COMMISSION OF THE EUROPEAN COMMUNITIES

COM(76) 189 final.

Brussels, 10 May 1976.

Proposal for a

COUNCIL DIRECTIVE

on the approximation of the laws of member states relating to veterinary medicinal products

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Proposal for a

COUNCIL DIRECTIVE

on the approximation of the laws of member states relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products

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(submitted to the Council by the Commission)

PROPOSAL FOR A COUNCIL DIRECTIVE ON THE APPROXIMATION OF THE LAWS OF MEMBER STATES RELATING TO VETERINARY MEDICINAL PRODUCTS

EXPLANATORY MEMORANDUM

1. General considerations

1. Medicinal products for veterinary use, like those for human therapy, are governed by different legal provisions from one Member State to another.

The need for Community rules is obvious from the economic point of view. Although the number of preparations is distinctly smaller than in human medicine - the proportion may be assessed at 1 to 10 - the consumption of and, therefore, the trade in these preparations are considerable. Stock-raising is becoming more and more industrialized. The concentration and intensification of stock-raising which results from this and the selection of highly productive breeds increase the risks of diseases and their economic consequences. With the achievement of the common agricultural market, the objectives of production, profitability, freedom of movement and undistorted competition have become vital in this field.

The need for rules is even more evident from the standpoint of public health. With the growing consumption of animal products, it is essential that the consumer of the treated animal should suffer no harm. At this time, when problems of quality are again claiming attention, it is hardly necessary to stress the benefit to health which rules in this field would confer.

2. This proposal for a directive is based on the principle that the requirements laid down for veterinary medicinal products should not be less stringent than those specified for pharmaceutical products for human use. This is in the interests of consumers of products of animal origin, who must suffer no harm, and also in the interests of effective therapy.

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That is why, wherever possible, the provisions concerning proprietary medicinal products for human use (1) have been taken across to this field. Nevertheless, in order to make allowance for problems peculiar to the veterinary field, it was necessary to add certain special provisions.

3. The scope of the directives relating to human use and that of this Directive do not coincide. The structures of the two markets are different. On the markets of certain countries, veterinary medicinal products are commercialized in the form of ready-made medicinal products and not proprietary medicinal products, in order to keep down the cost of packaging. For the same reasons international trade is carried on mainly in ready-made medicinal products.

In order to include most of the products entering into international trade it is therefore necessary to widen the scope of the Directive. This is also necessary for reasons of competition, since the strict regulation of one category of products would cause production to swing towards other less supervised categories, and this would ultimately be harmful to public health.

Another peculiarity of veterinary medicinal products is the danger of residues in animal products. It must be borne in mind that people may be harmed by ingesting products derived from animals to which medicinal products have been administered. This raises the questions of the persistence of the medicinal product, the route and duration of elimination, and the necessary waiting period between use of the medicinal product and consumption of the animal product. This problem of residues only arises in the case of products administered to animals which are likely to provide Man with food. Less stringent demands might therefore have been expected in the case of medicinal products administered to certain animal species, pets, for instance. It nevertheless seemed hazardous to create two separate categories of medicinal products in view of the corrupt and fraudulent practices which might have ensued and the problems of supervision which would then have arisen. It appeared wiser to allow certain waivers within the framework of the standards and protocols applicable to tests on veterinary medicinal products.

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(1) Council Directive No 65/65/EEC, OJ 22 of 0.2.1965
Council Directive No 75/318/EEC, OJ L 147 of 9.6.1975
Council Directive No 75/319/EEC, OJ L 147 of 9.6.1975

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4. The aim of this work on the approximation of laws is to introduce free movement of veterinary medicinal products while providing every safeguard for public health.

Having taken steps to safeguard public health at the product testing, manufacturing and marketing stage, the next problem which arose was that of the free movement of these products.

The introduction, at this stage, of freedom of movement might seem feasible since the position with regard to veterinary medicinal products is not identical with that of medicinal products for human use. The public health hazards may seem less serious, since the animal is used as an intermediary and therefore acts as a screen between the medicinal product and Man. Community rules adopted for agriculture have made it possible to ensure freedom of movement for agricultural products while securing the protection of public health.

These arguments were not devoid of weight but they clashed with other arguments concerning the need to progress by stages in a field which is closely related to health and is of prime importance for the economy of certain countries.

Instead of weighing up conflicting arguments which contribute nothing towards health and postpone free movement indefinitely, it appeared preferable to put forward more moderate proposals for introducing, in the case of veterinary medicinal products, the system of movement already adopted with regard to medicinal products for human use. This should enable the periods for the adoption and implementation of the texts to be shortened and hence make it possible to introduce free movement for veterinary medicinal products more rapidly than over-ambitious proposals would allow.

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II. Commentary on certain articles

Article 1

It goes without saying that the word "animal" refers to the whole of the animal kingdom and not merely to farm animals. New definitions to supplement those in Council Directive 65/65/EEC are necessary as the scope of the present Directive has been widened to make allowance for the special circumstances which prevail in this sector. Between the domain of the medicinal product defined by the Directive of 1965 and that of additives in feeding-stuffs, defined by Council Directive No 70/524 of 23 November 1970 (OJ No L 270 of 14 December 1970), there is a whole range of products that must be covered by the regulations if manufacturers are to be prevented from evading the requirements by marketing under uncontrolled forms.

The ready-made veterinary medicinal product differs from the proprietary medicinal product by the absence of a special name (trivial name). It has only a chemical name or an international non-proprietary name. Furthermore, it is not necessarily offered for sale in a special pack but may be supplied in bulk. It is specified that the ready-made product is marketed in a pharmaceutical form which may be used without further processing and it is therefore at this stage that authorization must be obtained for it.

The pre-mix for medicated feeds is defined fundamentally by its purpose: it is intended for ulterior use in a medicated feed. This is how it is distinguished from the ready-made product which may be used without further processing and is not intended for this ulterior use. On the other hand, a pre-mix is not necessarily a mixture: it is a medicinal preparation at the stage preceding mixing.

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In contrast, the medicated feed is a mixture of one or more medicinal preparations with one or more feeding-stuffs, made before marketing. It can be used without further processing and this distinguishes it from the pre-mix. Its therapeutic purpose differentiates it from the compound feeding-stuff.

Article 2

1. Apart from the economic goals to be reached, the chief concern was to ensure that substances harmful to Man are not administered to him via his food. A medicinal preparation is a product likely to be hazardous and must therefore be made subject to authorization irrespective of the way in which it will be employed subsequently. Aside from the economic considerations already mentioned, this is the reason which has led to the widening of the scope of this Directive as compared with the proposed directive on proprietary medicinal substances for human use.

2. On the other hand, the provisions of this Directive do not adequately cover certain specific cases (sera and vaccines, medicinal products based on radioactive isotopes) and it is advisable not to apply them to these products at present.

   Similarly, it was not considered advisable to make these provisions mandatory in the case of products which can have no effect on intra-Community trade, namely, veterinary medicinal products not prepared in advance; this refers to medicinal products which correspond to drugs prepared according to prescription in human medicine, i.e. medicinal products prepared by a veterinarian for one particular animal, following diagnosis.

   Finally, in order to make the present rules effective, it has been necessary to regulate one aspect of the manufacture of medicated feeding-stuffs [Article 2 (3)] pending rules applicable to medicated feeding-stuffs.

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Article 3

Paragraph 1 of this Article is wholly comparable to the provisions governing proprietary medicinal products for human use.

Paragraph 2 has been made necessary by the special situation which could arise in this sector;for a "parallel" market, subject to no supervision whatsoever, might emerge if the rule simple stated that any medicinal product placed on the market must be subject to prior authorization. It would be possible to get round the rules. The first step would be to procure, as a raw material, such and such a substance for which no prophylactic or curative properties are claimed; no authorization would be necessary since it would be a raw material and not a medicinal substance. Thereafter, the purchaser would employ this substance as medication for his own livestock; no authorization would be necessary since this medicinal product would not have been placed on the market as such.
Such a possibility would be unacceptable from the point of view of both public health and the economy.

It has therefore been necessary to go beyond the idea of marketing and to lay down an unqualified prohibition of administration to an animal of a medicinal product, in any form whatsoever, which has not been authorized pursuant to the provisions of this Directive. This provision assumes its full meaning if reference is made to the concept of a medicinal product as laid down in Article 1(2) of Council Directive No 65/65 of 26 January 1965.

It is very certain that such a provision gives rise to difficult problems of supervision. At the same,time, however, public authorities must be able to counter the corrupt practices which could stem from the purchase of substances not subject to the Directive's provisions and yet employed for a therapeutic purpose. If such practices are discovered they must be penalized; this justifies such a provision even if it is difficult to implement it.

An exception must be made in order to allow tests to be carried out on medicinal products for which authorization has not yet been granted.

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Article 4

Paragraph 5

The therapeutic indications must be taken in a broad sense: the "therapeutic effect" concept must be understood to be the effect promised by the manufacturer. Mutatis mutandis, the therapeutic indications cover the indications quoted for medicinal products alleged to possess curative or prophylactic properties and also those quoted for medicinal products intended for making a medical diagnosis or restoring, correcting or modifying physiological functions in animals.

Paragraph 6

The phrase "dosage for the various animal species for which the medicinal product is intended must be interpreted with common sense: if a different dose has to be administered to calves, cows, heifers etc., the dosage must of course be given for these sub-categories.

Paragraph 7

The person responsible for placing the product on the market must provide all necessary information concerning the precautions to be taken during use of the product in order to ensure the safety of the person administering it.

Article 10

It may be forbidden by law to use certain substances for particular purposes; an example is the use of oestrogens to fatten cattle. But if these substances exert a therapeutic effect, they must be allowed to qualify for authorization as medicinal products. In order to reconcile these requirements, authorization may be refused if the medicinal product is offered for sale, for a use prohibited under other Community provisions (Paragraph 3). On the other hand, this refusal would be rescinded if this possible use were no longer advertised.

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Article 11

1. In order to allow the marketing of medicinal products which are useful but which also present definite hazards, the authorization may entail the obligation to print the necessary warnings on the label and the package insert. The reference to clinical and pharmacological trials is designed to confer an objective character on this provision. The second paragraph of Article 13 enables the authorities to take account of items of information which emerge after the medicinal product is marketed and to reconsider the need to make warnings obligatory.

2. At present the question of tracer substances does not appear important enough to require a study at Community level of all tracer substances and of all medicinal products which must be tagged. Nevertheless it would be desirable for Member States not to specify different tracer substances. If joint consultation proved unsatisfactory and if this problem were to hamper freedom of movement, approximation measures would then be necessary. In any event, the manufacturer should be informed about the obligation to employ a tracer substance before and not after he determines the formula of his medicinal product.

Article 13

This Article makes it incumbent on the person responsible for placing the product on the market to modify his testing methods if an improvement in testing may result therefrom.

It also makes it incumbent on him to notify the competent authorities of any new factors which appear after the grant of marketing authorization:

- new factors over which the person responsible for marketing has no control, such as side-effects, interactions, contra-indications, etc. (second paragraph);

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- any new factors which result from its use: modifications in the composition, dosage, indications etc. (third paragraph). Naturally, in accordance with the provisions of the Directive, he will have to give the reasons for these proposed changes.

It did not appear to be necessary to specify the obligations of the competent authorities; they follow from the provisions of the Directive. The investigation measures which they will be led to take will depend on the new factors communicated by the person responsible and, in accordance with the national regulations, they will be led either to grant fresh authorization or to agree to the modification simply by a letter to the person responsible.

Article 16

In regard to the Committee for Veterinary Medicinal Products it is proposed to apply provisions based on those specified for the Committee for Proprietary Medicinal Products in Chapter III of Directive 75/319/EEC, for the reasons put forward in the General Considerations.

Article 23

It is proposed to apply all the provisions concerning manufacture and import from third countries, contained in Directive 75/319/EEC, to veterinary medicinal products. Moreover, it should be noted that veterinary medicine appears among the scientific discipline listed in Article 23 of Directive 75/319/EEC: an article which lays down the minimum qualifications required of persons who assume responsibility for the manufacture and testing controls of proprietary medicinal products for human use.

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Article 33

Paragraph 8

The expiration date has been made mandatory in all cases in order to ensure the correct use of medicinal products and to avoid wastage which may be caused by the absence of this item of information. In order not to give the user an unjustified feeling of security when the medicinal product, although not out-dated, may have decomposed owing to bad storage,conditions, the next paragraph makes it obligatory to mention any particular storage precautions that are necessary.

Article 35

In particular, this concerns capsules on which it would be difficult to print even the name.

Article 39

The package insert must, without exception, be included in the package of the veterinary medicinal product for the purpose of information and the correct use of the product. For example, the farmer must be informed concerning the significance of the waiting period. A certain number of items are needed so that the package insert may fulfil this object and these items must correspond to the information and documents supplied pursuant to Article 4 and verified by the competent authorities in accordance with Article 10.

On the other hand, the package insert must not contain any advertising matter; it must concern solely the medicinal product which it accompanies. In the interests of economy, this does not preclude mentioning the various forms of this medicinal product on one and the same package insert.

Similarly, the name of another medicinal product may be included on it if the marketing authorization prescribes such a reference pursuant to the first paragraph of Article 11. This would apply, for instance, to the antidote.

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Instructions for correct administration are necessary when the medicinal products are completely effective only in certain functional states of the organism (e.g. when fasting) or in certain stages of the disease (e.g. treatment of parasitoses) or in combination with certain concomitant measures (e.g. stimulation of circulation).

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THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100 thereof,

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Parliament,

Having regard to the Opinion of the Economic and Social Committee,

Whereas the primary purpose of any rules for the production and distribution of veterinary medicinal products must be the safeguarding of public health;

Whereas, however, this objective must be achieved by means which will not hinder the development of industry and trade in medicinal products within the Community;

Whereas, insofar as the Member States already have certain provisions laid down by law, regulation or administrative action governing veterinary medicinal products, such provisions differ in essential principles and whereas this results in the hindering of trade in medicinal products within the Community and thereby directly affects the establishment and functioning of the common market;

Whereas such hindrances must accordingly be removed; and whereas this entails approximation of the relevant provisions;

Whereas the provisions of this Directive which concern veterinary medicinal products are not adequate, although appropriate, for veterinary medicinal products used to confer active immunity, to diagnose the state of immunity and to confer passive immunity and for medicinal products based on radioactive isotopes; whereas it is therefore advisable not to prescribe their application to such products for the present;

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Whereas medicated feeding-stuffs do not come within the ambit of this Directive, but whereas it is necessary, as much for public health as economic reasons, to prohibit the use of unauthorized medicinal products in the manufacture of medicated feeding-stuffs;

Whereas marketing authorization shall be refused where a medicinal product lacks therapeutic effect or where there is insufficient proof of such effect promised by the manufacturers;

Whereas it is advisable, in order gradually to achieve freedom of movement of veterinary medicinal products, to facilitate the granting of marketing authorisations in several Member States for one and the same medicinal product;

Whereas, for this purpose, a Committee for Veterinary Medicinal Products should be set up, composed of representatives of the Member States and of the Commission, responsible for giving an opinion as to whether a particular veterinary medicinal product complies with the requirements set out in this Directive;

Whereas thisDirective is only one stage in the achievement of the aim of freedom of movement of veterinary medicinal products; whereas, for this purpose, new measures will prove necessary, in the light of experience gained [illegible], especially within the said Committee, for the removal of the remaining barriers to freedom of movement;

Whereas, in order to facilitate the movement of veterinary medicinal products and to prevent the checks carried out in one Member State from being repeated in another, minimum requirements for manufacture and imports from third countries and the grant of authorization relating thereto, should be applied to veterinary medicinal products, as specified in Council Directive 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products.

HAS ADOPTED THIS DIRECTIVE :

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(1) OJ No L 147, 9.6.1975, p. 13

Chapter I - Definitions and scope of application

Article 1

1. The definitions laid down in Article 1 of Council Directive No 65/65 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products[1] shall apply to this Directive.

2. Furthermore, for the purposes of this Directive, the following definitions shall apply
   - veterinary medicinal product shall mean any medicinal product intended for animals,
   - Ready-made veterinary medicinal product shall mean any veterinary medicinal product prepared in advance and marketed in a pharmaceutical form which may be used without further processing;
   - pre-mix for medicated feeding-stuffs shall mean any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feeding-stuffs,
   - medicated feeding-stuffs shall mean any mixture of a veterinary medicinal product or products and feed or feeds which is ready prepared for marketing and intended to be fed to animals without further processing, because of its curative or preventive proportion or other proportion of the medicinal substance covered by Article 1 (2) of the said Council Directive.

3. The additives incorporated in animal feeding-stuffs and the supplementary animal feeding-stuffs covered by Council Directive No 70/524 concerning additives in feeding-stuffs[2] shall, for the purposes of the present Directive, not be considered as medicinal products.

Article 2

1. The provisions of this Directive shall apply to veterinary medicinal products

(1) OJ No 22 of 9.2.1965, p. 20

(2) OJ No L 270 of 14.12.1970

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whether offered for sale in the form of proprietary medicinal products, ready-made veterinary medicinal products or pre-mixes.

2. The provisions of this Directive shall not apply to:

(a) medicated feeding-stuffs,

(b) veterinary medicinal products used with a view to producing active immunity, diagnosing the state of immunity and producing passive immunity,

(c) veterinary medicinal products based on radioactive isotopes,

(d) veterinary medicinal products not prepared in advance and intended for one particular animal.

3. However, pending separate provisions for medicated feeding-stuffs, a pre-mix shall not be used for the manufacture of medicated feeding-stuffs if it has not received the authorization referred to in Article 3.

Chapter II - Application for marketing authorization for veterinary medicinal products

Article 3

1. A veterinary medicinal product shall not be marketed in a Member State if authorization has not been previously issued by the competent authority of that Member State.

2. A veterinary medicinal product shall not be administered to animals if the authorization provided for in the preceding paragraph has not been issued, except where tests of medicinal products referred to in Article 4 (10) are concerned.

Article 4

For the purpose of obtaining the marketing authorization provided for in Article 3, the person responsible for placing the product on the market shall lodge an application with the competent authority of the Member State.

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The following particulars and documents shall be appended to this application:

1. name or corporate name and domicile or permanent address of the person responsible for placing the medicinal product on the market and, where applicable, of the manufacturer also ;

2. name of the medicinal product (trivial name, common name, with or without a trade mark or name of the manufacturer; scientific name or formula, with or without a trade mark or name of the manufacturer);

3. qualitative and quantitative particulars of all the components of the medicinal product expressed in the usual terms, but excluding empirical chemical formulae, with mention of the international non-proprietary name recommended by the World Health Organization , if such name exists;

4. brief description of the method of preparation;

5. therapeutic indications, contra-indications and side-effects;

6. dosage for the various species of animal for which the medicinal product is intended, its pharmaceutical form, method and means of administration and expected shelf life;

7. reasons for the precautionary and safety measures to be taken when using the medicinal product, if applicable;

8. indication of the necessary delay between the administration of the medicinal product to animals under normal conditions of use and the production of food stuffs from such animals, in order to ensure that such food does not contain any residues which might jeopardize the health of the consumer;

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9. Description of the testing methods employed by the manufacturer (qualitative and quantitative analysis of the components and the finished product, special tests, e.g. sterility tests, tests for the presence of pyrogenic substances, for the presence of heavy metals, biological and toxicity tests, tests on intermediate products);

10. Results of:

- physicochemical, biological or microbiological tests;
- toxicological and pharmacological tests;
- clinical trials.

The results of the toxicological and pharmacological tests shall relate more particularly to the metabolism of the active components in the animal and in particular to the mode and duration of their elimination, if such data are important for the purpose of checking the indicated delay;

Notwithstanding the foregoing,

a) a list of published references relating to the toxicological and pharmacological tests the clinical trials, and the data concerning the delay shall be substituted for the relevant test results in the case of:

i) a medicinal product with an established use, which has been adequately tested on animals so that its effects, including side-effects, are already known and are included in the published references;

ii) a new medicinal product, in which the active components are identical to those of a known medicinal product with an established use;

iii) a new medicinal product containing only known components that have already been used together in comparable proportions in adequately tested medicinal products with an established use;

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b) in the case of a new medicinal product containing known components not hitherto used together for therapeutic purposes, references to published data shall be substituted for the tests of such components;

11. one or more specimens or mock-ups of the sales presentation of the medicinal product together with a package insert;

12. a document showing that the manufacturer is authorized in his own country to produce medicinal products;

13. any authorization to place the relevant medicinal product on the market, which may have been obtained in another Member State or in a third country.

Article 5

Member States shall make all necessary arrangements to ensure that the documents and particulars listed in points 8, 9 and 10, of the second paragraph of Article 4, are drafted by experts with the requisite technical or professional qualifications before being submitted to the competent authorities. These documents and particulars shall be signed by the experts.

Article 6

According to their particular qualifications, the rôle of the experts shall be:

1. to carry out such work as falls within their particular discipline (analysis, pharmacology and similar experimental sciences, clinical trials) and to describe objectively the quantitative and qualitative results obtained;

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2. to describe their findings in accordance with Council Directive of ..... on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products, and in particular to state:

   a) in the case of analysts, whether the product conforms with the stated composition, providing any reasons for the testing methods which the manufacturer may use;

   b) in the case of pharmacologists or similarly qualified specialists,

      - the toxicity of the product and the pharmacological properties observed,

      - whether, after administration of the medicinal product under normal conditions of use and observance of the prescribed delay, food stuffs obtained from the treated animals contain residues which might constitute a health hazard to the consumer;

   c) in the case of clinicians, whether they have found effects in animals treated with the product corresponding to the information furnished by the manufacturer pursuant to Article 4, whether the product is well tolerated, what dosage they recommend and what are the contra-indications and side-effects, if any;

3. to give reasons for the use of the references to published data referred to in provisos a) and b) of item 10 in the second paragraph of Article 4, according to the conditions laid down by Council Directive of ..... on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products.

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The experts' detailed reports shall form part of the dossier which the applicant shall lodge with the competent authorities.

Chapter III - Instructions for application for authorization Authorization - Renewal of authorization

Article 7

Member States shall take all appropriate measures to ensure that the procedure for granting authorization to place a veterinary medicinal product on the market is completed within 120 days from the date of submission of the application.

In exceptional cases this time-limit shall be extended for a further 90 days. The applicant shall be notified of such extension before the expiry of the initial time-limit.

Article 8

In order to examine the application submitted pursuant to Article 4, the competent authorities of the Member States shall :

1. check that the particulars submitted in support of the application comply with the said Article 4 and, on the basis of the reports drawn up by the experts pursuant to Article 6, ascertain whether the conditions for the issue of the marketing authorization have been fulfilled;

2. submit the medicinal product for testing by a State laboratory or a laboratory designated for this purpose, in order to ensure that the testing methods of control employed by the manufacturer and described in the dossier, in accordance with iton 9 of the second paragraph of Article 4, are satisfactory;

3. where appropriate, require the applicant to supplement the dossier as regards the items listed in Article 4. Where the competent authorities avail themselves of this course of action, the time-limits specified

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in Article 7 shall be deferred until the supplementary data required have been provided. Similarly, these time-limits shall be deferred for the period allowed to the applicant, where appropriate, to explain himself orally or in writing.

Article 9

Member States shall take all appropriate measures in order that:

1. the competent authorities may ascertain that the manufacturers and importers of veterinary medicinal products from third countries are able to carry out manufacture in compliance with the details supplied pursuant to item 4 of the second paragraph of Article 4 and/or to carry out the tests in accordance with the methods described in the dossier under item 9 of the second paragraph of Article 4 ;

2. the competent authorities may authorize manufacturers and importers of veterinary medicinal products from third countries, in exceptional and justified cases, to have certain stages of manufacture and/or certain of the tests referred to in paragraph 1 carried out by third parties; in such cases the investigations by the competent authorities shall also be carried out in those establishments.

Article 10

The authorization provided for in Article 3 shall be withheld if, after examination of the documents and particulars listed in Article 4, it appears:

1. that the medicinal product is harmful as regards the conditions of use stated at the time of application for authorization, or that there is no therapeutic effect or insufficient proof thereof by the applicant as regards the species of animal which is to be treated, or that the qualitative or quantitative composition of the medicinal product is not as declared ;

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2. that the waiting period recommended by the applicant is not long enough to ensure that foodstuffs obtained from the treated animal do not contain residues which might jeopardize the health of the consumer, or is insufficiently substantiated;

3. that the medicinal product is offered for sale for a use prohibited under other Community provisions.

Authorization shall also be withheld if the dossier submitted to the competent authorities does not comply with Articles 4, 5 and 6.

Article 11

The grant of authurization provided for in Article 3 shall require the person responsible for placing the veterinary medicinal product on the market to indicate on the container and/or the outside wrapping and the package insert other particulars essential for safety or health protection , including any special precautions relating to use and any other warnings resulting from the clinical and pharmacological trials specified in item 10 of Article 4, or from experience gained during the use of the medicinal product once it has been marketed.

Authorization shall also require the inclusion of a tracer substance in the medicinal product.

Article 12

The granting of authorization shall not diminish the legal liability of the manufacturer and, where appropriate, of the person responsible for placing the veterinary medicinal product on the market.

Article 13

The person responsible for marketing shall accept the test method provided for in item 9 of article 4 in accordance with the advancement of technology and the progress of science if such adaptation ensures more reliable testing of the medicinal product.

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The person responsible for placing the veterinary medicinal product on the market shall forthwith inform the competent authorities of any new information which entails amendment of the particulars and documents referred to in Article 4 or additional examination, and more especially any prohibition or restriction prescribed by the competent authorities of the States in which the medicinal product is marketed.

The person responsible for placing the veterinary medicinal product on the market shall immediately inform the competent authorities of any alteration he proposes to make in the particulars and documents referred to in Article 4.

Article 14

Authorization shall be valid for five years and shall be renewable for five-year periods, on application by the holder within the three months preceding the date of expiry, in accordance with the previsions of Article 13.

Chapter IV - Committee for Veterinary Medicinal Products

Article 15

1. In order to facilitate the adoption of a common position by the Member States with regard to marketing authorizations, a Committee for Veterinary Medicinal Products, hereinafter called the "Committee", is hereby set up; it shall be composed of representatives of the Member States and of the Commission.

2. The Committee shall, when so requested by a Member State, examine questions relating to the implementation of Articles 10, 20 and 33, in accordance with Articles 16-21.

3. The Committee shalldraw up its own rules of procedure.

Article 16

1. The Member State which has issued a marketing authorization for a veterinary medicinal product shall transmit to the Committee a dossier containing a copy of this authorization together with the particulars and documents specified in the second paragraph of Article 4, if the person responsible for marketing has requested their transmission to at least five

other Member States.

2. The Committee shall forthwith transmit the dossier to the competent authorities of the specified Member States.

3. Such transmission shall be deemed to be equivalent to the submission of an application for marketing authorization to the said authorities within the meaning of Article 4.

Article 17

1. If, within a period of 120 days after the date of transmission referred to in Article 16 (2), no objection has been notified to the Committee by the competent authorities of the Member States specified, the Committee shall formally record the fact and forthwith inform the Member States concerned.

2. Where a Member State considers that it is unable to authorize the marketing of the veterinary medicinal product, it shall forward its reasoned objection, founded in Article 19 within the said period of 120 days.

Article 18

1. In the cases referred to in Article 17 (2), the Committee shall consider the matter and shall deliver its reasoned opinion within 60 days from the expiry of the time limit laid down in Article 17.

2. The opinion of the Committee shall deal with the compliance of the veterinary medicinal product with the conditions set out in Article 10.

The Committee shall forthwith inform the Member States concerned of its opinion or, in the event of dissension, of the opinions of its members.

3. The Member States concerned shall reach a decision on the application for marketing authorization not later than 30 days after the date on which the information provided for in Article 17 (1) or paragraph 2 hereof is given. They shall forthwith inform the Committee of their decision.

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Article 19

1. If several applications have been submitted in accordance with Article 4 for marketing authorization for the same veterinary medicinal product, and one or more Member States has granted such authorization while one or more of the other Member States have refused it, one of the Member States concerned may bring the matter before the Committee.

The same shall apply where one or more Member States have suspended or withdrawn marketing authorization while one or of the other Member States have not done so.

2. The Committee shall consider the matter and shall deliver its reasoned opinion within 120 days at the latest.

3. The opinion of the Committee shall only deal with the grounds on which authorization was refused, suspended or withdrawn.

The Committee shall forthwith inform the Member States concerned of its opinion on, in the event of dissension, of the opinions of its members.

4. The Member States concerned shall give notice, within 30 days, of the action they intend to take following the Committee's opinion.

Article 20

The Committee shall set a time limit for a fresh examination on the basis of particulars relating to the conditions laid down in Articles 10, 26 or 40 obtained in the meantime by Member States and in particular by those which have authorized the veterinary medicinal product.

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Article 21

The competent authorities of Member States shall, in specific cases where the interests of the Community are involved, refer the matter to the Committee before reaching a decision on an application for marketing authorization, its suspension or withdrawal.

Article 22

1. The Commission shall report to the Council annually on the operation of the procedure laid down in this Chapter and its effects on the development of intra-Community trade. It shall make its first report two years after the entry into force of this Directive.

2. In the light of experience the Commission shall, not later than four years after the entry into force of this Directive, submit to the Council a proposal containing appropriate measures leading to the abolition of any remaining barriers to the free movement of veterinary medicinal products still in existence.

The Council shall take a decision on the Commission proposal not later than one year after its submission.

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Chapter V - Manufacture and imports from third countries

Article 23

1. Member States shall take all appropriate measures to ensure that the manufacture and imports from third countries of veterinary medicinal products are subject to the holding of an authorization.

2. The provisions concerning manufacture and imports from third countries referred to in Chapter IV of the second Directive 75/319/EEC shall apply.

Chapter VI - Supervision and sanctions

Article 24

The competent authority of the Member State concerned shall ensure by means of inspection, that the legal requirements relating to veterinary medicinal products are complied with.

Such inspections shall be carried out by officials representing the competent authority who shall be empowered to :

1. Inspect manufacturing or commercial establishments and any laboratories entrusted by the holder of the authorization referred to in Article 23 (1) with the task of carrying out checks pursuant to Article 9 (2);

2. Take samples;

3. Examine any documents relating to the object of the inspection, subject to current provisions in the Member States at the time of notification of this Directive which place restrictions on these powers with regard to the description of the method of preparation.

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Article 25

Member States shall take all appropriate measures to ensure that the person responsible for marketing a veterinary medicinal product and, where appropriate, the holder of the authorization referred to in Article 23(1) furnish proof of the tests carried out on the finished product and/or on the components and intermediate products of the manufacturing process, in accordance with the methods laid down for the purposes of marketing authorization.

Article 26

The competent authorities of the Member States shall suspend or withdraw marketing authorization when it is clear that:

1. the medicinal product may be harmful under the conditions of use stated at the time of application for authorization or subsequently, or that the medicinal product lacks therapeutic effect or that its qualitative and quantitative composition is not as declared;

2. the recommended delay is inadequate to ensure that foodstuffs obtained from the treated animal do not contain residues which might endanger the health of the consumer;

3. the medicinal product is offered for sale for a use which is prohibited by other Community provisions;

4. the information given in the dossier pursuant to Articles 4 and 13 is incorrect;

5. the tests referred to in Article 25 have not been carried out;

6. the obligations referred to in the second paragraph of Article 11 have not been fulfilled.

The therapeutic effect is missing when it is established that the medicinal product cannot produce thereapeutic results in the species of animal for which the treatment is intended.

Authorization may also be suspended or withdrawn where :

.../...

- the particulars supporting the application, as provided for in Article 4, have not been amended in accordance with the first and third paragraphs of Article 13;

- any new information referred to in the second paragraph of Article 13 has not been communicated to the competent authorities.

Article 27

1. Notwithstanding the provisions of Article 26, Member States shall take all necessary measures to ensure that supply of the veterinary medicinal product is prohibited and that such medicinal product is withdrawn from the market where:

   a. it is clear that the medicinal product is harmful under the conditions of use stated at the time of the application for authorization or subsequently, pursuant to the third paragraph of Article 13;

   b. the medicinal product lacks therapeutic effect on the species of animal for which the treatment was intended;

   c. the qualitative and quantitative composition of the medicinal product is not as declared;

   d. the recommended delay is inadequate to ensure that foodstuffs obtained from the treated animal do not contain residues which might endanger the health of the consumer;

   e. the tests referred to in Article 25 have not been carried out or where another requirement or obligation relating to the grant of the authorization referred to in Article 23(1) has not been complied with.

2. The competent authority may confine its order prohibiting supply and the withdrawal from the market solely to manufacturing batches over which there is a dispute.

.../...

Article 28

1. The competent authority of a Member State shall suspend or withdraw the authorization referred to in Article 23 for a category of preparations or for all preparations when one of the requirements laid down for the obtaining of this authorization is no longer met.

2. The competent authority of a Member State may, in addition to the measures set out in Article 27, either suspend manufacture or imports of veterinary medicinal products from third countries or suspend or withdraw the authorization referred to in Article 23 for a category of preparations or for all preparations in the event of non-observance of the provisions regarding manufacture or imports from third countries.

Article 29

Member States shall take all appropriate measures to ensure that the competent authorities concerned communicate to each other such information as is appropriate to secure compliance with the requirements for the authorization referred to in Article 23 (1) or for marketing authorization.

Article 30

All decisions taken pursuant to Articles 10, 26 and 27, all negative decisions taken pursuant to Articles 9(12) and 18(3) of this Directive and all decisions to withhold authorization to manufacture or to import from third countries or to suspend or withdraw manufacturing authorization shall state in detail the reasons on which they are based. Such decisions shall be notified to the party concerned who shall at the same time be informed of the remedies available to him under current legislation and the time-limit within which such remedies must be sought.

Authorizations to place veterinary medicinal productson the market and decisions to revoke such authorizations shall be published by each Member State in its official gazette.

.../...

Article 31

Decisions to grant authorization to market, withhold, suspend or withdraw authorization, to prohibit supply, to withdraw a product from the market or to suspend manufacture or imports from third countries of veterinary medicinal products shall only be taken on the grounds set out in this Directive.

Article 32

Each Member State shall take all appropriate measures to ensure that decisions authorizing marketing, refusing or withdrawing a marketing authorization, cancelling a decision refusing or withdrawing marketing authorization, prohibiting supply or withdrawing a product from the market, together with the reasons on which such decisions are based, are brought to the attention of the Committee forthwith.

.../...

Chapter VII - Labelling and package inserts in the packaging of veterinary medicinal products

Article 33

The following particulars shall appear in legible characters on containers and outer packages of medicinal products:

1. Name of the medicinal product, which may be a trivial name or a common name with or without a trade mark or name of the manufacturer or a scientific name or formula with or without a trade mark or name of the manufacturer.

2. Next to the name of the medicinal product, its qualitative and quantitative composition expressed in active components per dose-unit or as a percentage, according to the pharmaceutical form and, in addition in the cases referred to in the second paragraph of Article 11 the tracer substances.

   The international non-proprietary names recommended by the World Health Organization shall be used wherever they exist.

3. Reference number for production identification (manufacturer's batch number).

4. Number of the authorization for placing the veterinary medicinal product on the market.

5. Name or corporate name and permanent address or headquarters of the person responsible for placing the veterinary medicinal product on the market and, where applicable, of the manufacturer also.

6. The species of animal for which the medicinal product is intended ; the method and means of administration.

7. Delay, if any.

.../...

8. Date of expiry.

9. Special storage precautions, if any.

10. The particulars laid down in the first paragraph of Article 11, if necessary.

11. The words "For veterinary use".

The pharmaceutical form and the contents by weight, volume or number of dose-units need only be shown on the outer package .

The provisions of the Annex, Part 1, A to Council Directive of.....on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products in so far as they concern the active components of veterinary medicinal products described qualitatively and quantitatively shall apply to the particulars given in point 2. Article 34

As regards ampoules, the particulars listed in the first paragraph of Article 33 shall be given on the outer package . On the actual containers, however, only the following particulars shall be necessary:

- name of the medicinal product,
- quantity of active substances,
- means of administration
- reference number for production identification (manufactuer's batch number)
- date of expiry
- the words "For veterinary use".

.../...

Article 35

As regards small single-dose containers, other than ampoules, on which it is impossible to give the particulars mentioned in Article 34, the requirements of Article 33 shall apply only to the outer package.

Article 36

As regards narcotics, in addition to the particulars mentioned in Article 33, both the outer package and the container shall bear a special sign consisting of a double red line.

Article 37

Where there is no outer package, all the particulars which should feature on such package pursuant to the preceding Articles shall be shown on the container.

Article 38

The particulars mentioned in items 6,7,8,9, 10 and 11 of the first paragraph of Article 33 and in the 3rd and 6th indents of Article 34 shall appear on the outer package and on the container of medicinal products in the language or languages of the country in which they are being placed on the market.

Article 39

Member States shall take all appropriate measures to ensure that the package insert which must be included in the package of a veterinary medicinal product relates solely to that medicinal product.

The package insert shall contain only the following particulars, which shall conform with the information and documents provided pursuant to Article 4 and which have been approved by the competent authorities:

.../...

a) Name or corporate name and permanent address or headquarters of the person responsible for placing the veterinary medicinal product on the market and, where applicable, of the manufacturer also ;

b) Name of the medicinal product and a statement of its active components expressed qualitatively and quantitatively.

The international non-proprietary names recommended by the World Health Organization shall be used wherever they exist.

c) The main therapeutic indications, contra-indications and side-effects in so far as these particulars are necessary for the use of the medicinal products ;

d) The species of animal for which the medicinal product is intended, the dosage suitable for this species, the method and means of administration and advice on correct administration, if necessary;

e) If necessary, all details concerning the delay ;

f) Special storage precautions, if necessary;

g) The particulars required by the first paragraph of Article 11, if necessary.

Article 40

Where the provisions of this Chapter are not observed and a formal notice addressed to the person concerned has been ineffective, the competent authorities of the Member States may suspend or withdraw the authorization to place the veterinary medicinal product on the market.

All decisions taken by virtue of the preceding paragraph shall state in detail the reasons on which they are based. A decision shall be notified to the party concerned, along with the remedies available to him under current legislation and the time allowed for seeking such remedies.

.../...

Article 41

The requirements of Member States concerning conditions of supply to the public, the marking of prices on medicinal products for veterinary use and industrial property rights shall not be affected by the provisions of this Chapter.

Chapter VIII - Implementing provisions and transitional measures

Article 42

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive within eighteen months of its notification and shall forthwith inform the Commission thereof.

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

Article 43

1. As regards the authorizations referred to in Article 23 which are issued before the expiry of the time-limit laid down in Article 42, Member States shall grant an additional period of one year to the undertakings concerned to enable them to comply with the provisions of Chapter V.

2. The other provisions of this Directive shall be applied progressively, within fifteen years of the notification referred to in Article 42, to veterinary medicinal products placed on the market by virtue of previous provisions.

.../...

3. Member States shall notify the Commission, within three years following the notification of this Directive, of the number of veterinary medicinal products covered by paragraph 2, and, in each subsequent year, of the number of such products for which the marketing authorization referred to in Article 3 has not yet been issued.

Article 44

This Directive is addressed to the Member States.

PROPOSAL FOR A COUNCIL DIRECTIVE ON THE APPROXIMATION OF THE LAWS OF MEMBER STATES RELATING TO ANALYTICAL, PHARMACO-TOXICOLOGICAL AND CLINICAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF VETERINARY MEDICINAL PRODUCTS

Explanatory memorandum

As with proprietary medicinal products for human beings, it is necessary, in the case of veterinary medicinal products, to make certain additions to the principles laid down by the basic Directive in order to allow veterinary medicinal products freedom of movement. By defining the data to be supplied concerning the characteristics of medicinal products, by setting out a common plan for the presentation of these data and by laying down the broad lines for testing medicinal products, this Directive will, at one and the same time, assist manufacturers, competent national authorities and the Committee on veterinary medicinal products envisaged in the Council Directive ..... of ..... on the approximation of the laws of Member States relating to veterinary medicinal products.

This proposal was drawn up on the basis of the studies made in the field of proprietary medicinal products for use in human beings. However, the special problems raised by veterinary medicinal products have led to a certain number of original provisions being made.

In the first place, it is important to protect the health of people who consume animal products. Advanced pharmaco-toxicological studies have been planned in order to determine the possible presence of residues in foodstuffs obtained from treated animals and the effects of such residues. These tests must make it possible to establish the necessary waiting period from the time when the medicinal product is administered to the animal until foodstuffs are obtained from the animal, in order to eliminate human health hazards. It is also important, however, to consider the protection of the treated animal, since, after all, this is the prime object of veterinary medicinal products; but this gives rise to a difficult question, i.e. the extent of the assurances which the competent authorities may require as to the safety of the product for the intended species of animal. In the case of medicinal products for human use the answer is obvious - every possible assurance is required. Where veterinary medicinal products are concerned the answer is not so easy.

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From the scientific standpoint it is clear that all the toxicity tests (single dose toxicity tests, repeated dose toxicity tests and tolerance tests) must be carried out in every case. By means of the first type of test it is possible to determine whether the product is highly or fairly toxic and generally to describe the acute symptoms of intoxication. The second type of test provides information concerning the mechanism of the intoxication process and make it possible to identify the side-effects which are masked in the acute toxicity tests. Similarly, the tolerance tests in the intended species of animal enable the maximum tolerated dose and the intolerance symptoms to be established.

From the economic standpoint one must nevertheless consider whether all these tests to safeguard the health of the treated animal will excessively penalize veterinary medicinal products as against medicinal products for human use. In the case of veterinary medicinal products, the toxicity tests are numerous: one range of tests is intended to protect the treated animal's health, another range is intended to protect the consumer of animal products (residue tests). One must therefore prevent the cost burden imposed on veterinary research from handicapping the sales prospects of such medicinal products too heavily and thus fostering illegal dealings in this market, which would run counter to the aims pursued.

A compromise solution is therefore proposed: it is desirable that all the tests for toxicity be carried out; nevertheless, [illegible], considering in particular the directions for the use of the medicinal product, the investigator may submit reasons for not carrying out the repeated dose toxicity tests; these reasons will of course be appraised by the competent authorities who can always insist that these tests be carried out.

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THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100 thereof,

Having regard to the proposal from the Commission,

Whereas the approximation begun by Council Directive ..... of ..... on the approximation of the laws of the Member States relating to veterinary medicinal products should be continued and the implementation of the principles laid down in that Directive should be ensured;

Whereas among existing disparities those relating to the control of veterinary medicinal products are of fundamental importance and point 10 of the second paragraph of Article 4 of the said Directive requires that applications for authorization to place a veterinary medicinal product on the market should be accompanied by particulars and documents relating to the results of tests and trials carried out on the product concerned;

Whereas standards and protocols for the performance of tests and trials on veterinary medicinal products are an effective means of control of these products and hence of protecting public health and can facilitate the movement of these products by laying down uniform rules applicable to tests and trials and the compilation of dossiers;

Whereas the adoption of the same standards and protocols by all the Member States will enable the competent authorities to arrive at their decisions on the basis of uniform tests and by reference to uniform criteria and will therefore help to obviate differences in evaluation;

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

Whereas the waiting period referred to in point 8 of the second paragraph of the said Article 4 must be determined in accordance with the results of the tests and trials provided for in point 10 thereof;

Whereas the concepts of harmfulness and therapeutic efficacy referred to in Article 10 of the said Directive can only be examined in relation to each other and have only a relative significance depending on the progress of scientific knowledge and the use for which the medicinal product is intended; whereas the particulars and documents which must accompany an application for authorization to place a veterinary medicinal product on the market must demonstrate that potential hazards are outweighed by the therapeutic efficacy of the product; whereas, failing such demonstration, the application must be rejected;

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

Whereas technical progress requires rapid adjustment of the provisions of the Annex to this Directive; whereas to make it easier to adapt to the measures required for this purpose, provision should be made for a procedure to ensure close cooperation between the Member States and the Commission within the Standing Committee on Medicinal Products,

HAS ADOPTED THIS DIRECTIVE:

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Article 1

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

Where, under point 10(a) or (b) of the second paragraph of Article 4 of the said Directive, references to published data are submitted, the provisions of this Directive shall apply in like manner.

Article 2

The amendments necessary for adapting the requirements of the Annex to this Directive to technical progress shall be adopted in accordance with the procedure laid down in Article 3(5) and (6) (as amended) of the Council Directive of ..... relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products.

The Committee referred to in Article 3 (as amended) of the said Directive may examine any question relating to the application of this Directive which is brought up by its Chairman, either on his own initiative or at the request of the representative of a Member State.

Article 3

Member States shall put into force the laws, regulations and administrative provisions needed in order to comply with this Directive within 18 months of its notification and shall forthwith inform the Commission thereof.

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

Article 4

This Directive is adressed to the Member States.

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A N N E X

Part 1

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

A. Qualitative and quantitative particulars of the components

The particulars and documents which must accompany applications for marketing authorizations pursuant to Article 4, point 3, second paragraph, of Council Directive ..... of ..... on the approximation of the laws of Member States relating to veterinary medicinal products shall be submitted in accordance with the following requirements :

1. "Qualitative particulars" of all the components of the midicinal product means the designation or description of :

- the active substance(s)
- the component(s) of the excipients, whatever their nature or the quantity used, including colouring agents, preservatives, stabilizers, thickeners, emulsifiers, anti-agglutinating agents, flavouring and aromatic substances, gas propellants, etc....
- components of the pharmaceutical form (e.g. capsule, cachet) intended to be ingested or otherwise administered to animals.

These particulars shall be supplemented by any relevant data concerning the container and, where appropriate, the way of closing it.

2. The "usual terminology", to be used in describing the components of medicinal products, means, without prejudice to the application of the other provisions of Article 4, point 3, of the said Directive :

- compulsorily, in respect of substances which appear in the European Pharmacopoeia or, failing this, in the national pharmacopoeia of one of the Member States, the principal designation used in the relevant monograph, with reference to the pharmacopoeia concerned;

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- in respect of other substances, the international non-proprietary name recommended by 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, any other relevant details;

- in respect of colouring agents, designation by the "E" code assigned to them in a future Council Directive on the approximation of the rules of the Member States concerning the colouring agents authorized for use in proprietary medicinal products.

3. In order to give "quantitative particulars of all the components of the medicinal product" it is necessary, depending on the pharmaceutical form concerned, to specify in regard to the active substance(s) the weight or the number of international units, either per dosage-unit or per unit of weight or volume and in regard to the components of the excipient, the weight or the volume of each of them, with due allowance for the details provided in section B below.

This information shall be supplemented:

- in respect of parenteral preparations, by the weight of each active substance in the unit container, taking into account the usable volume of the product;
- in respect of medicinal products to be administered in drops, by the weight of each active substance contained in the number of drops corresponding to an average dose;
- in respect of syrups, emulsions, granules and other pharmaceutical forms to be administered in measured quantities, by the weight of each active substance per measured quantity.

Active substances present in the form of compounds or derivatives shall be described quantitatively by their total weight, and if necessary or relevant, by the weight of the active moiety or moieties of the molecule (in the case of chloramphenicol palmitate, for example, the weight of the ester and that of the corresponding chloramphenicol shall be given).

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The biological units of activity of products which have not been defined chemically, and on which there is insufficient bibliographical information, shall be expressed in such a way as to provide unambiguous information on the activity of the substance, e.g. by stating the physiological effect on which the method of determining the dose is based.

B. Description of method of preparation

The "brief description of the method of preparation" accompanying the application for marketing authorization pursuant to Article 4, second paragraph, point 4, of Council Directive ..... of ....., shall be drafted in such a way as to give an adequate idea 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 brought about an adverse change in the components;

- in the case of a continuous process, full details concerning precautions taken to ensure the homogeneity of the final product;

- the actual manufacturing formula, with the quantitative particulars of all the substances used, the quantities of excipients, however, being given in approximate terms in so far as the pharmaceutical form makes this necessary; mention shall be made of any substances that may disappear in the course of manufacture;

- a statement of the stages of manufacture at which sampling is carried out for in-process control tests, where other data in the documents supporting the application show such tests to be necessary for quality control of the medicinal product.

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Checking of basic substances

For the purposes of this paragraph, "basic substances" shall mean all the components of the medicinal product and, if necessary, of its container, as referred to in paragraph A, point 1, above.

The particulars and documents which must accompany the application for marketing authorization pursuant to Article 4, second paragraph, points 9 and 10, of Council Directive ..... of ..... shall include the results of the tests relating to quality control of all the components used. These particulars and documents shall be submitted in accordance with the following provisions.

1. Basic substances 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 pharmacopeia 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 Article 4, second paragraph, point 9, of Council Directive ..... of ..... In this case, the description of the analytical methods may be replaced by a detailed reference to the pharmacopoeia in question.

Reference to any of the pharmacopoeias of non Member countries may be permitted in cases where the substance is described neither in the European Pharmacopoeia nor in the national pharmacopoeia concerned; in that case the monograph shall be submitted, accompanied where necessary by a translation for which the applicant shall be responsible.

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Colouring agents shall, in all cases, satisfy the requirements of a future Council Directive on the approximation of the laws of the Member States concerning the colouring agents authorized for use in proprietary medicinal products.

For routine tests on each batch of basic substance, only that part of the pharmacopoeia relating to verification tests (purity and strengths) shall be mandatory; the full range of identity tests need not necessarily be performed where those that have been performed permit an unambiguous characterization. In this case, the reference to the monograph of the pharmacopoeia mentioned above shall include details relating to this aspect.

2. Basic substances not in a pharmacopoeia

Components which are not given in any pharmacopoeia shall be described in the form of a monograph under the following headings:

(a) The name of the substance, meeting the requirements of paragraph A, point 2, shall be supplemented by any trade or scientific synonyms;

(b) The description of the substance, set down in a form similar to that used in a descriptive item in the European Pharmacopoeia, shall be accompanied by any necessary explanatory evidence, especially concerning the molecular structure where appropriate; it must, in such a case, be accompanied by a brief indication of the method of synthetic preparation. Where substances can only be described by their method of preparation, the description will have to be sufficiently detailed to characterize a substance which is constant both in its composition and in its effects;

(c) Methods of identification may be divided into complete techniques as used for the formulation of the medicinal product, and tests which ought to be carried out as a routine matter.

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(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 medicinal association to which the application refers, might adversely affect the stability of the medicinal product or distort analytical results.

(e) The assay technique(s) must be described in sufficiently precise detail so as to be reproducible in checking tests carried out at the request of the competent authority; any special apparatus and equipment which may be used shall be described in adequate detail, possibly accompanied by a diagram. The formulae of the laboratory reagents shall be supplemented, if necessary, by the method of preparation.

The standard deviation of the method, its reliability and the acceptability limits of the results shall be specified and, if necessary, justified in the light of feasibility and the progress of scientific knowledge.

With regard to complex substances of plant or animal origin, a distinction must be made between the case where multiple pharmacological effects render a chemical, physical or biological check of the principal components necessary, and the case of substances containing one or more groups of principles exerting similar action, in respect of which an overall method of determination may be accepted.

(f) Any special precautions that may be necessary during storage of the basic substance and, if necessary, its storage life shall be given.

D. Checks during manufacture

The particulars and documents which must accompany an application for marketing authorization, pursuant to Article 4, second paragraph, points 9 and 10, of Council Directive ..... of ..... shall more especially include particulars relating to the product checks that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring consistency of the technical characteristics and the production process.

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These tests are essential to verify the conformity of the medicinal product with the formula when, exceptionally, an applicant proposes an analytical technique for testing the finished product which does not include the assay of all the active substances (or of all the components of the excipient subject to the same requirements as the active substances).

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

E. Checks on the finished product

The particulars and documents which must accompany the application for marketing authorization pursuant to Article 4, second paragraph, points 9 and 10, of Council Directive ..... of ....., shall include particulars relating to checks on the finished product. They shall be submitted in accordance with the following requirements.

1. General characteristics of the various pharmaceutical forms

Certain checks on the general characteristics of a product which can be carried out in the course of the manufacturing process shall be included among the tests on the finished product.

As a guideline, and subject to the requirements of the European Pharmacopoeia or the national pharmacopoeias of Member States, the general characteristics which are to be verified for various pharmaceutical forms are given at point 5 below.

These checks shall, wherever applicable, relate to the verification of average weights and maximum deviations, to mechanical, physical or microbiological tests, organoleptic characteristics such as clarity, colour and taste, and physical characteristics such as density, pH, refractive index, etc. For each of these characteristics, standards and limits must be specified by the applicant in each particular case.

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2. Identification and assay of active substance(s)

The description of the techniques for analysing the finished product shall set out, in such precise detail that they can be reproduced readily, the methods used for identification and assay of the active substance(s) either in a representative average sample from the production batch or in a number of dosage-units considered individually.

In every case, the methods must correspond to the state of scientific progress at the time and give details and explanations concerning the standard deviations, the reliability of the analytical method and the maximum acceptable deviations.

In certain exceptional cases of particularly complex mixtures, where the assay of active substances which are either very numerous or present in very small amounts would necessitate an intricate investigation difficult to carry out in respect of each manufacturing batch, the assay of one or more active substances 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 cover the characterization of the substances concerned. This simplified technique shall then be supplemented by a method of quantitative evaluation, enabling the competend authority to have the conformity of the medicinal product with its formula verified after it has been placed on the market.

An assay of biological activity shall be obligatory when physico-chemical methods cannot provide adequate information on the quality of the product.

Where the particulars given in paragraph B show that a significant overage of an active substance was employed in the manufacture of the medicinal product, the description of the methods for checking the finished product shall include, where appropriate, the chemical and even the toxico-pharmacological investigation of the changes that this substance has undergone, and the characterization or determination of the degradation products, if any.

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3. Identification and assay of components of excipients

An upper-limit test shall be mandatory in respect of excipient components which are subject to rules relating to toxic substances or which are used as preservatives; furthermore, components liable to affect physiological functions shall be subjected to an assay.

The method proposed for identifying colouring agents must enable a verification to be made that such agents appear in the list to be appended to a future Council Directive on the approximation of the laws of the Member States concerning the colouring agents authorized for use in proprietary medicinal products.

In so far as is necessary, the components of the excipient shall be subjected at least to characterization tests.

4. Safety tests

Apart from the toxico-pharmacological tests submitted with the application for marketing authorization, particulars of safety tests (abnormal toxicity) or local tolerance in animals shall be included in the analytical dossier wherever such tests must be undertaken as a matter of routine in order to verify the quality of the medicinal product.

5. General characteristics of medicinal products to be verified systematically, depending on the pharmaceutical form of each product

The following requirements are given for guidance and without prejudice to any requirements of the European Pharmacopoeia or national pharmacopoeias of Member States; for example, microbiological testing of preparations to be ingested orally shall be performed in accordance with the requirements of the European Pharmacopoeia.

- Tablets and pills: colour, weight and acceptable variations in unit weight; if necessary, disintegration time with the method used to determine this.

- Coated tablets: colour, disintegration time with the method used to determine this; weight of finished tablet; weight of core and acceptable variations in unit weight.

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- Hard gelatine capsules and soft gelatine capsules: colour, disintegration time with the method used to determine this; appearance and weight of content, with acceptable variations in unit weight.

- Enteric-coated preparations (tablets, hard and soft gelatine capsules, granules): in addition to the requirements of the particular pharmaceutical form, resistance time in an artificial gastric fluid, with the method used to determine this; disintegration time in an artificial intestinal fluid, with the method used to determine this.

- Preparations with special protective coating (tablets, hard and soft gelatine capsules, granules): in addition to the requirements peculiar to each pharmaceutical form, verification of the effectiveness of the coating for the desired purpose.

- Preparations ensuring gradual release of the active substance; in addition to the requirements peculiar to each pharmaceutical form, requirements relating to gradual release, with the method used to determine this.

- Cachets, packets and sachets: nature and weight of contents and acceptable variations in unit weight.

- Parenteral preparations: colour, volume of contents and acceptable variations in this volume; pH, clarity of solutes, size limit of particulate matter in the case of suspensions; sterility tests, with description of test methods and, if necessary, a pyrogen test with description of method.

- Ampoules with solid content: quantity of medicinal product per ampoule and permitted variations in weight; sterility requirements and tests.

- Drinkable ampoules: colour, appearance, volume of content and acceptable variations.

- Ointments, creams, etc.: colour and consistency; weight and acceptable margin of variation; nature of container; in certain cases, microbiological tests.

- Suspensions: colour; where settlement occurs, the ease of re-suspendability.

- Emulsions: colour; type; stability.

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- Suppositories, bougies and preparations for intra-uterine administration: colour, weight and acceptable variations in unit weight; melting temperature or disintegration time, and description of the method.

- Aerosols: description of container and valve with details of output; particle size-limit, where the product is intended to be inhaled.

- Eye drops, ophthalmic ointments, eye lotions: colour; appearance; sterility tests, with description of the method used; where appropriate, clarity and size-limit of particulate matter in the case of suspensions; pH determination.

- Syrups, solutes, etc.: colour, appearance

- Pre-mix formulations for medicated feeds: in addition to the requirements peculiar to each pharmaceutical form, all useful information on the characteristics of the pre-mix formulation enabling a sufficiently homogeneous medicated feed to be prepared.

- Preparations for administration within the udder via the teat canal: colour, consistency; weight of content and, in the case of products presented in single slow-release dose formulations, usable weight with acceptable deviation; sterility test; pH determination.

F. Stability tests

The particulars and documents which must accompany the application for marketing authorization pursuant to Article 4, second paragraph, points 6 and 9, of Council Directive ..... of ..... shall be submitted in accordance with the following requirements.

A description shall be given of the investigations by which the shelf life proposed by the applicant has been determined.

Where a finished product is liable to give rise to toxic degradation products the applicant must report these and indicate characterization or assay methods.

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The conclusions shall contain the results of analyses, justifying the proposed shelf life under normal, or, where appropriate, under special storage conditions.

A study of the interaction between the medicinal product and the container shall be submitted wherever the risk of such interaction is regarded as possible, especially where parenteral preparations or aerosols for internal use are concerned.

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Part 2

TOXICOLOGICAL AND PHARMACOLOGICAL TESTS

The particulars and documents which must accompany the application for marketing authorization pursuant to Article 4, second paragraph, point 10, of Council Directive ..... of ..... shall be submitted in accordance with the requirements of Chapters I and II below.

Chapter I: Performance of tests

A. Introduction

The toxicological and pharmacological tests must show:

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

2. its pharmacological properties, in both qualitative and quantitative relationship to the proposed use in animals;

3. to what extent and for how long after use of this medicinal product in animals there exist residues in food products obtained from the animals, what are their possible harmful effects on Man and what are their drawbacks for the industrial processing of food.

All results must be reliable and of general applicability. Whenever appropriate, mathematical and statistical procedures shall be used in working out the experimental methods and in evaluating the results. Furthermore, it is necessary for clinicians to be given information about the therapeutic potential of the product and about the hazards connected with its use.

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B. Toxicity study

1. Single-dose toxicity

Single-dose toxicity test means a qualitative and quantitative study of the toxic reactions which may result from a single administration of the active substances contained in the medicinal product, in the proportions in which they are present in the actual medicinal product.

Wherever practicable, the product in its actual pharmaceutical form shall be subjected to an acute toxicity test.

The single-dose toxicity test must be carried out in at least two mammalian species of known strain, and at least two different routes of administration shall normally be used. The study with two mammalian species can be replaced by study with one mammalian species and an animal species of another class for which the medicinal product is intended. One of the forms of administration must be identical with or similar to that proposed for use in the animal for which the medicinal product is intended and the other must be a route ensuring systemic absorption of the product. The study must be carried out on equal numbers of male and female animals.

This study will describe the symptoms observed, including local reactions. Where possible, the LD_{50} value with its confidence limits (95 %) will be noted. The period during which the test animals are observed shall be fixed by the investigator and shall not be less than one week.

In the case of active substances in association, the study must be carried out in such a way as to check whether or not potentiation phenomena or new toxic effects occur.

2. Repeated-dose toxicity

Repeated-dose toxicity tests are intended to reveal any physiological and/or morbid anatomical changes induced by repeated administration of the active substance or association of active substances under examination, and to determine how such changes are related to dosage.

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Generally, it is desirable to perform at least one test the duration of which shall depend on the conditions of clinical use; its purpose shall be to determine by experiment the non-toxic dose range of the product examined during the trial. The investigator must give reasons for the extent and duration of the trials and the dosages chosen.

If, however, having regard in particular to the directions for use of the medicinal product, the responsible investigator sees fit not to carry out this examination he must give adequate reasons for his decision.

Repeated-dose toxicity tests must be carried out on two species of mammals one of which must be a non-rodent. Wherever it is feasible, the study with two mammalian species shall be replaced by a study with one species and another animal species for which the medicinal product is intended. The choice of the route(s) of administration must depend on those envisaged for therapeutic use and on the possibilities of systemic absorption. The method and frequency of administration and the length of the trials shall be clearly stated.

The maximum dose should be chosen, so as to bring harmful effects to light. The lower doses will then enable the animal's tolerance of the new product to be determined.

The evaluation of the toxic effects shall be based on observation of behaviour, growth, blood picture 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 will depend on the species of animal used and the state of scientific knowledge at the time.

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In the case of new combinations of known substances that have been investigated in accordance with the provisions of this Directive, the long-term tests may, except where acute and subacute toxicity tests have demonstrated potentiation or novel toxic effects, be suitably modified by the investigator who shall submit his reasons for such modifications. Substances that have been shown to be safe by wide usage over at least three years in clinical treatment of human beings, and by the result of controlled trials shall be treated in the same way as known substances which have already been investigated in accordance with these standards and protocols.

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

3. Tolerance in the intended species of animal

This study must be carried out with all animal species for which the medicinal product is intended. Its purpose is to carry out in all the animal species for which the medicinal product is intended local and general tolerance assays to establish the maximum does tolerated and the clinical symptoms of intolerance using the recommended route or routes, in so far as

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it is possible to attain this aim by increasing the therapeutic dose. The report on the trials must contain as many details as possible on the expected pharmacological effects and the adverse side-effects; the latter must be assessed with due regard to the fact that the experimental animals may be of very high value.

The medicinal product shall be administered via the routes likely to produce the appearance of the pharmacological effects sought.

Where the trials must be carried out with animals of high unit price the sequential method may be used.

This method consists in calculating a non-lethal theoretical dose for the animal concerned on the basis of the pharmacologically effective doses determined during the experimental trials with the medicinal product, bearing in mind the maximum tolerated doses observed during the single-dose toxicity study, in accordance with point B.1. This dose shall then be administered to an animal which shall be watched very carefully in order to obtain as much information as possible regarding the effects of the medicinal product. If the animal presents no symptoms of intolerance the test shall be recommenced with another animal using a higher dose the strength of which shall be left to the investigator's discretion. If the animal easily tolerates this new dose the test shall be continued with a yet higher dose. The dose which must not be exceeded will be found when symptoms of toxicity appear. If the animal dies, the test shall be recommenced with a lower dose and so on. In every case the aim is to determine a single dosage which enables a favourable pharmacological effect to be obtained without harming the animal.

Any excipient employed for the first time in the pharmaceutical field shall be treated as an active substance.

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4. Foetal toxicity

This study consists in examining the toxic and abortifacient effects observed in the progeny when the medicinal product under investigation is also intended to be administered to the female during pregnancy. The tests in question may be carried out as part of the clinical trials.

5. Examination of reproductive function

If the results of the clinical trials reveal anything suggesting impairment of male or female reproductive function or harmful effects on progeny, the reproductive function must be investigated by appropriate tests.

C. Study of pharmacological properties

1. Pharmacodynamics

Pharmacodynamics means the study of the variations caused by the medicinal product in the functions of the organism, irrespective of whether these functions are normal or experimentally modified.

This study must follow two distinct lines of approach.

First, the actions on which the recommended application in practice is based shall be adequately described. The results shall be expressed in quantitative terms (dose-effect curves, time-effect curves etc.) and, wherever possible, to comparison with a product whose activity is well known. Where a higher therapeutic coefficient is claimed for a product, the difference shall be demonstrated by reference to the confidence limits.

Secondly, the investigator shall give a general pharmacological assessment of the substance, referring in particular to the possibility of side-effects. In general, the main functions of the physiological systems should be investigated; the more closely the doses liable to produce side effects approximate to those producing the therapeutic effects for which the product is being proposed, the more thorough this investigation must be.

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The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and the investigator must establish their heuristic value. The experimental results shall be set out clearly and for certain types of tests their statistical significance shall be quoted.

Unless good reasons are given to the contrary, any quantitative modification of effects resulting from repeated administration of the doses shall also be investigated.

Medicinal associations may result either from pharmacological premisses or from clinical indications. In the first case, the pharmacodynamic study shall demonstrate those interactions which might make the association itself recommendable in clinical use. In the second case, where scientific justification for the medicinal association is sought through clinical experimentation, the investigation must determine whether the effects expected from the association can be demonstrated in animals, and at least the importance of any side-effects shall be investigated. If an association includes a new active substance, the latter must previously have been studied in depth.

2. Pharmacokinetics

Pharmacokinetics means the study of the fate of medicinal products within the organism, and covers the study of the absorption, distribution, biotransformation (or metabolism) and elimination of the products.

The study of these different phases may be carried out by means of physical, chemical or biological methods and by observation of the actual pharmacodynamic activity of the medicine.

Data concerning distribution and elimination shall be necessary in respect of chemotherapeutic products (antibiotics, etc.) and products whose use depends on their non-pharmacodynamic effects, and in all cases where such data are indispensable to determine the dosage for animals.

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In the case of new associations of known substances which have been investigated in accordance with the provisions of this Directive, pharmacokinetic studies shall not be required if the toxicity tests and clinical trials justify their omission. The same applies to substances that have been shown to be effective and safe by very wide usage over a period of at least three years in human or animal therapy and by controlled trials.

D. Study of residues

For the implementation of this Directive "residues" shall mean all active ingredients or metabolites thereof which remain in meats or other food produced from the animal to which the medicinal product in question has been administered in accordance with the recommended directions for use.

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

Assessment of the hazard due to residues entails ascertaining the presence of residues, if any, and the investigation of the effects of these residues in the treatment of animals under normal conditions of use.

1. Determination of residues

The determination of residues shall be carried out with due regard for the results of the pharmacokinetic tests. 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 must be specified. The results must be checked as far as possible, and at the least, by sampling, in the sick animals for which the medicinal product is recommended.

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2. Investigation of the effects of residues

a) [illegible] toxicity of orally administered residues

The study of the chronic (several months) toxicity of orally administered residues shall be performed differently according to whether it is a medicinal product that is eliminated without transformation or one that is metabolized. In the first case the researcher can work directly on the medicinal product. In the second case he must work similarly on the principal metabolites which are found chiefly in food. If the metabolites cannot be isolated or synthesized, recourse shall be had to the study of "relayed toxicity" which consists of operating with tissues in which the greatest quantity of residues has been traced or with products from treated animals.

The trials must be carried out, using the oral route, in two mammalian species one of which must be non-rodent. The usual duration of the trials shall be 3 - 6 months. If one works directly on the medicinal product or a metabolite, the doses must be fixed with due regard for the residues actually present and must be selected in such a way that the highest dose causes harmful effects to appear as far as possible, while the lower doses then enable the limit of tolerance in animals to be found. If the study of "relayed toxicity" is adopted, the upward gradation of the doses is limited by the quantity of residues actually present.

The evaluation of the toxic effects shall be based on observation of behaviour, growth, blood picture 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 will depend on the species of animal used and the state of scientific knowledge at the time.

b) Other effects of orally administered residues

The effects of residues on reproductive functions must be tested in rodents.

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Tests to reveal carcinogenic effects are indispensable:

1. in respect of substances having a close chemical analogy with known carcinogenic or cocarcinogenic compounds;
2. in respect of substances which have given rise to suspicious changes during the repeated-dose toxicity study.

Tests to reveal teratogenic effects are indispensable:

1. in respect of substances having a close chemical analogy with known teratogenic products;
2. in respect of substances which have given rise to suspicious changes during the study of effects on the reproductive functions.

The study of teratogenic effects shall be carried out with at least two animal species: a breed of rabbit sensitive to known teratogenic substances, and rats or mice (specifying the strain). The details of the test (number of animals, amounts administered and criteria for evaluation of results) shall depend on the state of scientific knowledge at the time when the application is lodged, and the level of statistical significance that the results must attain.

Furthermore, the study of mutagenic effects and allergic phenomena is also desirable.

Tests on the origination of resistant pathogenic germs are necessary in the case of residues of the medicinal products used to prevent or treat contagious diseases in Man or animals.

c) Disadvantages for the industrial processing of food

In certain cases it may be necessary to carry out tests to determine whether residues constitute disadvantages for technological procedures in the industrial processing of food.

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The study of the effects of residues in accordance with points a) to c) shall not be required if it has been established that the medicinal product has been rapidly and completely eliminated or if it is only used occasionally. In such cases the waiting period shall be determined in such a way that measurable residues are not included in the food.

E. Medicinal products for topical use

Where a medicinal product is intended for topical use, systemic absorption must be investigated in the intended species of animal. If it is proved that systemic absorption is negligible, the repeated-dose toxicity tests, the foetal toxicity tests and the studies of reproductive function referred to at points B.2, B.4 and B.5 may be omitted.

If the medicinal product is absorbed systemically in a significant quantity from the standpoint of view of residues or from that of pharmacodynamics (concentration) or if such systemic absorption has to be expected in the case of accidental oral ingestion of the medicinal product by the animal, the medicinal product must be investigated in accordance with the requirements of points B to D.

In all cases, tests of local tolerance after repeated administration shall be carried out and shall include histological examinations. Where a medicinal product which is not systemically absorbed may enter a food product obtained from the treated animal (mammary implants, etc.), the assay of residues in accordance with point D shall be carried out each time.

Chapter II: Presentation of particulars and documents

As in any scientific work, the dossier of toxicological and pharmacological tests shall include the following:

a) an introduction defining the subject, accompanied by any useful bibliographical references, particularly where the medicine has been used on human beings.

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b) 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 specific pathogen-free (SPF) or not;

c) all the important results obtained, whether favourable or unfavourable. The original data should be described in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author. By way of explanation and illustration, the results may be accompanied by reproductions of kymograms, photomicrographs, etc.;

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

e) an objective discussion of the results obtained, leasing to conclusions on the toxicological and pharmacological properties of the substance, on its safety margins in the intended animal and its possible side-effects, on its fields of application, on its active dose levels and any possible incompatibilities;

f) information showing whether the components of the 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 Man and on their cause, where appropriate in the light of trial results or bibliographical documents; where components of the medicinal product are themselves not used as medicinal products in human therapy the reasons should be stated;

g) a detailed description and a thorough discussion of the results of the study on the presence of residues in food and an assessment of the hazards they constitute for Man. Account should be taken of all the factors which may be of importance, particularly with regard to customary diet and levels of contamination by foreign matter present in the environment. In the case of each recommended use, this description shall be followed by proposals concerning the waiting periods which, allowing for an adequate

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safety margin, must be so established as to ensure that no further residue remains in food or, if this is impossible, to ensure that any danger to Man is eliminated by applying internationally recognized assessment criteria (dose devoid of effect in animals, acceptable daily dose, safety margin of 1 : 100 or </> 1 : 100 according to available information, etc.);

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

i) a summary together with precise bibliographical references.

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Part 3

CLINICAL TRIALS

The particulars and documents which must accompany applications for marketing authorizations pursuant to Article 4, point 10, second paragraph, of Council Directive ..... of ..... shall be submitted in accordance with the provisions of Chapters I and II below.

Chapter I: Conduct of trials

The purpose of clinical trials is to demonstrate or to ascertain the therapeutic effect of the medicinal product, to specify its indications and contra-indications according to species, its directions for use, any side-effects it may have and its harmlessness under normal conditions of use.

Clinical trials must be preceded by adequate pharmacological and toxicity tests carried out in accordance with the provisions of this Directive and, where they are practicable, by tests carried out preferably on the one or more animal species for which the medicinal product is intended. The investigator must acquaint himself with the conclusions of these preliminary trials.

As far as possible, clinical trials must be carried out with control animals (controlled clinical trials); if it is economically justifiable, the therapeutic effect obtained should be compared both with a placebo and with absence of treatment and/or with the effect of a medicinal product of known therapeutic value that has already been used. All the results obtained, whether positive or negative, must be reported.

The methods used to make the diagnosis must be specified. The results must be set out by making use of quantitative criteria or criteria represented by symbols (crosses, etc.).

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Chapter II: Particulars and documents

Particulars concerning clinical trials must be sufficiently detailed to enable an objective judgement to be made.

1. Records of clinical observations

All the particulars must be supplied by each of the investigators on individual record-sheets of clinical observations in the case of collective treatment.

The particulars supplied shall be classified as follows:

a) name, address, function and university qualifications of investigator;

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

c) in the case of individual treatment and collective treatment, if the latter has been given, full identification of the trial animals, names or registered numbers, species, breeds or strains, age, weight, sex (in the case of females, specify whether pregnant or in milk and, in the case of birds, in lay, etc.);

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

e) case history (as full as possible); occurrence and course of any intercurrent diseases;

f) diagnosis and means used to make it;

g) symptoms and severity of the disease, if possible giving criteria represented by symbols (crosses, etc.);

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

i) duration of treatment and period of subsequent observation;

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j) all details concerning medicinal products (other than that being assayed) 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;

k) 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 alone suffice to justify conclusions concerning any therapeutic effect;

l) all particulars of the observed side-effects, whether harmful or not, and of any measures taken in consequence; relation of cause and effect must be investigated with the same care normally accorded to identifying a therapeutic effect;

m) effect on animals' performances (egg-laying, milk production and reproductive function);

n) an opinion concerning each individual case or, where several series of collective treatment are concerned, an opinion on each collective case.

Omission of one or more of items a) to n) must be explained.

When, 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,

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marketing authorization may be granted subject to the following conditions:

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

b) the package insert and any other information shall 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 inadequate.

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 as from the date of transmission of the dossier to the competent authority.

2. Summary and conclusions

The clinical observations referred to in paragraph 1 above shall be summarized in a synopsis of the trials and their results, indicating:

a) 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 medicinal product of known effect;

d) the frequency of observed side-effects;

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e) 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 whose physiological or pathological condition requires special consideration;

f) a statistical evaluation of the results, when this is entailed by the programming of the trials and the variability of the factors involved.

Finally, the investigator shall draw general conclusions from the experimental evidence, expressing his opinion on the harmlessness of the medicinal product, under normal 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.

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FICHE FINANCIERE

1. Le Comité des médicaments vétérinaires (ch. IV) est composé de représentants des Etats membres et de la Commission.

   Il doit émettre un avis dans 3 cas :

   - lorsque le responsable de la mise sur le marché qui a obtenu une 1ère autorisation nationale le demande pour accéder à 5 autres marchés au moins,

   - lorsque des décisions nationales divergentes sont prises pour un même produit,

   - lorsqu'un Etat membre souhaite prendre l'avis du Comité avant de se prononcer sur une demande, une suspension ou un retrait d'autorisation.

2. Le nombre de réunions de ce Comité est purement conjectural puisqu'il dépend à la fois de la volonté des fabricants et des Etats membres; il est proposé de le fixer à 12 par an. Chaque Etat membre doit pouvoir envoyer un maximum de 4 experts (un administratif, un analyste, un toxicologue, un clinicien). Les experts gouvernementaux bénéficieront uniquement du remboursement des frais de voyage.

3. Compte tenu du nombre des experts (4 par Etat membre), les frais à prévoir pour la Commission s'élèveront par réunion à la somme de 230.400 FB, soit annuellement à la somme de 230.400 x 12 = 2.764.800 FB.