II

(Acts whose publication is not obligatory)

COMMISSION

COMMISSION DIRECTIVE 92/18/EEC

of 20 March 1992

modifying the Annex to Council Directive 81/852/EEC on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community,

Having regard to Council Directive 81/852/EEC of 28 September 1981 on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products (1), as amended by Council Directive 87/20/EEC (2),

Having regard to Council Directive 90/677/EEC of 13 December 1990 extending the scope of Directive 81/851/EEC on the approximation of laws of the Member States relating to veterinary medicinal products, and laying down additional provisions for immunological veterinary medicinal products (3), and in particular Article 5 thereof,

Whereas following the adoption of Directive 90/677/EEC, it is necessary to amend the Annex to Directive 81/852/EEC in order to lay down special requirements for the testing of immunological veterinary medicinal products;

Whereas it is further necessary to adapt to technical progress the existing requirements laid down in the Annex to Directive 81/852/EEC;

Whereas the provisions of this Directive are in accordance with the opinion of the Committee on the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Veterinary Medicinal Products Sector established under Article 2b of Directive 81/852/EEC,

HAS ADOPTED THIS DIRECTIVE:

Article 1

The text of the Annex to Directive 81/852/EEC is hereby replaced by the text of the Annex to this Directive.

Article 2

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive no later than 1 April 1993. They shall forthwith inform the Commission thereof.

2. When the Member States adopt these provisions, the provisions shall contain a reference to this Directive or shall be accompanied by such a reference when they are published in official form. The arrangements for this reference shall be decided by Member States.

Article 3

This Directive is addressed to Member States.

Done at Brussels, 20 March 1992.

For the Commission
Martin BANGEMANN
Vice-President

(1) OJ No L 317, 6. 11. 1981, p. 16.
(2) OJ No L 15, 17. 1. 1987, p. 34.
(3) OJ No L 373, 31. 12. 1990, p. 26.

ANNEX

INTRODUCTION

The particulars and documents accompanying an application for marketing authorization pursuant to Article 5 of Council Directive 81/851/EEC (1) shall be presented in accordance with the requirements set out in this Annex and taking account of the guidance contained in the 'Notice to applicants for marketing authorizations for veterinary medicinal products in the Member States of the European Community', published by the Commission in *The rules governing medicinal products in the European Community,* volume V: *Veterinary Medicinal Products.*

In assembling the dossier for application for marketing authorization, applicants shall take into account the Community guidelines relating to the quality, safety and efficacy of veterinary medicinal products published by the Commission in *The rules governing medicinal products in the European Community.*

All information which is relevant to the evaluation of the medicinal product concerned shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned test or trial relating to the veterinary medicinal product. Moreover, after marketing authorization, any information not in the original application, pertinent to the benefit/risk assessment, shall be submitted forthwith to the competent authorities.

Member States ensure that all experiments on animals are conducted in accordance with Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (2).

The provisions of Title I of this Annex shall apply to veterinary medicinal products other than immunological veterinary medicinal products intended for administration to animals in order to produce active or passive immunity or to diagnose the state of immunity.

The provisions of Title II of this Annex shall apply to veterinary medicinal products intended for administration to animals to produce active or passive immunity or to diagnose the state of immunity, hereinafter referred to as 'immunological veterinary medicinal products'.

TITLE I

REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS OTHER THAN IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

PART 1

SUMMARY OF THE DOSSIER

A. ADMINISTRATIVE DATA

The veterinary medicinal product which is the subject of the application shall be identified by name and by name of the active ingredient(s), together with the strength and pharmaceutical form, the method and route of administration and a description of the final sales presentation of the product.

The name and address of the applicant shall be given, together with the name and address of the manufacturers and the sites involved in the different stages of the manufacture (including the manufacturer of the finished product and the manufacturer(s) of the active ingredient(s)), and where relevant the name and address of the importer.

The applicant shall identify the number and titles of volumes of documentation submitted in support of the application and indicate what samples, if any, are also provided.

Annexed to the administrative data shall be a document showing that the manufacturer is authorized to produce the veterinary medicinal products concerned, as defined in Article 24 of Directive 81/851/EEC, together with a list of countries in which authorization has been granted, copies of all the summaries of product characteristics in accordance with Article 5a of Directive 81/851/EEC as approved by Member States and a list of countries in which an application has been submitted.

B. SUMMARY OF PRODUCT CHARACTERISTICS

The applicant shall propose a summary of the product characteristics, in accordance with Article 5a of Directive 81/851/EEC.

In addition the applicant shall provide one or more specimens or mock-ups of the sales presentation of the veterinary medicinal product, together with a package insert where one is required.

C. EXPERT REPORTS

In accordance with Article 7 of Directive 81/851/EEC, expert reports must be provided on the analytical documentation, the pharmacotoxicological documentation, the residues documentation and the clinical documentation.

Each expert report shall consist of a critical evaluation of the various tests and/or trials which have been carried out in accordance with this Directive, and bring out all the data relevant for evaluation. The expert shall give his opinion as to whether sufficient guarantees have been provided as to the quality, safety and efficacy of the product concerned. A factual summary is not sufficient.

(1) OJ No L 317, 6. 11. 1981, p. 1.

(2) OJ No L 358, 18. 12. 1986, p. 1.

All important data shall be summarized in an appendix to the expert report, whenever possible in tabular or graphic form. The expert report and the summaries shall contain precise cross references to the information contained in the main documentation.

Each expert report shall be prepared by a suitably qualified and experienced person. It shall be signed and dated by the expert, and attached to the report shall be brief information about the educational background, training and occupational experience of the expert. The professional relationship of the expert to the applicant shall be declared.

PART 2

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

All test procedures shall correspond to the state of scientific progress at the time and shall be validated procedures; results of the validation studies shall be provided.

All the test procedure(s) shall 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. In the case of test procedures included in the *European Pharmacopoeia* or the pharmacopoeia of a Member State, this description may be replaced by a detailed reference to the pharmacopoeia in question.

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 5, second paragraph, of Directive 81/851/EEC shall be submitted in accordance with the following requirements.

1. **Qualitative particulars**

'Qualitative particulars' of all the constituents of the 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, adjuvants, stabilizers, thickeners, emulsifiers, flavouring and aromatic substances, etc,

— the constituents, intended to be ingested or otherwise administered to animals, of the outer covering of the medicinal products — capsules, gelatine capsules, etc.

These particulars shall be supplemented by any relevant data concerning the container and, where appropriate, its manner of closure, together with details of devices with which the medicinal product will be used or administered and which will be delivered with the product.

2. The 'usual terminology', to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions of point 3 of Article 5, second paragraph, 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, with reference to the pharmacopoeia concerned,

— in respect of other substances, the international non-proprietary name recommended by the World Health Organization (WHO), 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 Council Directive 78/25/EEC of 12 December 1977 on the approximation of the rules of the Member States concerning the colouring matters authorized for use in medicinal products [1].

3. **Quantitative particulars**

3.1. In order to give 'quantitative particulars' of the active ingredients of the medicinal products, it is necessary, depending on the pharmaceutical form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active ingredient.

Units of biological activity shall be used for substances which cannot be defined chemically. Where an International Unit of biological activity has been defined by the World Health Organization, this shall be used. Where no International Unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances.

Whenever possible, biological activity per units of mass or volume shall be indicated.

This information shall be supplemented:

— in respect of injectable preparations, by the mass or units of biological activity of each active ingredient in the unit container, taking into account the usable volume of the product, after reconstitution, where appropriate,

— in respect of medicinal products to be administered by drops, by the mass or units of biological activity of each active ingredient contained in the number of drops corresponding to 1 ml or 1 g of the preparation,

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

3.2. Active ingredients present in the form of compounds or derivatives shall be described quantitatively by their total mass, and if necessary or relevant, by the mass of the active entity or entities of the molecule.

[1] OJ No L 11, 14. 1. 1978, p. 18.

3.3. For medicinal products containing an active ingredient which is the subject of an application for marketing authorization in any Member State for the first time, the quantitative statement of an active ingredient which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity or entities in the molecule. All subsequently authorized medicinal products in the Member States shall have their quantitative composition stated in the same way for the same active ingredient.

4. **Development pharmaceutics**

An explanation shall be provided with regard to the choice of composition, constituents and container and the intended function of the excipients in the finished product. This explanation shall be supported by scientific data on development pharmaceutics. The overage, with justification thereof, shall be stated.

B. DESCRIPTION OF METHOD OF PREPARATION

The description of the method of preparation accompanying the application for marketing authorization pursuant to point 4 of Article 5, second paragraph, of Directive 81/851/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 finished 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; any overage shall be indicated and justified,

— 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 the quality control of the finished product,

— experimental studies validating the manufacturing process, where a non-standard method of manufacture is used or where it is critical for the product,

— for sterile products, details of the sterilization processes and/or aseptic procedures used.

C. CONTROL OF STARTING MATERIALS

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

In the case of:

— an active ingredient not described in the *European Pharmacopoeia* or in the pharmacopoeia of a Member State,

or

— an active ingredient described in the *European Pharmacopoeia* or in the pharmacopoeia of a Member State when prepared by a method liable to leave impurities not mentioned in the pharmacopoeial monograph and for which the monograph is inappropriate adequately to control its quality,

which is manufactured by a person different from the applicant, the latter may arrange for the detailed description of the manufacturing method, quality control during manufacture and process validation to be supplied directly to the competent authorities by the manufacturer of the active ingredient. In this case, the manufacturer shall however provide the applicant with all the data which may be necessary for the latter to take responsibility for the medicinal product. The manufacturer shall confirm in writing to the applicant that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing the applicant. Documents and particulars supporting the application for such a change shall be supplied to the competent authorities.

The particulars and documents accompanying the application for marketing authorization pursuant to points 9 and 10 of Article 5, second paragraph, of Directive 81/851/EEC shall include the results of the tests, including batch analyses particularly for active ingredients, relating to quality control of all the constituents used. These shall be submitted in accordance with the following provisions.

1.1. *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 Article 5, second paragraph, 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 controlled in the pharmacopoeia monograph these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described.

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

The routine tests carried out on each batch of starting materials must be as stated in the application for marketing authorization. If tests other than those mentioned in the pharmacopoeia are used, proof must be supplied that the starting materials meet the quality requirements of that pharmacopoeia.

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.

The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The person responsible for placing the product on the market shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.

In cases where a starting material is described neither in the *European Pharmacopoeia* nor in the pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia can be accepted; in such cases, the applicant shall submit a copy of the monograph accompanied where necessary by the validation of the test procedures contained in the monograph and by a translation where appropriate.

1.2. *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 definition of the substance, set down in a form similar to that used in the *European Pharmacopoeia,* shall be accompanied by any necessary explanatory evidence, especially concerning the molecular structure where appropriate; it must be accompanied by an appropriate description of the method of synthesis. Where substances can only be described by their method of preparation, the description shall be sufficiently detailed to characterize a substance which is constant both on its composition and in its effects;

(c) methods of identification 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 medicinal product or distort analytical results;

(e) 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) when materials of animal origin are used, measures to ensure freedom from potentially pathogenic agents shall be described;

(g) any special precautions that may be necessary during storage of the starting material and, if necessary, the maximum period of storage before retesting shall be given.

1.3. *Physico-chemical characteristics liable to affect bio-availability*

The following items of information concerning active ingredients, whether or not listed in the pharmacopoeias, shall be provided as part of the general description of the active ingredients if the bio-availability of the medicinal product depends on them:

— crystalline form and solubility coefficients,

— particle size, where appropriate after pulverization,

— state of solvation,

— oil/water coefficient of partition (1).

The first three indents are not applicable to substances used solely in solution.

2. Where source materials such as micro-organisms, tissues of either plant or animal origin, cells or fluids (including blood) of human or animal origin or biotechnological cell constructs are used in the manufacture of veterinary medicinal products, the origin and history of starting materials shall be described and documented.

The description of the starting material shall include the manufacturing strategy, purification/inactivation procedures with their validation and all in-process control procedures designed to ensure the quality, safety and batch to batch consistency of the finished product.

2.1. When cell banks are used, the cell characteristics shall be shown to have remained unchanged at the passage level used for the production and beyond.

2.2. Seed materials, cell banks, pools of serum and other materials of biological origin and, whenever possible, the source materials from which they are derived shall be tested for adventitious agents.

If the presence of potentially pathogenic adventitious agents is inevitable, the material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated.

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

The particulars and documents accompanying an application for marketing authorization, pursuant to points 9 and 10 of Article 5, second paragraph, of Directive 81/851/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 medicinal product with the formula when, exceptionally, an applicant proposes an analytical method 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.

(1) The competent authorities may also request the pK and pH values if they think this information is essential.