II

(Acts whose publication is not obligatory)

COUNCIL

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

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[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.