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Legislation

Contents

I *Acts whose publication is obligatory*

.....

II *Acts whose publication is not obligatory*

Council

(Continued overleaf)

Acts whose titles are printed in light type are those relating to day-to-day management of agricultural matters, and are generally valid for a limited period.

Contents (continued)

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.

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 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 20 May 1975

on the approximation of the laws of the Member States relating to the steering equipment of wheeled agricultural or forestry tractors

(75/321/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 technical requirements with which tractors must comply pursuant to national laws relate, *inter alia,* to steering equipment;

Whereas these requirements differ from one Member State to another; whereas it is therefore necessary that all Member States adopt the same requirements either in addition to or in place of their existing rules in order, in particular, to allow the EEC type approval procedure which was the subject of Council Directive 74/150/EEC (3) of 4 March 1974 on the approximation of the laws of the Member States relating to the type approval of wheeled agricultural or forestry tractors to be applied in respect of each type of tractor,

HAS ADOPTED THIS DIRECTIVE :

Article 1

1. 'Agricultural or forestry tractor' means any motor vehicle fitted with wheels or caterpillar tracks and having at least two axles, the main function of which lies in its tractive power and which is specially designed to tow, push, carry or power certain tools, machinery or trailers intended for agricultural or forestry use. It may be equipped to carry a load and passengers.

2. This Directive shall apply only to tractors defined in the preceding paragraph which are fitted with pneumatic tyres and which have two axles and a maximum design speed of between 6 and 25 kilometres per hour.

Article 2

No Member State may refuse to grant EEC type approval or national type approval of a tractor on grounds relating to the steering equipment if this satisfies the requirements set out in the Annex.

Article 3

No Member State may refuse the registration or prohibit the sale, entry into service, or use of tractors on grounds relating to the steering equipment if this satisfies the requirements set out in the Annex.

Article 4

The amendments necessary for adapting the requirements of the Annex to technical progress shall be adopted in accordance with the procedure laid down in Article 13 of Directive 74/150/EEC.

Article 5

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

2. Member States shall ensure that the texts of the main provisions of national law which they adopt in the field covered by this Directive are communicated to the Commission.

Article 6

This Directive is addressed to the Member States.

Done at Brussels, 20 May 1975.

For the Council

The President

R. RYAN

(1) OJ No C 160, 18. 12. 1969, p. 29.
(2) OJ No C 48, 16. 4. 1969, p. 21.
(3) OJ No L 84, 28. 3. 1974, p. 10.

ANNEX

1. DEFINITIONS

1.1. **'Steering equipment'**

'Steering equipment' means all the equipment the purpose of which is to alter the direction of movement of the tractor.

The steering equipment may be considered to include:

— the steering control;

— the steering gear;

— the steered wheels;

— where applicable, special equipment to produce additional or independent power.

1.1.1. '*Steering control*'

'Steering control' means the part directly operated by the driver in order to steer the tractor.

1.1.2. '*Steering gear*'

'Stearing gear' means all the components between the steering control and the steered wheels, with the exception of the special equipment referred to in 1.1.4. The steering gear may be mechanical, hydraulic, pneumatic, electric or a combination of any of these.

1.1.3. '*Steered wheels*'

'Steered wheels' means:

— the wheels the alignment of which may be altered directly or indirectly in relation to that of the tractor in order to obtain a change in the direction of movement of the tractor;

— all wheels of articulated tractors;

— wheels on the same axle, the speed of which may be varied in order to obtain a change in the direction of movement of the tractor.

Self-tracking castor wheels are not steered wheels.

1.1.4. '*Special equipment*'

'Special equipment' means that part of the steering equipment by which additional or independent power is produced. Additional or independent power may be produced by any mechanical, hydraulic, pneumatic or electrical system, or by any combination of these (for example by an oil pump, air pump or battery, etc.).

1.2. **'Different types of steering equipment'**

1.2.1. Depending on the source of power which is necessary for the deflection of the steered wheels, the following types of steering equipment are identified:

1.2.1.1. *Manual steering equipment*, in which the steering power is provided solely by the muscular power of the driver;

1.2.1.2. *Assisted steering equipment*, in which the steering power is provided both by the muscular power of the driver and by the special equipment referred to in 1.1.4;

Steering equipment where the steering power is normally provided solely by the special equipment referred to in 1.1.4, but which in the event of failure of the special equipment enables the muscular power of the driver to be used for steering, shall be considered as 'assisted steering equipment'.

1.2.1.3. *Servo-steering equipment*, in which the steering power is provided solely by the special equipement referred to in 1.1.4.

1.3. **Steering effort**

'Steering effort' means the force exerted by the driver on the steering control in order to steer the tractor.

2. CONSTRUCTION, FITTING AND INSPECTION REQUIREMENTS

2.1. **General requirements**

2.1.1. The steering equipment must ensure easy and safe handling of the tractor and must comply with the detailed requirements set out in 2.2.

2.2. **Detailed requirements**

2.2.1. *Steering control*

2.2.1.1. The steering control must be easy to use and grip. It must be designed in such a way as to permit gradual deflection. The direction of movement of the steering control must correspond to the desired change in the direction of the tractor.

2.2.1.2. The steering effort required to achieve a turning circle of 12 m radius, starting from the straight ahead position, must not exceed 25 daN. In the case of assisted steering equipment, if the auxiliary power supply fails the steering effort required must not exceed 60 daN.

2.2.1.3. In order to check compliance with the requirement in 2.2.1.2, the tractor shall describe a spiral movement at a speed of 10 kilometres per hour, starting from the straight ahead position, on a dry, flat road surface offering good tyre adhesion. The steering effort on the steering control shall be noted until it reaches the position corresponding to the tractor entering a turning circle of 12 m radius. The duration of the manoeuvre (time between the moment when the steering control is first operated and the moment when it reaches the position where the measurements are taken) must not exceed five seconds in normal cases and eight seconds if the special equipment fails. One manoeuvre must be made to the left and one to the right.

For the test, the tractor must be loaded to its technically permissible maximum weight; tyre pressures and weight distribution between the axles must conform to the manufacturer's instructions.

2.2.2. *Steering gear*

2.2.2.1. The steering equipment may not include either electrical or wholly pneumatic steering gear.

2.2.2.2. The steering gear must be so designed as to meet any operational requirements It must be easily accessible for maintenance and inspection.

2.2.2.3. In the case of steering gear which is not wholly hydraulic, it must be possible to drive the tractor even in the event of failure of the hydraulic or pneumatic components of the steering gear.

2.2.2.4. Steering gear which is operated purely hydraulically and the special equipment mentioned in 1.1.4, must meet the following requirements:

2.2.2.4.1. One or more pressure limitation devices must protect the whole or part of the circuit against excess pressure;

2.2.2.4.2. The pressure limitation devices must be set so as not to exceed a pressure T equal to the maximum operating pressure stated by the manufacturer.

2.2.2.4.3. The characteristics and dimensions of the pipe work must be such that the pipes withstand four times the pressure T (permitted by the pressure limitation devices), and must be protected in places and arranged in such a way that the risks of damage by impact or interference are reduced to a minimum, and the risks of damage by rubbing can be considered negligible.

2.2.3. *Steered wheels*

2.2.3.1. All the wheels may be steered wheels.

2.2.4. *Special equipment*

2.2.4.1. The special equipment defined in 1.1.4, used in the types of steering equipment defined in 1.2.1.2 and 1.2.1.3, shall be acceptable in the following circumstances:

2.2.4.1.1. If the tractor is equipped with assisted steering equipment as defined in 1.2.1.2, it must be possible to drive it even in the event of failure of the special equipment as already stated in 2.2.1.2. If the assisted steering equipment does not have its own source of power, it must be fitted with a power reservoir. This power reservoir may be replaced by a self-contained device providing power supply to the steering equipment with priority over the other systems which are linked to the common energy source. The steering and braking systems must not have a common source of energy. If the source of power is compressed air, the air reservoir must be protected by a non-return valve.

Where the steering power is normally provided solely by the special equipment referred to in 1.1.4, the assisted steering equipment must be fitted with a device such that if, in the event of failure of the special equipment, the steering effort exceeds 25 daN, a visual or acoustic signal must give warning of such failure.

2.2.4.1.2. If the tractor is fitted with servo-steering equipment as defined in 1.2.1.3, and provided that such equipment has a wholly hydraulic steering gear, it must be possible, should the special device fail, to carry out the two manoeuvres specified in 2.2.1.3 using a special additional device. The special additional device may be a compressed air or gas reservoir. An oil pump or compressor may be used as the special additional device if that device is worked by the rotation of the tractor wheels and cannot be disconnected from them. In the event of failure of the special equipment, a visual or acoustic signal must give warning of such failure.

2.2.4.1.2.1. If the special device is pneumatic, it must be fitted with a compressed air reservoir protected by a non-return valve. The capacity of the compressed air reservoir must be calculated so that at least seven complete turns (from lock to lock) are possible before the reservoir pressure falls to half its operating pressure; the test must be carried out with the steered wheels off the ground.

COUNCIL DIRECTIVE

of 20 May 1975

on the approximation of the laws of the Member States relating to the suppression of radio interference produced by spark-ignition engines fitted to wheeled agricultural or forestry tractors

(75/322/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 technical requirements with which tractors must comply pursuant to national laws relate, *inter alia,* to the suppression of radio interference;

Whereas these requirements differ from one Member State to another; whereas it is therefore necessary that all Member States adopt the same requirements either in addition to or in place of their existing rules, in particular to allow the EEC type approval procedure which was the subject of Council Directive 74/150/EEC (3) of 4 March 1974 on the approximation of the laws of the Member States relating to the type approval of wheeled agricultural or forestry tractors to be applied in respect of each type of tractor,

HAS ADOPTED THIS DIRECTIVE :

Article 1

1. 'Agricultural or forestry tractor' means any motor vehicle fitted with wheels or caterpillar tracks and having at least two axles, the main function of which lies in its tractive power and which is specially designed to tow, push, carry or power certain tools, machinery or trailers intended for agricultural or forestry use. It may be equipped to carry a load and passengers.

2. This Directive shall apply only to tractors defined in the preceding paragraph, fitted with pneumatic tyres, and which have two axles and a maximum design speed of between 6 and 25 km/h and a spark-ignition engine.

Article 2

No Member State may refuse to grant EEC type approval or national type approval of a tractor on grounds relating to the radio interference produced by the spark-ignition system of its propulsion engine if such tractors are fitted with interference suppression equipment meeting the requirements of the Annexes.

Article 3

No Member State may refuse the registration or prohibit the sale, entry into service or use of a tractor on grounds relating to the radio interference produced by the spark-ignition system of its propulsion engine if such tractors are fitted with interference suppression equipment meeting the requirements of the Annexes.

Article 4

A Member State which has granted type approval shall take the necessary measures to be informed of any modification of a part or characteristic referred to in 2.2 — Annex I. The competent authorities of that State shall determine whether fresh tests should be carried out on the modified type of the tractor and a fresh report drawn up. Where such tests reveal failure to comply with the requirements of this Directive, the modification shall not be approved.

(1) OJ No C 160, 18. 12. 1969, p. 29.
(2) OJ No C 48, 16. 4. 1969, p. 21.
(3) OJ No L 84, 28. 3. 1974, p. 10.

Article 5

The amendments necessary for adapting the requirements of the Annexes to technical progress shall be adopted in accordance with the procedure laid down in Article 13 of Directive 74/150/EEC.

Article 6

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

2. Member States shall ensure that the texts of the main provisions of national law which they adopt in the field covered by this Directive are communicated to the Commission.

Article 7

This Directive is addressed to the Member States.

Done at Brussels, 20 May 1975.

For the Council

The President

R. RYAN

ANNEX I (1)

DEFINITIONS, APPLICATION FOR EEC TYPE APPROVAL, MARKINGS, EEC TYPE APPROVAL, SPECIFICATIONS, TESTS, CONFORMITY OF PRODUCTION

(1.)

2. DEFINITIONS

For the purposes of this Directive,

(2.1.)

2.2. 'Tractor type as regards radio interference suppression' means tractors which do not differ in such essential respects as:

2.2.1. The shapes and constituent materials of the part of the body forming the engine compartment and the part of the passenger compartment nearest to it.

2.2.2. The type of engine (whether two- or four-stroke, number and capacity of cylinders, number of carburettors, arrangement of valves, maximum power and corresponding r.p.m.).

2.2.3 The position or model of the ignition circuit components (coil, distributor, sparking plugs, screening, etc.).

2.2.4. The position of metal components housed in the engine compartment (e.g. heating appliances, spare wheel, air filter, etc.).

2.3. 'Limitation of radio interference' means a reduction of radio interference in the sound-broadcasting and television frequency bands to a level such that there is no appreciable interference with the functioning of receivers not carried on the vehicle itself; this condition is fulfilled if the level of interference remains below the limits laid down in 6.2.2 below;

2.4. 'Radio interference suppression equipment' means a complete set of components necessary for limiting radio interference from the ignition system of a tractor. Radio interference suppression equipment also includes earthing strips and screening components incorporated specially for radio interference suppression;

2.5. 'Suppression equipment of different types' means sets of equipment which differ in such essential respects as:

2.5.1. That their components bear different trade names or marks.

2.5.2. That the 'high-frequency' characteristics of a component are different or their components differ in shape or size.

2.5.3. That the operating principles of at least one component are different.

2.5.4. That their components are assembled differently.

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(1) The text of the Annexes corresponds to that of Council Directive 72/245/EEC of 20 June 1972 on the approximation of the laws of the Member States relating to the suppression of radio interference produced by spark-ignition engines fitted to motor vehicles (OJ No L 152, 6. 7. 1972, p. 15).

2.6. 'Suppression equipment component' means one of the individual constituent parts of the suppression equipment.

3. APPLICATION FOR EEC TYPE APPROVAL

3.1. The application for EEC type approval of a tractor type with regard to radio interference suppression shall be submitted by the vehicle manufacturer or by his authorized representative.

3.2. It shall be accompanied by the following documents in triplicate and by the following particulars:

3.2.1. A description of the tractor type with regard to the items mentioned in 2.2 above, accompanied by an exploded view or a photograph of the engine compartment. The numbers and/or symbols identifying the engine type and the tractor type shall be shown.

3.2.2. A list of the components, duly identified, constituting the radio interference suppression equipment.

3.2.3. Detailed drawings of each component to enable it to be easily located and identified.

3.2.4. Particulars of the nominal value of the direct-current resistances, and, in the case of resistive ignition cables, of their nominal resistance per metre.

3.3. In addition, the application for EEC type approval shall be accompanied by a sample of the radio interference suppression equipment.

3.4. A vehicle representative of the tractor type to be approved shall be submitted to the technical service responsible for the type approval tests.

4. MARKINGS

4.1. The radio interference suppression equipment components shall bear:

4.1.1. The trade name or mark of the manufacturers of the equipment and its components.

4.1.2. The trade description given by the manufacturer.

4.2. The markings shall be repeated on the radio interference suppression cables at intervals of not more than twelve centimetres.

4.3. These markings shall be clearly legible and indelible.

5. TYPE APPROVAL

(5.1.)

(5.2.)

5.3. A form conforming to the model in Annex IV shall be attached to the EEC type approval certificate.

(5.4.)

(5.5.)

(5.6.)

6. SPECIFICATIONS

6.1. **General specifications**

The components of the radio interference suppression equipment shall be so designed, constructed and fitted as to enable the tractor, in normal conditions of use, to comply with the requirements of this Directive.

6.2. **Specifications concerning radio interference**

6.2.1. *Method of measurement*

The interfering radiation set up by the tractor type submitted for approval shall be measured by the method described in Annex II.

6.2.2. *Reference limits*

6.2.2.1. The radiation limits based on quasi-peak measurements shall be 50 μV/m in the 40-75 MHz frequency band and 50-120 μ/Vm in the 75-250 MHz frequency band, this limit increasing linearly with frequencies above 75 MHz.

6.2.2.2. If measurements are made with peak measuring equipment, the readings, expressed in μ/Vm, shall be divided by 10.

6.2.3. On the tractor type submitted for approval in respect of radio interference suppression, the measured values shall be not less than 20 per cent below the reference limits.

7. TESTS

Compliance with the requirements of section 6 above shall be checked in accordance with the method shown in Annex II.

(8.)

9. CONFORMITY OF PRODUCTION

(9.1.)

9.2. When the conformity of a tractor taken from the series is being verified, production shall be deemed to conform to the requirements of this Directive if the levels measured do not exceed by more than 25 % the limits prescribed in 6.2.2.

9.3. If at least one of the levels measured on the tractor taken from the series exceeds the limits prescribed in 6.2.2. by more than 25 %, the manufacturer may request that measurements be made on a sample of at least six tractors taken from the series. The results for each frequency band shall be interpreted by the statistical method shown in Annex III.

(10.)

(11.)

ANNEX II

METHOD OF MEASUREMENT OF RADIO INTERFERENCE PRODUCED BY HIGH-VOLTAGE IGNITION SYSTEMS

1. MEASURING APPARATUS

The measuring equipment shall comply with the requirements of Publication No 2 (first edition, 1961) of the International Special Committee on Radio Interference (CISPR) or with the specifications applicable to peak type measuring apparatus given in CISPR Publication No 5 (first edition, 1967).

Note:

Where the available equipment does not fully meet all the CISPR specifications, discrepancies must be clearly stated.

2. EXPRESSION OF RESULTS

The results of measurements must be expressed in μV/m for 120 kHz bandwidth. For statistical purposes, the logarithmic unit dB (μV/m) shall be used. If for certain frequencies the actual bandwidth B (expressed in kHz) of the measuring apparatus differs slightly from 120 kHz, the readings taken should be converted to 120 kHz bandwidth through multiplication by a factor $\frac{120}{B}$.

3. MEASURING SITE

The measuring site shall be a level area free from appreciable wave-reflecting surfaces within an ellipse having a major axis of 20 m and a minor axis of 17·3 m. The antenna and the centre of the engine must be located on the major axis of the ellipse, the plane of symmetry of the tractor being parallel to the minor axis. The antenna and the point of intersection of the side of the engine nearest to the antenna with the major axis must each be located at a focal point of the ellipse. The measuring set, or the test hut or vehicle in which the set is located, may be within the ellipse but horizontally not closer than 3 m to the antenna, in a direction opposite to the tractor being measured. Furthermore, the absence of any extraneous or signal which could materially affect the measurement must be ensured; a check is therefore made, with the engine stopped, before and after taking the measurements, which can be considered satisfactory only if the readings are at least 10 dB above the highest obtained at the pre- and post-measurement checks.

4. TRACTOR

4.1. Only the ancillary electrical equipment necessary for the running of the engine shall be operating.

4.2. The engine shall be at its normal operating temperature. During each measurement, the engine shall be operated as follows:

Number of cylinders	Method of measurement	
	Peak	Quasi-peak
One	Above idling	2 500 r.p.m.
More than one	Above idling	1 500 r.p.m.

4.3. Measurements shall not be made while rain is falling on the vehicle or within 10 minutes after rain has stopped.

5. ANTENNA

5.1. **Height**

The centre of the dipole shall be 3 m above the ground.

5.2. **Distance of measurement**

The horizontal distance from the antenna to the nearest metal part of the tractor shall be 10 m.

5.3. **Antenna location relative to tractor**

The antenna shall be placed successively on the left- and right-hand sides of the tractor at two positions of measurement, with the aerial parallel to the plane of symmetry of the tractor and in line with the engine. (See Appendix to this Annex).

5.4. **Antenna position**

At each of the measuring points, readings shall be taken with the dipole in a horizontal and in a vertical position. (See Appendix to this Annex).

5.5. **Readings**

The maximum of four readings shall be taken as the characteristic reading at the frequency at which the measurements were made.

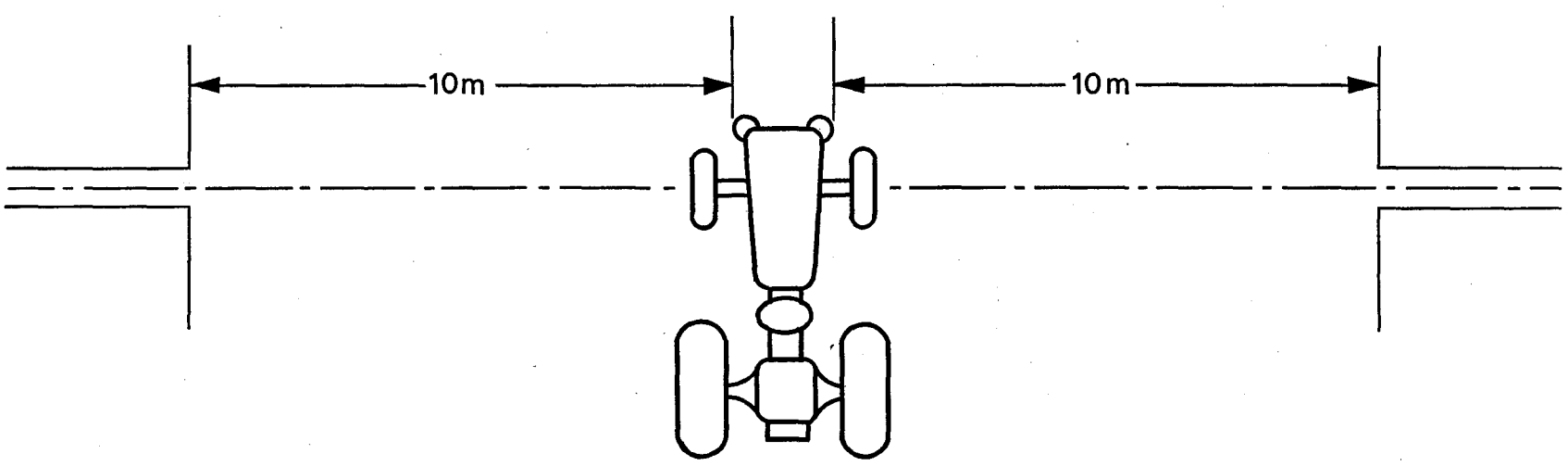
6. FREQUENCIES

Measurements shall be made within the 40 to 250 MHz range. A tractor is considered as very likely to meet the required suppression limits over the whole frequency range if it meets them at the following six frequencies: 45, 65, 90, 150, 180 and 220 ($\pm$ 5 MHz). (The 5 MHz tolerance for the six frequencies chosen should make it possible to avoid interference from transmissions operating on the nominal frequencies).

Appendix

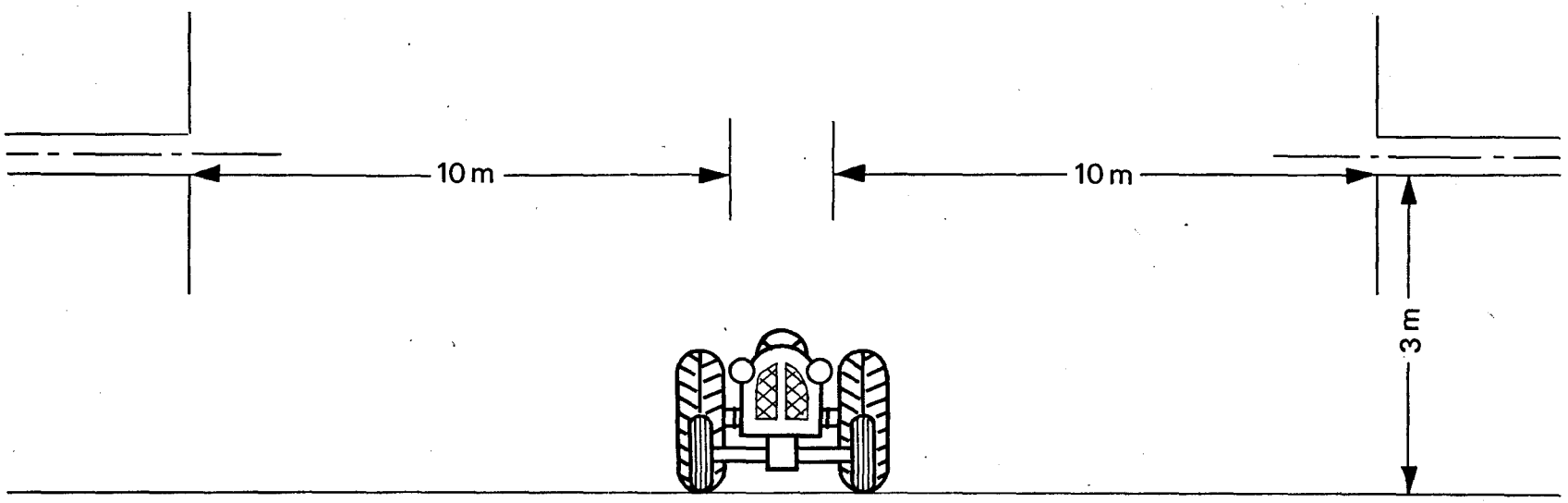
ANTENNA DIRECTION RELATIVE TO TRACTOR

Example



Plan

Dipole antenna in position to measure horizontal component of the radiation



Elevation

Dipole antenna in position to measure horizontal component of the radiation

ANNEX III

STATISTICAL METHOD OF CHECKING RADIO INTERFERENCE SUPPRESSION

In order to ensure with an 80 % probability that 80 % of the vehicles conform to a specified limit L, the following condition must be satisfied:

$$\bar{x} + kS_n \leq L$$

where $\bar{x}$ = arithmetic mean of the results on n tractors

k = statistical factor which depends on n as shown in the following table:

n = 6	7	8	9	10	11	12
k = 1·42	1·35	1·30	1·27	1·24	1·21	1·20

S_n = standard deviation of results on n tractors

$S_n 2 = \Sigma (x - \bar{x})^2 / (n - 1)$

x = individual result

L = specified limit

S_n , x, $\bar{x}$ and L expressed in dB (μV/m).

If a first sample of n tractors does not meet the specification, a second sample of n tractors shall be tested and the overall results assessed as coming from a sample of 2n tractors.

ANNEX IV

Name of administration

MODEL

COMMUNICATION CONCERNING THE APPROVAL OF AN AGRICULTURAL OR FORESTRY TRACTOR TYPE WITH REGARD TO RADIO INTERFERENCE SUPPRESSION

Type Approval No .....

1. Mark (Trade name) .....
2. Tractor type and commercial description .....

   .....
3. Name and address of manufacturer .....
4. If applicable, name and address of manufacturer's authorized representative .....

   .....
5. Brief description of the radio interference suppression equipment and of the tractor fitted with such equipment .....

   .....
6. Tractor submitted for type approval on .....
7. Technical service responsible for type approval tests .....

   .....
8. Date of report issued by that service .....
9. Number of report issued by that service .....
10. Type approval as regards radio interference suppression has been granted/refused (1)
11. Place .....
12. Date .....
13. Signature .....
14. The following documents, bearing the type approval number shown above, are annexed to this communication:

    ..... drawings, diagrams and plans of the engine and of the engine compartment;

    ..... photographs of the engine and of the engine compartment;

    ..... list of components, duly identified, constituting the radio interference suppression equipment.

(1) Delete whichever is inapplicable.

COUNCIL DIRECTIVE

of 20 May 1975

on the approximation of the laws of the Member States relating to the power connection fitted on wheeled agricultural or forestry tractors for lighting and light-signalling devices on tools, machinery or trailers intended for agriculture or forestry

(75/323/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 technical requirements with which tractors must comply pursuant to national laws relate, *inter alia,* to the power connection for lighting and light-signalling devices on tools, machinery or trailers;

Whereas these requirements differ from one Member State to another; whereas it is therefore necessary that all Member States adopt the same requirements either in addition to or in place of their existing rules, in particular to allow the EEC type approval procedure which was the subject of Council Directive 74/150/EEC (3) of 4 March 1974 on the approximation of the laws of the Member States relating to the type approval of wheeled agricultural or forestry tractors to be applied in respect of each type of tractor;

Whereas the technical requirements should be those adopted by the International Standards Organization in its recommendation ISO R/1724 — Electrical linkages for vehicles with 6 or 12V electrical equipment (First edition, April 1970),

HAS ADOPTED THIS DIRECTIVE:

Article 1

1. 'Agricultural or forestry tractor' means any motor vehicle fitted with wheels or caterpillar tracks and having at least two axles, the main function of which lies in its tractive power and which is specially designed to tow, push, carry or power certain tools, machinery or trailers intended for agricultural or forestry use. It may be equipped to carry a load and passengers.

2. This Directive shall apply only to tractors defined in the preceding paragraph which are fitted with pneumatic tyres and which have two axles and a maximum design speed of between 6 and 25 kilometres per hour.

Article 2

No Member State may refuse to grant EEC type approval or national type approval of a tractor on grounds relating to the power connection for lighting and light-signalling devices on tools, machinery or trailers if the tractor is fitted with a power connection which satisfies the requirements set out in the Annex.

Article 3

No Member State may refuse the registration or prohibit the sale, entry into service or use of tractors on grounds relating to the power connections for lighting and light-signalling devices on tools, machinery or trailers if the tractors are fitted with power connections which satisfy the requirements set out in the Annex.

Article 4

The amendments necessary for adapting the requirements of the Annex to technical progress shall

(1) OJ No C 160, 18. 12. 1969, p. 29.
(2) OJ No C 48, 16. 4. 1969, p. 21.
(3) OJ No L 84, 28. 3. 1974, p. 10.

be adopted in accordance with the procedure laid down in Article 13 of Directive 74/150/EEC.

Article 5

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

2. Member States shall ensure that the texts of the main provisions of national law which they adopt in the field covered by this Directive are communicated to the Commission.

Article 6

This Directive is addressed to the Member States.

Done at Brussels, 20 May 1975.

For the Council

The President

R. RYAN

ANNEX

The tractor must be equipped with a fixed socket with seven contacts in accordance with recommendation ISO R/1724, first edition, April 1970, allowing for a 12-volt power supply to the lighting and light-signalling devices on tools, machinery or trailers intended for agricultural or forestry use.

COUNCIL DIRECTIVE

of 20 May 1975

on the approximation of the laws of the Member States relating to aerosol dispensers

(75/324/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, in certain Member States, aerosol dispensers are required to comply with certain mandatory technical specifications; whereas such specifications differ from one Member State to another and, by so doing, hinder trade within the Community;

Whereas these barriers to the establishment and functioning of the common market can be removed if all the Member States adopt the same specifications, either in addition to or in place of those laid down in their present laws, and whereas these specifications must relate, more particularly, to the manufacture, filling and nominal capacities of aerosol dispensers;

Whereas, at the present stage of technical progress, the field of application of this Directive should be limited to aerosol dispensers made of metal, glass or plastic;

Whereas the technical specifications listed in the Annex to this Directive will need to be promptly adapted in line with technical progress; whereas, to facilitate the implementation of the appropriate necessary measures, a procedure should be laid down for close cooperation between the Member States and the Commission within a Committee on the adaptation to technical progress of the Directive on aerosol dispensers;

Whereas it is possible that some aerosol dispensers placed on the market may represent a safety risk even though they satisfy the requirements of this Directive and of the Annex thereto; whereas a procedure should therefore be laid down to obviate this risk,

HAS ADOPTED THE FOLLOWING DIRECTIVE :

Article 1

This Directive shall apply to aerosol dispensers as defined in Article 2, with the exception of those with a maximum capacity of less than 50 ml, and those with a maximum capacity greater than that specified in points 3.1, 4.1.1, 4.2.1, 5.1 and 5.2 respectively of the Annex to this Directive.

Article 2

For the purpose of this Directive, the term 'aerosol dispenser' shall mean any non-reusable container made of metal, glass or plastic and containing a gas compressed, liquefied or dissolved under pressure, with or without a liquid, paste or powder, and fitted with a release device allowing the contents to be ejected as solid or liquid particles in suspension in a gas, as a foam, paste or powder or in a liquid state.

Article 3

The person responsible for the marketing of aerosol dispensers shall affix the symbol '3' (inverted epsilon) to aerosol dispensers, as proof that they satisfy the requirements of this Directive and the Annex thereto.

Article 4

The Member States may not, for reasons related to the requirements laid down in this Directive and the Annex thereto, refuse, prohibit or restrict the marketing of any aerosol dispenser which complies with the requirements of this Directive and the Annex thereto.

(1) OJ No C 83, 11. 10. 1973, p. 24.
(2) OJ No C 101, 23. 11. 1973, p. 28.

Article 5

The amendments required to adapt to technical progress the Annex to this Directive shall be adopted according to the procedure laid down in Article 7.

Article 6

1. A committee on the adaptation to technical progress of the Directive on aerosol dispensers, hereinafter called the 'Committee', is hereby set up and shall consist of representatives of the Member States with a Commission representative as Chairman.

2. The Committee shall adopt its rules of procedure.

Article 7

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

2. The Commission representative shall submit to the Committee a draft of the measures to be taken. The Committee shall deliver its opinion on the draft within a period of two months. Opinions shall be adopted 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. (a) The Commission shall adopt the proposed measures where they are in accordance with the Opinion of the Committee.

(b) Where the proposed measures are not in accordance with the opinion of the Committee or if no opinion is delivered, the Commission shall without delay propose to the Council the measures to be adopted. The Council shall act by a qualified majority.

(c) If the Council has not acted within three months of the proposal's being submitted to it, the proposed measures shall be adopted by the Commission.

Article 8

1. Without prejudice to other Community Directives, in particular to Directives on dangerous substances and preparations, each aerosol dispenser or, where particulars cannot be put on the aerosol dispenser due to its small dimensions (maximum capacity of 150 ml or less) a label attached thereto must bear the following particulars in visible, legible and indelible characters:

(a) the name and address or trade mark of the person responsible for marketing the aerosol dispenser,

(b) the symbol '℮' (inverted epsilon) certifying conformity with the requirements of this Directive,

(c) code markings enabling the filling batch to be identified,

(d) the details referred to in point 2.2 of the Annex,

(e) the net contents by weight and by volume.

2. Member States may make the marketing of aerosol dispensers in their territory conditional on the use of their national language or languages for the wording on the label.

Article 9

Member States shall take all necessary measures to prevent the use on aerosol dispensers of markings or inscriptions which might be confused with the symbol '℮' (inverted epsilon).

Article 10

1. If a Member State notes, on the basis of a substantive justification, that one or more aerosol dispensers, although complying with the requirements of the Directive, represent a hazard to safety or health, it may provisionally prohibit the sale of the dispenser or dispensers in its territory or subject it or them to special conditions. It shall immediately inform the other Member States and the Commission thereof, stating the grounds for its decision.

2. The Commission shall, within six weeks, consult the Member States concerned, following which it shall deliver its opinion without delay and take the appropriate steps.

3. If the Commission is of the opinion that technical adaptations to the Directive are necessary, such adaptations shall be adopted by either the Commission or the Council in accordance with the procedure laid down in Article 7. In that case, the Member State having adopted safeguard measures may maintain them until the entry into force of the adaptations.

Article 11

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

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

Article 12

This Directive is addressed to the Member States.

Done at Brussels, 20 May 1975.

For the Council

The President

R. RYAN

ANNEX

1. DEFINITIONS

1.1. **Pressures**

'Pressures' means the internal pressures expressed in bars (relative pressures).

1.2. **Test pressure**

'Test pressure' means the pressure to which an unfilled aerosol dispenser container may be subjected for 25 seconds without any leakage being caused or, in the case of metal or plastic containers, any visible or permanent distortion except as allowed under 6.1.1.2.

1.3. **Bursting pressure**

'Bursting pressure' means the minimum pressure which causes the aerosol dispenser container to burst or rupture.

1.4. **Total capacity of the container**

'Total capacity of the container' means the volume in millilitres of an open container up to the rim of the opening.

1.5. **Net capacity**

'Net capacity' means the volume in millilitres of a filled and closed aerosol dispenser.

1.6. **Volume of liquid phase**

'Volume of liquid phase' means the volume of the non-gaseous phases in the filled and closed aerosol dispenser.

1.7. **Test conditions**

'Test conditions' means the values of test and bursting pressures exerted hydraulically at 20° C (± 5° C).

1.8. **Flammable contents**

'Flammable contents' means:

(a) gases which are flammable in air at normal pressure;

(b) substances and preparations in liquid form which have a flash point less than, or equal to, 100° C.

The method of determining the flash point is defined in Annex V to Council Directive 67/548/EEC [1] of 27 June 1967 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling, of dangerous substances, as last amended by Directive 73/146/EEC [2];

2. GENERAL PROVISIONS

2.1. **Construction and equipment**

2.1.1. The filled aerosol dispenser must be such that, under normal conditions of use and storage, it complies with the provisions of this Annex.

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[1] OJ No 196, 16. 8. 1967, p. 1.
[2] OJ No L 167, 25. 6. 1973, p. 1.

2.1.2. The valve must enable the aerosol dispenser to be virtually hermetically sealed under normal conditions of storage or transport and must be protected, for example by means of a protective cap, against any unintentional opening and any deterioration.

2.1.3. There must be no possibility that the mechanical resistance of the aerosol dispenser can be impaired by the action of the substances contained in it, even during prolonged storage.

2.2. **Inscriptions**

Without prejudice to the Directives relating to dangerous substances and preparations, each aerosol dispenser or its packing shall be marked clearly and legibly as follows:

(a) 'Pressurized container: protect from sunlight and do not expose to temperatures exceeding 50° C. Do not pierce or burn, even after use.';

(b) 'Do not spray on a naked flame or any incandescent material', unless the aerosol dispenser is designed for that purpose;

(c) 'Flammable' or the symbol of a naked flame if the contents include more than 45 % by weight, or more than 250 g of flammable components.

3. SPECIAL PROVISIONS FOR METAL AEROSOL DISPENSERS

3.1. **Capacity**

The total capacity of these containers may not exceed 1 000 ml.

3.1.1. *Test pressure of the container*

(a) For containers filled at a pressure of less than 6·7 bars at 50° C, the test pressure must be equal to at least 10 bars.

(b) For containers filled at a pressure equal to or greater than 6·7 bars at 50° C, the test pressure must be 50 % higher than the internal pressure at 50° C.

3.1.2. *Filling*

At 50° C, the pressure in the aerosol dispenser must not exceed 12 bars, whatever kind of gas is used for filling.

3.1.3. *Volume of the liquid phase*

The volume of the liquid phase at 50° C must not exceed 87 % of the net capacity. However, for containers with a concave base which becomes convex before bursting, the volume of the liquid phase at 50° C may be as much as 95 % of the net capacity.

4. SPECIAL PROVISIONS FOR GLASS AEROSOL DISPENSERS

4.1. **Plastic coated or permanently protected containers**

Containers of this type may be used for filling with compressed, liquefied or dissolved gas.

4.1.1. *Capacity*

The total capacity of such containers may not exceed 220 ml.

4.1.2. *Coating*

The coating must be a protective envelope of plastic or other suitable material, intended to prevent the risk of flying particles of glass if the container is accidently broken, and must be so designed that there are no flying particles of glass if the filled aerosol dispenser, brought to a temperature of 20° C, is dropped from a height of 1·8 m onto a concrete floor.

4.1.3. *Test pressure of the container*

(a) Containers used for filling with compressed or dissolved gas must resist a test pressure equal to at least 12 bars.

(b) Containers used for filling with liquefied gas must resist a test pressure equal to at least 10 bars.

4.1.4. *Filling*

(a) Aerosol dispensers filled with compressed gas shall not be required to withstand a pressure of more than 9 bars at 50° C.

(b) Aerosol dispensers filled with dissolved gas shall not be required to withstand a pressure of more than 8 bars at 50° C.

(c) Aerosol dispensers containing liquefied gas or mixtures of liquefied gas shall not be required to withstand, at 20° C, pressures higher than those shown in the following table:

Total capacity	Percentage by weight of liquefied gas in the total mixture		
	20 %	50 %	80 %
50 to 80 ml	3·5 bars	2·8 bars	2·5 bars
< 80 to 160 ml	3·2 bars	2·5 bars	2·2 bars
< 160 to 220 ml	2·8 bars	2·1 bars	1·8 bars

This table shows the pressure limits permitted at 20° C in relation to the percentage of gas.

Pressure limits for percentages of gas not shown in the table shall be extrapolated from it.

4.1.5. *Volume of the liquid phase*

At 50° C, thevolume of the liquid phase of a filled aerosol dispenser must not exceed 90 % of the net capacity.

4.2. **Unprotected glass containers**

Aerosol dispensers using unprotected glass containers shall be filled exclusively with liquefied or dissolved gases.

4.2.1. *Capacity*

The total capacity of these containers may not exceed 150 ml.

4.2.2. *Test pressure of the container*

The test pressure of the container must be equal to at least 12 bars.

4.2.3. *Filling*

(a) Aerosol dispensers filled with dissolved gas shall not be required to withstand a pressure of more than 8 bars at 50° C.

(b) Aerosol dispensers containing liquefied gas shall not be required to withstand, at 20° C, pressures in excess of those shown in the following table:

Total capacity	Percentage by weight of liquefied gas in the total mixture		
	20 %	50 %	80 %
50 to 70 ml	1·5 bar	1·5 bar	1·25 bar
< 70 to 150 ml	1·5 bar	1·5 bar	1 bar

This table shows the pressure limits permitted at 20° C in relation to the percentage of liquefied gas.

Pressure limits for percentages of gas not shown in the table shall be extrapolated from it.

4.2.4. *Volume of the liquid phase*

At 50° C, the volume of the liquid phase of an aerosol dispenser filled with liquefied or dissolved gas must not exceed 90 % of the net capacity.

5. SPECIAL PROVISIONS APPLYING TO PLASTIC AEROSOL DISPENSERS

5.1. Plastic aerosol dispensers which may splinter on bursting shall be treated in the same way as unprotected glass aerosol dispensers.

5.2. Plastic aerosol dispensers which cannot splinter on bursting shall be treated in the same way as glass aerosol dispensers with a protective coating.

6. TESTS

6.1. Test requirements to be guaranteed by the person responsible for marketing

6.1.1. *Hydraulic test on empty containers*

6.1.1.1. Metal, glass or plastic aerosol dispensers must be able to withstand a hydraulic pressure test as laid down in 3.1.1, 4.1.3 and 4.2.2.

6.1.1.2. Metal containers showing assymetrical or major distortions or other similar faults shall be rejected. A slight symmetrical distortion of the base or one affecting the profile of the upper casing shall be allowed provided that the container passes the bursting test.

6.1.2. *Bursting test for empty metal containers*

The person responsible for marketing must ensure that the bursting pressure of containers is at least 20 % higher than the test pressure laid down.

6.1.3. *Dropping test for protected glass containers*

The manufacturer must ensure that the containers satisfy the test requirements laid down in 4.1.2.

6.1.4. *Individual inspection of filled aerosol dispensers*

6.1.4.1. (a) Each filled aerosol dispenser shall be immersed in a bath of water. The temperature of the water and the period of immersion must be such as to enable:

— the contents of the aerosol dispenser to reach a uniform temperature of 50° C or

— the pressure in the aerosol dispenser to reach that exerted by its contents at a uniform temperature of 50° C.

(b) Any aerosol dispenser showing visible permanent distortion or a leak must be rejected.

6.1.4.2. However, any test system enabling a result equivalent to that of the water bath method to be obtained may be used by the person responsible for marketing, on his own responsibility and with the agreement of the Committee referred to in Article 6 of the Directive.

6.2. **Examples of inspection tests which may be carried out by Member States**

6.2.1. *Test on unfilled containers*

The test pressure shall be applied for 25 seconds on five containers selected at random from a homogeneous batch of 2 500 unfilled containers, i.e. manufactured from the same materials by the same continuous batch manufacturing process, or from a batch constituting one hour's production.

If any one of these containers does not pass the test, ten additional containers shall be drawn at random from the same batch and put through the same test.

If any one of these aerosol containers does not pass the test, the whole batch shall be unsuitable for use.

6.2.2. *Tests on filled aerosol dispensers*

Air and water-tightness inspection tests shall be carried out by immersing a representative number of filled aerosol dispensers in a bath of water. The temperature of the bath and the period of immersion must be such as to enable the contents of the aerosol dispenser to attain a uniform temperature of 50° C during the time required to ensure that there is no bursting or rupture.

Any batch of aerosol dispensers which does not pass these tests must be considered unsuitable for use.