COUNCIL DIRECTIVE

of 28 September 1981

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 veterinary medicinal products

(81/852/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 (1),

Whereas the approximation begun by Council Directive 81/851/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to veterinary medicinal products (2) should continue and the principles laid down in that Directive should be implemented;

Whereas, among existing disparities, those relating to the control of veterinary medicinal products are of fundamental importance; whereas point 10 of the second paragraph of Article 5 of Directive 81/851/EEC requires that applications for authorization to place a veterinary 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 veterinary 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 and the compilation of dossiers;

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 obviate differences in evaluation;

Whereas the physico-chemical, biological or microbiological tests provided for in point 10 of the second paragraph of Article 5 of Directive 81/851/EEC are closely related to points 3, 4, 6 and 9 of the said paragraph; whereas it is necessary, therefore, to specify the data to be provided under those points;

Whereas the waiting period referred to in point 8 of the second paragraph of the said Article 5 of Directive 81/851/EEC must be determined in accordance with the results of the tests and trials provided for in point 10 thereof;

Whereas the concepts of harmfulness and therapeutic efficacy referred to in Article 11 of Directive 81/851/EEC can be examined only in relation to one another and have only a relative significance, depending on the progress of scientific knowledge and the use for which the medicinal product is intended; whereas the particulars and documents which must accompany an application for authorization to place a veterinary medicinal product on the market must demonstrate that potential hazards are outweighed by the therapeutic efficacy of the product; whereas, failing such demonstration, the application must be rejected;

Whereas it is the quality of the tests and trials which is pre-eminent; whereas the tests and trials carried out pursuant to these provisions must, therefore, be taken into consideration, irrespective of the nationality of the experts who perform them and of the country in which they are carried out,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Member States shall take all appropriate measures to ensure that the particulars and documents which shall accompany applications for authorization to place a veterinary medicinal product on the market, pursuant to points 3, 4, 6, 8, 9 and 10 of the second paragraph of Article 5 of Directive 81/851/EEC, are submitted by the persons concerned in accordance with the Annex to this Directive.

Where, pursuant to point 10 (a) or (b) of the second paragraph of Article 5 of the abovementioned Direc-

(1) OJ No C 152, 5. 7. 1976, p. 11.
(2) See page 1 of this Official Journal.

tive, references to published data are submitted, the provisions of this Directive shall apply in like manner.

Article 2

The Committee for Veterinary Medicinal Products referred to in Article 16 of Directive 81/851/EEC may examine any question relating to the application of this Directive.

Article 3

Member States shall bring into force the provisions necessary to comply with this Directive within 24 months following its notification and shall forthwith inform the Commission thereof.

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 4

This Directive is addressed to the Member States.

Done at Brussels, 28 September 1981.

For the Council
The President
P. WALKER

ANNEX

PART 1

ANALYTICAL (PHYSICO-CHEMICAL, BIOLOGICAL OR MICROBIOLOGICAL) TESTS OF VETERINARY MEDICINAL PRODUCTS

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

The particulars and documents which shall accompany applications for marketing authorization pursuant to point 3 of the second paragraph of Article 5 of Directive 81/851/EEC shall be submitted in accordance with the following requirements; if any amendments are made to these requirements for reasons of scientific progress, all grounds shall be stated.

1. Qualitative particulars of all the constituents of the medicinal product means the designation or description of:

   — the active ingredient(s),

   — the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring agents, preservatives, stabilizers, thickeners, emulsifiers, anti-agglutinating agents, flavouring and aromatic substances, propellents, etc.,

   — the constituents of the pharmaceutical form intended to be ingested or otherwise administered to animals.

   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 means, notwithstanding the application of the other provisions of point 3 of the second paragraph of Article 5 of Directive 81/851/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, which will be obligatory for all such substances, with a reference to the pharmacopoeia concerned,

   — in respect of other substances, the international non-proprietary name recommended by the WHO, which may be accompanied by another non-proprietary name, or, failing this, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement indicating how and from what they were prepared, together with any other necessary relevant details,

   — in respect of colouring matters, designation by the 'E' code assigned to them in Council Directive 78/25/EEC of 12 December 1977 on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products [1], as last amended by Directive 81/464/EEC [2].

3. In order to give 'quantitative particulars' of the active constituents of the medicinal product, 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 and with regard to the constituents of the excipient, the weight or the volume of each of them, with due allowance for the details provided in section B below.

   This information shall be supplemented:

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

   — in respect of syrups, emulsions, granule or 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, e.g. by stating the physiological effect on which the method of determining the dose is based.

(1) OJ No L 11, 14. 1. 1978, p. 18.
(2) OJ No L 183, 4. 7. 1981, p. 33.

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 the second paragraph of Article 5 of Directive 81/851/EEC shall be so drafted as to provide 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 which 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 tests to be necessary for quality control of the proprietary medicinal product.

C. CONTROL OF STARTING MATERIALS

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

The particulars and documents accompanying the application for marketing authorization pursuant to points 9 and 10 of the second paragraph of Article 5 of Directive 81/851/EEC must 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 9 of the second paragraph of Article 5 of Directive 81/851/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 shall be responsible.

Colouring matters shall, in all cases, satisfy the requirements of Directive 78/25/EEC.

The routine tests to be carried out on each batch of starting materials shall be declared in an application for authorization to market. These tests must make it possible to provide evidence that each batch of starting material satisfies the quality requirements of the relevant pharmacopoeial monograph.

Should a specification contained in a monograph of the European Pharmacopoeia or in the national pharmacopoeia of a Member State 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 point 2 of paragraph A, 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 shall, in such cases be accompanied by a brief indication of the method of synthetic preparation. Where substances can be described only by their method of preparation, the description shall be sufficiently detailed to characterize a substance which is constant in both its composition and its effects;

(c) 'Methods of identification' may be divided into complete techniques as used for the development of the medicinal product and 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, may adversely effect the stability of the medicinal product or distort analytical results.

(e) 'The assay technique(s)' shall be described in sufficiently precise detail 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, if necessary, be supplemented by a description of 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, justified in the lights of feasibility and the progress of scientific knowledge.

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

(f) 'Any special precautions which may be necessary during storage' of the starting material and, if necessary, its storage life shall be given.

D. CONTROL TESTS DURING MANUFACTURE

The particulars and documents which shall accompany an application for marketing authorization, pursuant to points 9 and 10 of the second paragraph of Article 5 of Directive 81/851/EEC, shall include particulars relating to the product control tests which 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 to verify the conformity of the 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 which are subject to the same requirements as the active ingredients).

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

E. CONTROL TESTS ON THE FINISHED PRODUCT

The particulars and documents which shall accompany the application for marketing authorization pursuant to points 9 and 10 of the second paragraph of Article 5 of Directive 81/851/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 be included among the tests on the finished product.

As a guideline, and subject to the possible 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 in point 5.

These tests shall relate, wherever necessary, 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 shall 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, to enable them to be reproduced readily, the methods used for identification and assay of the active ingredient(s) in either a representative average sample from the production batch or a number of dosage-units considered individually.

In every case, the methods shall correspond to the state of scientific progress at the time and give details and explanations of the standard errors, the reliability of the analytical method and the 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 then be supplemented, if possible, by a method of quantitative evalution, enabling the competent authorities to have the conformity of the medicinal product with its formula verified after it has been placed on the market.

An assay of biological activity is obligatory when physicochemical 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 medicinal product, the descrip-