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.

E. CONTROL TESTS ON THE FINISHED PRODUCT

1. For the control of the finished product, a batch of a finished product comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilization operations or, in the case of a continuous production process, all the units manufactured in a given period of time.

The application for marketing authorization shall list those tests which are carried out routinely on each batch of finished product. The frequency of the tests which are not carried out routinely shall be stated. Release limits shall be indicated.

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 particulars relating to control tests on the finished product at release. They shall be submitted in accordance with the following requirements.

The provisions of the general monographs of the *European Pharmacopoeia,* or failing that, of a Member State, shall be applicable to all products defined therein.

If test procedures and limits other than those mentioned in the general monographs of the *European Pharmacopoeia,* or failing this, in the national pharmacopoeia of a Member State, are used, proof shall be supplied that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned.

1.1. *General characteristics of the finished product*

Certain tests of the general characteristics of a product shall always be included among the tests on the finished product. These tests shall, wherever applicable, relate to the control of average masses and maximum deviations, to mechanical, physical or microbiological tests, organoleptic characteristics, physical characteristics such as density, pH, refractive index, etc. For each of these characteristics, standards and tolerance limits shall be specified by the applicant in each particular case.

The conditions of the tests, where appropriate, the equipment/apparatus employed and the standards shall be described in precise details whenever they are not given in the *European Pharmacopoeia* or the pharmacopoeia of the Member States; the same shall apply in cases where the methods prescribed by such pharmacopoeias are not applicable.

Furthermore, solid pharmaceutical forms having to be administered orally shall be subjected to *in vitro* studies on the liberation and dissolution rate of the active ingredient or ingredients; these studies shall also be carried out where administration is by another means if the competent authorities of the Member State concerned consider this necessary.

1.2. *Identification and assay of active ingredient(s)*

Identification and assay of the active ingredient(s) shall be carried out either in a representative sample from the production batch or in a number of dosage-units analysed individually.

Unless there is appropriate justification, the maximum acceptable deviation in the active-ingredient content of the finished product shall not exceed ± 5% at the time of manufacture.

On the basis of the stability tests, the manufacturer must propose and justify maximum acceptable tolerance limits in the active-ingredient content of the finished product up to the end of the proposed shelf-life.

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 medicinal product with its specification verified after it has been placed on the market.

An *in vivo* or *in vitro* biological assay shall be obligatory when physico-chemical methods cannot provide adequate information on the quality of the product. Such an assy shall, whenever possible, include reference materials and statistical analysis allowing calculation of confidence limits. Where these tests cannot be carried out on the finished product, they may be performed at an intermediate stage, as late as possible in the manufacturing process.

Where the particulars given in section B show that a significant overage of an active ingredient is employed in the manufacture of the 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 and/or assay of the degradation products.

1.3. *Identification and assay of excipient constituents*

In so far as is necessary, the excipient(s) shall be subject at least to identification tests.

The test procedure proposed for identifying colouring matters must enable a verification to be made that such matters appear in the list annexed to Directive 78/25/EEC.

An upper and lower limit test shall be obligatory in respect of preserving agents and an upper limit test for any other excipient constituent liable to affect adversely physiological functions; an upper and lower limit test shall be obligatory in respect of the excipient if it is liable to affect the bio-availability of an active substance, unless bio-availability is guaranteed by other appropriate tests.

1.4. *Safety tests*

Apart from the toxico-pharmacological tests submitted with the application for marketing authorization, particulars of safety tests, such as sterility, bacterial endotoxin, pyrogenicity and 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.

F. STABILITY TEST

The particulars and documents accompanying the application for marketing authorization pursuant to points 6 and 9 of Article 5, second paragraph, of Directive 81/851/EEC shall be submitted in accordance with the following requirements.

A description shall be given of the investigations by which the shelf life, the recommended storage conditions and the specifications at the end of the shelf life proposed by the applicant have been determined.

In the case of pre-mixes for medicated feedingstuffs, information shall also be given as necessary on the shelf life of the medicated feedingstuffs manufactured from these pre-mixes in accordance with the recommended instructions for use.

Where a finished product requires reconstitution prior to administration, details of the proposed shelf life for the reconstituted product are required, supported by relevant stability data.

In the case of multi-dose vials, stability data shall be presented to justify a shelf life for the vial after it has been punctured for the first time.

Where a finished product is liable to give rise to degradation products, the applicant must declare these and indicate characterization methods and test procedures.

The conclusions shall contain the results of analyses, justifying the proposed shelf life under the recommended storage conditions and the specifications of the finished product at the end of the shelf life of the finished product under these recommended storage conditions.

The maximum acceptable level of degradation products at the end of shelf life shall be indicated.

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 3

SAFETY AND RESIDUES TESTING

The particulars and documents which shall accompany the application for marketing authorization pursuant to point 10 of the second paragraph of Article 5 of Directive 81/851/EEC shall be submitted in accordance with the requirements below.

Member States shall ensure that the tests are carried out in accordance with the provisions relating to good laboratory practice laid down by Council Directives 87/18/EEC (1) and 88/320/EEC (2).

A. Safety testing

CHAPTER I

PERFORMANCE OF TESTS

1. **Introduction**

The safety documentation shall show:

1. the potential toxicity of the medicinal product and any dangerous or undesirable effects which may occur under the proposed conditions of use in animals; these should be evaluated in relation to the severity of the pathological condition concerned;

2. the potential harmful effects to man of residues of the veterinary medicinal product or substance in foodstuffs obtained from treated animals and what difficulties these residues may create in the industrial processing of foodstuffs;

3. the potential risks which may result from the exposure of human beings to the medicinal product, for example during its administration to the animal;

4. the potential risks for the environment resulting from the use of the medicinal product.

All results shall be reliable and valid generally. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results. Additionally, clinicians shall be given information about the therapeutic potential of the product and about the hazards connected with its use.

In some cases it may be necessary to test the metabolites of the parent compound where these represent the residues of concern.

An excipient used in the pharmaceutical field for the first time shall be treated like an active ingredient.

2. **Pharmacology**

Pharmacological studies are of fundamental importance in clarifying the mechanisms by which the medicinal product produces its therapeutic effects and therefore pharmacological studies conducted in experimental and target species of animal should be included in Part 4.

However, pharmacological studies may also assist in the understanding of toxicological phenomena. Moreover, where a medicinal product produces pharmacological effects

(1) OJ No L 15, 17. 1. 1987, p. 29.
(2) OJ No L 145, 11. 6. 1988, p. 35.

in the absence of a toxic response, or at doses lower than those required to elicit toxicity, these pharmacological effects shall be taken into account during the evaluation of the safety of the product.

Therefore the safety documentation shall always be preceded by details of pharmacological investigations undertaken in laboratory animals and all relevant information observed during clinical studies in the target animal.

3. Toxicology

3.1. *Single-dose toxicity*

Single-dose toxicity studies can be used to predict:

— the possible effects of acute overdosage in the target species,

— the possible effects of accidental administration to humans,

— the doses which may usefully be employed in the repeat dose studies.

Single dose toxicity studies should reveal the acute toxic effects of the substance and the time course for their onset and remission.

These studies should normally be carried out in at least two mammalian species. One mammalian species may be replaced, if appropriate, by an animal species for which the medicinal product is intended. At least two different routes of administration should normally be studied. One of these may be the same as, or similar to, that proposed for the target species. If substantial exposure of the user of the medicinal product is anticipated, for example by inhalation or dermal contact, these routes should be studied.

In order to reduce the number and suffering of the animals involved, new protocols for single dose toxicity testing are continually being developed. Studies carried out in accordance with these new procedures when properly validated will be accepted, as well as studies carried out in accordance with established internationally recognized guidelines.

3.2. *Repeated-dose 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.

In the case of substances or medicinal products intended solely for use in animals which do not produce food for human consumption, a repeated dose toxicity study in one species of experimental animal will normally be sufficient. This study may be replaced by a study conducted in the target animal. The frequency and route of administration, and the duration of the study should be chosen having regard to the proposed conditions of clinical use. The investigator shall give his reasons for the extent and duration of the trials and the dosages chosen.

In the case of substances or medicinal products intended for use in food producing animals, the study should be conducted in at least two species, one of which should be a non-rodent. The investigator shall give his reasons for the choice of species, having regard to the available knowledge of the metabolism of the product in animals and man. The test substance shall be administered orally. The duration of the test shall be at least 90 days. The investigator shall clearly state and give his reasons for the method and frequency of administration and the length of the trials.

The maximum dose should normally be selected so as to bring harmful effects to light. The lowest dose level should not produce any evidence of toxicity.

Evaluation of the toxic effects shall be based on observation of behaviour, growth, haematology and physiological tests, especially those relating to the excretory organs, and also on autopsy reports and accompanying histological data. The choice and range of each group of tests depends on the species of animal used and the state of scientific knowledge at the time.

In the case of new combinations of known substances which have been investigated in accordance with the provisions of this Directive, the repeated-dose tests may, except where toxicity test have demonstrated potentiation or novel toxic effects, be suitably modified by the investigator, who shall submit his reasons for such modifications.

3.3. *Tolerance in the target species*

Details should be provided of any signs of intolerance which have been observed during studies conducted in the target species in accordance with the requirements of Part 4, Chapter I, Section B. The studies concerned, the dosages at which the intolerance occurred and the species and breeds concerned should be identified. Details of any unexpected physiological changes should also be provided.

3.4. *Reproductive toxicity including teratogenicity*

3.4.1. Study of the effects on reproduction

The purpose of this study is to identify possible impairment of male or female reproductive function or harmful effects on progeny resulting from the administration of the medicinal products or substance under investigation.

In the case of substances or medicinal products intended for use in food-producing animals, the study of the effects on reproduction shall be carried out in the form of a two-generation study on at least one species, usually a rodent. The substance or product under investigation shall be administered to males and females at an appropriate time prior to mating. Administration should continue until the weaning of the F2 generation. At least three dose levels shall be used. The maximum dose should be selected so as to bring harmful effects to light. The lowest dose level should not produce any evidence of toxicity.

Evaluation of the effects on reproduction shall be based upon fertility, pregnancy and maternal behaviour; the suckling,

growth and development of the F1 offspring from conception to maturity; the development of the F2 offspring to weaning.

3.4.2. Study of embryotoxic/fetotoxic effects including teratogenicity

In the case of substances or medicinal products intended for use in food producing animals, studies of embryotoxic/fetotoxic effects, including teratogenicity, shall be carried out. These studies shall be carried out in at least two mammalian species, usually a rodent and the rabbit. The details of the test (number of animals, doses, time at which administered and criteria for the evaluation of results) shall depend on the state of scientific knowledge at the time the application is lodged and the level of statistical significance which the results should attain. The rodent study may be combined with the study of effects on reproductive function.

In the case of substances or medicinal products which are not intended for use in food producing animals, a study of embryotoxic/fetotoxic effects, including teratogenicity, shall be required in at least one species, which may be the target species, if the product is intended for use in animals which might be used for breeding.

3.5. *Mutagenicity*

Mutagenicity tests are intended to assess the potential of substances to cause transmissible changes in the genetic material of cells.

Any new substance intended for use in veterinary medicinal products must be assessed for mutagenic properties.

The number and types of tests and the criteria for the evaluation of the results shall depend on the state of scientific knowledge when the application is submitted.

3.6. *Carcinogenicity*

Long term animal carcinogenicity studies will usually be required for substances to which human beings will be exposed

— which have a close chemical analogy with known carcinogens,

— which during mutagenicity testing produced results indicating a possibility of carcinogenic effects,

— which have given rise to suspect signs during toxicity testing.

The state of scientific knowledge at the time the application is submitted shall be taken into account when designing carcinogenicity studies and evaluating their results.

3.7. *Exceptions*

Where a medicinal product is intended for topical use, systemic absorption shall be investigated in the target species of animal. If it is proved that systemic absorption is negligible, the repeated dose toxicity tests, the tests for reproductive toxicity and the carcinogenicity tests may be omitted, unless:

— under the conditions of use laid down, oral ingestion of the medicinal product by the animal is to be expected, or

— the medicinal particular may enter foodstuffs obtained from the treated animal (intramammary preparations).

4. **Other requirements**

4.1. *Immunotoxicity*

Where the effects observed during repeated dose studies in animals include specific changes in lymphoid organ weights and/or histology and changes in the cellularity of lymphoid tissues, bone marrow or peripheral leukocytes, the investigator shall consider the need for additional studies of the effects of the product on the immune system.

The state of scientific knowledge at the time the application is submitted shall be taken into account when designing such studies and evaluating their results.

4.2. *Microbiological properties of residues*

4.2.1. Potential effects on the human gut flora

The microbiological risk presented by residues of anti-microbial compounds for the human intestinal flora shall be investigated in accordance with the state of scientific knowledge at the time the application is submitted.

4.2.2. Potential effects on the microorganisms used for industrial food processing

In certain cases, it may be necessary to carry out tests to determine whether residues cause difficulties affecting technological processes in industrial foodstuff processing.

4.3. *Observations in humans*

Information shall be provided showing whether the constituents of the veterinary medicinal product are used as medicinal products in human therapy; if this is so, a report should be made on all the effects observed (including side-effects) in humans and on their cause, to the extent that they may be important for the assessment of the veterinary medicinal product, where appropriate in the light of trial results of bibliographical documents; where constituents of the veterinary medicinal products are themselves not used or are no longer used as medicinal products in human therapy, the reasons should be stated.

5. **Ecotoxicity**

5.1. The purpose of the study of the ecotoxicity of a veterinary medicinal product is to assess the potential harmful effects which the use of the product may cause to the environment and to identify any precautionary measures which may be necessary to reduce such risks.

5.2. An assessment of ecotoxicity shall be compulsory for any application for marketing authorization for a veterinary medicinal product other than applications submitted in accordance with point 10 of Article 5, second paragraph, of Directive 81/851/EEC.

5.3. This assessment shall normally be conducted in two phases.

In the first phase, the investigator shall assess the potential extent of exposure to the environment of the product, its active ingredients or relevant metabolites, taking into account:

— the target species, and the proposed pattern of use (for example, mass-medication or individual animal medication),

— the method of administration, in particular the likely extent to which the product will enter directly into environmental systems,

— the possible excretion of the product, its active ingredients or relevant metabolites into the environment by treated animals; persistence in such excretia,

— the disposal of unused or waste product.

5.4. In a second phase, having regard to the extent of exposure of the product to the environment, and the available information about the physical/chemical, pharmacological and/or toxicological properties of the compound which has been obtained during the conduct of the other tests and trials required by this Directive, the investigator shall then consider whether further specific investigation of the effects of the product on particular eco-systems is necessary.

5.5. As appropriate, further investigation may be required of:

— fate and behaviour in soil,

— fate and behaviour in water and air,

— effects on aquatic organisms,

— effects on other non-target organisms.

These further investigations shall be carried out in accordance with the test protocols laid down in Annex V of Directive 67/548/EEC (1), at last amended by Commission Directive 91/632/EEC (2), or where an end point is not adequately covered by these protocols, in accordance with other internationally recognized protocols on the veterinary medicinal product and/or the active substance(s) and/or the excreted metabolites as appropriate. The number and types of tests and the criteria for their evaluation shall depend upon the state of scientific knowledge at the time the application is submitted.

CHAPTER II

PRESENTATION OF PARTICULARS AND DOCUMENTS

As in any scientific work, the dossier of safety tests shall include the following:

(a) an introduction defining the subject, accompanied by any useful bibliographical references;

(b) the detailed identification of the substance under review, including:

— international non-proprietary name (INN),

— International Union of Pure and Applied Chemistry Name (IUPAC),

— Chemical Abstract Service (CAS) number,

— therapeutical and pharmacological classification,

— synonyms and abbreviations

— structural formula,

— molecular formula,

— molecular weight,

— degree of impurity,

— qualitative and quantitative composition of impurities,

— description of physical properties,

— melting point,

— boiling point,

— vapour pressure,

— solubility in water and organic solvents expressed in g/l, with indication of temperature,

— density,

— spectra of refraction, rotation, etc;

(c) a detailed experimental protocol giving the reasons for any omission of certain tests listed above, a description of the methods, apparatus and materials used, details of the species, breed or 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 free from specific pathogens (SPF);

(d) all the 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, the results may be accompanied by illustrations;

(e) a statistical analysis of the results, where such is called for by the test programme, and variance within the data;

(f) an objective discussion of the results obtained, leading to conclusions on the safety of the substance, on its safety margin in the test animal and the target animal and its possible side-effects, on its fields of application, on its active dose levels and any possible incompatibilities;

(g) a detailed description and a thorough discussion of the results of the study of the safety of residues in food, and its relevance for the evaluation of potential risks presented by residues to humans. This discussion shall be followed by proposals to ensure that any danger to man is eliminated by applying internationally recognized assessment criteria, for example: no observed effect level in animals, proposals for a choice of safety factor and for acceptable daily intake (ADI);

(h) a thorough discussion of any risks for persons preparing the medicinal product or administering it to animals, followed by proposals for appropriate measures to reduce such risks;

(1) OJ No L 196, 16. 8. 1967, p. 1.
(2) OJ No L 338, 10. 12. 1991, p. 23.

(i) a thorough discussion of the risks which use of the veterinary medicinal product under the practical conditions proposed may represent for the environment followed by appropriate proposals to reduce such risks;

(j) all information necessary to acquaint the clinician as fully as possible with the utility of the proposed product. The discussion will be supplemented by suggestions as to side-effects and possible treatment for acute toxic reactions in animals to which the product is to be administered;

(k) a concluding expert report which provides a detailed critical analysis of the information referred to above in the light of the state of scientific knowledge at the time the application is submitted together with a detailed summary of all the results of the relevant safety tests and precise bibliographical references.

B. Residue testing

CHAPTER I

PERFORMANCE OF TESTS

1. Introduction

For the purposes of this Directive, 'residues' means all active ingredients or metabolites thereof which remain in meat or other foodstuffs produced from the animal to which the medicinal product in question has been administered.

The purpose of studying residues is to determine whether, and if so under what conditions and to what extent, residues persist in foodstuffs produced from treated animals and to ascertain the withdrawal periods to be adhered to in order to obviate any hazard to human health and/or difficulties in the industrial processing of foodstuffs.

Assessment of the hazard due to residues entails establishing whether residues are present in the animals treated under recommended conditions of use and investigating the effects of those residues.

In the case of veterinary medicinal products intended for use in food-producing animals, the residue documentation shall show:

1. to what extent, and how long, do residues of the veterinary medicinal product or its metabolites persist in the tissues of the treated animal or foodstuffs obtained therefrom;

2. that in order to prevent any risk to the health of the consumer of foodstuffs of treated animals, or difficulties in the industrial processing of foodstuffs, it is possible to establish realistic withdrawal periods which can be observed under practical farming conditions;

3. that practical analytical methods suitable for routine use are available to verify compliance with the withdrawal period.

2. Metabolism and residue kinetics

2.1. *Pharmacokinetics (absorption, distribution, biotransformation, excretion)*

The purpose of pharmacokinetic studies with respect to residues of veterinary medicinal products is to evaluate the absorption, distribution, biotransformation and excretion of the product in the target species.

The final product, or a formulation which is bioequivalent, shall be administered to the target species at the maximum recommended dose.

Having regard to the method of administration, the extent of absorption of the medicinal product shall be fully described. If it is demonstrated that systemic absorption of products for topical application is negligible, further residue studies will not be required.

The distribution of the medicinal product in the target animal shall be described; the possibility of plasma protein binding, or passage into milk or eggs and of the accumulation of lipophilic compounds shall be considered.

The pathways for the excretion of the product from the target animal shall be described. The major metabolites shall be identified and characterized.

2.2. *Depletion of residues*

The purposes of these studies, which measure the rate at which residues deplete in the target animal after the last administration of the medicinal product, is to permit the determination of withdrawal periods.

At varying times after the test animal has received the final dose of the medicinal product, the quantities of residues present shall be determined by appropriate physical, chemical or biological methods; the technical procedures and the reliability and sensitivity of the methods employed shall be specified.

3. Routine analytical method for the detection of residues

Analytical procedures shall be proposed which can be carried out in the course of a routine examination and which have a level of sensitivity such as to enable violations of legally permitted maximum residue limits to be detected with certainty.

The analytical method proposed shall be described in detail. It shall be validated and shall be sufficiently rugged for use under normal conditions of routine monitoring for residues.

The following characteristics shall be described:

— specificity,

— accuracy, including sensitivity,

— precision,

— limit of detection,

— limit of quantitation,

— practicability and applicability under normal laboratory conditions,

— susceptibility to interference.

The suitability of the analytical method proposed shall be evaluated in the light of the state of scientific and technical knowledge at the time the application is submitted.

CHAPTER II

PRESENTATION OF PARTICULARS AND DOCUMENTS

As in any scientific work, the dossier of residue tests shall include the following:

(a) an introduction defining the subject, accompanied by any useful bibliographical references;

(b) a detailed identification of the product, including:

— composition,

— purity,

— batch identification,

— relationship to the final product,

— specific activity and radio-purity of labelled substances,

— position of labelled atoms in the molecule;

(c) a detailed experimental protocol giving the reasons for any omission of certain tests listed above, a description of the methods, apparatus and materials used, details of the species, breed or strain of animals, where they were obtained, their number and the conditions under which they were housed and fed;

(d) all the 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. The results may be accompanied by illustrations;

(e) a statistical analysis of the results, where such is called for by the test programme, and variance within the data;

(f) an objective discussion of the results obtained, followed by proposals for maximum residue limits for the active substances contained in the product, specifying the marker residue and target tissues concerned, and proposals concerning the withdrawal periods necessary to ensure that no residues which might constitute a hazard for consumers are present in foodstuffs obtained from treated animals;

(g) a concluding expert report which provides a detailed critical analysis of the information referred to above in the light of the state of scientific knowledge at the time the application is submitted together with a detailed summary of the results of the residue tests and precise bibliographical references.

PART 4

PRE-CLINICAL AND CLINICAL TESTING

The particulars and documents which shall accompany applications for marketing authorizations pursuant to point 10 of the second paragraph of Article 5 of Directive 81/851/EEC shall be submitted in accordance with the provisions of Chapters I, II and III below.

CHAPTER I

PRE-CLINICAL REQUIREMENTS

Pre-clinical studies are required to establish the pharmacological activity and the tolerance of the product.

A. Pharmacology

A.1. *PHARMACODYNAMICS*

The study of pharmacodynamics shall follow two distinct lines of approach:

First, the mechanism of action and the pharmacological effects on which the recommended application in 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, in comparison with a substance the activity of which is well known. Where a higher efficacy is being claimed for an active ingredient, the difference shall be demonstrated and shown to be statistically significant.

Secondly, the investigator shall give an overall pharmacological assessment of the active ingredient, with special reference to the possibility of side-effects. In general, the main functions shall be investigated.

The investigator shall identify the effect of the route of administration, formulation, etc, on the pharmacological activity of the active ingredient.

The investigations shall be intensified where the recommended dose approaches that liable to produce effects.

The experimental techniques, unless they are standard procedures, shall be described in such detail as to allow them to be reproduced, and the investigator shall establish their validity. The experimental results shall be set out clearly and, for certain types of tests, 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 also be investigated.

Medicinal combinations may be prompted either on pharmacological grounds or by clinical indications. In the first case, the pharmacodynamic and/or pharmacokinetic studies shall demonstrate those interactions which might make the combination itself of value in clinical use. In the second case, where scientific justification for the medicinal combination is sought through clinical experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals and, at least, the importance of any side-effects shall be checked. If a combination includes a novel active substance, the latter shall have been previously studied in depth.

A.2. *Pharmacokinetics*

Basic pharmacokinetic information concerning a new active substance is generally useful in the clinical context.

Pharmacokinetic objectives can be divided into two main areas:

(i) descriptive pharmacokinetics leading to the evaluation of basic parameters such as body clearance, volume(s) of distribution, mean residence time, etc;

(ii) use of these parameters to investigate the relationships between dosage regimen, plasma and tissue concentration and pharmacologic, therapeutic or toxic effects.

In target species, pharmacokinetic studies are, as a rule, necessary in order to employ drugs with the greatest possible efficacy and safety. Such studies are especially useful to assist the clinician in establishing dosage-regimens (route and site of administration, dose, dosing interval, number of administrations, etc.) and to adopt dosage regimens according to certain population variables (e.g. age, disease). Such studies can be more efficient in number of animals and generally provide more information than classical dose titration studies.

In the case of new combinations of known substances which have been investigated in accordance with the provisions of this Directive, pharmacokinetic studies of the fixed combination are not required if it can be justified that the administration of the active ingredients as a fixed combination does not change their pharmacokinetic properties.

A.2.1. Bioavailability/bioequivalence

Appropriate bioavailability studies shall be undertaken to establish bioequivalence:

— when comparing a reformulated product with the existing one,

— when comparing a new method or route of administration with an established one,

— in all cases referred to in Article 5 second paragraph point 10 (i), (ii), and (iii) of Directive 81/851/EEC.

B. **Tolerance in the target species of animal**

The purpose of this study, which shall be carried out with all animal species for which the medicinal product is intended, is to carry out in all such animal species local and general tolerance trials designed to establish a tolerated dosage wide enough to allow an adequate safety margin and the clinical symptoms of intolerance using the recommended route or routes, in so far as this may be achieved by increasing the therapeutic dose and/or the duration of treatment. The report on the trials shall contain as many details as possible of the expected pharmacological effects and the adverse side-effects; the latter shall be assessed with due regard to the fact that the animals used may be of very high value.

The medicinal product shall be administered at least via the recommended route of administration.

C. **Resistance**

Data on the emergence of resistant organisms are necessary in the case of medicinal products used for the prevention or treatment of infectious diseases or parasitic infestations in animals.

CHAPTER II

CLINICAL REQUIREMENTS

1. **General principles**

The purposes of clinical trials are to demonstrate or substantiate the effect of the veterinary medicinal product after administration of the recommended dosage, to specify its indications and contra-indications according to species, age, breed and sex, its directions for use, any side-effects which it may have and its safety and tolerance under normal conditions of use.

Unless justified, clinical trials shall be carried out with control animals (controlled clinical trials). The effect obtained should be compared with a placebo or with absence of treatment and/or with the effect of an authorized medicinal product known to be of therapeutic value. All the results obtained, whether positive or negative, shall be reported.

The methods used to make the diagnosis shall be specified. The results shall be set out by making use of quantitative or conventional clinical criteria. Adequate statistical methods shall be used and justified.

In the case of a veterinary medicinal product intended primarily for use as a performance enhancer, particular attention shall be given to:

— the yield of animal produce,

— the quality of animal produce (organoleptic, nutritional, hygienic and technological qualities)

— nutritional efficiency and growth of animal,

— the general status of health of the animal.

Experimental data shall be confirmed by data obtained under practical field conditions.

Where, in respect of particular therapeutic indications, the applicant can show that he is unable to provide comprehensive data on therapeutic effect because:

(a) the indications for which the medicinal product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence;

(b) in the present state of scientific knowledge, comprehensive information cannot be provided;

the marketing authorization may only be granted subject to the following conditions;

(a) the medicinal product in question is to be supplied on veterinary prescription only and may, in certain cases, be administered only under strict veterinary supervision;

(b) the package insert and any other information must draw the attention of the veterinary practitioner to the fact that, in certain specified respects, the particulars available concerning the medicinal product in question are as yet incomplete.

2. **Performance of trials**

All veterinary clinical trials shall be conducted in accordance with a fully considered detailed trial protocol which shall be recorded in writing prior to commencement of the trial. The welfare of the trial animals shall be subject to veterinary supervision and shall be taken fully into consideration during the elaboration of any trial protocol and throughout the conduct of the trial.

Pre-established systematic written procedures for the organization, conduct, data collection, documentation and verification of clinical trials shall be required.

Before the commencement of any trial, the informed consent of the owner of the animals to be used in the trial shall be obtained and documented. In particular, the animal owner shall be informed in writing of the consequences of participation in the trial for the subsequent disposal of treated animals or for the taking of foodstuffs from treated animals. A copy of this notification, countersigned and dated by the animal owner, shall be included in the trial documentation.

Unless the trial is conducted with a blind design, the provisions of Articles 43 to 47 of Directive 81/851/EEC concerning the labelling of veterinary medicinal products shall apply by analogy to the labelling of formulations intended for use in veterinary clinical trials. In all cases, the words 'for veterinary clinical trial use only' shall appear prominently and indelibly upon the labelling.

CHAPTER III

PARTICULARS AND DOCUMENTS

As in any scientific work, the dossier on efficacy shall include an introduction defining the subject accompanied by any useful bibliographical documentation.

All pre-clinical and clinical documentation must be sufficiently detailed to enable an objective judgement to be made. All studies and trials must be reported, whether favourable or unfavourable to the applicant.

1. **Records of pre-clinical observations**

Wherever possible, particulars shall be given of the results of:

(a) tests demonstrating pharmacological actions;

(b) tests demonstrating the pharmacological mechanisms underlying the therapeutic effect;

(c) tests demonstrating the main pharmacokinetic processes.

Should unexpected results occur during the course of the tests, these should be detailed.

Additionally the following particulars shall be provided in all pre-clinical studies:

(a) a summary;

(b) a detailed experimental protocol giving a description of the methods, apparatus and materials used, details such as species, age, weight, sex, number, breed or strain of animals, identification of animals, dose, route and schedule of administration;

(c) a statistical analysis of the results where relevant;

(d) an objective discussion of the results obtained, leading to conclusions on the safety and efficacy of the product.

Total or partial omission of these data must be explained.

2.1. *Records of clinical observations*

All the particulars shall be supplied by each of the investigators on individual record-sheets in the case of individual treatment and collective record-sheets in the case of collective treatment.

The particulars supplied shall take the following form:

(a) name, address, function and qualifications of investigator in charge;

(b) place and date of treatment; name and address of owner of the animals;

(c) details of the trial protocol giving a description of the methods used, including methods of randomization and blinding, details such as the route of administration, schedule of administration, the dose, identification of trial animals, species, breeds or strains, age, weight, sex, physiological status;

(d) method of rearing and feeding, stating the composition of the feed and the nature and quantity of any additives contained in the feed;

(e) case history (as full as possible), occurrence and course of any inter-current diseases;

(f) diagnosis and means used to make it;

(g) symptoms and severity of the disease, if possible according to conventional criteria;

(h) the precise identification of the clinical trial formulation used in the trial;

(i) dosage of the medicinal product, method, route and frequency of administration and precautions, if any, taken during administration (duration of injection, etc.);

(j) duration of treatment and period of subsequent observation;

(k) all details concerning medicinal products (other than that under study) which have been administered during the period of examination, either prior to or concurrently with the test product and, in the latter case, details of the interactions observed;

(l) all results of the clinical trials (including unfavourable or negative results) with a full statement of the clinical observations and the results of the objective tests of activity (laboratory analyses, physiological tests), 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 the medication); demonstration of the pharmacodynamic effect in animals shall not in itself suffice to justify conclusions concerning any therapeutic effect;

(m) all particulars of any unintended effects, whether harmful or not, and of any measures taken in consequence; the cause-and-effect relationship shall be investigated if possible;

(n) effect of animals' performance (for example: egg-laying, milk production and reproductive function);

(o) effects on the quality of foodstuffs obtained from treated animals, particularly in the case of medicinal products intended for use as performance enhancers;

(p) a conclusion on each individual case or, where collective treatment is concerned, on each collective case.

Omission of one or more items (a) to (p) shall be justified.

The person responsible for placing the veterinary medicinal product on the market shall make all necessary arrangements to ensure that the original documents, which formed the basis of the data supplied, are kept for at least five years after the product is no longer authorized.

2.2. *Summary and conclusions of clinical observations*

In respect of each clinical trial, the clinical observations shall be summarized in a synopsis of the trials and the results thereof, indicating in particular:

(a) the number of controls, the number of animals treated either individually or collectively, with a breakdown according to species, breed or strain, age and sex;

(b) the number of animals withdrawn prematurely from the trials and the reasons for such withdrawal;

(c) in the case of control animals, whether they have:

— received no treatment;

— received a placebo,

— received another authorized medicinal product of known effect,

— received the active ingredient under investigation in a different formulation or by a different route;

(d) the frequency of observed side-effect;

(e) observations as to the effect on performance (for example, egg-laying, milk production, reproductive function and food quality);

(f) details concerning test animals which may be at increased risk owing to their age, their mode of rearing or feeding, or the purpose for which they are intended, or animals the physiological or pathological condition of which requires special consideration;

(g) a statistical evaluation of the results, when this is called for by the test programme.

Finally, the investigator shall draw general conclusions from the experimental evidence, expressing his opinion on the harmlessness of the medicinal product under the proposed conditions of use, its therapeutic effect and any useful information relating to indications and contra-indications, dosage and average duration of treatment and where appropriate, any interactions observed with other medicinal products or feed additives as well as any special precautions to be taken during treatment and the clinical symptoms of overdosage.

In the case of fixed combination products, the investigator shall also draw conclusions concerning the safety and the efficacy of the product when compared with the separate administration of the active ingredients involved.

3. **Concluding expert report**

The concluding expert report shall provide a detailed critical analysis of all the pre-clinical and clinical documentation in the light of the state of scientific knowledge at the time the application is submitted together with a detailed summary of the results of the tests and trials submitted and precise bibliographic references.

TITLE II

REQUIREMENTS FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Without prejudice to the specific requirements laid down by Community legislation for the control and eradication of animal desease, the following requirements shall apply to immunological veterinary medicinal products.

PART 5

SUMMARY OF THE DOSSIER

A. ADMINISTRATIVE DATA

The immunological veterinary medicinal product which is the subject of the application shall be identified by name and by name of the active ingredients, 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 adress of the manufacturer and the sites involved in the different stages of 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 copies of a document showing that the manufacturer is authorized to produce

immunological veterinary medicinal products, as defined in Article 24 of Directive 81/851/EEC (with a brief description of the production site). Moreover, the list of organisms handled at the production site shall be given.

The applicant shall submit 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 immunological 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 all aspects of the 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.

All important data shall be summarised 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 6

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

All test procedures used 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 immunological veterinary medicinal product shall mean the designation or description of:

   — the active ingredient(s),

   — the constituents of the adjuvants,

   — the constituent(s) of the excipients, whatever their nature or the quantity used, including preservatives, stabilizers, emulsifiers, colouring matter, flavouring, aromatic substances, markers, etc.,

   — the constituents of the pharmaceutical form administered to animals.

   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 immunological veterinary 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 immunological veterinary 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 of the monograph in question, which will be obligatory for all such substances, 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 Council Directive 78/25/EEC.

3. **Quantitative particulars**

   In order to give the 'quantitative particulars' of the active ingredients of an immunological veterinary medicinal product, it is necessary to specify whenever possible the number of organisms, the specific protein content, the mass, the number of International Units (IU) or units of biological activity, either per dosage-unit or volume, and with regard to the adjuvant and to

the constituents of the excipients, the mass or the volume of each of them, with due allowance for the details provided in section B below.

Where an International Unit of biological activity has been defined, this shall be used.

The units of biological activity for which no published data exist shall be expressed in such a way as to provide unambiguous information on the activity of the ingredients, eg. by stating the immunological effect on which the method of determining the dose is based.

4. **Development pharmaceutics**

An explanation shall be provided with regard to the composition, constituents and containers, supported by scientific data on development pharmaceutics. The overage, with justification thereof, shall be stated. The efficacy of any preservative system shall be demonstrated.

B. DESCRIPTION OF METHOD OF PREPARATION OF THE FINISHED PRODUCT

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 description of the nature of the operations employed.

For this purpose the description shall include at least:

— the various stages of manufacture (including purification procedures) so that an assessment can be made of the reproducibility of the manufacturing procedure and of the risks of adverse effects on the finished products, such as microbiological contamination,

— in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity and consistency of each batch of the finished product,

— mention of substances which cannot be recovered in the course of manufacture,

— the details of the blending, with the quantitative particulars of all the substances used,

— a statement of the stage of manufacture at which sampling is carried out for in-process control tests.

C. PRODUCTION AND CONTROL OF STARTING MATERIALS

For the purposes of this paragraph 'starting materials' means all components used in the production of the immunological veterinary medicinal product. Culture media used for the production of the active ingredient are considered as one single starting material.

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 the second paragraph of Article 5 of Directive 81/851/EEC shall include the results of the tests relating to quality control of all the components used and 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.

Components 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, 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.

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 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 or other provisions 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. For active ingredients, demonstration of the ability of the monograph adequately to control their quality shall be presented.

2. **Starting materials not in a pharmacopoeia**

2.1. *Starting materials of biological origin*

The description shall be given in the form of a monograph.

Whenever possible, vaccine production shall be based on a seed lot system and on established cell banks. For the production of immunological veterinary medicinal products consisting of serums, the origin, general health and immunological status of the producing animals shall be indicated; defined pools of source materials shall be used.

The origin and history of starting materials shall be described and documented. For genetically engineered starting materials this information shall include details such as the description of the starting cells or strains, the construction of the expression vector (name, origin, function of the replicon, promoter enhancer and other regulator elements), control of the sequence of DNA or RNA effectively inserted, oligonucleotidic sequences of plasmid vector in cells, plasmid used for cotransfection, added or deleted genes, biological properties of the final construct and the genes expressed, copy number and genetic stability.

Seed materials, including cell banks and raw serum for anti-serum production shall be tested for identity and adventitious agents.

Information shall be provided on all substances of biological origin used at any stage in the manufacturing procedure. The information shall include:

— details of the source of the materials,

— details of any processing, purification and inactivation applied, with data on the validation of these process and in-process controls,

— details of any tests for contamination carried out on each batch of the substance.

If the presence of adventitious agents is detected or suspected, the corresponding material shall be discarded or used in very exceptional circumstances only when further processing of the product ensures their elimination and/or inactivation; elimination and/or inactivation of such adventitious agents shall be demonstrated.

When cell banks are used, the cell characteristics shall be shown to have remained unchanged up to the highest passage level used for the production.

For live attenuated vaccines, proof of the stability of the attenuation characteristics of the seed has to be given.

When required, samples of the biological starting material or reagents used in the testing procedures shall be provided to enable the competent authority to arrange for check tests to be carried out.

2.2. *Starting materials of non-biological origin*

The description shall be given in the form of a monograph under the following headings:

— the name of the starting material meeting the requirements of point 2 of paragraph A shall be supplemented by any trade or scientific synonyms,

— the description of the starting material, set down in a form similar to that used in a descriptive item in the *European Pharmacopoeia,*

— the function of the starting material,

— methods of identification,

— purity 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 affect the stability of the medicinal product or distort analytical results. A brief description shall be provided of the tests undertaken to establish the purity of each batch of the starting material,

— 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 PRODUCTION

1. 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 control tests which are carried out on intermediate products with a view to verifying the consistency of the production process and the final product.

2. For inactivated or detoxified vaccines, inactivation or detoxification shall be tested during each production run immediately after the inactivation or detoxification process.

E. CONTROL TESTS ON THE FINISHED PRODUCT

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 particulars relating to control tests on the finished product. Where appropriate monographs exist, if test procedures and limits other than those mentioned in the monographs of the *European Pharmacopoeia,* or failing this, in the national pharmacopoeia of a Member State, are used, proof must be supplied that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned. The application for marketing

authorization shall list those tests which are carried out on representative samples of each batch of finished product. The frequency of the tests which are not carried out on each batch shall be stated. Release limits shall be indicated.

1. **General characteristics of the finished product**

Certain tests of the general characteristics of a product shall be included among the tests on the finished product, even if they have been carried out in the course of the manufacturing process.

These tests shall, wherever applicable, relate to the control of average masses and maximum deviations, to mechanical, physical, chemical or microbiological tests, physical characteristics such as density, pH, refractive index, etc. For each of these characteristics, specifications, with appropriate confidence limits, shall be established by the applicant in each particular case.

2. **Identification and assay of active ingredient(s)**

For all tests, the description of the techniques for analyzing the finished product shall be set out in sufficiently precise detail, so that they can be reproduced readily.

The assay of biological activity of the active ingredient(s) shall be carried out either in a representative sample from the production batch or in a number of dosage-units analysed individually.

Where necessary, a specific test for identification shall also be carried out.

In certain exceptional cases 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 as late as possible 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 verify that the immunological veterinary medicinal product is in accordance with its formula after it has been placed on the market.

3. **Identification and assay of adjuvants**

In so far as testing procedures are available, the quantity and nature of the adjuvant and its constituents shall be verified on the finished product.

4. **Identification and assay of excipient constituents**

In so far as is necessary, the excipient(s) shall be subject at least to identification tests.

The test procedure proposed for identifying colouring matters must enable a verification to be made that such matters are permitted under Directive 78/25/EEC.

An upper and lower limit test shall be obligatory in respect of preserving agents; an upper limit test for any other excipient constituent liable to give rise to an adverse reaction shall be obligatory.

5. **Safety tests**

Apart from the results of tests submitted in accordance with Part 7 of this Annex, particulars of safety tests shall be submitted. These tests shall preferably be overdosage studies carried out in at least one of the most sensitive target species and by at least the recommended route of administration posing the greatest risk.

6. **Sterility and purity test**

Appropriate tests to demonstrate the absence of contamination by adventitious agents or other substances shall be carried out according to the nature of the immunological veterinary medicinal product, the method and the conditions of preparation.

7. **Inactivation**

Where applicable, a test to verify inactivation shall be carried out on the product in the final container.

8. **Residual humidity**

Each batch of lyophilized product shall be tested for residual humidity

9. **Batch-to-batch consistency**

In order to ensure that efficacy of the product is reproducible from batch to batch and to demonstrate conformity with specifications, potency tests based upon *in vitro* or *in vivo* methods, including appropriate reference materials whenever available, shall be carried out on each final bulk or each batch of finished product, with appropriate confidence limits; in exceptional circumstances, potency testing may be carried out at an intermediate stage, as late as possible in the production process.

F. STABILITY TESTS

The particulars and documents accompanying the application for marketing authorization pursuant to points 6 and 9 of Article 5, second paragraph, of Directive 81/851/EEC shall be submitted in accordance with the following requirements.

A description shall be given of the tests undertaken to support the shelf life proposed by the applicant. These tests shall always be real-time studies; they shall be carried out on a sufficient number of batches produced according to the described production process and on products stored in the final container(s); these tests include biological and physico-chemical stability tests.

The conclusions shall contain the results of analyses, justifying the proposed shelf-life under all proposed storage conditions.

In the case of products administered in the feed, information shall also be given as necessary on the shelf-life of the product, at the different stages of mixing, when mixed in accordance with the recommended instructions.

Where a finished product requires reconstitution prior to administration, details of the proposed shelf-life are required for the

product reconstituted as recommended. Data in support of the proposed shelf-life for the reconstituted product shall be submitted.

PART 7

SAFETY TESTING

A. INTRODUCTION

1. The safety tests shall show the potential risks from the immunological veterinary medicinal product which may occur under the proposed conditions of use in animals: these shall be evaluated in relation to the potential benefits of the product.

   Where immunological veterinary medicinal products consist of live organisms, especially those which could be shed by vaccinated animals, the potential risk to unvaccinated animals of the same or of any other potentially exposed species shall be evaluated.

2. The particulars and documents which shall accompany the application for marketing authorization pursuant to point 10 of the second paragraph of Article 5 of Directive 81/851/EEC shall be submitted in accordance with the requirements of section B below.

3. Member States shall ensure that the laboratory tests are carried out in conformity with the principles of good laboratory practice laid down in Council Directives 87/18/EEC and 88/320/EEC.

B. GENERAL REQUIREMENTS

1. The safety tests shall be carried out in the target species.

2. The dose to be used shall be that quantity of the product to be recommended for use and containing the maximum titre or potency for which the application is submitted.

3. The sample used for safety testing shall be taken from a batch or batches produced according to the manufacturing process described in the application for marketing authorization.

C. LABORATORY TESTS

1. **Safety of the administration of one dose**

   The immunological veterinary medicinal product shall be administered at the recommended dose and by each recommended route of administration to animals of each species and category in which it is intended for use, including animals of the minimum age of administration. The animals shall be observed and examined for signs of systemic and local reactions. Where appropriate, these studies shall include detailed post-mortem macroscopic and microscopic examinations of the injection site. Other objective criteria shall be recorded, such as rectal temperature and performance measurements.

   The animals shall be observed and examined until reactions may no longer be expected, but in all cases, the observation and examination period shall be at least 14 days after administration.

2. **Safety of one administration of an overdose**

   An overdose of the immunological veterinary medicinal product shall be administered by each recommended route of administration to animals of the most sensitive categories of the target species. The animals shall be observed and examined for signs of systemic and local reactions. Other objective criteria shall be recorded, such as rectal temperature and performance measurements.

   The animals shall be observed and examined for at least 14 days after administration.

3. **Safety of the repeated administration of one dose**

   Repeated administration of one dose may be required to reveal any adverse effects induced by such administration. These tests shall be carried out on the most sensitive categories of the target species, using the recommended route of administration.

   The animals shall be observed and examined for at least 14 days after the last administration for signs of systemic and local reactions. Other objective criteria shall be recorded, such as rectal temperature and performance measurements.

4. **Examination of reproductive performance**

   Examination of reproductive performance shall be considered when data suggest that the starting material from which the product is derived may be a potential risk factor. Reproductive performance of males and non-pregnant and pregnant females shall be investigated with the recommended dose and by each of the recommended routes of administration. In addition, harmful effects on the progeny, as well as teratogenic and abortifacient effects, shall be investigated.

   These studies may form part of the safety studies described in paragraph 1 above.

5. **Examination of immunological functions**

   Where the immunological veterinary medicinal product might adversely affect the immune response of the vaccinated animal or of its progeny, suitable tests on the immunological functions shall be carried out.

6. **Special requirements for live vaccines:**

6.1. *Spread of the vaccine strain*

   Spread of the vaccine strain from vaccinated to unvaccinated target animals shall be investigated, using the recommended route of administration most likely to result in spread. Moreover, it may be necessary to investigate spread to non target species which could be highly susceptible to a live vaccine strain.

6.2. *Dissemination in the vaccinated animal*

   Faeces, urine, milk, eggs, oral, nasal and other secretions shall be tested for the presence of the organism. Moreover, studies may be required of the dissemination of the vaccine strain in the body, with particular attention being paid to the predilection

sites for replication of the organism. In the case of live vaccines for well established zoonotic diseases for food producing animals, these studies must be undertaken.

6.3. *Reversion to virulence of attenuated vaccines*

Reversion to virulence shall be investigated with material from the passage level which is least attenuated between the master seed and the final product. The initial vaccination shall be carried out using the recommended route of administration most likely to lead to reversion to virulence. At least five serial passages through animals of the target species shall be undertaken. Where this is not technically possible due to failure of the organism to replicate adequately, as many passages as possible shall be carried out in the target species. If necessary, *in vitro* propagation of the organism may be carried out between passages *in vivo*. The passages shall be undertaken by the route of administration most likely to lead to reversion to virulence.

6.4. *Biological properties of the vaccine strain*

Other tests may be necessary to determine as precisely as possible the intrinsic biological properties of the vaccine strain (e.g. neurotropism).

6.5. *Recombination or genomic reassortment of strains*

The probability of recombination or genomic reassortment with field or other strains shall be discussed.

7. **Study of residues**

For immunological veterinary medicinal products, it will normally not be necessary to undertake a study of residues. However, where adjuvants and/or preservatives are used in the manufacture of immunological veterinary medicinal products, consideration shall be given to the possibility of any residue remaining in the foodstuffs. If necessary, the effects of such residues shall be investigated. Moreover, in the case of live vaccines for zoonotic diseases, the determination of residues at the injection site may be required in addition to the studies described in paragraph 6.2 above.

A proposal for a withdrawal period shall be made and its adequacy shall be discussed in relation to any residue studies which have been undertaken.

8. **Interactions**

Any knwon interactions with other products shall be indicated.

D. FIELD STUDIES

Unless justified, results from laboratory studies shall be supplemented with supportive data from field studies.

E. ECOTOXICITY

The purpose of the study of the ecotoxicity of an immunological veterinary medicinal product is to assess the potential harmful effects which the use of the product may cause to the environment and to identify any precautionary measures which may be necessary to reduce such risks.

An assessment of ecotoxicity shall be compulsory for any application for marketing authorization for an immunological veterinary medicinal product other than applications submitted in accordance with point 10 of Article 5, second paragraph, of Directive 81/851/EEC.

This assessment shall normally be conducted in two phases.

The first phase of the assessment shall always be carried out: the investigator shall assess the potential extent of exposure of the environment to the product, its active ingredients, or relevant metabolites, taking into account:

— the target species and the proposed pattern of use (for example, mass medication or individual animal medication),

— the method of administration, in particular the likely extent to which the product will enter directly into environmental system,

— the possible excretion of the product, its active ingredients or relevant metabolites into the environment by treated animals, persistence in such excretia,

— the disposal of unused or waste product.

Where the conclusions of the first phase indicate potential exposure of the environment to the product, the applicant shall proceed to the second phase and evaluate the potential ecotoxicity of the product. For this purpose, he shall consider the extent and duration of exposure of the environment to the product, and the information about the physical/chemical, pharmacological and/or toxicological properties of the compound obtained during the conduct of the other tests and trials required by this Directive. Where necessary further investigations on the impact of the product (soil, water, air, aquatic systems, non-target organisms) shall be carried out.

These further investigations shall be carried out in accordance with the test protocols laid down in Annex V to Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances [1], as last amended by Commission Directive 91/632/EEC [2], or where an end point is not adequately covered by these protocols, in accordance with other internationally recognised protocols on the immunological veterinary medicinal product and/or the active substances and/or the excreted metabolites as appropriate. The number and types of tests and the criteria for their evaluation shall depend upon the state of scientific knowledge at the time the application is submitted.

PART 8

EFFICACY TRIALS

A. INTRODUCTION

1. The purpose of the trials described in this Part is to demonstrate or to confirm the efficacy of the immunological veterinary medicinal product. All claims made by the applicant with regard

[1] OJ No 196, 16. 8. 1967, p. 1.
[2] OJ No 338, 10. 12. 1991, p. 23.

to the properties, effects and use of the product shall be fully supported by results of specific trials contained in the application for marketing authorization.

2. The particulars and documents which shall accompany applications for marketing authorizations pursuant to point 10 of Article 5, second paragraph, of Directive 81/851/EEC shall be submitted in accordance with the provisions below.

3. All veterinary clinical trials shall be conducted in accordance with a fully considered detailed trial protocol which shall be recorded in writing prior to commencement of the trial. The welfare of the trial animals shall be subject to veterinary supervision and shall be taken fully into consideration during the elaboration of any trial protocol and throughout the conduct of the trial.

   Pre-established systematic written procedures for the organization, conduct, data collection, documentation and verification of clinical trials shall be required.

4. Before the commencement of any trial, the informed consent of the owner of the animals to be used in the trial shall be obtained and documented. In particular, the animal owner shall be informed in writing of the consequences of participation in the trial for the subsequent disposal of treated animals or for the taking of foodstuffs from treated animals. A copy of this notification, countersigned and dated by the animal owner, shall be included in the trial documentation.

5. Unless the trial is conducted with a blind design, the provisions of Articles 43 to 47 of Directive 81/851/EEC shall apply by analogy to the labelling of formulations intended for use in veterinary clinical trials. In all cases, the words 'for veterinary clinical trial use only' shall appear prominently and indelibly upon the labelling.

B. GENERAL REQUIREMENTS

1. The choice of vaccine strains shall be justified on the basis of epizoological data.

2. 'Efficacy trials carried out in the laboratory shall be controlled trials, including untreated control animals.

   In general, these trails shall be supported by trials carried out in field conditions, including untreated control animals.

   All trials shall be described in sufficiently precise details so as to be reproducible in control trials, carried out at the request of the competent authorities. The investigator shall demonstrate the validity of all the techniques involved. All results shall be presented as precisely as possible.

   All results obtained, whether favourable or unfavourable, shall be reported.

3. The efficacy of an immunological veterinary medicinal product shall be demonstrated for each category of each target species recommended for vaccination, by each recommended route of administration and using the proposed schedule of administration. The influence of passively acquired and maternally derived antibodies on the efficacy of a vaccine shall be adequately evaluated. Any claims regarding onset and duration of protection shall be supported by data from trials.

4. The efficacy of each of the components of multivalent and combined immunological veterinary medicinal products shall be demonstrated. If the product is recommended for administration in combination with or at the same time as another veterinary medicinal product, they shall be shown to be compatible.

5. Whenever a product forms part of a vaccination scheme recommended by the applicant the priming or booster effect or the contribution of the product to the efficacy of the scheme as a whole shall be demonstrated.

6. The dose to be used shall be that quantity of the product to be recommended for use and containing the minimum titre or potency for which the application is submitted.

7. The samples used for efficacy trials shall be taken from a batch or batches produced according to the manufacturing process described in the application for marketing authorization.

8. For diagnostic immunological veterinary medicinal products administered to animals, the applicant shall indicate how reactions to the product are to be interpreted.

C. LABORATORY TRIALS

1. In principle, demonstration of efficacy shall be undertaken under well controlled laboratory conditions by challenge after administration of the immunological veterinary medicinal product to the target animal under the recommended conditions of use. In so far as possible, the conditions under which the challenge is carried out shall mimic the natural conditions for infection, for example with regard to the amount of challenge organism and the route of administration of the challenge.

2. If possible, the immune mechanism (cell-mediated/humoral, local/general classes of immunoglobulin) which is initiated after the administration of the immunological veterinary medicinal product to target animals by the recommended route of administration shall be specified and documented.

D. FIELD TRIALS

1. Unless justified, results from laboratory trials shall be supplemented with data from field trials.

2. Where laboratory trials cannot be supportive of efficacy, the performance of field trials alone may be acceptable.

PART 9

PARTICULARS AND DOCUMENTS CONCERNING SAFETY TESTING AND EFFICACY TRIALS OF IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

A. INTRODUCTION

As in any scientific work, the dossier of safety and efficacy studies shall include an introduction defining the subject and indicating the tests which have been carried out in compliance with Parts 7 and 8,

as well as a summary, with references to the published literature. Omission of any tests or trials listed in Parts 7 and 8 shall be indicated and discussed.

B. LABORATORY STUDIES

The following shall be provided for all studies:

1. a summary;
2. the name of the body having carried out the studies;
3. a detailed experimental protocol giving a description of the methods, apparatus and materials used, details such as species, breed or strain of animals, categories of animals, where they were obtained, their identification and number, the conditions under which they were housed and fed (stating *inter alia* whether they were free from any specified pathogens and/or specified antibodies, the nature and quantity of any additives contained in the feed), dose, route, schedule and dates of administration, a description of the statistical methods used;
4. in the case of control animals, whether they received a placebo or no treatment;
5. all general and individual observations and results obtained (with averages and standard deviations), whether favourable or unfavourable. The data shall be described in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author. The raw data shall be presented in tabular form. By way of explanation and illustration, the results may be accompanied by reproductions of recordings, photomicrographs, etc.;
6. the nature, frequency and duration of observed side-effects;
7. the number of animals withdrawn prematurely from the studies and reasons for such withdrawal;
8. a statistical analysis of the results, where such is called for by the test programme, and variance within the data;
9. occurrence and course of any intercurrent disease;
10. all details concerning medicinal products (other than the product under study), the administration of which was necessary during the course of the study;
11. an objective discussion of the results obtained, leading to conclusions on the safety and efficacy of the product.

C. FIELD STUDIES

Particulars concerning field studies shall be sufficiently detailed to enable an objective judgment to be made. They shall include the following:

1. a summary;
2. name, address, function and qualifications of the investigator in charge;
3. place and date of administration, name and address of the owner of the animal(s);
4. details of the trial protocol, giving a description of the methods, apparatus and materials used, details such as the route of administration, the schedule of administration, the dose, the categories of animals, the duration of observation, the serological response and other investigations carried out on the animals after administration;
5. in the case of control animals, whether they received a placebo or no treatment;
6. identification of the treated and control animals (collective or individual, as appropriate), such as species, breeds or strains, age, weight, sex, physiological status;
7. a brief description of the method of rearing and feeding, stating the nature and quantity of any additives contained in the feed;
8. all the particulars on observations, performances and results (with averages and standard deviation); individual data shall be indicated when tests and measurements on individuals have been carried out;
9. all observations and results of the studies, whether favourable or unfavourable, with a full statement of the observations and the results of the objective tests of activity required to evaluate the product; the techniques used must be specified and the significance of any variations in the results explained;
10. effect on the animals' performances (e.g. egg laying, milk production, reproductive performance);
11. the number of animals withdrawn prematurely from the studies and reasons for such withdrawal;
12. the nature, frequency and duration of observed side-effects;
13. occurrence and course of any intercurrent disease;
14. all details concerning medicinal products (other than the product under study) which have been administered either prior to or concurrently with the test product or during the observation period; details of any interactions observed;
15. an objective discussion of the results obtained, leading to conclusions on the safety and efficacy of the product.

D. GENERAL CONCLUSIONS

General conclusions on all results of tests and trials carried out in compliance with Parts 7 and 8 shall be given. They shall contain an objective discussion of all the results obtained and lead to a conclusion on the safety and efficacy of the immunological veterinary medicinal product.

E. BIBLIOGRAPHICAL REFERENCES

The bibliographical references cited in the summary mentioned under item A shall be listed in detail.