COMMISSION OF THE EUROPEAN COMMUNITIES

THE RULES GOVERNING MEDICAMENTS IN THE EUROPEAN COMMUNITY

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INTRODUCTION

After the implementation of Council Directive 65/65/EEC, 75/318/EEC and 75/319/EEC the most important aspects of proprietary medicinal products are now subject matter of common regulation in the nine Member States. The main purpose of such regulation is to safeguard public health while at the same time ensuring that the development of the pharmaceutical industry and trade in medicinal products within the Community will not be hindered.

The Directives regulate the following matters :

- conditions for marketing authorizations; requirements for tests and trials to be carried out on proprietary medicinal products;
- manufacture and control of proprietary medicinal products;
- labelling and package leaflets;
- supervisory duties of national authorities;
- the Committee for Proprietary Medicinal Products.

Council Directive 78/25/EEC which comes into force on 15 June 1979, governs which colouring matters may be added to medicinal products.

The Committee for Proprietary Medicinal Products has been set up by Directive 75/319/EEC to ensure cooperative between the national competent authorities, especially with a view to obviating inconsistent decisions relating to marketing authorizations which are still issued at national level. The Rules of Procedure of the Committee are reproduced in this booklet. The Committee will issue an opinion as to whether a particular product complies with the conditions for the granting of a marketing authorization :

- when the holder of an initial marketing authorization applies for its extension to at least five other Member States through the Committee. The procedure to be applied by the applicant is explained in the Notice for applicants for marketing authorizations for proprietary medicinal products;
- when inconsistent decisions are taken by Members States in respect of one and the same product;
- when a Member State wishes, in specific cases where the interest of the Community is concerned, to obtain the opinion of the Committee before reaching a decision.

The Committee for Proprietary Medicinal Products has elaborated a standard application form in accordance with which the Committee wishes the particulars in support of applications for marketing authorizations to be presented.

The Council has clearly stated that the present level of harmonization merely represents one step towards achievement of the objective of the free movement of proprietary medicinal products. Hence the Commission is obliged to submit to the Council before the 22 November 1980 a proposal containing

appropriate measures leading towards the abolition of any remaining barrier to the free movement of proprietary medicinal products.

An important task in this further development will lie with the Pharmaceutical Committee set up by Council Decision 75/320/EEC. The duty of this Committee which consists of senior officials from the Member States is to advise the Commission on general questions in the field of proprietary medicinal products.

COUNCIL DIRECTIVE

of 26 January 1965

on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products

(65/65/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 proprietary 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 proprietary 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 feeding-stuffs 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;

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(1) OJ No 84, 4.6.1963, p. 1571/63
(2) OJ No 158, 16.10.1964, p. 2508/64

HAS ADOPTED THIS DIRECTIVE :

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.

Article 2

The provisions of Chapters II to V shall apply only to proprietary medicinal products for human use intended to be placed on the market in Member States.

Chapter II

Authorisation to place proprietary medicinal products on the market

Article 3

No proprietary medicinal product may be placed on the market in a Member State unless an authorisation has been issued by the competent authority of that Member State.

Article 4

In order to obtain an authorisation to place a proprietary 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 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.

5. Therapeutic indications, contra-indications and side-effects.

6. Posology, pharmaceutical form, method and route of administration and expected shelf life if less than three years.

7. Control methods employed by the manufacturer (analysis and assay 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).

8. Results of :

   - physico-chemical, biological or microbiological tests;
   - pharmacological and toxicological tests;
   - clinical trials.

However :

a) a List of published references relating to the pharmacological tests, toxicological tests and clinical trials may be substituted for the relevant test results in the case of :

   i) a proprietary product with an established use, which has been adequately tested on human beings so that its effects, including side-effects, are already known and are included in the published references;

   ii) a new proprietary product, in which the combination of active constituents is identical with that of a known proprietary product with an established use;

   iii) a new proprietary product consisting solely of known constituents that have been used in combination in comparable proportions in adequately tested medicinal products with an established use;

b) In the case of a new proprietary product containing known constituents not hitherto used in combination for therapeutic purposes, references to published data may be substituted for the tests of such constituents.

9. 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. Any authorisation obtained in another Member State or in a third country to place the relevant proprietary product on the market.

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 proprietary 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 or 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

The competent authorities of Member States may refuse to authorise the placing on the market of a proprietary medicinal product for use as a contraceptive where the sale of proprietary products intended principally for such purposes is prohibited under their laws.

Article 7

Member States shall take all appropriate measures to ensure that the procedure for granting an authorisation to place a proprietary medicinal product on the market is completed within 120 days of the date of submitting the application.

In exceptional cases this time limit may be extended for a futher ninety days. The applicant shall be notified of such extension before the expiry of the initial time limit.

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 proprietary medicinal product on the market.

Article 10

Authorisations shall be valid for five years and shall be renewed for five-year periods, on application by the holder within the three months preceding expiry.

Chapter III

Suspension and revocation of authorisation to market proprietary medicinal products

Article 11

The competent authorities of the Member States shall suspend or revoke an authorisation to place a proprietary 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 proprietary product.

An authorisation shall also be suspended or revoked where the particulars supporting the application as provided for in Article 4 are found to be incorrect, or when the controls on the finished product referred to in Article 8 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 proprietary 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 proprietary medicinal products

Article 13

The following particulars shall appear on containers and outer packages of proprietary medicinal products :

1. Name of the proprietary product which may be a brand name, or a common name together with a trade mark or name of the manufacturer, or a scientific name together with a trade mark or name of the manufacturer.

2. Next to the name of the proprietary product, a statement of the active constituents expressed qualitatively and quantitatively per dose-unit or as a percentage, according to the pharmaceutical form. The international non-proprietary names recommended by the World Health Organisation shall be used wherever they exist.

3. Reference number for production identification (manufacturer's batch number).

4. Number of the authorisation to place the proprietary product on the market.

5. 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.

6. Method of administration.

7. Expiry date for proprietary products with a shelf life of less than three years.

8. Special storage precautions, if any.

The pharmaceutical form and the contents by weight, by volume or by number of dose-units need only be shown on the outer packages.

Article 14

In the case of ampoules, the particulars required under the first paragraph of Article 13 shall be given on the outer packages. However, on the actual containers, only the following particulars are required :

- name of the proprietary medicinal product;
- quantity of active constituents;
- route of administration;
- expiry date.

Article 15

As regards small single-dose containers, other than ampoules, on which it is impossible to give the particulars mentioned in Article 14, the requirements of Article 13 shall apply only to the outer package.

Article 16

In the case of narcotics, in addition to the particulars mentioned in Article 13, a special sign consisting of a double red line shall appear on both the outer package and the container.

Article 17

Where there is no outer package, the particulars which should feature on such a package pursuant to the preceding Articles shall be shown on the container.

Article 18

The particulars mentioned in items 6, 7 and 8 of the first paragraph of Article 13 shall appear on the outer package and on the container of proprietary medicinal products in the language or languages of the country where they are being placed on the market.

Article 19

The provisions of this Chapter shall not prevent the particulars required by rules other than those to which this Directive relates from being given on outer packages or on containers.

Article 20

Where the provisions of this Chapter are not observed and an order addressed to the person concerned has remained without effect, the competent authorities of the Member States may suspend or revoke the authorisation to place the proprietary medicinal product on the market.

All decisions taken in pursuance of the preceding paragraph 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.

Chapter V

General and final provisions

Article 21

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

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

In the five years following the notification mentioned in Article 22, the rules for which provision is made in this Directive shall be applied progressively to proprietary medicinal products covered by an authorisation 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

COUNCIL DIRECTIVE

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

(75/318/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;

Whereas the approximation begun by Council Directive 65/65/EEC [1] of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products should be continued and the implementation of the principles laid down in that Directive should be ensured;

Whereas among existing disparities those relating to the control of proprietary medicinal products are of fundamental importance and point 8 of Article 4, second paragraph of the said Directive requires that applications for authorization to place a proprietary medicinal product on the market should be accompanied by particulars and documents relating to the results of tests and trials carried out on the product concerned;

Whereas standards and protocols for the performance of tests and trials on proprietary medicinal products are an effective means of control of these products and hence of protecting public health and can facilitate the movement of these products by laying down uniform rules applicable to tests and trials, the compilation of dossiers and the examination of applications;

Whereas the adoption of the same standards and protocols by all the Member States will enable the competent authorities to arrive at their decisions on the basis of uniform tests and by reference to uniform criteria and will therefore help to avoid differences in evaluation;

Whereas the physico-chemical, biological or microbiological tests provided for in point 8 of Article 4, second paragraph, of Directive 65/65/EEC are closely related to points 3, 4, 6 and 7 of the same paragraph and it is therefore necessary to specify the data to be provided pursuant to these points;

Whereas the quality of the tests is the essential consideration; whereas therefore tests carried out in accordance with these provisions must be taken into consideration irrespective of the nationality of the experts who perform them or the country in which they are carried out;

Whereas the concepts of 'harmfulness' and 'therapeutic efficacy' referred to in Article 5 of Directive 65/65/EEC can only be examined in relation to each other and have only a relative significance depending on the progress of scientific knowledge and the use for which the proprietary medicinal product is

[1] OJ No 22, 9. 2. 1965, p. 369/65.

intended; whereas the particulars and documents which must accompany an application for authorization to place a proprietary medicinal product on the market demonstrate that potential risks are outweighed by the therapeutic efficacy of the product; whereas failing such demonstration, the application must be rejected;

Whereas the evaluation of 'harmfulness' and 'therapeutic efficacy' may be modified in the light of new discoveries and standards and protocols must be amended periodically to take account of scientific progress,

HAS ADOPTED THIS DIRECTIVE :

Article 1

Member States shall take all appropriate measures to ensure that the particulars and documents which must accompany applications for authorization to place a proprietary medicinal product on the market (marketing authorization), pursuant to points 3, 4, 6, 7 and 8 of Article 4, second paragraph, of Directive 65/65/EEC, are submitted by the persons concerned in accordance with the Annex to this Directive.

Where, pursuant to point 8 (a) and (b) of Article 4, second paragraph, of the abovementioned Directive, references to published data are submitted, the provisions of this Directive shall apply in like manner.

Article 2

Notwithstanding the provisions of other Directives on proprietary medicinal products, Member States shall take all appropriate measures to ensure that the competent authorities examine the particulars and documents submitted in support of applications for marketing authorization in accordance with the criteria of the Annex to this Directive.

Article 3

Member States shall bring into force the 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 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 4

This Directive is addressed to the Member States.

Done at Brussels, 20 May 1975.

For the Council

The President

R. RYAN

ANNEX

PART 1

PHYSICO-CHEMICAL, BIOLOGICAL OR MICROBIOLOGICAL TESTS OF PROPRIETARY MEDICINAL PRODUCTS

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

The particulars and documents which must accompany applications for marketing authorization, pursuant to point 3 of Article 4, second paragraph, of Directive 65/65/EEC shall be submitted in accordance with the following requirements.

1. 'Qualitative particulars' of all the constituents of the proprietary medicinal product shall mean the designation or description of:

   — the active ingredient(s);

   — the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, stabilizers, thickeners, emulsifiers, flavouring and aromatic substances, etc.;

   — the constituents, intended to be ingested or otherwise administered to the patient, of the outer covering of the proprietary medicinal products — capsules, gelatine capsules, cachet shells, rectal capsules, etc.

   These particulars shall be supplemented by any relevant data concerning the container and, where appropriate, its manner of closure.

2. The 'usual terminology', to be used in describing the constituents of proprietary medicinal products, shall mean, notwithstanding the application of the other provisions of point 3 of Article 4, second paragraph, of Directive 65/65/EEC:

   — in respect of substances which appear in the European Pharmacopoeia or, failing this, in the national pharmacopoeia of one of the Member States, the main title at the head of the monograph in question, with reference to the pharmacopoeia concerned;

   — in respect of other substances, the international non-proprietary name recommended by the World Health Organization, which may be accompanied by another non-proprietary name, or, failing these, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details;

   — in respect of colouring matter, designation by the 'E' code assigned to them in a future Council Directive on the approximation of the rules of the Member States concerning the colouring matters authorized for use in proprietary medicinal products.

3. In order to give 'quantitative particulars' of the active constituents of the proprietary medicinal products, it is necessary, depending on the pharmaceutical form concerned, to specify the weight, or the number of international units, either per dosage-unit or per unit of weight or volume, of each active ingredient.

   This information shall be supplemented:

   — in respect of injectable preparations, by the weight of each active ingredient in the unit container, taking into account the usable volume of the product;

   — in respect of proprietary medicinal products to be administered by drops, by the weight of each active ingredient contained in the number of drops corresponding to an average dose;

   — in respect of syrups, emulsions, granular preparations and other pharmaceutical forms to be administered in measured quantities, by the weight of each active ingredient per measured quantity.

Active ingredients present in the form of compounds or derivatives shall be described quantitatively by their total weight, and if necessary or relevant, by the weight of the active moiety or moieties of the molecule (in the case of chloramphenicol palmitate, for example, the weight of the ester and that of the corresponding chloramphenicol shall be given).

The biological units of activity of substances which have not been defined chemically, and on which there is insufficient bibliographical information, shall be expressed in such a way as to provide unambiguous information on the activity of the substances.

B. DESCRIPTION OF METHOD OF PREPARATION

The 'brief description of the method of preparation' accompanying the application for marketing authorization pursuant to point 4 of Article 4, second paragraph, of Directive 65/65/EEC, shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.

For this purpose it shall include at least:

— mention of the various stages of manufacture, so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced an adverse change in the constituents;

— in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the final product;

— the actual manufacturing formula, with the quantitative particulars of all the substances used, the quantities of excipients, however, being given in approximate terms in so far as the pharmaceutical form makes this necessary; mention shall be made of any substances that may disappear in the course of manufacture;

— a statement of the stages of manufacture at which sampling is carried out for in-process control tests, where other data in the documents supporting the application show such texts to be necessary for the quality control of the proprietary medicinal product.

C. CONTROL OF STARTING MATERIALS

For the puposes of this paragraph, 'starting materials' shall mean all the constituents of the proprietary medicinal product and, if necessary, of its container, as referred to in paragraph A point 1, above.

The particulars and documents accompanying the application for marketing authorization pursuant to points 7 and 8 of Article 4, second paragraph, of Directive 65/65/EEC shall include the results of the tests relating to quality control of all the constituents used. These shall be submitted in accordance with the following provisions.

1. Starting materials listed in pharmacopoeias

The monographs of the European Pharmacopoeia shall be applicable to all substances appearing in it.

In respect of other substances, each Member State may require observance of its own national pharmacopoeia with regard to products manufactured in its territory.

Constituents fulfilling the requirements of the European Pharmacopoeia or the pharmacopoeia of one of the Member States shall be deemed to comply sufficiently with point 7 of Article 4, second paragraph, of Directive 65/65/EEC. In this case the description of the analytical methods may be replaced by a detailed reference to the pharmacopoeia in question.

However, where a starting material in the European Pharmacopoeia or in the pharmacopoeia of a Member State has been prepared by a method liable to leave impurities not mentioned in the pharmacopoeia monograph these impurities and their maximum tolerance levels must be declared and a suitable test method advanced.

Reference to pharmacopoeias of third countries may be permitted in cases where the substance is described neither in the European Pharmacopoeia nor in the national pharmacopoeia concerned; in that case the monograph shall be submitted, accompanied where necessary by a translation for which the applicant will be responsible.

Colouring matter shall, in all cases, satisfy the requirements of a future Council Directive on the approximation of the rules of the Member States concerning the colouring matters authorized for use in proprietary medicinal products.

For routine tests on each batch of starting material, only that part of the pharmacopoeia relating to control tests (purity and strengths) shall be mandatory; the full range of identity tests need not necessarily be performed where those that have been performed permit an unambiguous characterization. In this case, the reference to the monograph of the pharmacopoeia mentioned above shall include details relating to this aspect.

In cases where a specification contained in a monograph of the European Pharmacopoeia or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the person responsible for placing the product on the market.

2. Starting materials not in a pharmacopoeia

Constituents which are not given in any pharmacopoeia shall be described in the form of a monograph under the following headings:

(a) *The name of the substance,* meeting the requirements of paragraph A, point 2, shall be supplemented by any trade or scientific synonyms;

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

(c) *methods of indentification* may be described in the form of complete techniques as used for production of the substance, and in the form of tests which ought to be carried out as a routine matter;

(d) *purity tests* shall be described in relation to the sum total of predictable impurities, especially those which may have a harmful effect, and, if necessary, those which, having regard to the combination of substances to which the application refers, might adversely affect the stability of the proprietary medicinal product or distort analytical results;

(e) *the assay technique(s)* must be described in sufficiently precise detail so as to be reproducible in control tests, carried out at the request of the competent authority; any special apparatus and equipment which may be used shall be described in adequate detail, possibly accompanied by a diagram. The formulae of the laboratory reagents shall be supplemented, if necessary, by the method of preparation.

The standard error of the method, its reliability and the acceptability limits of the results shall be specified and, if necessary, explained.

With regard to complex substances of plant or animal origin, a distinction must be made between the case where multiple pharmacological effects render chemical, physical or biological control of the principal constituents necessary, and the case of substances containing one or more groups of principles having similar activity, in respect of which an overall method of assay may be accepted;

(f) *any special precautions that may be necessary during storage* of the starting material and, if necessary, its *storage life* shall be given.

D. CONTROL TESTS CARRIED OUT AT AN INTERMEDIATE STAGE OF THE MANUFACTURING PROCESS

The particulars and documents accompanying an application for marketing authorization; pursuant to points 7 and 8 of Article 4, second paragraph, of Directive 65/65/EEC, shall include particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the technical characteristics and the production process.

These tests are essential for checking the conformity of the proprietary medicinal product with the formula when, exceptionally, an applicant proposes an analytical technique for testing the finished product which does not include the assay of all the active ingredients (or of all the excipient constituents subject to the same requirements as the active ingredients).

The same applies where the quality control of the finished product depends on in-process control tests, particularly if the substance is essentially defined by its method of preparation.

E. CONTROL TESTS ON THE FINISHED PRODUCT

The particulars and documents accompanying the application for marketing authorization pursuant to points 7 and 8 of Article 4, second paragraph, of Directive 65/65/EEC, shall include particulars relating to control tests on the finished product. They shall be submitted in accordance with the following requirements.

1. General characteristics of the various pharmaceutical forms

Certain tests of the general characteristics of a product which can be carried out in the course of the manufacturing process shall always be included among the tests on the finished product.

As a guideline, and subject to the possible future requirements of the European Pharmacopoeia or the national pharmacopoeias of Member States, the general characteristics which are to be verified for various pharmaceutical forms are given at point 5 below.

These tests shall, wherever applicable, relate to the control of average weights and maximum deviations, to mechanical, physical, or microbiological tests, organoleptic characteristics, such as clarity, colour, taste, physical characteristics such as density, pH, refractive index, etc. For each of these characteristics, standards and tolerances must be specified by the applicant in each particular case.

2. Identification and assay of active ingredient(s)

The description of the techniques for analyzing the finished product shall set out in sufficiently precise detail, so that they can be reproduced readily, the methods used for identification and assay of the active ingredient(s) either in a representative sample from the production batch or in a number of dosage-units analyzed individually.

In every case, the methods must correspond to the state of scientific progress at the time and give details and explanations of the standard errors and reliability of the analytical method and also of maximum acceptable deviations.

In certain exceptional cases of particularly complex mixtures, where assay of active ingredients which are very numerous or present in very low amounts would necessitate an intricate investigation difficult to carry out in respect of each production batch, the assay of one or more active ingredients in the finished product may be omitted, on the express condition that such assays are made at intermediate stages in the production process. This relaxation may not be extended to the characterization of the substances concerned. This simplified technique shall be supplemented by a method of quantitative evaluation, enabling the competent authority to have the conformity of the proprietary medicinal product with its formula verified after it has been placed on the market.

An assay of biological activity shall be obligatory when physico-chemical methods cannot provide adequate information on the quality of the product.

Where the particulars given in paragraph B show that a significant overage of an active ingredient was employed in the manufacture of the proprietary medicinal product, the description of the control tests on the finished product shall include, where appropriate, the chemical and, if necessary, the toxico-pharmacological investigation of the changes that this substance has undergone, and possibly the characterization or assay of the degradation products.

3. **Identification and assay of excipient constituents**

In so far as is necessary, the constituents of the excipient shall be subject at least to characterization tests.

The method proposed for identifying colouring matters must enable a verification to be made that such matters appear in the list to be annexed to a future Council Directive on the approximation of the rules of the Member States concerning the colouring matters authorized for use in proprietary medicinal products.

An upper limit test shall be obligatory in respect of excipient constituents which are subject to rules relating to toxic substances or which are being used as preservatives, while an assay shall be obligatory in respect of constituents liable to affect physiological functions.

4. **Safety tests**

Apart from the toxico-pharmacological tests submitted with the application for marketing authorization, particulars of safety tests (abnormal toxicity) or local tolerance in animals shall be included in the analytical particulars wherever such tests must be undertaken as a matter of routine in order to verify the quality of the product.

5. **General characteristics of finished products to be verified systematically, depending on the pharmaceutical form of each product**

The following requirements are given as an indication and without prejudice to any future requirements of the European Pharmacopoeia or national pharmacopoeias of Member States; for example, microbiological control tests of preparations for oral administration shall be performed in accordance with the requirements of the European Pharmacopoeia.

Tablets and pills: colour, weight and acceptable variations in unit weight; if necessary, disintegration time with the method used to determine this.

Coated tablets: colour, disintegration time with the method used to determine this; weight of finished tablet; weight of core and acceptable variations in unit weight.

Capsules and gelatine capsules: colour, disintegration time with the method used to determine this; appearance and weight of content with acceptable variations in unit weight.

Enteric-coated preparations (tablets, capsules, gelatine capsules, granular preparations): in addition to the requirements of the particular pharmaceutical form, resistance time in an artificial gastric medium, with the method used to determine this; disintegration time in an artificial intestinal medium, with the method used to determine this.

Preparations with special protective coating (tablets, capsules, gelatine capsules, granular preparations): in addition to the requirements of the particular pharmaceutical form, verification of the effectiveness of the coating for the desired purpose.

Preparations with gradual release of the active principle: in addition to the requirements of the particular pharmaceutical form, requirements relating to gradual release, with the method used to determine this.

Cachets, packets and sachets: nature and weight of contents and acceptable variations in unit weight.

Injectable preparations: colour, volume of contents and acceptable variations of this volume; pH, clarity of solution, size limit of particulate matter in the case of suspensions; sterility tests, with description of test methods; except in special cases, in respect of preparations to be administered in single doses of 10 ml or more, a pyrogen test with description of method.

Ampoules with solid content: quantity of product per ampoule and permitted variations in weight; sterility requirements and tests.

Ampoules to be taken orally: colour, appearance, volume of content and acceptable variations.

Ointments, creams, etc.: colour and consistency; weight and acceptable margin of variation; nature of container; in certain cases microbiological control tests.

Suspensions: colour; where settlement occurs, the ease of re-suspendability.

Emulsions: colour, type, stability.

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

Aerosols: description of container and valve with details of output; particle size-limit, where the product is intended to be inhaled.

Collyria, eye ointments, eye lotions: colour, appearance, sterility controls, with description of the method used; where appropriate, clarity and size limit of particulate matter in the case of suspensions, pH determination.

Syrups, solutions, etc: colour, appearance.

F. STABILITY TESTS

The particulars and documents accompanying the application for marketing authorization pursuant to points 6 and 7 of Article 4, second paragraph, of Directive 65/65/EEC shall be submitted in accordance with the following requirements:

A description shall be given of the investigations by which the shelf life proposed by the applicant has been determined.

Where a finished product is liable to give rise to toxic degradation products the applicant must declare these and indicate characterization and assay methods.

The conclusions shall contain the results of analyses, justifying the proposed shelf life under normal, or, where appropriate, under special storage conditions.

A study of the interaction between product and container shall be submitted wherever the risk of such interaction is regarded as possible, especially where injectable preparations or aerosols for internal use are concerned.

PART 2

TOXICOLOGICAL AND PHARMACOLOGICAL TESTS

The particulars and documents accompanying the application for marketing authorization pursuant to point 8 of Article 4, second paragraph, of Directive 65/65/EEC shall be given in accordance with the requirements of Chapters I and II below.

CHAPTER I

PERFORMANCE OF TESTS

A. INTRODUCTION

The toxicological and pharmacological tests must show:

1. the potential toxicity of the product and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human beings; these should be evaluated in relation to the gravity of the pathological condition concerned;
2. the pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in human beings. All results must be reliable and of general applicability. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results.

Additionally, it is necessary for clinicians to be given information about the therapeutic potential of the product.

B. TOXICITY

1. Single dose toxicity (acute toxicity)

Acute toxicity test means a qualitative and quantitative study of the toxic reactions which may result from a single administration of the active substance or substances contained in the proprietary medicinal product, in the proportions in which they are present in the actual product.

Wherever practicable, the product in its actual pharmaceutical form shall be subjected to an acute toxicity test.

This study will cover the symptoms observed, including local reactions. Where possible, the LD_{50} value with its fiducial limits (95%) will be determined. The period during which the test animals are oberserved shall be fixed by the investigator and shall not be less than one week.

The acute toxicity test must be carried out on at least two mammalian species of known strain, and at least two different routes of administration shall normally be used: one being indentical with or similar to that proposed for use in human beings and the other ensuring systemic absorption of the substance. This determination must be carried out on equal numbers of male and female animals.

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

2. Repeated dose toxicity (sub-acute or chronic toxicity)

Repeated dose toxicity tests are intended to reveal any physiological and/or pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.

Generally, it is desirable that two tests be performed: one short-term, lasting two to four weeks, the other long-term. The duration of the latter shall depend on the conditions of clinical use. Its purpose shall be to determine by experiment the non-toxic dose range of the product and normally it shall last three to six months.

In respect of proprietary medicinal products to be administered once only to humans, a single test lasting two to four weeks shall be performed.

If, however, having regard to the proposed duration of use in human beings, the investigator sees fit to carry out experiments of greater or lesser duration than indicated above, he must give adequate reasons for doing so.

Reasons should also be given for the dosages chosen.

Repeated dose toxicity tests shall be carried out on two species of mammals one of which must be a non-rodent. The choice of route(s) of administration employed shall

depend on the intended therapeutic use and the possibilities of systemic absorption. The method and frequency of dosage shall be clearly stated.

The maximum dose should be chosen so as to bring harmful effects to light. The lower doses will then enable the animal's tolerance of the product to be determined.

Wherever possible, and always in experiments on small rodents, the design of the experiment and the control procedures must be suited to the scale of the problem being tackled and enable fiducial limits to be determined.

The evaluation of the toxic effects shall be based on observation of behaviour, growth, haematological and biochemical tests, especially those relating to the excretory mechanism, and also on autopsy reports and accompanying histological data. The choice and range of each group of tests will depend on the species of animal used and the state of scientific knowledge at the time.

In the case of new combinations of known substances that have been investigated in accordance with the provisions of this Directive, the long-term tests may, except where acute and subacute toxicity tests have demonstrated potentiation or novel toxic effects, be suitably modified by the investigator who shall submit his reasons for such modification. Substances that have been shown to be safe by wide usage over at least three years in clinical treatment of human beings, and by the result of controlled trials shall be treated in the same way as known substances which have already been investigated in accordance with these standards and protocols.

An excipient used for the first time in the pharmaceutical field shall be treated like an active ingredient.

C. FOETAL TOXICITY

This investigation comprises a demonstration of the toxic and especially the teratogenic effects observed in the issue of conception when the substance under investigation has been administered to the female during pregnancy.

Although up to the present these tests have had only a limited predictive value in regard to the application of the results to human beings, they are thought to provide important information where the results show effects such as resorptions and other anomalies.

Omission of these tests, either because the proprietary medicinal product will not normally be used by women capable of childbearing or for other reasons, must be adequately justified.

The tests in question shall be carried out on at least two animal species: a breed of rabbits sensitive to known teratogenic substances and rats or mice (specifying the strain) or, if appropriate, in some other animal species.

The details of the test (number of animals, amounts administered, timing of administration and criteria for evaluation of results) shall depend on the state of scientific knowledge at the time when the application is lodged, and the level of statistical significance that the results must attain.

D. EXAMINATION OF REPRODUCTIVE FUNCTION

If the results of other tests reveal anything suggesting harmful effects on progeny or impairment of male or female reproductive function, this shall be investigated by appropriate tests.

E. CARCINOGENICITY

Tests to reveal carcinogenic effects shall be essential:

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.

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.

F. PHARMACODYNAMICS

This heading covers the variations caused by the substance in the functions of the physiological systems, whether these functions are normal or experimentally modified.

This study shall follow two distinct lines of approach.

Firstly, the actions on which the recommended application in therapeutic practice is based shall be adequately described. The results shall be expressed in quantitative terms using, for example, dose-effect curves, time-effect curves etc., and wherever possible, compared with data relating to a substance whose activity is known. Where a higher therapeutic potency is being claimed for a substance, the difference shall be demonstrated and shown to be statistically significant.

Secondly, the investigator shall provide a general pharmacological characterization of the substance, with special reference to collateral effects. In general, the main functions of the physiological systems should be investigated. The depth of this investigation must be increased as the doses liable to produce side-effects approach those producing the main effect for which the substance is being proposed.

The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and the investigator must

establish their validity. The experimental results shall be set out clearly and, when relevant to the test, their statistical significance quoted.

Unless good reasons are given to the contrary, any quantitative modification of responses resulting from repeated administration of the substance shall be investigated.

Tests on combinations of active substances may be prompted either by pharmacological premises or by indications of therapeutic effect.

In the first case, the pharmacodynamic study shall demonstrate those interactions which might make the combination of value in therapeutic use.

In the second case, where scientific justification for the combination is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and the importance of any collateral effects shall at least be investigated.

If a combination includes a novel active substance, the latter must previously have been studied in depth.

G. PHARMACOKINETICS

Pharmacokinetics means the study of the fate of the active substance within the organism, and covers the study of the absorption, distribution, biotransformation and elimination of the substance.

The study of these different phases may be carried out both by means of physical, chemical or biological methods, and by observation of the actual pharmacodynamic activity of the substance itself.

Information on distribution and elimination shall be necessary in all cases where such data are indispensable to determine the dosage for humans, and in respect of chemotherapeutic substances (antibiotics, etc.) and substances whose use depends on their non-pharmacodynamic effects (e. g. numerous diagnostic agents etc.)

Pharmacokinetic investigation of pharmacologically active substances is desirable.

In the case of new combinations of known substances which have been investigated in accordance with the provisions of this Directive pharmacokinetic studies shall not be required, if the toxicity tests and therapeutic experimentation justify their omission. The same applies to substances that have been shown to be efficaceous and safe by wide usage over a period of at least three years in the clinical treatment of human beings and by controlled trials.

H. PRODUCTS FOR TOPICAL USE

Where a proprietary medicinal product is intended for topical use systemic absorption must be investigated, due account also being taken of the possible use of the product on broken skin. Only if it is proved that systemic absorption under these conditions is negligible may repeated dose systemic toxicity tests, foetal toxicity tests and studies of reproductive function be omitted.

If, however, systemic absorption is demonstrated during therapeutic experimentation, toxicity tests shall be carried out on animals, and where necessary, foetal toxicity tests.

In all cases tests of local tolerance after repeated application shall be carried out with particular care and include histological examinations; the possibility of sensitization shall be investigated and any carcinogenic potential investigated in the cases referred to in paragraph E.

CHAPTER II

PRESENTATION OF PARTICULARS AND DOCUMENTS

As in all scientific work, the dossier of toxicological and pharmacological tests shall be arranged as follows:

(a) an introduction defining the subject accompanied possibly by references to published data;

(b) a detailed experimental protocol giving a description of the methods, apparatus and materials used, details of the species, and the breed and strain of animals, where they were obtained, their number and the conditions under which they were housed and fed, stating, *inter alia*, whether they were specific pathogen-free (SPF) or not; omission of any of the tests listed above shall be explained;

(c) all the important results obtained, whether favourable or unfavourable. The original data should be described in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author. By way of explanation and illustration, the results may be accompanied by reproductions of kymographic charts, microphotographs, etc.;

(d) a statistical analysis of the results, where such is called for by the test programme, and variance within the data;

(e) an objective discussion of the results obtained, leading to conclusions on the toxicological and pharmacological properties of the substance, on its safety margins in the animal and its possible side-effects, on its fields of application, on its active dose levels and any possible incompatibilities;

(f) all information necessary to acquaint the clinician as fully as possible with the potential of the proposed proprietary medicinal product. The discussion shall be supplemented by suggestions as to possible treatment for acute toxic reactions and any side-effects that may occur in human beings;

(g) a summary together with precise references to published data.

PART 3

CLINICAL TRIALS

The particulars and documents accompanying applications for marketing authorizations pursuant to point 8 of Article 4, second paragraph, of Directive 65/65/EEC shall be submitted in accordance with the provisions of Chapters I and II below.

CHAPTER I

CONDUCT OF TRIALS

1. Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of this Directive relevant to such tests. The clinician must acquaint himself with the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide him with the complete pharmacological and toxicological reports.

2. Clinical trials must be carried out in the form of 'controlled clinical trials'. The design of the trials will vary from case to case and also will depend on ethical considerations; thus it may, in some instances, be more pertinent to compare the therapeutic effect of a new proprietary medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.

3. As far as possible, and particularly in trials where the effect of the product cannot be objectively measured, the 'double blind' method of controlled study should be used.

4. If statistical methods are necessary to determine the therapeutic effect, the criteria upon which the trial is based must be sufficiently precise to permit a statistical analysis to be undertaken. Inclusion of a large number of patients in a trial must not be regarded as an adequate substitute for a properly controlled trial.

CHAPTER II

PRESENTATION OF PARTICULARS AND DOCUMENTS

1. The clinical particulars to be provided pursuant to point 8 of Article 4, second paragraph, of Directive 65/65/EEC must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the proprietary medicinal product satisfies the criteria governing the granting of a marketing authorization. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.

2. The results of the trials shall be presented in accordance with the following scheme:

A. PHARMACOLOGICAL PARTICULARS
(Clinical pharmacology)

1. Wherever possible particulars shall be given of the results of:

   (a) tests demonstrating pharmacological actions;

   (b) tests demonstrating the pharmacodynamic mechanisms underlying the therapeutic effect;

   (c) tests demonstrating biotransformation and the main pharmacokinetic processes.

   Total or partial omission of these data must be explained.

   Should unexpected results occur during the course of the tests, further preliminary toxicological and pharmacological tests on animals must be undertaken and reviewed.

2. If the proprietary medicinal product is intended for long-term administration, particulars shall be given of any modification of the pharmacological action following repeated administration.

3. If the product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

4. All side-effects noted during the tests shall be described individually.

B. CLINICAL PARTICULARS

1. Individual case histories — Clinical records

Particulars of clinical trials must contain sufficient detail to allow an objective judgment to be made. As a general rule, these trials should be carried out in a medical care establishment.

The aim of the trials shall be stated, together with the criteria, both favourable and unfavourable, for evaluating the results.

Each investigator shall give his name, address, appointments, university qualifications and clinical duties, state where the trial was carried out and assemble the following information in respect of each patient individually:

1. identification of the patient (e.g., by reference to the number of his medical file);
2. criteria determining admission of the patient to the trials;
3. patient's age;
4. patient's sex;
5. diagnosis and indication for which the product was administered and the patient's history; relevant particulars of any previous illnesses shall be given;
6. dosage and method of administration of the product;
7. frequency of administration and any precautions taken at the time of administration;
8. duration of treatment and of the subsequent observation period;
9. details of medicinal products administered previously or concomitantly, i.e. at any time during the period covered by the investigation;
10. dietary regime, if pertinent;
11. all results of the clinical trials (including unfavourable or negative results) with a full statement of clinical observations and results of clinical investigations (such as X-rays, electroencephalograms, electrocardiograms, laboratory analyses, physiological tests etc.), required to evaluate the application. The techniques used must be specified, and the significance of any variations in the results explained (for example, variance in method, variance between individuals or the effects of treatment);
12. all particulars of the observed side-effects, whether harmful or not, and any measures taken in consequence. Relation of cause and effect must be investigated with the same care normally accorded to identifying therapeutic action;
13. an opinion concerning each individual case.

Omission of one or more of items 1 to 13 must be explained.

The information referred to above must be forwarded to the competent authorities.

The competent authorities may waive this requirement in whole or in part if the documentation is very extensive or if there are other adequate reasons of the same order, subject, however, to there being no doubt as to the sound basis of the summary and conclusions referred to in point 2 below.

The person responsible for placing the proprietary medicinal product on the market must make arrangements to ensure that the original documents which formed the basis of the data supplied, including the codes for associating those documents with the patients in question, are kept for at least five years following transmission of the dossier to the competent authority.

2. Summary and conclusions

1. The clinical observations referred to in items 1 to 13 of paragraph 1 above, shall be summarized in a synopsis of the trials and their results, indicating:

   (a) the number and sex of patients treated;

   (b) the selection and age-distribution of the groups of patients being investigated and the control groups;

   (c) the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal;

   (d) where controlled trials were carried out under the above conditions, whether the control group:
   - received no treatment,
   - received a placebo,
   - received another medicinal product of known effect;

   (e) the frequency of observed side-effects;

   (f) details concerning patients who may be at increased risk, e.g. elderly people, children, women during pregnancy or menstruation, or whose physiological or pathological condition requires special consideration;

   (g) a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.

2. Finally the investigator shall, in the general conclusions on the experimental evidence, express an opinion on the safety of the product under normal conditions of use, its compatibility, its therapeutic efficacy and any useful information relating to indications and contra-indications, dosage and average duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of overdosage.

C. GENERAL CONSIDERATIONS

1. The clinician shall always indicate his observations on:

   (a) any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;

(b) any interactions that have been observed with other medicinal products administered concomitantly;

(c) the criteria determining exclusion of certain patients from the trials.

2. Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and therapeutic efficacy of the combination.

CHAPTER III

EXAMINATION OF APPLICATIONS FOR AUTHORIZATION TO PLACE A PROPRIETARY MEDICINAL PRODUCT ON THE MARKET

In examining any application submitted pursuant to Article 4 of Directive 65/65/EEC, the competent authorities of Member States shall apply the following principles.

1. Evaluation of the application for marketing authorization shall be based on clinical trials or clinical pharmacological experiments designed to determine the therapeutic efficacy and safety of the product under normal conditions of use, having regard to the therapeutic indications for use in human beings. Therapeutic advantages must outweigh potential risks.

2. Clinical statements concerning the therapeutic efficacy or safety of a proprietary medicinal product under normal conditions of use which are not scientifically substantiated cannot be accepted as valid evidence.

3. Demonstration of pharmacodynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect.

4. The value of data on the therapeutic efficacy and safety of a proprietary medicinal product under normal conditions of use will be very greatly enhanced if such data come from several competent investigators working independently.

5. When, in respect of particular therapeutic indications, the applicant can show that he is unable to provide comprehensive data on therapeutic efficacy and safety under normal conditions of use, because:

(a) the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or

(b) in the present state of scientific knowledge comprehensive information cannot be provided, or

(c) it would be contrary to generally accepted principles of medical ethics to collect such information,

marketing authorization may be granted on the following conditions:

(a) the proprietary medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital;

(b) the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the proprietary medicinal product in question is as yet inadequate in certain specified respects.

SECOND COUNCIL DIRECTIVE

of 20 May 1975

on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products

(75/319/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 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 proprietary 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 proprietary 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 proprietary medicinal products, the issue of authorizations to place one and the same proprietary 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 proprietary 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 proprietary medicinal products; whereas, therefore, further measures with a view to abolishing any remaining barriers to the free movement of proprietary medicinal products will be necessary in the light of experience gained, particularly in the abovementioned Committee;

Whereas in order to facilitate the movement of proprietary 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 proprietary medicinal products is carried out by a person who fulfils minimum conditions of qualification;

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

Whereas certain rules in this Directive entail amendments to various provisions of Directive 65/65/EEC,

HAS ADOPTED THIS DIRECTIVE:

CHAPTER I

Application for authorization to place proprietary medicinal products on the market

Article 1

Member States shall take all appropriate measures to ensure that the documents and particulars listed

(1) OJ No 96, 2. 6. 1965, p. 1677/65.
(2) OJ No 107, 19. 6. 1965, p. 1825/65.
(3) OJ No 22, 9. 2. 1965, p. 369/65.

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, pharmaco-toxicological 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;

— 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.

[1] See page 1 of this Official Journal.

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 proprietary medical 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 proprietary medicinal products on the market (marketing authorization) are complied with;

(b) may submit the proprietary medicinal product 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 point 7 of Article 4, second paragraph, 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 out 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.

Article 6

Where a leaflet is enclosed with the packaging of a proprietary medicinal product Member States shall take all appropriate measures to ensure that it applies to the product in question only.

All the information given in the leaflet must be in accordance with the particulars and documents supplied pursuant to Article 4 of Directive 65/65/EEC and must be approved by the competent authorities.

The leaflet must include at least the following information:

(a) name and domicile or corporate name and domicile or registered place of business of the person responsible for marketing the product and, where applicable, of the manufacturer;

(b) name and qualitative and quantitative particulars of the product in terms of its active ingredients.

The international non-proprietary names recommended by the World Health Organization should be used where such names exist;

(c) in the absence of a decision to the contrary by the competent authorities:

— therapeutic indications,

— contra-indications, side effects and special precautions for use.

Information and decisions under the first and second indents shall take into account the results of the clinical trials and pharmacological tests provided for in point 8 of Article 4, second paragraph, of Directive 65/65/EEC and in the case of the information referred to under the second indent, of experience acquired in use after marketing;

(d) directions for use of the product (method of administration, duration of treatment if this should be limited, normal dosage);

(e) special storage precautions, where applicable.

Other information shall be clearly separate from that referred to above.

Member State may require that a leaflet be included with the packaging.

Article 7

Notwithstanding the provisions of Chapter IV and of Article 21 of Directive 65/65/EEC, Member States may require that the proprietary medicinal product shall be labelled so as to indicate on the container and/or outer packaging and/or on the package leaflet other requirements essential to safety or for the protection of public health, including any particular precautions to be taken in using the product and any other warnings based on the results of the clinical trials and pharmacological tests mentioned in point 8 of Article 4, second paragraph, of Directive 65/65/EEC, or resulting from experience in the course of use of the proprietary medicinal product after marketing.

CHAPTER III

Committee for Proprietary Medicinal Products

Article 8

1. In order to facilitate the adoption of a common position by the Member States regarding marketing authorizations, a Committee for Proprietary Medicinal Products, hereinafter referred to as 'the Committee', is hereby set up. The Committee shall consist of representatives of the Member States and of the Commission.

2. The responsibility of the Committee shall be to examine, in accordance with Articles 9 to 14, the questions referred to it by a Member State 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. The Member State which has issued a marketing authorization for a proprietary medicinal product shall forward to the Committee a dossier containing a copy of the authorization together with the particulars and documents specified in Article 4,

second paragraph, of Directive 65/65/EEC, if the person responsible for marketing has requested the forwarding to at least five other Member States.

2. The Committee shall forthwith forward the dossier to the competent authorities of the Member States so specified.

3. Such forwarding shall be deemed to be equivalent to submitting an application for marketing authorization, within the meaning of Article 4 of Directive 65/65/EEC, to the said authorities.

Article 10

1. If, within a period of 120 days after the date of the forwarding referred to in Article 9 (2), no objection is notified to the Committee by the competent authorities of the Member States specified, the Committee shall formally record the fact and forthwith inform the Member States concerned.

2. Where a Member State considers that it is unable to authorize the marketing of the proprietary medicinal product, it shall forward its reasoned objection, within the said period of 120 days, on the basis of Article 5 of Directive 65/65/EEC.

Article 11

1. In the cases referred to in Article 10 (2), the Committee shall consider the matter and give a reasoned opinion within not more than 60 days from the expiry of the time limit laid down in Article 10.

2. The opinion of the Committee shall deal with the compliance of the proprietary medicinal product with the conditions set out in Article 5 of Directive 65/65/EEC.

The Committee shall forthwith inform the Member States concerned of its opinion or, in the event of a divergence, of the opinions of its members.

3. The Member States concerned shall reach a decision on the application for marketing authorization not more than 30 days after the date on which the information provided for in Article 10 (1) or paragraph 2 of this Article is given. They shall forthwith inform the Committee of their decision.

Article 12

1. If several applications submitted in accordance with Article 4 of Directive 65/65/EEC have been made for 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 may bring the matter before the Committee.

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

2. The Committee shall consider the matter and give a reasoned opinion within 120 days at the most.

3. The opinion of the Committee shall only deal with the grounds on which authorization was refused, suspended or revoked.

The Committee shall forthwith inform the Member States concerned of its opinion or, in the event of a divergence, of the opinions of its members.

4. The Member States concerned shall give notice within 30 days of the action they intend to take following the Committee's opinion.

Article 13

The Committee may set a time limit for a fresh examination on the basis of particulars relating to the conditions laid down in Articles 5, 11 or 20 of Directive 65/65/EEC obtained in the meantime by the Member States, in particular by those which have authorized the proprietary medicinal product.

Article 14

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 an application for a marketing authorization, its suspension or revocation.

Article 15

1. The Commission shall report to the Council annually on the operation of the procedure laid down in this Chapter and its effects on the development of intra-Community trade. It shall report for the first time two years after the entry into force of this Directive.

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. The Council shall take a decision on the Commission proposal no later than one year after 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 the proprietary medicinal products is subject to the holding of an authorization.

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 proprietary 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 proprietary 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.

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 proprietary medicinal products manufactured within the Member States concerned that each batch of proprietary 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 proprietary 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 proprietary 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.

A Member State may relieve the qualified person of responsibility for the controls prescribed under (b) for imported proprietary medicinal products which are to remain in that Member State, if appropriate arrangements have been made with the exporting country to ensure that those controls have been carried out in the exporting country. Where these products are imported in the packaging in which they are to be sold by retail, Member States may allow exceptions to the requirements laid down in Article 17.

2. In all cases and particularly where the proprietary 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 proprietary 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 proprietary 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 proprietary 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 inspections that the legal requirements relating to proprietary medicinal products are complied with.

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 proprietary 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 proprietary medicinal product shall be prohibited and the proprietary medicinal product withdrawn from the market if:

(a) the proprietary 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 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 proprietary 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 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.

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 proprietary medicinal products coming from third countries, prohibition of supply or withdrawal from the market of a proprietary medicinal product may be taken except on the ground set out in Articles 28 and 29.

Article 33

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.

Article 34

This Directive shall apply only to proprietary medicinal products for human use.

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

Article 35

The following shall be substituted for point 7 of Article 4, second paragraph, of Directive 65/65/EEC:

'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).'

Article 36

The following shall be substituted for Article 11, second paragraph, of Directive 65/65/EEC:

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

The following footnote shall be added:

'[1] OJ No L 147, 9. 6. 75, p. 13.'

Article 37

The following shall be substituted for Article 24 of Directive 65/65/EEC:

'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'.

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 proprietary 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 proprietary 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).

COUNCIL DIRECTIVE

of 2 May 1978

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

(78/420/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 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) set up a Committee for Proprietary Medicinal Products, hereinafter referred to as 'the Committee', and entrusted it with the task of giving opinions on whether particular proprietary medicinal products comply with the requirements of 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 (4);

Whereas Articles 9 and 10 of Directive 75/319/EEC provide that, where the Community procedure is to be applied, the Member State which has issued a marketing authorization shall forward a dossier to the Committee which shall forthwith forward the dossier to the competent authorities of the Member States specified by the person responsible for marketing;

Whereas experience has shown that the provision that the dossiers shall pass through the Committee instead of being sent directly to the Member States concerned results in administrative problems in the forwarding of voluminous documentation and in delays in the work of the Committee;

Whereas, in order to solve these problems and to reduce the delays, it is necessary to amend these provisions to enable the Member State which initially issued the marketing authorization to send the dossier directly to the Member States concerned as well as to the Committee,

HAS ADOPTED THIS DIRECTIVE:

Article 1

The following shall be substituted for Article 9 of Directive 75/319/EEC:

'*Article 9*

1. The Member State which has issued a marketing authorization for a proprietary medicinal product shall, if the person responsible for marketing has requested forwarding to at least five other Member States, forward a dossier containing a copy of this request and a copy of the authorization together with the particulars and documents listed in the second paragraph of Article 4 of Directive 65/65/EEC to the Committee and to the competent authorities of the Member States specified.

2. Such forwarding shall be deemed to be equivalent to the submission of an application for marketing authorization, within the meaning of Article 4 of Directive 65/65/EEC, to the said authorities.

3. The Committee shall without delay inform the Member States concerned that the dossier has been received by the Committee.'

Article 2

In Article 10 (1) of Directive 75/319/EEC the words 'transmission of the information referred to in Article 9 (3)' shall be substituted for 'forwarding referred to in Article 9 (2)'.

Article 3

This Directive is addressed to the Member States.

Done at Brussels, 2 May 1978.

For the Council

The President

K. B. ANDERSEN

(1) OJ No C 266, 7. 11. 1977, p. 45.
(2) OJ No C 18, 23. 1. 1978, p. 11.
(3) OJ No L 147, 9. 6. 1975, p. 13.
(4) OJ No 22, 9. 2. 1965, p. 369/65.

COUNCIL DECISION

of 20 May 1975

setting up a pharmaceutical committee

(75/320/EEC)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community;

Having regard to the proposal from the Commission;

Whereas the implementation of the measures adopted by the Council as regards the approximation of the laws relating to proprietary medicinal products for human use may raise problems which should be jointly examined;

Whereas, to this end, a Committee should be set up, chaired by a representative of the Commission and composed of representatives of the Member States from those States' administrations,

HAS DECIDED AS FOLLOWS:

Article 1

A Committee called the 'Pharmaceutical Committee' shall be set up and attached to the Commission.

Article 2

Without prejudice to the tasks of the Committee for Proprietary Medicinal Products referred to in Article 8 of the Second Council Directive 75/319/EEC [1] of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products, the task of this Committee shall be to examine:

— any question relating to the application of Directives on proprietary medicinal products which are brought up by its Chairman — either on his initiative or at the request of the representative of a Member State;

— any other question in the field of proprietary medicinal products brought up by its Chairman — either on his initiative or at the request of the representative of a Member State.

The Commission shall consult the Committee when preparing proposals for Directives in the field of proprietary medicinal products, and in particular when it considers any amendments to Council Directive 65/65/EEC [2] of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products which it might have occasion to propose.

Article 3

1. The Committee shall consist of senior experts in public health matters from the Member States' administrations and each Member State shall have one representative.

2. There shall be one deputy for each representative. This deputy shall be entitled to participate in meetings of the Committee.

3. A representative of the Commission shall chair the Committee.

Article 4

The Committee shall adopt its rules of procedure.

Done at Brussels, 20 May 1975.

For the Council

The President

R. RYAN

[1] See page 13 of this Official Journal.

[2] OJ No 22, 9. 2. 1965, p. 369/65.

COUNCIL DIRECTIVE

of 12 December 1977

on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products

(78/25/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 primary purpose of any laws concerning 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, although the Council Directive of 23 October 1962 [3], as last amended by Directive 76/399/EEC [4], established a single list of colouring matters authorized for use in foodstuffs intended for human consumption, the disparities between the laws of Member States concerning the colouring of medicinal products still exist; whereas certain Member States apply the rules laid down for foodstuffs to medicinal products; whereas others have separate lists of authorized colouring matters for medicinal products and for foodstuffs;

Whereas these disparities tend to hinder trade in medicinal products within the Community and trade in colouring matters which may be added to these products; whereas such disparities therefore directly affect the establishment and functioning of the common market;

Whereas experience has shown that on health grounds there is no reason why the colouring matters authorized for use in foodstuffs intended for human consumption should not also be authorized for use in medicinal products; whereas, consequently, Annexes I and III to the Directive of 23 October 1962, as they stand or as they subsequently may be amended, should also apply for medicinal products;

Whereas when the use of a colouring matter in foodstuffs and medicinal products is prohibited in order to safeguard public health, technological and economic disturbances should be avoided as far as is possible; whereas to this end a procedure should be provided which establishes close cooperation between the Member States and the Commission within a Committee for the adjustment to technical progress of the Directives on the elimination of technical barriers to trade in the sector of colouring matters which may be added to medicinal products;

Whereas special consideration must be given to certain colouring matters hitherto permitted by certain Member States, in particular for colouring medicinal products for external use,

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[1] OJ No C 62, 30. 5. 1974, p. 23.
[2] OJ No C 116, 30. 9. 1974, p. 24.
[3] OJ No 115, 11. 11. 1962, p. 2645/62.
[4] OJ No L 108, 26. 4. 1976, p. 19.

HAS ADOPTED THIS DIRECTIVE:

Article 1

Member States shall not authorize, for the colouring of medicinal products for human and veterinary use as defined in Article 1 of 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], any colouring matters other than those covered by Annex I, Sections I and II, to the Directive of 23 October 1962 as subsequently amended. Any transitional provisions laid down for certain of these colouring matters shall also apply.

Article 2

Member States shall take all measures necessary to ensure that the colouring matters covered by Annex I, Sections I and II, to the Directive of 23 October 1962 satisfy the general and specific criteria of purity laid down in Annex III to that Directive.

Article 3

The methods of analysis needed to verify that the general and specific criteria of purity adopted pursuant to the Directive of 23 October 1962 are satisfied shall also apply for the purpose of this Directive.

Article 4

Where a colouring matter is deleted from Annex I to the Directive of 23 October 1962 but the marketing of foodstuffs containing this colouring matter is permitted to continue for a limited period, this provision shall also apply to medicinal products. This limited period of use may however be amended for medicinal products according to the procedure laid down in Article 6.

Article 5

1. A committee for the adaptation to technical progress of the Directives on the elimination of technical barriers to trade in the sector of colouring matters which may be added to medicinal products, hereinafter called the 'Committee', is hereby set up and shall consist of representatives of the Member States with a representative of the Commission as chairman.

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

Article 6

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

2. The Commission representative shall submit a draft of the measures to be adopted. The Committee shall deliver its opinion on such measures within a time limit set by the chairman according to the urgency of the matter. Opinions shall be delivered by a majority of 41 votes, the votes of the Member States being weighted as provided in Article 148 (2) of the Treaty. The chairman shall not vote.

3. The Commission shall adopt the proposed measures where they are in accordance with the opinion of the Committee.

If these measures are not in accordance with the opinion of the Committee, or if the Committee does not deliver an opinion, the Commission shall forthwith submit to the Council a proposal regarding the measures to be adopted.

The Council shall act by a qualified majority.

If the Council has not taken a decision within three months of the matter being referred to it, the Commission shall adopt the proposed measures.

Article 7

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

2. However, any Member State may permit, on its own territory, until the end of a period of four years from the notification of this Directive, the marketing of medicinal products containing colouring matters which do not comply with the requirements of this Directive so long as these colouring matters were authorized in that Member State before the adoption of the Directive.

3. Depending on the opinion of the Scientific Committee for Food and of the Committee referred to in Article 5 the Commission shall if appropriate submit to the Council within two years of the adoption of this Directive a proposal for amendment of the Directive to allow the use of:

— the colouring matters:

= Brilliant Blue FCF CI 42090,
= Red 2G CI 18050,

— other colouring matters for medicinal products for external use only.

The Council shall take a decision on the Commission proposal no later than two years after its submission.

[1] OJ No 22, 9. 2. 1965, p. 369/65.

4. 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 8

This Directive is addressed to the Member States.

Done at Brussels, 12 December 1977.

For the Council

The President

A. HUMBLET

ANNEX

LIST OF COLOURING MATERIALS

AUTHORISED FOR COLOURING MEDICINAL PRODUCTS

UP TO 1.1.1978

(Annex I, sections I and II of the Directive of October 23, 1962 *)

No.	Common Name
E 100	Curcumin
E 101	Lactoflavin (Riboflavin)
E 102	Tartrazine
E 104	Quinoline yellow
E 110	Orange yellow S sunset yellow FCF
E 120	Cochineal carminic acid
E 122	Azorubine Carmoisine
E 123	Amaranth
E 124	Cochineal Red A Ponceau 4R
E 127	Erythrosine
E 131	Patent Blue V
E 132	Indigotin (indigo carmine)
E 140	Chlorophylls
E 141	Copper complexes of chlorophylls and chlorophyllins
E 142	Acid brilliant green BS (lissamine green)
E 150	Caramel
E 151	Brillant Black BN, Black PN
E 153	Carbo medicinalis vegetalis (charcoal)

* Council Directive of 23 October 1962 concerning the approximation of legislation of Member States concerning colouring materials which can be utilised in foodstuffs destined for human consumption - OJ 115 of 11.11.1962, p. 2645/62

amended by :

- Directive 65/469/EEC of 25 October 1965 - OJ 178 of 26.10.1965, p.2793/65
- Directive 67/653/EEC of 24 October 1967 - OJ 263 of 30.10.1967, p. 4
- Directive 68/419/EEC of 20 December 1968 - OJ L 309 of 24.12.1968, p. 24
- Directive 70/358/EEC of 13 July 1970 - OJ L 157 of 18.7.1970, p. 36
- Act of Accession - OJ L 73 of 27.3.1972, p. 14
- Directive 76/399/EEC of 4 April 1976 - OJ L 108 of 26.4.1976, p. 19
- Directive 78/144/EEC of 34 January 1978 - OJ L 44 of 15.2.1978

No.	Common Name
E 160	Carotenoids : a) Alpha-, beta-, gamma-carotene b) Bixin, Norbixin (Roucou Annatto) c) Capsanthin, Capsorubin d) Lycopene e) Beta-apo-8' carotenal (C 30) f) Ethyl ester of beta-apo-8' carotenoic acid (C 30)
E 161	Xanthophylls a) Flavoxanthin b) Lutein c) Kryptoxanthin d) Rubixanthin e) Violoxanthin f) Rhodoxant g) Canthaxanthin
E 162	Beetroot red, betanin
E 163	Anthocyanins
E 170 **)	Calcium carbonate
E 171 **)	Totanium dioxide
E 172 **)	Iron oxides and hydroxides
E 173 **)	Aluminium
E 174 **)	Silver
E 175 **)	Gold

**) For surface colouring only.

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

rules of procedure

THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS,

Having regard to 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, and in particular Article 8(3) thereof, (1)

HAS DRAWN UP ITS RULES OF PROCEDURE AS FOLLOWS :

(1) OJ No L 147, 9.6.75

Article 1

1. The Committee shall consist of one representative for each Member State and one representative of the Commission. One alternate shall be appointed for each of the representatives.

2. The Committee members and the alternates shall be appointed by the Member States for three years provided they continue to be national officials responsible for examining applications for authorization to market proprietary medicinal products. Their appointments shall be renewable.

3. An alternate shall sit in this capacity on the Committee only if the full member is absent or is unable to discharge his duties.

4. Each representative may arrange to be accompanied at Committee meetings by not more than three experts.

5. Even after their duties have ceased, members, alternates and experts shall be required not to disclose information of the kind covered by the obligation of professional secrecy.

Article 2

The Committee shall elect its Chairman from among its members by absolute majority and secret ballot. If, after two ballots, nobody has obtained an absolute majority of the votes, the member who obtains the relative majority at the third ballot shall be elected. In the event of a tie the oldest candidate shall be declared elected.

Article 3

The term of office of the Chairman shall be three years. He shall be eligible for re-election once only.

Article 4

As soon as he takes up his duties, the Chairman shall cease to be a representative and shall be replaced in that capacity.

Article 5

Two Deputy Chairmen shall be appointed to replace the Chairman when he is absent or unable to discharge his duties. One shall be elected by the Committee and the other appointed by the Commission.

The provisions of Articles 2 and 3 of these Rules of Procedure shall apply to the election and the term of office of the elected Deputy Chairman.

Article 6

The Committee shall be convened by its Chairman, either on his own initiative or at the request of a member.

Article 7

The Chairman shall draw up the agenda, in which distinctions shall be made between :

a) objections to applications for marketing authorizations submitted to the Committee for an opinion under Article 11 (1) of Directive 75/319/EEC;

b) refusals, suspensions or revocations of marketing authorizations submitted to the Committee for an opinion under Article 12 (2) of Directive 75/319/EEC;

c) fresh examinations of previous opinions under Article 13 of Directive 75/319/EEC;

d) specific cases submitted under Article 14 of Directive 75/319/EEC.

Article 8

Requests to convene the Committee which are made by a member must be drawn up in accordance with the classification set out in the foregoing Article and be reasoned such that they may constitute the working paper of the Committee.

Article 9 *

1. Pursuant to Article 9 (1) of Directive 75/319/EEC, the Member State concerned shall forward to the Committee a dossier containing :

   a) a copy of the request for forwarding to the competent authorities of the Member States specified;

   b) a copy of the marketing authorization;

   c) the particulars and documents listed in the second paragraph of Article 4 of Directive 65/65/EEC.

   There shall be forwarded as many dossiers as there are Member States specified, plus one for the secretariat of the Committee.

2. Pursuant to Article 9 (2) of Directive 75/319/EEC, the Committee shall forthwith forward this dossier to the competent authorities of the Member States specified.

3. The Committee shall send to the members of the Committee the documents referred to in paragraph 1 (a) and (b) above.

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* To be amended cf. Council Directive 78/420/EEC of 2nd May 1978.

Article 10

The dossier kept by the secretariat of the Committee may be consulted by any member of the Committee or by the experts referred to in Article 1 (4) having the written authority of the member.

Article 11

1. The notification of the meeting, the agenda and the working papers shall be forwarded by the Chairman to the members of the Committee in accordance with the procedure laid down in Article 18 (2) and (3).

2. These papers shall be delivered to the Permanent Representatives of the Member States and to the Commission not later than fifteen days before the date of the meeting.

3. In urgent cases, the Chairman may, at the request of a member of the Committee or on his own initiative, shorten this period of notice by up to three clear working days, stating the grounds for his decision.

Article 12

1. Meetings of the Committee shall be validly held if six Member States are represented.

2. The representative of a Member State may, if necessary, undertake the representation of one other Member State. The Chairman of the Committee shall be informed accordingly by the Permanent Representative of the Member State wishing to be so represented.

Article 13

The Committee may convene panels of experts to study matters of common interest.

Article 14

The secretariat services for the Committee shall be provided by the Commission, assisted, if necessary, by experts.

Article 15

1. The Member States concerned shall be informed forthwith of the reasoned opinions delivered pursuant to Articles 11 and 12 of Directive 75/319/EEC in accordance with the procedure set out in the first subparagraph of Article 18 (2).

2. A summary record shall be prepared under the responsibility of the Chairman for each meeting; it shall be forwarded to the members of the Committee in accordance with the procedure set out in Article 18 (2) and (3). Any comments which the members may wish to make shall be communicated to the Chairman in writing. The Chairman shall pass them on to the Committee; if there is disagreement, the proposed amendment shall be discussed at the following meeting. If disagreement persists, this amendment shall be appended to the relevant record.

Article 16

The Chairman of the Committee shall act as proxy for the Committee to perform the formal recording referred to in Article 10 (1) of Directive 75/319/EEC.

He shall forthwith inform the Member States of this formal recording in accordance with the procedure set out in the first paragraph of Article 18 (2).

Article 17

1. The secretariat of the Committee shall act as proxy for the Committee to forward the dossier referred to in Article 9 (2) to the competent authorities of the Member States in accordance with the procedure set out in the first paragraph of Article 18 (2) and, in the same way, the documents referred to in Article 9 (3).

2. The information forwarded to the Committee in accordance with Article 11 (3), Article 12 (4) and Article 33 of Directive 75/319/EEC shall be brought to the knowledge of the members of the Committee by the secretariat in accordance with the procedure set out in the second paragraph of Article 18 (2).

Article 18

1. Correspondence of concern to the Committee shall be addressed to the secretariat of the Committee, Directorate-General for Internal Market and Industrial Affairs, for the attention of the Chairman.

2. Correspondence intended for the representatives of the Member States shall be addressed to the Permanent Representations.

   Copies of such correspondence shall be addressed directly to the representatives of the Member States.

3. Correspondence intended for the representative of the Commission shall be addressed to the Commission, Directorate-General for Internal Market and Industrial Affairs.

Article 19

Notwithstanding the provisions of Article 214 of the Treaty, the work of the Committee and of the panels of experts and all the documents submitted to them shall be treated as confidential. Nevertheless, the representatives of the Member States may, in accordance with the national laws in force, inform the person responsible for marketing a medicinal product or products of the reasoned objection of a Member State, as referred to in Article 10 (2) of Directive 75/319/EEC.

Notice to applicants for marketing authorizations for proprietary medicinal products

I. A new procedure for placing proprietary medicinal products on the market

Following the European Community Directives adopted in 1975 *(Official Journal of the European Communities* No L 147 of 9 June 1975) all manufacturers of and persons responsible for marketing proprietary medicinal products may now use a new procedure for placing their products on the markets of the Member States: they may go through the Committee for Proprietary Medicinal Products attached to the Commission of the European Communities in Brussels.

II. Conditions to be fulfilled in order to use this procedure:

1. The proprietary medicinal product in question must first have obtained a marketing authorization (subsequently referred to as M.A.) in one of the Member States, as laid down in Directives 65/65/EEC, 75/318/EEC and 75/319/EEC.

   Vaccines, toxins and serums, proprietary medicinal products based on human blood or blood constituents, radioactive isotopes and homeopathic proprietary medicinal products may not benefit from this procedure (Article 34 of Directive 75/319/EEC).

2. Applications for M.A. via the Committee must relate to at least five other Member States.

III. Procedure to be followed:

(a) Documents to be supplied to the competent authority of the Member State which has granted the initial M.A.:

   1. Request that the documents be forwarded to at least five named Member States through the Committee for Proprietary Medicinal Products;

   2. Information and documents listed in the second paragraph of Article 4 of Directive 65/65/EEC;

   3. Copy of the M.A.

(b) The number of copies of these documents to be supplied is one for each Member State concerned plus one for the Committee secretariat.

(c) The languages in which the documents must be presented:

   1. The documents referred to in the second paragraph of Article 4 of Directive 65/65/EEC must be provided in one of the official languages of each of the Member States concerned; except that the documents referred to in item 8 of the second paragraph of Article 4 may, alternatively, be presented in:

      — English for Germany,

      — English for Belgium,

      — English, French or German for Denmark,

      — English or French for Italy,

      — Dutch, English, German or Italian for Luxembourg,

      — English, French or German for the Netherlands.

2. The copy intended for the Committee secretariat may be in English or French.

(d) No special fee is payable to the Committee for Proprietary Medicinal Products, but national registration fees remain applicable.

(e) A reasoned opinion of the Committee, which will be based on information contained in the application for an M.A., shall not be regarded as an M.A. in any Member State.

IV. **Consideration of divergent decisions:**

Directive 75/319/EEC also makes provision for consideration by the Committee of divergent decisions taken by the Member States as regards the authorization, suspension or revocation of an M.A.

Any one of the Member States concerned may request the opinion of the Committee concerning the grounds for refusal, suspension or revocation of the M.A. as given by the authorities of another Member State.

Within 30 days, the Member States shall notify the Committee of the action they intend to take following the opinion.

V. **Force of the opinions of the Committee:**

The opinions of the Committee shall not be binding on Member States and shall not replace national decisions.

VI. **Additional information:**

For additional information, please apply to the Secretariat, Committee for Proprietary Medicinal Products, 3 Rond-Point Schuman, B-1049 Brussels; or to the appropriate national licensing authority.

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

Application for marketing authorization for
a proprietary medicinal product

The Committee for Proprietary Medicinal specialities wishes in respect of Council Directives 65/65/EEC, 75/318/EEC and 75/319/EEC that the particulars in support of applications for authorizations to place proprietary medicinal products on the market are presented in the following way in order to facilitate the task of the applicants and the competent authorities.

Flyleaf

1. Name or business name of applicant for marketing authorization

2. Full address

3. a) Name and address of manufacturer

   b) Name and address of importer

4. Name of the proprietary medicinal product

5. Pharmaceutical form

6. Method and route of administration

7. Number of annexes supplied in support of the application

Annex I : General Information

- Name of the proprietary medicinal product
- Pharmaceutical form
- Qualitative and quantitative composition in terms of active principles
- Therapeutic indications
- Dosage
- Contra-indications
- Warnings and precautions (including during pregnancy)
- Side-effects
- Directions for use (where applicable)
- Shelf life and storage precautions

Annex II : Information and documents concerning physico-chemical, biological or microbiological tests

Annex II A : Complete qualitative and quantitative composition

- Name of product

- Composition

Names of constituents	Quantity	Reference to standards
Active principles		
Other constituents		

- Container (brief description)

Annex II B : Method of preparation

1. Manufacturing formula

2. Manufacturing process including in-process control and the pharmaceutical assembly process

Annex II C : Control of starting materials

1. Active principles

a) Active principles described in a pharmacopoeia

b) Active principles not described in a pharmacopoeia

Annex II C : Control of starting materials

2. Other constituents

a) Constituents described in a pharmacopoeia

b) Constituents not described in a pharmacopoeia

Annex II D : Control tests on intermediate products
(if necessary)

Annex II E : Control tests on the finished product

1. General characteristics, other quality control tests required by the nature of the product;

   (appearance, dimension, shape, colour, odour, distinguishing features, etc.)

Annex II E : Control tests on the finished product

2. Identification and quantitative determination of the active principle or principles, other quality control tests, with a description of the methods employed (including, if necessary, and depending on the nature of the product, biological and microbiological methods).

Annex II E : Control tests on the finished product

3. Identification and quantitative determination of the other constituents (if necessary)

Annex II F : Stability tests

1. Proposed shelf life (depending on the type of container)

2. Information concerning stability, including physical stability :
   - number of batches tested
   - storage conditions
   - methods employed
   - description of containers

Annex II F : Stability tests

3. Results and interpretations

Annex II G : Conclusions

Certificate by the expert analyst on the application of the methods and justification of the control methods to be used by the manufacturer

Annex III : Toxicological and pharmacological tests *
(Summary of the tasks performed by the expert pharmacologist)

The following information must be provided in respect of each test :

1. Animals used (species, strain, sex, etc.)
2. Experimental conditions including diet
3. Results

Annex III A : Acute toxicity

* If use is made of a list of published references pursuant to point 8 of the second paragraph of Article 4 of Council Directive 65/65/EEC (OJ No 22 of 9 February 1966), the expert must show that this is justified.

Annex III : Toxicological and pharmacological tests

Annex III B : Toxicity with repeated administration

1. Subacute toxicity trials

Annex III : Toxicological and pharmacological tests

Annex III B : Toxicity with repeated administration

2. Chronic toxicity trials

Annex III : Toxicological and pharmacological tests

Annex III C : Foetal toxicity

a) tests for teratogenicity (dosing during period of organogenesis)
b) pre- and postnatal dosing of the mother to demonstrate effects on late pregnancy, parturition and lactation

Annex III : Toxicological and pharmacological tests

Annex III D : Fertility studies

Annex III : Toxicological and pharmacological tests

Annex III E : Carcinogenicity and mutagenicity

Annex III : Toxicological and pharmacological tests

Annex III F : Pharmacodynamics

1. Actions relevant to the proposed therapeutic uses
2. Other actions investigated
3. Interactions

Annex III : Toxicological and pharmacological tests

Annex III G : Pharmacokinetics

1. Absorption (serum levels of the medicinal product)
2. Distribution of the medicinal product
3. Biotransformation
4. Excretion of the medicinal product or metabolites

Annex IV : Clinical trials *
(Summary of the tasks performed by the expert clinician)

Annex IV A : Human pharmacology

* If use is made of a list of published references pursuant to point 8 of the second paragraph of Article 4 of Council Directive 65/65/EEC (OJ No 22 of 9 February 1965), the expert must show that this is justified.

Annex IV : Clinical trials

Annex IV B : Clinical data

1. Individual data - clinical reports

Annex IV : Clinical trials

Annex IV B : Clinical data

2. Summary

Annex IV : Clinical trials

Annex IV B : Clinical data

3. Conclusions

Annex IV : Clinical trials

Annex IV C : Side-effects and interactions

Information on side-effects and interactions observed when used in other countries (the extent of usage in terms of number of prescriptions and duration of use is useful in assessing the frequency of the adverse reaction)

Annex V : Special particulars

Annex V A : Dosage form

1. Packaging
2. Label
3. Package insert

Annex V : Special particulars

Annex V B : Samples

Annex V : Special particulars

Annex V C : Manufacturer's authorization

Annex V : Special particulars

Annex V D : Marketing authorization

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The rules governing medicaments in the European Community

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The conditions in which proprietary medicinal products can be manufactured and marketed within various Member States of the European Communities are regulated by Community rules which are contained in a number of Directives. These texts afford protection on the ground of public health and improve the free movement of medicines. As regards public health, this protection is designed to ensure that medicines are soundly based and of high quality of manufacture.

To facilitate free movement of medicines a Committee for Proprietary Medicinal Products has been set up to ensure close co-operation between the competent authorities of the nine Member States so that decisions made upon applications for marketing authorization are as consistent as possible. Another factor in facilitating free movement of medicines is the suppression of regular controls at the time of importation.

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