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.