and collated at a single point within the Community;

b) the preparation for the competent authorities of the reports referred to in Article 29d, in such form as may be laid down by those authorities, in accordance with the relevant national or Community guidelines;

c) ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned.

Article 29d

1. The person responsible for placing the medicinal product on the market shall be required to record and to report all suspected serious adverse reactions which are brought to his attention by a health care professional to the competent authorities immediately, and in any case within 15 days of their receipt at the latest.

2. In addition, the person responsible for placing the medicinal product on the market shall be required to maintain detailed records of all other suspected adverse reactions which are reported to him by a health care professional.

Unless other requirements have been laid down as a condition of the granting of authorization, these records shall be submitted to the competent authorities immediately upon request or at least every six months during the first two years following authorization, and once a year for the following three years. Thereafter, the records shall be submitted at five-yearly intervals together with the application for renewal of the authorization, or immediately upon request. These records shall be accompanied by a scientific evaluation.

Article 29e

The Member States shall take all appropriate measures to encourage doctors and other health care professionals to report suspected adverse reactions to the competent authorities.

The Member States may impose specific requirements on medical practitioners, in respect of the reporting of suspected serious or unexpected adverse reactions, in particular where such reporting is a condition of the authorization.

Article 29f

The Member States shall ensure that reports of suspected serious adverse reactions are immediately brought to the attention of the Agency and the person responsible for placing the medicinal product on the market, and in any case within 15 days of their notification, at the latest.

Article 29g

In order to facilitate the exchange of information about pharmacovigilance within the Community, the Commission, in consultation with the Agency, Member States and interested parties, shall draw up guidance on the collection, verification and presentation of adverse reaction reports.

This guidance shall take account of international harmonization work carried out with regard to terminology and classification in hte field of pharmacovigilance.

Article 29h

Where as a result of the evaluation of adverse reaction reports a Member State considers that a marketing authorization should be varied, suspended or withdrawn, it shall forthwith inform the Agency and the person responsible for placing the medicinal product on the market.

In case of urgency, the Member State concerned may suspend the marketing of a medicinal product, provided the Agency is informed at the latest on the following working day.

Article 29i

Any amendments which may be necessary to update provisions of this Chapter to take account of scientific and technical progress shall be adopted in accordance with the procedure laid down in Article 37a.

CHAPTER VI

Miscellaneous provisions

Article 30

Member States shall take all appropriate measures to ensure that the competent authorities concerned communicate to each other such information as is appropriate to guarantee that the requirements for the authorizations referred to in Article 16 or marketing authorizations are fulfilled.

Upon reasoned request, Member States shall forthwith communicate the reports referred to in the third subparagraph of Article 26 to the competent authorities of another Member State. If, after considering the reports, the Member State receiving the reports considers that it cannot accept the conclusions reached by the competent authorities of the Member State in which the report was established, it shall inform the competent authorities concerned of its reasons and may request further information. The Member States concerned shall use their best endeavours to reach agreement. If necessary, in the case of serious differences of opinion, the Commission shall be informed by one of the Member States concerned.

Article 31

All decisions taken pursuant to Articles 18, 28 and 29 and all negative decisions taken pursuant to Articles 5 b) and 11 (3) shall state in detail the reasons on which they are based. Such decisions 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 applying for such remedies.

Article 32

No decision concerning suspension of manufacture or of importation of medicinal products coming from third countries, prohibition of supply or withdrawal from the market of a medicinal product may be taken except on the ground set out in Articles 28 and 29.

Article 33

1. Each Member State shall take all the appropriate measures to ensure that decisions authorizing marketing, refusing or revoking a marketing authorization, cancelling a decision refusing or revoking a marketing authorization, prohibiting supply, or withdrawing a product from the market, together with the reasons on which such decisions are based, are brought to the attention of the Committee forthwith.

2. The person responsible for the marketing of a medicinal product shall be obliged to notify the Member States concerned forthwith of any action taken by him to suspend the marketing of a product or to withdraw a product from the market, together with the reasons for such action if the latter concerns the efficacy of the medicinal product or the protection of public health. Member States shall ensure that this information is brought to the attention of the committee.

3. Member States shall ensure that appropriate information about action taken pursuant to paragraphs 1 and 2 which may affect the protection of public health in third countries is forthwith brought to the attention of the World Health Organization, with a copy to the committee.

4. The Commission shall publish annually a list of the medicinal products which are prohibited in the Community.

Article 34

This Directive shall apply to medicinal products for human use within the limits referred to in Article 2 of Directive 65/65/EEC.

Chapters II to V of Directive 65/65/EEC and this Directive shall not apply to medicinal products consisting of vaccines, toxins or serums, to medicinal products based on human blood or blood constituents or radioactive isotopes, or to homeopathic medicinal products. A list, for information purposes, of these vaccines, toxins and serums is given in the annex.

Articles 35 – 37

This text has been inserted into Directive 65/65/CEE.

CHAPTER VIa

Standing Committee procedures

Article 37a

Where the procedure laid down in this Article is to be followed the Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use.

The representative of the Commission shall submit to the Committee a draft of the measures to be taken. The Committee shall deliver its opinion on the draft within a time-limit which the Chairman may lay down according to the urgency of the matter. The opinion shall be delivered by the majority laid down in Article 148 (2) of the Treaty in the case of decisions which the Council is required to adopt on a proposal from the Commission. The votes of the representatives of the Member States within the Committee shall be weighted in the manner set out in that Article. The Chairman shall not vote.

The Commission shall adopt the measures envisaged if they are in accordance with the opinion of the Committee.

If the measures envisaged are not in accordance with the opinion of the Committee, or if no opinion is delivered, the Commission shall, without delay, submit to the Council a proposal relating to the measures to be taken. The Council shall act by a qualified majority.

If on the expiry of a period of three months from the date of referral to the Council, the Council has not acted, the proposed measures shall be adopted by the Commission.

Article 37b

Where the procedure laid down in this Article is to be followed the Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use.

The representative of the Commission shall submit to the Committee a draft of the measures to be taken. The Committee shall deliver its opinion on the draft within a time-limit which the Chairman may lay down according to the urgency of the matter. The opinion shall be delivered by the majority laid down in Article 148 (2) of the Treaty in the case of decisions which the Council is required to adopt on a proposal from the Commission. The votes of the representatives of the Member States within the Committee shall be weighted in the manner set out in that Article. The Chairman shall not vote.

The Commission shall adopt the measures envisaged if they are in accordance with the opinion of the Committee.

If the measures envisaged are not in accordance with the opinion of the Committee, or if no opinion is delivered, the Commission shall, without delay, submit to the Council a proposal relating to the measures to be taken. The Council shall act by a qualified majority.

If on the expiry of a period of three months from the date of referral to the Council, the Council has not acted, the proposed measures shall be adopted by the Commission, save where the Council has decided against the said measures by a simple majority.

CHAPTER VII

Implementing provisions and transitional measures

Article 38

Member States shall bring into force the laws, regulations and administrative provisions needed in order to comply with this Directive within 18 months of its notification and shall forthwith inform the Commission thereof.

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 39

1. As regards the authorizations referred to in Article 16 issued before the expiry of the time-limit laid down in Article 38, Member States may grant an additional period of one year to the undertakings concerned to enable them to comply with the provisions of Chapter IV.

2. Within 15 years of the notification referred to in Article 38, the other provisions of this Directive shall be applied progressively to medicinal products placed on the market by virtue of previous provisions.

3. Member States shall notify the Commission, within three years following the notification of this Directive, of the number of medicinal products covered by paragraph 2, and, each subsequent year, of the number of these products for which a marketing authorization referred to in Article 3 of directive 65/65/EEC, has not yet been issued.

Article 40

This Directive is addressed to the Member States.

Done at Brussels, 20 May 1975.

For the Council

The President

R. RYAN

ANNEX

The expression 'vaccines, toxins or serums' used in Article 34 shall cover in particular:

— agents used to produce active immunity;

(such as cholera vaccine, BCG, polio vaccine, smallpox vaccine);

— agents used to diagnose the state of immunity;

including in particular tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin;

— agents used to produce passive immunity;

(such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin).