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Acts whose titles are printed in light type are those relating to day-to-day management of agricultural matters, and are generally valid for a limited period.

The titles of all other acts are printed in bold type and preceded by an asterisk.

I

(Acts whose publication is obligatory)

DIRECTIVE 2001/82/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 6 November 2001

on the Community code relating to veterinary medicinal products

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the Economic and Social Committee [1],

Acting in accordance with the procedure laid down in Article 251 of the Treaty [2],

Whereas:

(1) Council Directive 81/851/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to veterinary medicinal products [3], Council Directive 81/852/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products [4], Council Directive 90/677/EEC of 13 December 1990 extending the scope of Directive 81/851/EEC on the approximation of the laws of the Member States relating to veterinary medicinal products and laying down additional provisions for immunological veterinary medicinal products [5], and Council Directive 92/74/EEC of 22 September 1992 widening the scope of Directive 81/851/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to veterinary medicinal products and laying down additional provisions on homeopathic veterinary medicinal products [6] have been frequently and substantially amended; in the interests of clarity and rationality, the said Directives should therefore be codified by assembling them in a single text.

(2) The primary purpose of any rules for the production and distribution of veterinary medicinal products must be the safeguarding of public health.

(3) However, this objective must be achieved by means which will not hinder the development of industry and trade in medicinal products within the Community.

(4) In so far 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. This results in the hindering of trade in medicinal products within the Community, thereby directly affecting the functioning of the internal market.

(5) Such hindrances must, accordingly, be removed; whereas this entails approximation of the relevant provisions.

(6) It is necessary from the point of view of public health and the free movement of veterinary medicinal products for the competent authorities to have at their disposal all useful information on authorized veterinary medicinal products in the form of approved summaries of the characteristics of products.

(7) With the exception of those medicinal products which are subject to the centralised Community authorization procedure established by Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products [7], a marketing authorization in one Member State ought to be recognized by the competent authority of the other Member States unless there are serious grounds for supposing that the authorization of the veterinary medicinal product concerned may present

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[1] OJ C 75, 15.3.2000, p. 11.

[2] Opinion of the European Parliament of 3 July 2001 (not yet published in the Official Journal) and Council Decision of 27 September 2001.

[3] OJ L 317, 6.11.1981, p. 1. Directive as last amended by Commission Directive 2000/37/EC (OJ L 139, 10.6.2000, p. 25).

[4] OJ L 317, 6.11.1981, p. 16. Directive as last amended by Commission Directive 1999/104/EC (OJ L 3, 6.1.2000, p. 18).

[5] OJ L 373, 31.12.1990, p. 26.

[6] OJ L 297, 13.10.1992, p. 12.

[7] OJ L 214, 24.8.1993, p. 1. Regulation as amended by Commission Regulation (EC) No 649/98 (OJ L 88, 24.3.1998, p. 7).

a risk to human or animal health, or to the environment; in the event of a disagreement between Member States about the quality, the safety or the efficacy of a medicinal product, a scientific evaluation of the matter should be undertaken at a Community level, lead to a single decision on the area of disagreement, binding on the Member States concerned. This Decision should be adopted by a rapid procedure ensuring close cooperation between the Commission and the Member States.

(8) For this purpose, a Committee for Veterinary Medicinal Products should be set up in accordance with the European Agency for the Evaluation of Medicinal Products laid down in the aforementioned Regulation (EEC) No 2309/93.

(9) This Directive is only one stage in the achievement of the aim of freedom of movement of veterinary medicinal products. However, for this purpose, new measures will prove necessary, in the light of experience gained — especially within the Committee for Veterinary Medicinal Products — for the removal of the remaining barriers to freedom of movement.

(10) Medicated feedingstuffs do not come within the scope of this Directive. However, it is necessary, for both public health and economic reasons, to prohibit the use of unauthorized medicinal products in the manufacture of medicated feedingstuffs.

(11) The concepts of harmfulness and therapeutic efficacy can be examined only in relation to one another and have only a relative significance, depending on the progress of scientific knowledge and the use for which the medicinal product is intended. The particulars and documents which must accompany an application for marketing authorization must demonstrate that potential hazards are outweighed by the benefits due to efficacy. Failing such demonstration, the application must be rejected.

(12) Marketing authorization should be refused where a medicinal product lacks therapeutic effect or where there is insufficient proof of such effect. The concept of therapeutic effect must be understood as being the effect promised by the manufacturers.

(13) Such marketing authorization should also be refused where the withdrawal period indicated is not long enough to eliminate health hazards arising from residues.

(14) Before an authorization to market an immunological veterinary medicinal product can be granted, the manufacturer must demonstrate his ability to attain batch-to-batch consistency.

(15) The competent authorities should also be empowered to prohibit the use of an immunological veterinary medicinal product when the immunological responses of the treated animal will interfere with a national or Community programme for the diagnosis, eradication or control of animal disease.

(16) It is desirable in the first instance to provide users of homeopathic medicinal products with a very clear indication of their homeopathic character and with sufficient guarantees of their quality and safety.

(17) The rules relating to the manufacture, control and inspection of homeopathic veterinary medicinal products must be harmonised to permit the circulation throughout the Community of medicinal products which are safe and of good quality.

(18) Having regard to the particular characteristics of these homeopathic veterinary medicinal products, such as the very low level of active principles they contain and the difficulty of applying to them the conventional statistical methods relating to clinical trials, it is desirable to provide a special, simplified registration procedure for those traditional homeopathic medicinal products which are placed on the market without therapeutic indications in a pharmaceutical form and dosage which do not present a risk for the animal.

(19) The usual rules governing the authorization to market veterinary medicinal products must be applied to homeopathic veterinary medicinal products marketed with therapeutic indications or in a form which may present risks which must be balanced against the desired therapeutic effect. Member States should be able to apply particular rules for the evaluation of the results of tests and trials intended to establish the safety and efficacy of these medicinal products for pet animals and exotic species, provided that they notify them to the Commission.

(20) In order to better protect human and animal health and avoid any unnecessary duplication of effort during the examination of application for a marketing authorization, Member States should systematically prepare assessment reports in respect of each veterinary medicinal product which is authorized by them, and exchange the reports upon request. Furthermore, a Member State should be able to suspend the examination of an application for authorization to place a veterinary medicinal product on the market which is currently under active consideration in another Member State with a view to recognizing the decision reached by the latter Member State.

(21) 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 corresponding authorizations, should be applied to veterinary medicinal products.

(22) The quality of veterinary medicinal products manufactured within the Community should be guaranteed by requiring compliance with the principles of good manufacturing practice for medicinal products irrespective of the final destination of the medicinal products.

(23) Measures should also be taken to ensure that distributors of veterinary medicinal products are authorized by Member States and maintain adequate records.

(24) 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 the compilation of dossiers, allowing the competent authorities to arrive at their decisions on the basis of uniform tests and by reference to uniform criteria, and therefore helping to obviate differences in evaluation.

(25) It is advisable to stipulate more precisely the cases in which the results of pharmacological and toxicological tests or clinical trials do not have to be provided with a view to obtaining authorization for a veterinary medicinal product which is essentially similar to an innovative product, while ensuring that innovative forms are not placed at a disadvantage. However, there are reasons of public policy for not repeating tests carried out on animals without overriding cause.

(26) Following the establishment of the internal market, specific controls to guarantee the quality of veterinary medicinal products imported from third countries can be waived only if appropriate arrangements have been made by the Community to ensure that the necessary controls are carried out in the exporting country.

(27) In order to ensure the continued safety of veterinary medicinal products in use, it is necessary to ensure that pharmacovigilance systems in the Community are continually adapted to take account of scientific and technical progress.

(28) For public health protection, relevant data on adverse effects in humans related to the use of veterinary medicines should be collected and evaluated.

(29) The pharmacovigilance systems should consider the available data on lack of efficacy.

(30) In addition, collection of information on adverse reactions due to off-label use, investigations of the validity of the withdrawal period and on potential environmental problems may contribute to improve regular monitoring of good usage of veterinary medicines.

(31) It is necessary to take account of changes arising as a result of international harmonisation of definitions, terminology and technological developments in the field of pharmacovigilance.

(32) The increasing use of electronic means of communication of information on adverse reactions to veterinary medicinal products marketed in the Community is intended to allow a single reporting point for adverse reactions, at the same time ensuring that this information is shared with the competent authorities in all Member States.

(33) It is the interest of the Community to ensure that the veterinary pharmacovigilance systems for centrally authorised medicinal products and those authorised by other procedures are consistent.

(34) Holders of marketing authorisations should be proactively responsible for ongoing pharmacovigilance of the veterinary medicinal products they place on the market.

(35) The measures necessary for the implementation of this Directive should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission [1].

(36) In order to improve the protection of public health, it is necessary to specify that foodstuffs for human consumption may not be taken from animals which have been used in clinical trials of veterinary medicinal products unless a maximum residue limit has been laid down for residues of the veterinary medicinal product concerned in accordance with the provisions of Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin [2].

(37) The Commission should be empowered to adopt the changes necessary in order to adapt Annex I to scientific and technical progress.

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[1] OJ L 184, 17.7.1999, p. 23.

[2] OJ L 224, 18.8.1990, p. 1. Regulation as last amended by Commission Regulation (EC) No 1274/2001 (OJ L 175, 28.6.2001, p. 14).

(38) This Directive should be without prejudice to the obligations of the Member States concerning the time-limits for transposition of the Directives set out in Annex II, Part B,

HAVE ADOPTED THIS DIRECTIVE:

TITLE I

DEFINITIONS

Article 1

For the purposes of this Directive, the following terms shall bear the following meanings:

1. *Proprietary medicinal product:*

Any ready-prepared medicinal product placed on the market under a special name and in a special pack.

2. *Veterinary medicinal product:*

Any substance or combination of substances presented for treating or preventing disease in animals.

Any substance or combination of substances which may be administered to animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in animals is likewise considered a veterinary medicinal product.

3. *Ready-made veterinary medicinal product:*

Any veterinary medicinal product prepared in advance which does not comply with the definition of proprietary medicinal products and which is marketed in a pharmaceutical form which may be used without further processing.

4. *Substance:*

Any matter irrespective of origin which may be:

— human, e.g.

human blood and human blood products;

— animal, e.g.

micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products;

— vegetable, e.g.

micro-organisms, plants, parts of plants, vegetable secretions, extracts;

— chemical, e.g.

elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis.

5. *Pre-mix for medicated feedingstuffs:*

Any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feedingstuffs.

6. *Medicated feedingstuffs:*

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 properties or other properties as a medicinal product covered by point 2.

7. *Immunological veterinary medicinal product:*

A veterinary medicinal product administered to animals in order to produce active or passive immunity or to diagnose the state of immunity.

8. *Homeopathic veterinary medicinal product:*

Any veterinary medicinal product prepared from products, substances or compositions called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States.

A homeopathic veterinary medicinal product may also contain a number of principles.

9. *Withdrawal period:*

Period necessary between the last administration of the veterinary medicinal product to animals under normal conditions of use and the production of foodstuffs from such animals, in order to ensure that such foodstuffs do not contain residues in quantities in excess of the maximum limits laid down in application of Regulation (EEC) No 2377/90.

10. *Adverse reaction:*

A reaction which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function.

11. *Human adverse reaction:*

A reaction which is noxious and unintended and which occurs in a human being following exposure to a veterinary medicine.

12. *Serious adverse reaction:*

An adverse reaction which results in death, is life-threatening, results in significant disability or incapacity, is a congenital anomaly/birth defect, or which results in permanent or prolonged signs in the animals treated.

13. *Unexpected adverse reaction:*

An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of the product characteristics.

14. *Periodic safety update reports:*

The periodical reports containing the records referred to in Article 75.

15. *Post-marketing surveillance studies:*

Pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorization, conducted with the aim of identifying and investigating a safety hazard relating to an authorized veterinary medicinal product.

16. *Off-label use:*

The use of a veterinary medicinal product that is not in accordance with the summary of the product characteristics, including the misuse and serious abuse of the product.

17. *Wholesale dealing in veterinary medicinal products:*

Any activity which includes the purchase, sale, import, export, or any other commercial transaction in veterinary medicinal products, whether or not for profit, except for:

— the supply by a manufacturer of veterinary medicinal products manufactured by himself,

— retail supplies of veterinary medicinal products by persons entitled to carry out such supplies in accordance with Article 66.

18. *Agency:*

European Agency for the Evaluation of Medicinal Products established by Regulation (EEC) No 2309/93.

19. *Risk to human or animal health or the environment:*

Any risk relating to the quality, safety and efficacy of the veterinary medicinal product.

TITLE II

SCOPE

Article 2

The provisions of this Directive shall apply to veterinary medicinal products intended to be placed on the market *inter alia* in the form of medicinal products, ready-made veterinary medicinal products or pre-mixes for medicated feeedingstuffs.

Article 3

This Directive shall not apply to:

1. Medicated feedingstuffs as defined in Council Directive 90/167/EEC of 26 March 1990 laying down the conditions governing the preparation, placing on the market and use of medicated feedingstuffs in the Community ([1]);

   However, medicated feedingstuffs may be prepared only from pre-mixes which have been authorized under this Directive;

2. Inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals from a holding and used for the treatment of that animal or the animals of that holding in the same locality;

3. Any medicinal product prepared in a pharmacy in accordance with a prescription for an individual animal (commonly known as the magistral formula);

4. Any medicinal product prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the end-user (commonly known as the officinal formula);

5. Veterinary medicinal products based on radio-active isotopes;

6. Any additives covered by Council Directive 70/524/EEC of 23 November 1970 concerning additives in feedingstuffs ([2]), where they are incorporated in animal feedingstuffs and supplementary animal feedingstuffs in accordance with that Directive. Nevertheless, Member States may, when implementing Articles 10(1)(c) and(2) take acount of the medicinal products referred to in points 3 and 4 of the first paragraph.

Nonetheless, Member States may, when implementing Article 10(1)(c) and (2) take account of the medicinal products referred to in points 3 and 4 of the first paragraph.

Article 4

1. Member States may provide that this Directive shall not apply to non-inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals from a holding and used for the treatment of that animal or the animals of that holding in the same locality.

([1]) OJ L 92, 7.4.1990, p. 42.
([2]) OJ L 270, 14.12.1970, p. 1. Directive as last amended by Commission Regulation (EC) No 45/1999 (OJ L 6, 12.1.1999, p. 3).

2. Member States may permit exemptions on their territory in respect of veterinary medicinal products intended solely for aquarium fish, cage birds, homing pigeons, terrarium animals and small rodents, from the provisions in Articles 5, 7 and 8, provided that such products do not contain substances the use of which requires veterinary control and that all possible measures have been taken to prevent unauthorized use of the products for other animals.

TITLE III

MARKETING

CHAPTER 1

Marketing authorization

Article 5

No veterinary medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive or a marketing authorization has been granted in accordance with Regulation (EEC) No 2309/93.

Article 6

In order that a veterinary medicinal product may be the subject of a marketing authorization for the purpose of administering it to food-producing animals, the active substances which it contains must be shown in Annexes I, II or III of Regulation (EEC) No 2377/90.

Article 7

Where the health situation so requires, a Member State may authorise the marketing or administration to animals of veterinary medicinal products which have been authorized by another Member State in accordance with this Directive.

Article 8

In the event of serious disease epidemic, Member States may provisionally allow the use of immunological veterinary medicinal products without an authorization for placing on the market, in the absence of a suitable medicinal product and after informing the Commission of the detailed conditions of use.

Article 9

No veterinary medicinal product may be administered to animals unless the marketing authorization has been issued, except for the tests of veterinary medicinal products referred to in Article 12(3)(j) which have been accepted by the competent national authorities, following notification or authorization, in accordance with the national rules in force.

Article 10

1. Where there is no authorized medicinal product for a condition, Member States may exceptionally, in particular in order to avoid causing unacceptable suffering to the animals concerned, permit the administration by a veterinarian or under his/her direct personal responsibility to an animal or to a small number of animals on a particular holding:

(a) of a veterinary medicinal product authorized in the Member State concerned under this Directive or under Regulation (EEC) No 2309/93 for use in another animal species, or for another condition in the same species; or

(b) if there is no product as referred to in point (a), of a medicinal product authorized for use in the Member State concerned in human beings in accordance with Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use [1] or under Regulation (EEC) No 2309/93; or

(c) if there is no product as referred to in point (b) and within the limits of the law of the Member State concerned, of a veterinary medicinal product prepared extemporaneously by a person authorized to do so under national legislation in accordance with the terms of a veterinary prescription.

For the purposes of this paragraph, the phrase 'an animal or a small number of animals on a particular holding' also covers pets, and shall be interpreted more flexibly for minor or exotic animal species which do not produce food.

2. The provisions of paragraph 1 shall apply provided that the medicinal product, where administered to food-producing animals, contains only substances to be found in a veterinary medicinal product authorized for such animals in the Member State concerned and that in the case of food-producing animals the veterinarian responsible specifies an appropriate withdrawal period.

Unless the medicinal product used indicates a withdrawal period for the species concerned, the specified withdrawal period shall not be less than:

7 days	eggs,
7 days	milk,
28 days	meat from poultry and mammals including fat and offal,
500 degree days	meat from fish.

[1] See p. 67 of this edition of the Official Journal.

With regard to homeopathic veterinary medicinal products in which the level of active principles is equal to or less than one part per million, the withdrawal period referred to in the first and second subparagraphs is reduced to zero.

Article 11

When a veterinarian has recourse to the provisions of Article 10, he shall keep adequate records of the date of examination of the animals, details of the owner, the number of animals treated, the diagnosis, the medicinal products prescribed, the dosages administered, the duration of treatment and the withdrawal periods recommended, and make these records available for inspection by the competent authorities for a period of at least three years. This requirement may be extended by the Member States to non food-producing animals.

Article 12

1. For the purposes of obtaining a marketing authorization in respect of a veterinary medicinal product, other than under the procedure established by Regulation (EEC) No 2309/93, an application shall be lodged with the competent authority of the Member State concerned.

2. A marketing authorization may only be granted to an applicant established in the Community.

3. The following particulars and documents shall accompany an application in accordance with Annex I:

(a) name or business name and permanent address or registered place of business of the person responsible for placing the product on the market and, if different, of the manufacturer or manufacturers involved and of the sites of manufacture;

(b) name of the veterinary medicinal product (brand name, non-proprietary name, with or without a trademark, or name of the manufacturer or scientific name or formula, with or without a trademark, or the name of the manufacturer);

(c) qualitative and quantitative particulars of all the constituents of the veterinary medicinal product, using the usual terminology, but not empirical chemical formulae and giving the international non-proprietary name recommended by the World Health Organization, where such a name exists;

(d) description of the method of manufacture;

(e) therapeutic indications, contra indications and adverse reactions;

(f) dosage for the various species of animal for which the veterinary medicinal product is intended, its pharmaceutical form, method and route of administration and proposed shelf life;

(g) if applicable, explanations of the precautionary and safety measures to be taken when the product is stored, when it is administered to animals and when waste therefrom is disposed of, together with an indication of any potential risks the medicinal product might pose to the environment and the health of humans, animals or plants;

(h) indication of the withdrawal period. Where necessary, the applicant shall propose and justify a tolerance level for residues which may be accepted in foodstuffs without risk for the consumer, together with routine analysis methods which could be used by the competent authorities to trace residues;

(i) description of the control testing methods employed by the manufacturer (qualitative and quantitative analysis of the constituents and the finished product, specific tests e.g. sterility tests, test for the presence of pyrogens, for the presence of heavy metals, stability tests, biological and toxicity tests, tests on intermediate products);

(j) results of:

— physico-chemical, biological or microbiological tests,

— toxicological and pharmacological tests,

— clinical trials.

(k) a summary in accordance with Article 14 of the product characteristics, one or more specimens or mock-ups of the sales presentation of the veterinary medicinal product together with the package insert;

(l) a document showing that the manufacturer is authorized in his own country to produce veterinary medicinal products;

(m) copies of any marketing authorization obtained in another Member State or in a third country for the relevant veterinary medicinal product, together with a list of those Member States in which an application for authorization submitted in accordance with this Directive is under examination. Copies of the summary of the product characteristics proposed by the applicant in accordance with Article 14 or approved by the competent authority of the Member State in accordance with Article 25 and copies of the package insert proposed, details of any decision to refuse authorization, whether in the Community or a third country and the reasons for that decision.

This information shall be updated on a regular basis;

(n) in the case of medicinal products containing new active substances which are not mentioned in Annex I, II or III to Regulation (EEC) No 2377/90, a copy of the documents submitted to the Commission in accordance with Annex V to that Regulation.

Article 13

1. By way of derogation from point (j) of Article 12(3), and without prejudice to the law relating to the protection of industrial and commercial property:

(a) the applicant shall not be required to provide the results of toxicological and pharmacological tests and clinical trials if he can demonstrate:

(i) either that the veterinary medicinal product is essentially similar to a medicinal product authorized in the Member State concerned by the application and that the marketing authorization holder has agreed that the toxicological, pharmacological and/or clinical references contained in the file on the original veterinary medicinal product may be used for the purpose of examining the application in question;

(ii) or that the constituent or constituents of the veterinary medicinal product have a well-established medicinal use, with recognized efficacy and an acceptable level of safety, by means of detailed references to scientific literature;

(iii) or that the veterinary medicinal product is essentially similar to a medicinal product which has been authorized within the Community, in accordance with Community provisions in force, for not less than six years and is marketed in the Member State for which the application is made; this period shall be extended to 10 years in the case of high-technology medicinal products having been authorized in pursuance of the procedure established by Article 2(5) of Council Directive 87/22/EEC ([1]). Furthermore, a Member State may also extend this period to 10 years by a single Decision covering all the medicinal products marketed in its territory where it considers this necessary in the interest of public health. Member States are at liberty not to apply the six-year period beyond the date of expiry of a patent protecting the original medicinal product;

(b) in the case of new veterinary medicinal products containing known constituents not hitherto used in combination for therapeutic purposes, the results of toxicological and pharmacological tests and of clinical trials relating to that combination must be provided, but it shall not be necessary to provide the relevant documentation for each individual constituent.

2. Annex I shall apply in like manner where, pursuant to point (a)(ii) of paragraph 1, references to published data are submitted.

Article 14

The summary of the product characteristics shall contain the following information:

1. Name of the veterinary medicinal products;

2. Qualitative and quantitative composition in terms of the active substances and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product; the international non-proprietary names recommended by the World Health Organization shall be used, where such names exist, or failing this, the usual non-proprietary name or chemical description;

3. Pharmaceutical form;

4. Pharmacological properties and, in so far as this information is useful for the therapeutic purposes, pharmacokinetic particulars;

5. Clinical particulars;

5.1 target species,

5.2 indications for use, specifying the target species,

5.3 contra-indications,

5.4 undesirable effects (frequency and seriousness),

5.5 special precautions for use,

5.6 use during pregnancy and lactation,

5.7 interaction with other medicaments and other forms of interaction,

5.8 posology and method of administration,

5.9 overdose (symptoms, emergency procedures, antidotes) (if necessary),

5.10 special warnings for each target species,

5.11 withdrawal periods,

5.12 special precautions to be taken by the person administering the medicinal product to animals;

6. Pharmaceutical particulars:

6.1 major incompatibilities,

6.2 shelf life, when necessary after reconstitution of the medicinal product or when the container is opened for the first time,

6.3 special precautions for storage,

6.4 nature and contents of container,

6.5 special precautions for the disposal of unused medicinal product or waste materials, if any;

7. Name or corporate name and address or registered place of business of the authorization holder.

([1]) OJ L 15, 17.1.1987, p. 38. Directive repealed by Directive 93/41/EEC (OJ L 214, 24.8.1993, p. 40).

Article 15

1. Member States shall make all necessary arrangements to ensure that the documents and particulars listed in Article 12(3)(h), (i), (j) and Article 13(1) 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 in question.

2. According to their particular qualifications, the role of the experts shall be:

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

(b) to describe their findings in accordance with Annex I and in particular to state:

(i) in the case of analysts, whether the medicinal product conforms with the stated composition, providing any reasons for the control testing methods which the manufacturer is to use;

(ii) in the case of pharmacologists and appropriately qualified specialists:

— the toxicity of the medicinal product and the pharmacological properties observed,

— whether, after administration of the veterinary medicinal product under normal conditions of use and observance of the recommended withdrawal period, foodstuffs obtained from the treated animals contain residues which might constitute a health hazard to the consumer;

(iii) in the case of clinicians, whether they have found in animals treated with the medicinal product effects corresponding to the information furnished by the manufacturer pursuant to Articles 12 and 13(1), whether the medicinal product is well tolerated, what dosage they recommend and what are the contra-indications and adverse reactions, if any;

(c) to give reasons for the use of the references to published data referred to in point (a)(ii) of Article 13(1).

3. The experts' detailed reports shall form part of the documentation which the applicant shall lodge with the competent authorities. A brief curriculum vitae of the expert shall be appended to each report.

CHAPTER 2

Particular provisions applicable to homeopathic veterinary medicinal products

Article 16

1. Member States shall ensure that homeopathic veterinary medicinal products manufactured and marketed within the Community are registered or authorized in accordance with the provisions of Articles 17(1) and (2), 18 and 19. Each Member State shall take due account of registrations and authorizations previously granted by another Member State.

2. A Member State may refrain from establishing a special, simplified registration procedure for the homeopathic veterinary medicinal products referred to in Article 17(1) and (2). A Member State applying this provision shall inform the Commission accordingly. The Member State concerned shall, by 31 December 1995 at the latest, allow use in its territory of homeopathic veterinary medicinal products registered by other Member States in accordance with Article 17(1) and (2) and Article 18.

Article 17

1. Only homeopathic veterinary medicinal products which satisfy all of the following conditions may be subject to authorization by means of a special, simplified registration procedure:

— they are intended for administration to pet animals or exotic species which are non food-producing,

— they are administered by a route described in the *European Pharmacopoeia* or, in absence thereof, by the pharmacopoeias currently used officially in the Member States,

— no specific therapeutic indication appears on the labelling of the veterinary medicinal product or in any information relating thereto,

— there is a sufficient degree of dilution to guarantee the safety of the medicinal product; in particular, the medicinal product may not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active principles whose presence in an allopathic medicinal product results in the obligation to submit a veterinary prescription.

At the time of registration, Member States shall determine the classification for the dispensing of the medicinal product.

2. The criteria and rules of procedure provided for in Chapter 3, with the exception of Article 25, shall apply by analogy to the special, simplified registration procedure for homeopathic veterinary medicinal products referred to in paragraph 1, with the exception of the proof of therapeutic effect.

3. The proof of therapeutic effect shall not be required for homeopathic veterinary medicinal products registered in accordance with paragraph 1 of this Article or, where appropriate, admitted in accordance with Article 16(2).

Article 18

A special, simplified application for registration may cover a series of medicinal products derived from the same homeopathic stock or stocks. The following documents shall be included with the application in order to demonstrate, in particular, the pharmaceutical quality and the batch-to-batch homogeneity of the products concerned:

— scientific name or other name given in a pharmacopoeia of the homeopathic stock or stocks, together with a statement of the various routes of administration, pharmaceutical forms and degree of dilution to be registered,

— dossier describing how the homeopathic stock or stocks is/are obtained and controlled, and justifying its/their homeopathic nature, on the basis of an adequate bibliography; in the case of homeopathic veterinary medicinal products containing biological substances, a description of the measures taken to ensure the absence of pathogens,

— manufacturing and control file for each pharmaceutical form and a description of the method of dilution and potentiation,

— manufacturing authorization for the medicinal products concerned,

— copies of any registrations or authorizations obtained for the same medicinal products in other Member States,

— one or more specimens or mock-ups of the outer packaging and immediate packaging of the medicinal products to be registered,

— data concerning the stability of the medicinal product.

Article 19

1. Homeopathic veterinary medicinal products other than those referred to in Article 17(1) shall be authorized in accordance with the provisions of Articles 12 to 15 and Chapter 3.

2. A Member State may introduce or retain in its territory specific rules for the pharmacological and toxicological tests and clinical trials of homeopathic veterinary medicinal products intended for pet animals and exotic species which are non food-producing other than those referred to in Article 17(1), in accordance with the principles and characteristics of homeopathy as practised in that Member State.

In this case, the Member State concerned shall notify the Commission of the specific rules in force.

Article 20

This Chapter shall not apply to immunological homeopathic veterinary medicinal products.

The provisions of titles VI and VII shall apply to homeopathic veterinary medicinal products.

CHAPTER 3

Procedure for marketing authorization

Article 21

1. Member States shall take all appropriate measures to ensure that the procedure for granting an authorization to place a veterinary medicinal product on the market is completed within 210 days of the submission of a valid application.

2. Where a Member State notes that an application for authorization submitted is already under active examination in another Member State in respect of that veterinary medicinal product, the Member State concerned may decide to suspend the detailed examination of the application in order to await the assessment report prepared by the other Member State in accordance with Article 25(4).

The Member State concerned shall inform the other Member State and the applicant of its decision to suspend detailed examination of the application in question. As soon as it has completed the examination of the application and reached a decision, the other Member State shall forward a copy of its assessment report to the Member State concerned.

Article 22

Where a Member State is informed in accordance with Article 12(3)(m), that another Member State has authorized a veterinary medicinal product which is the subject of an application for authorization in the Member State concerned, that Member State shall forthwith request the authorities of the Member State which has granted the authorization to forward to it the assessment report referred to in Article 25(4).

Within 90 days of receipt of the assessment report, the Member State concerned shall either recognise the decision of the first Member State and the summary of the product characteristics as approved by it or, if it considers that there are grounds for supposing that the authorization of the veterinary medicinal product concerned may present a risk to human or animal health or the environment, it shall apply the procedures set out in Articles 33 to 38.

Article 23

In order to examine the application submitted pursuant to Articles 12 and 13(1), the competent authorities of the Member States:

1. shall check that the documentation submitted in support of the application complies with Articles 12 and 13(1) and, on the basis of the reports drawn up by the experts pursuant to Article 15(2) and (3), ascertain whether the conditions for the issue of the marketing authorization have been fulfilled;

2. may submit the medicinal product, its raw materials and if necessary intermediate products or other constituent materials for testing by a State laboratory or by a laboratory designated for that purpose, in order to ensure that the testing methods employed by the manufacturer and described in the application documents, in accordance with Article 12(3)(i), are satisfactory;

3. may, where appropriate, require the applicant to provide further information as regards the items listed in Articles 12 and 13(1). Where the competent authorities take this course of action, the time-limits specified in Article 21 shall be suspended until the further data required have been provided. Similarly, these time-limits shall be suspended for any period which the applicant may be given to provide oral or written explanations;

4. may require the applicant to submit substances in the quantities necessary to verify the analytical detection method proposed by the applicant in accordance with Article 12(3)(h) and to put it into effect as part of routine checks to reveal the presence of residues of the veterinary medicinal products concerned.

Article 24

Member States shall take all appropriate measures to ensure that:

(a) the competent authorities ascertain that the manufacturers and importers of veterinary medicinal products from third countries are able to manufacture them in compliance with the details supplied pursuant to Article 12(3)(d), and/or to carry out control tests in accordance with the methods described in the application documents under Article 12(3)(i);

(b) the competent authorities may authorize manufacturers and importers of veterinary medicinal products from third countries, where circumstances so justify, to have certain stages of manufacture and/or certain of the control tests referred to in (a) carried out by third parties; in such cases, checks by the competent authorities shall also be carried out in the establishments concerned.

Article 25

1. When the marketing authorization is issued, the holder shall be informed by the competent authorities of the Member State concerned, of the summary of the product characteristics as approved by it.

2. The competent authorities shall take all necessary measures to ensure that the information given in the summary is in conformity with that accepted when the marketing authorization is issued or subsequently.

3. The competent authorities shall forward to the Agency a copy of the authorization together with the summary of the product characteristics.

4. The competent authorities shall draw up an assessment report and comments on the dossier as regards the results of the analytical and pharmacotoxicological tests and the clinical trials of the veterinary medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is of importance for the evaluation of the quality, safety or efficacy of the veterinary medicinal product concerned.

Article 26

1. The marketing authorization may require the holder to indicate on the container and/or the outer wrapping and the package insert, where the latter is required, 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 prescribed in Articles 12(3)(j) and 13(1) or from experience gained during the use of the veterinary medicinal product once it has been marketed.

2. The authorization may also require the inclusion of a tracer substance in the veterinary medicinal product.

3. In exceptional circumstances, and following consultation with the applicant, an authorization may be granted subject to certain specific obligations, and subject to annual review, including:

— the carrying out of further studies following the granting of authorization,

— the notification of adverse reactions to the veterinary medicinal product.

These exceptional decisions may only be adopted for objective and verifiable reasons.

Article 27

1. After a marketing authorization has been issued, the holder must, in respect of the manufacturing methods and control methods provided for in Article 12(3)(d) and (i), take account of scientific and technical progress and introduce any changes that may be required to enable that veterinary medicinal product to be manufactured and checked by means of generally accepted scientific methods.

These changes shall be subject to the approval of the competent authorities of the Member State concerned.

2. Upon request from the competent authorities, the marketing authorization holder shall also review the analytical detection methods provided for in Article 12(3)(h) and propose any changes which may be necessary to take account of scientific and technical progress.

3. The marketing authorization holder shall forthwith inform the competent authorities of any new information which might entail the amendment of the particulars and documents referred to in Articles 12 and 13(1) or of the approved summary of the product characteristics. In particular, he shall forthwith inform the competent authorities of any prohibition or restriction imposed by the competent authorities of any country in which the veterinary medicinal product is marketed and of any serious unexpected adverse effect occurring in the animals concerned or human beings.

4. The marketing authorization holder shall be required to maintain records of all adverse reactions observed in animals or human beings. The records so established shall be kept at least five years and shall be made available to the competent authorities upon request.

5. The marketing authorization holder shall immediately inform the competent authorities, with a view to authorization, of any alteration he proposes to make to the particulars and documents referred to in Articles 12 and 13(1).

Article 28

Authorization shall be valid for five years and shall be renewable for five-year periods, on application by the holder at least three months before the expiry date and after consideration of a dossier updating the information previously submitted.

Article 29

The granting of authorization shall not diminish the general legal liability of the manufacturer and, where appropriate, of the authorization holder.

Article 30

The marketing authorization shall be withheld if examination of the documents and particulars listed in Articles 12 and 13(1) establishes that:

(a) the veterinary medical product is harmful under the conditions of use stated at the time of application for authorization; or

(b) has no therapeutic effect or the applicant has not provided sufficient proof of such effect as regards the species of animal which is to be treated; or

(c) its qualitative or quantitative composition is not as stated; or

(d) the withdrawal period recommended by the applicant is not long enough to ensure that foodstuffs obtained from the treated animal do not contain residues which might constitute a health hazard to the consumer, or is insufficiently substantiated; or

(e) the veterinary medicinal product is offered for sale for a use prohibited under other Community provisions.

However, pending Community rules, the competent authorities may refuse to grant authorization for a veterinary medicinal product where such action is necessary for the protection of public health, consumer or animal health.

Authorization shall also be withheld if the application documents submitted to the competent authorities do not comply with Articles 12, 13(1) and 15.

CHAPTER 4

Mutual recognition of authorizations

Article 31

1. In order to facilitate the adoption of common decisions by Member States on the authorization of veterinary medicinal products on the basis of the scientific criteria of quality, safety and efficacy, and to achieve thereby the free movement of veterinary medicinal products within the Community, a Committee for Veterinary Medicinal Products, hereinafter referred to as 'the Committee', is hereby set up. The Committee shall be part of the Agency.

2. In addition to the other responsibilities conferred upon it by Community law, the Committee shall examine any question relating to the granting, variation, suspension or withdrawal of marketing authorization which is submitted to it in accordance with the provisions of this Directive. It shall also examine any question relating to tests of veterinary medicinal products.

3. The Committee shall adopt its own rules of procedure.

Article 32

1. Before submitting an application for mutual recognition of marketing authorizations, the holder of the authorization shall inform the Member State which granted the authorization on which the application is based (hereinafter: the reference Member State) that an application is to be made in accordance with this Directive and shall notify it of any additions to the original dossier; that Member State may require the applicant to provide it with all the particulars and documents necessary to enable it to check that the dossiers filed are identical.

In addition, the holder of the authorization shall request the reference Member State which granted the initial authorization

to prepare an assessment report in respect of the veterinary medicinal product concerned, or, if necessary, to update it. That Member State shall prepare it within 90 days of receipt of the request.

At the same time as the application is submitted in accordance with paragraph 2 the reference Member Sate which granted the initial authorization shall forward the assessment report to the Member State or Member States concerned by the application.

2. In order to obtain the recognition according to the procedure laid down in this Chapter in one or more of the Member States of a marketing authorization issued by a Member State, the holder of the authorization shall submit an application to the competent authority of the Member State or Member States concerned, together with the information and particulars referred to in Articles 12, 13(1), 14 and 25. He shall testify that the dossier is identical to that accepted by the reference Member State, or shall identify any additions or amendments it may contain. In the latter case, he shall certify that the summary of the product characteristics proposed by him in accordance with Article 14 is identical to that accepted by the reference Member State in accordance with Article 25. Moreover, he shall certify that all the dossiers filed as part of this procedure are identical.

3. The holder of the marketing authorization shall transmit the application to the Agency, inform it of the Member States concerned and of the dates of submission of the application and send it a copy of the authorization granted by the reference Member State. He shall also send the Agency copies of any such authorization which may have been granted by the other Member States in respect of the veterinary medicinal product concerned, and shall indicate whether any application for authorization is currently under consideration in any Member State.

4. Save in the exceptional case provided for in Article 33(1), each Member State shall recognise the marketing authorization granted by the reference Member State within 90 days of receipt of the application and the assessment report. It shall inform the reference Member State, the other Member States concerned by the application, the Agency, and the holder of the authorization for placing the product on the market.

Article 33

1. Where a Member State considers that there are grounds for supposing that the marketing authorization of the veterinary medicinal product concerned may present a risk to human or animal health or the environment, it shall forthwith inform the applicant, the reference Member State, any other Member States concerned by the application and the Agency. The Member State shall state its reason in detail and shall indicate what action may be necessary to correct any defect in the application.

2. All the Member States concerned shall use their best endeavours to reach agreement on the action to be taken in respect of the application. They shall provide the applicant with the opportunity to make his point of view known orally or in writing. However, if the Member States have not reached agreement within the time-limit referred to in Article 32(4) they shall forthwith refer the matter to the Agency, for referral to the Committee, for the application of the procedure laid down in Article 36.

3. Within the time-limit referred to in Article 32(4), the Member States concerned shall provide the Committee with a detailed statement of the matters on which they have been unable to reach agreement and the reasons for their disagreement. The applicant shall be provided with a copy of this information.

4. As soon as he is informed that the matter has been referred to the Committee, the applicant shall forthwith forward to the Committee a copy of the information and particulars referred to in Article 32(2).

Article 34

If several applications submitted in accordance with Articles 12, 13(1) and 14 have been made for marketing authorization for a particular veterinary medicinal product and Member States have adopted divergent decisions concerning the authorization of that veterinary medicinal product, or suspension or withdrawal of that authorization, a Member State, or the Commission, or the marketing authorization holder may refer the matter to the Committee for application of the procedure laid down in Article 36.

The Member State concerned, the marketing authorization holder or the Commission shall clearly identify the question which is referred to the Committee for consideration and, if appropriate, shall inform the aforementioned holder thereof.

The Member States and the marketing authorization holder shall forward to the Committee all available information relating to the matter in question.

Article 35

The Member States or the Commission or the applicant or holder of the marketing authorization may, in specific cases where the interests of the Community are involved, refer the matter to the Committee for the application of the procedure laid down in Article 36 before reaching a decision on a request for a marketing authorization or on the suspension or withdrawal of an authorization, or on any other variations to the terms of a marketing authorization which appears necessary, in particular to take account of the information collected in accordance with Title VII.

The Member State concerned or the Commission shall clearly identify the question which is referred to the Committee for consideration and shall inform the marketing authorization holder.

The Member States and the holder shall forward to the Committee all available information relating to the matter in question.

Article 36

1. When reference is made to the procedure described in this Article, the Committee shall consider the matter concerned and issue a reasoned opinion within 90 days of the date on which the matter was referred to it.

However, in cases submitted to the Committee in accordance with Articles 34 and 35, this period may be extended by 90 days.

In case of urgency, on a proposal from its Chairman, the Committee may agree to a shorter deadline.

2. In order to consider the matter, the Committee may appoint one of its members to act as rapporteur. The Committee may also appoint individual experts to advise it on specific questions. When appointing experts, the Committee shall define their tasks and specify the time-limit for the completion of these tasks.

3. In the cases referred to in Articles 33 and 34, before issuing its opinion, the Committee shall provide the marketing authorization holder with an opportunity to present written or oral explanations.

In the case referred to in Article 35, the marketing authorization holder may be asked to explain himself orally or in writing.

If it considers it appropriate, the Committee may invite any other person to provide information relating to the matter before it.

The Committee may suspend the time-limit referred to in paragraph 1 in order to allow the marketing authorization holder to prepare explanations.

4. The Agency shall forthwith inform the marketing authorization holder where the opinion of the Committee is that:

— the application does not satisfy the criteria for authorization, or

— the summary of the product characteristics proposed by the applicant in accordance with Article 14 should be amended, or

— the authorization should be granted subject to conditions, with regard to conditions considered essential for the safe and effective use of the veterinary medicinal product including pharmacovigilance, or

— a marketing authorization should be suspended, varied or withdrawn.

Within 15 days of the receipt of the opinion, the holder may notify the Agency in writing of his intention to appeal. In that case, he shall forward the detailed grounds for appeal to the Agency within 60 days of receipt of the opinion. Within 60 days of receipt of the grounds for appeal, the Committee shall consider whether its opinion should be revised, and the conclusions reached on the appeal shall be annexed to the assessment report referred to in paragraph 5.

5. Within 30 days of its adoption, the Agency shall forward the final opinion of the Committee to the Member States, the Commission and the marketing authorization holder together with a report describing the assessment of the veterinary medicinal product and the reasons for its conclusions.

In the event of an opinion in favour of granting or maintaining an authorization to place the veterinary medicinal product concerned on the market, the following documents shall be annexed to the opinion:

(a) a draft summary of the product characteristics, as referred to in Article 14; where necessary this will reflect differences in the veterinary conditions pertaining in the Member States;

(b) any conditions affecting the authorization within the meaning of paragraph 4.

Article 37

Within 30 days of receipt of the opinion, the Commission shall prepare a draft of the decision to be taken in respect of the application, taking into account Community law.

In the event of a draft decision which envisages the granting of marketing authorization, the documents referred to in Article 36(5)(2), (a) and (b) shall be annexed.

Where, exceptionally, the draft decision is not in accordance with the opinion of the Agency, the Commission shall also annex a detailed explanation of the reasons for the differences.

The draft decision shall be forwarded to the Member States and the applicant.

Article 38

1. A final decision on the application shall be adopted in accordance with the procedure referred to in Article 89(2).

2. The rules of procedure of the Standing Committee set up by Article 89(1) shall be adjusted to take account of the tasks incumbent upon it in accordance with this Chapter.

These adjustments shall involve the following:

— except in cases referred to in the third paragraph of Article 37, the opinion of the Standing Committee shall be obtained in writing,

— each Member State is allowed at least 28 days to forward written observations on the draft decision of the Commission,

— each Member State is able to require in writing that the draft decision be discussed by the Standing Committee, giving its reasons in detail.

Where, in the opinion of the Commission, the written observations of a Member State raise important new questions of a scientific or technical nature which have not been addressed in the opinion of the Agency, the Chairman shall suspend the procedure and refer the application back to the Agency for further consideration.

The provisions necessary for the implementation of this paragraph shall be adopted by the Commission in accordance with the procedure referred to in Article 89(2).

3. A decision as referred to in paragraph 1 shall be addressed to the Member States concerned by the matter and communicated to the marketing authorization holder. The Member States shall either grant or withdraw marketing authorization, or vary the terms of a marketing authorization as necessary to comply with the decision within 30 days of its notification. They shall inform the Commission and the Agency thereof.

Article 39

1. Any application by the marketing authorization holder to vary a marketing authorization which has been granted in accordance with the provisions of this Chapter shall be submitted to all the Member States which have previously authorized the veterinary medicinal product concerned.

The Commission shall, in consultation with the Agency, adopt appropriate arrangements for the examination of variations to the terms of a marketing authorization.

These arrangements shall include a notification system or administration procedures concerning minor variations and define precisely the concept of 'a minor variation'.

These arrangements shall be adopted by the Commission in the form of an implementing regulation in accordance with the procedure referred to in Article 89(2).

2. In case of arbitration submitted to the Commission, the procedure laid down in Articles 36, 37 and 38 shall apply by analogy to variations made to marketing authorizations.

Article 40

1. Where a Member State considers that the variation of the terms of a marketing authorization which has been granted in accordance with the provisions of this Chapter or its suspension or withdrawal is necessary for the protection of human or animal health or the environment, the Member State concerned shall forthwith refer the matter to the Agency for the application of the procedures laid down in Articles 36, 37 and 38.

2. Without prejudice to the provisions of Article 35, in exceptional cases, where urgent action is essential to protect human or animal health or the environment, until a definitive decision is adopted, a Member State may suspend the marketing and the use of the veterinary medicinal product concerned on its territory. It shall inform the Commission and the other Member States no later than the following working day of the reasons for its action.

Article 41

Articles 39 and 40 shall apply by analogy to veterinary medicinal products authorized by Member States following an opinion of the Committee given in accordance with Article 4 of Directive 87/22/EEC before 1 January 1995.

Article 42

1. The Agency shall publish an annual report on the operation of the procedures laid down in this Chapter and shall forward it to the European Parliament and the Council for information.

2. By 1 January 2001, the Commission shall publish a detailed review of the operation of the procedures laid down in this Chapter and shall propose any amendments which may be necessary to improve these procedures.

The Council shall decide, under the conditions provided for in the Treaty, on the Commission proposal within one year of its submission.

Article 43

The provisions of Articles 31 to 38 shall not apply to homeopathic veterinary medicinal products referred to in Article 19(2).

TITLE IV

MANUFACTURE AND IMPORTS

Article 44

1. Member States shall take all appropriate measures to ensure that the manufacture of veterinary medicinal products in their territory is subject to the holding of an authorization. This manufacturing authorization shall likewise be required for veterinary medicinal products intended for export.

2. The authorization referred to in paragraph 1 shall be required both for total and partial manufacture and for the various processes of dividing up, packaging or presentation.

However, such authorization shall not be required for preparation, dividing up, changes in packaging or presentation where these processes are carried out solely for retail supply by pharmacists in dispensing pharmacies or by persons legally authorized in the Member States to carry out such processes.

3. The authorization referred to in paragraph 1 shall also be required for imports from third countries into a Member State; this Title and Article 83 shall apply to such imports in the same way as to manufacture.

Member States shall take all appropriate measures to ensure that veterinary medicinal products brought into their territory from a third country and destined for another Member State are accompanied by a copy of the authorization referred to in paragraph 1.

Article 45

In order to obtain the manufacturing authorization, the applicant shall meet at least the following requirements:

(a) he shall specify the veterinary medicinal products and pharmaceutical forms which are to be manufactured or imported and also the place where they are to be manufactured and/or controlled;

(b) he shall have at his disposal, for the manufacture or import of the above, suitable and sufficient premises, technical equipment and control facilities complying with the legal requirements which the Member State concerned lays down as regards both manufacture and control and the storage of products, in accordance with Article 24;

(c) he shall have at his disposal the services of at least one qualified person within the meaning of Article 52.

The applicant shall provide particulars in his application to establish his compliance with the above requirements.

Article 46

1. The competent authority of the Member State shall not issue the manufacturing authorization until it has established the accuracy of the particulars supplied pursuant to Article 45 by means of an inquiry carried out by its representatives.

2. In order to ensure that the requirements referred to in Article 45 are complied with, authorization may be made conditional on the fulfilment of certain obligations imposed either when authorization is granted or at a later date.

3. The authorization shall apply only to the premises specified in the application and to the veterinary medicinal products and pharmaceutical forms specified in that application.

Article 47

The Member States shall take all appropriate measures to ensure that the time taken for the procedure for granting the manufacturing authorization does not exceed 90 days from the day on which the competent authority receives the application.

Article 48

If the holder of the manufacturing authorization requests a change in any of the particulars referred to in Article 45, first paragraph, (a) and (b), the time taken for the procedure relating to this request shall not exceed 30 days. In exceptional cases, this period of time may be extended to 90 days.

Article 49

The competent authority of the Member States may require from the applicant further information concerning both the particulars supplied pursuant to Article 45 and the qualified person referred to in Article 52; where the competent authority concerned exercises this right, application of the time-limits referred to in Articles 47 and 48 shall be suspended until the additional data required have been supplied.

Article 50

The holder of a manufacturing authorization shall at least be obliged to:

(a) have at his disposal the services of staff complying with the legal requirements existing in the Member State concerned as regards both manufacture and controls;

(b) dispose of the authorized veterinary medicinal products only in accordance with the legislation of the Member States concerned;

(c) give prior notice to the competent authority of any changes which he may wish to make to any of the particulars supplied pursuant to Article 45; the competent authority shall, in any event, be immediately informed if the qualified person referred to in Article 52 is replaced unexpectedly;

(d) allow the representatives of the competent authority of the Member State concerned access to his premises at any time;

(e) enable the qualified person referred to in Article 52 to carry out his duties, particularly by placing at his disposal all the necessary facilities;

(f) comply with the principles and the guidelines of good manufacturing practice for medicinal products laid down by Community law;

(g) keep detailed records of all veterinary medicinal products supplied by him, including samples, in accordance with the laws of the countries of destination. The following information at least shall be recorded in respect of each transaction, whether or not it is made for payment:

— date,

— name of the veterinary medicinal product,

— quantity supplied,

— name and address of the recipient,

— batch number.

These records shall be available for inspection by the competent authorities for a period of at least three years.

Article 51

The principles and guidelines of good manufacturing practice for veterinary medicinal products referred to in Article 50(f) shall be adopted in the form of a Directive addressed to the Member States in accordance with the procedure referred to in Article 89(2).

Detailed guidelines shall be published by the Commission and revised as appropriate to take account of scientific and technical progress.

Article 52

1. Member States shall take all appropriate measures to ensure that the holder of the manufacturing authorization has permanently and continuously at his disposal the services of at least one qualified person who fulfils the conditions laid down in Article 53 and is responsible, in particular, for carrying out the duties specified in Article 55.

2. If he personally fulfils the conditions laid down in Article 53, the holder of the authorization may himself assume the responsibility referred to in paragraph 1.

Article 53

1. Member States shall ensure that the qualified person referred to in Article 52 fulfils the minimum conditions of qualification set out in paragraphs 2 and 3.

2. The qualified person shall be in possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course of study, or a course recognized as equivalent by the Member State concerned, extending over a period of at least four years of theoretical and practical study in one of the following scientific disciplines: pharmacy, medicine, veterinary science, chemistry, pharmaceutical chemistry and technology, biology.

However, the minimum duration of the university course may be three and a half years where the course is followed by a period of theoretical and practical training of at least one year and includes a training period of at least six months in a pharmacy open to the public, corroborated by an examination at university level.

Where two university or recognized equivalent courses coexist in a Member State and where one of these extends over four years and the other over three years, the diploma, certificate or other evidence of formal qualifications awarded on completion of the three-year university course or its recognized equivalent shall be considered to fulfil the condition of duration referred to in the first subparagraph in so far as the diplomas, certificates or other evidence of formal qualifications awarded on completion of both courses are recognized as equivalent by the State in question.

The course shall include theoretical and practical tuition bearing upon at least the following basic subjects:

— experimental physics,

— general and inorganic chemistry,

— organic chemistry,

— analytical chemistry,

— pharmaceutical chemistry, including analysis of medicinal products,

— general and applied biochemistry (medical),

— physiology,

— microbiology,

— pharmacology,

— pharmaceutical technology,

— toxicology,

— pharmacognosy (study of the composition and effects of the active principles of natural substances of plant and animal origin).

Tuition in these subjects should be so balanced as to enable the person concerned to fulfil the obligations specified in Article 55.

In so far as certain diplomas, certificates or other evidence of formal qualifications mentioned in this paragraph do not fulfil the criteria laid down above, the competent authority of the Member State shall ensure that the person concerned provides evidence that he has, in the subjects involved, the knowledge required for the manufacture and control of veterinary medicinal products.

3. The qualified person shall have acquired practical experience over at least two years, in one or more undertakings which are authorized manufacturers, in the activities of qualitative analysis of medicinal products, of quantitative analysis of active substances and of the testing and checking necessary to ensure the quality of veterinary medicinal products.

The duration of practical experience may be reduced by one year where a university course lasts for at least five years and by a year and a half where the course lasts for at least six years.

Article 54

1. A person engaging, in a Member State, in the activities of the person referred to in Article 52 at the date on which

Directive 81/851/EEC became applicable, without complying with the provisions of Article 53 shall be eligible to continue to engage in those activities in the State concerned.

2. The holder of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course — or a course recognized as equivalent by the Member State concerned — in a scientific discipline allowing him to engage in the activities of the person referred to in Article 52 in accordance with the laws of that State may — if he began his course prior to 9 October 1981 — be considered as qualified to carry out in that State the duties of the person referred to in Article 52, provided that he has previously engaged in the following activities for at least two years before 9 October 1991 in one or more undertakings with a manufacturing authorization; production supervision and/or qualitative and quantitative analysis of active substances, and the necessary testing and checking under the direct authority of a person as referred to in Article 52 to ensure the quality of veterinary medicinal products.

If the person concerned has acquired the practical experience referred to in the first subparagraph before 9 October 1971, a further one year's practical experience in accordance with the conditions referred to in the first subparagraph shall be completed by him immediately before he engages in such activities.

Article 55

1. Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 52 is, without prejudice to his relationship with the holder of the manufacturing authorization, responsible, in the context of the procedures referred to in Article 56, for ensuring that:

(a) in the case of veterinary medicinal products manufactured within the Member State concerned, each batch of veterinary medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorization;

(b) in the case of veterinary medicinal products coming from third countries, each production batch imported has undergone in the importing Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of veterinary medicinal products in accordance with the requirements of the marketing authorization.

Batches of veterinary medicinal products which have undergone such controls in a Member State shall be exempt from the above controls if they are placed on the market in another Member State, accompanied by the control reports signed by the qualified person.

2. In the case of veterinary medicinal products imported from a third country, where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the veterinary medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the Community and to ensure that the controls referred to under point (b) of the first subparagraph of paragraph 1 have been carried out in the exporting country, the qualified person may be relieved of responsibility for carrying out those controls.

3. In all cases, and particularly where the veterinary medicinal products are released for sale, the qualified person shall certify, in a register or equivalent document provided for the purpose, that each production batch satisfies the provisions of this Article; the said register or equivalent document shall be kept up to date as operations are carried out and shall remain at the disposal of the representatives of the competent authority for the period specified in the provisions of the Member State concerned and, in any event, for at least five years.

Article 56

Member States shall ensure that the obligations of qualified persons referred to in Article 52 are fulfilled, either by means of appropriate administrative measures or by making such persons subject to a professional code of conduct.

Member States may provide for the temporary suspension of such a person upon the commencement of administrative or disciplinary proceedings against him for failure to fulfil his obligations.

Article 57

The provisions of this Title shall apply to homeopathic veterinary medicinal products.

TITLE V

LABELLING AND PACKAGE INSERT

Article 58

1. The following information, which shall conform with the particulars and documents provided pursuant to Articles 12 and 13(1) and be approved by the competent authorities, shall appear in legible characters on containers and outer packages of medicinal products:

(a) Name of the veterinary medicinal product, which may be a brand name or a non-proprietary name accompanied by a trade mark or the name of the manufacturer, or a scientific name or formula, with or without a trade mark, or the name of the manufacturer.

Where the special name of a medicinal product containing only one active substance is a brand name, this name must be accompanied in legible characters by the international non-propriety name recommended by the World Health Organization, where such name exists or, where no such name exists, by the usual non-proprietary name;

(b) A statement of the active substances expressed qualitatively and quantitatively per dosage unit or according to the form of administration for a particular volume or weight, using the international non-proprietary names recommended by the World Health Organization, where such names exist or, where no such names exist, the usual non-proprietary names;

(c) Manufacturer's batch number;

(d) Marketing authorization number;

(e) Name or corporate name and permanent address or registered place of business of the marketing authorization holder and of the manufacturer, if different;

(f) The species of animal for which the veterinary medicinal product is intended; the method and route of administration;

(g) The withdrawal period, even if nil, in the case of veterinary medicinal products administered to food-producing animals;

(h) Expiry date, in plain language;

(i) Special storage precautions, if any;

(j) Special precautions for disposal of unused medicinal products or waste material from medicinal products, if any;

(k) Particulars required to be indicated pursuant to Article 26(1), if any;

(l) The words 'For animal treatment only'.

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

3. The provisions of Part 1, A of Annex I, in so far as they concern the qualitative and quantitative composition of veterinary medicinal products in respect of active substances, shall apply to the particulars provided for in paragraph 1(b).

4. The particulars mentioned in paragraph 1(f) to (l) shall appear on the outer package and on the container of the medicinal products in the language or languages of the country in which they are placed on the market.

Article 59

1. As regards ampoules, the particulars listed in the first paragraph of Article 58(1) shall be given on the outer package. On the containers, however, only the following particulars shall be necessary:

— name of veterinary medicinal product,

— quantity of the active substances,

— route of administration,

— manufacturer's batch number,

— date of expiry,

— the words 'For animal treatment only'.

2. As regards small single-dose containers, other than ampoules, on which it is impossible to give the particulars mentioned in paragraph 1, the requirements of Article 58(1), (2) and (3), shall apply only to the outer package.

3. The particulars mentioned in the third and sixth indents of paragraph 1 shall appear on the outer package and on the container of the medicinal products in the language or languages of the country in which they are placed on the market.

Article 60

Where there is no outer package, all the particulars which should feature on such a package pursuant to the Articles 58 and 59 shall be shown on the container.

Article 61

1. The inclusion of a package insert in the packaging of veterinary medicinal products shall be obligatory unless all the information required by this Article can be conveyed on the container and the external packaging. Member States shall take all appropriate measures to ensure that the insert relates solely to the veterinary medicinal product with which it is included. The insert shall be in the official language or languages of the Member State in which the medicinal product is marketed.

2. The package insert shall contain at least the following information, which shall conform to the particulars and documents provided pursuant to Articles 12 and 13(1) and be approved by the competent authorities:

(a) name or corporate name and permanent address or registered place of business of the marketing authorization holder and of the manufacturer, if different;

(b) name of the veterinary medicinal product and a statement of its active substances expressed qualitatively and quantitatively;

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

(c) the therapeutic indications;

(d) contra-indications and adverse reactions in so far as these particulars are necessary for the use of the veterinary medicinal product;

(e) the species of animal for which the veterinary medicinal product is intended, the dosage for each species, the method and route of administration and advice on correct administration, if necessary;

(f) the withdrawal period, even if this is nil, in the case of veterinary medicinal products administered to food-producing animals;

(g) special storage precautions, if any;

(h) particulars required to be indicated pursuant to Article 26(1), if any;

(i) special precautions for the disposal of unused medicinal products or waste materials from medicinal products, if any.

3. The particulars referred to in paragraph 2 shall appear in the language or languages of the country in which the product is marketed. The other information shall be clearly separate from such particulars.

Article 62

Where the provisions of this Title are not observed and a formal notice addressed to the person concerned has been ineffectual, the competent authorities of the Member States may suspend or withdraw marketing authorization.

Article 63

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 Title.

Article 64

1. Without prejudice to paragraph 2, homeopathic veterinary medicinal products shall be labelled in accordance with the provisions of this title and identified by the inclusion on their labels, in clearly legible form, of the words 'homeopathic medicinal product for veterinary use'.

2. In addition to the clear mention of the words 'homeopathic veterinary medicinal product without approved therapeutic indications', the labelling and, where appropriate, package insert for the homeopathic veterinary medicinal products referred to in Article 17(1) shall bear the following information and no other information:

— the scientific name of the stock or stocks followed by the degree of dilution, using the symbols of the pharmacopoeia used in accordance with point 8 of Article 1,

— name and address of the marketing authorization holder and, where appropriate, of the manufacturer,

— method of administration and, if necessary, route,

— expiry date, in clear terms (month, year),

— pharmaceutical form,

— contents of the sales presentation,

— special storage precautions, if any,

— target species,

— a special warning if necessary for the medicinal product,

— manufacturer's batch number,

— registration number.

TITLE VI

POSSESSION, WHOLESALE DISTRIBUTION AND DISPENSING OF VETERINARY MEDICINAL PRODUCTS

Article 65

1. Member States shall take all appropriate measures to ensure that wholesale distribution of veterinary medicinal products is subject to the holding of an authorization and to ensure that the time taken for the procedure for granting this authorization does not exceed 90 days from the date on which the competent authority receives the application.

Member States may exclude supplies of small quantities of veterinary medicinal products from one retailer to another from the scope of the definition of wholesale distribution.

2. In order to obtain the authorization for distribution, the applicant shall have at his disposal technically competent staff and suitable and sufficient premises complying with the requirements laid down in the Member State concerned as regards the storage and handling of veterinary medicinal products.

3. The holder of the authorization for distribution shall be required to keep detailed records. The following minimum information shall be recorded in respect of each incoming or outgoing transaction:

(a) date;

(b) precise identity of the veterinary medicinal product;

(c) manufacturer's batch number, expiry date;

(d) quantity received or supplied;

(e) name and address of the supplier or recipient.

At least once a year a detailed audit shall be carried out to compare incoming and outgoing medicinal supplies with supplies currently held in stock, any discrepancies being recorded.

These records shall be available for inspection by the competent authorities for a period of at least three years.

4. Member States shall take all appropriate measures to ensure that wholesalers supply veterinary medicinal products only to persons permitted to carry out retail activities in accordance with Article 66, or to other persons who are lawfully permitted to receive veterinary medicinal products from wholesalers.

Article 66

1. Member States shall take all appropriate measures to ensure that the retail supply of veterinary medicinal products is conducted only by persons who are permitted to carry out such operations by the legislation of the Member State concerned.

2. Any person permitted under paragraph 1 to sell veterinary medicinal products shall be required to keep detailed records. The following information shall be recorded in respect of each incoming or outgoing transaction:

(a) date;

(b) precise identity of the veterinary medicinal product;

(c) manufacturer's batch number;

(d) quantity received or supplied;

(e) name and address of the supplier or recipient;

(f) where relevant, name and address of the prescribing veterinarian and a copy of the prescription.

At least once a year a detailed audit shall be carried out, and incoming and outgoing veterinary medicinal products shall be reconciled with products currently held in stock, any discrepancies being recorded.

These records shall be available for inspection by the competent authorities for a period of three years.

3. Member States may limit the number of detailed documenting requirements referred to in paragraph 2. However, these requirements shall always be applied in case of veterinary medicinal products which are intended for administration to food-producing animals and which are available only on veterinary prescription or in respect of which a withdrawal period must be observed.

4. Not later that 1 January 1992, Member States shall communicate to the Commission a list of the veterinary medicinal products which are available without prescription.

After having taken note of the communication from the Member States, the Commission shall examine whether suitable measures should be proposed for drawing up a Community list of such medicinal products.

Article 67

Without prejudice to stricter Community or national rules relating to dispensing veterinary medicinal products and to protect human and animal health, a prescription shall be required for dispensing to the public the following veterinary medicinal products;

(a) those products subject to official restrictions on supply or use, such as:

— the restrictions resulting from the implementation of the relevant United Nations conventions on narcotic and psychotropic substances,

— the restrictions on the use of veterinary medicinal products resulting from Community law;

(b) those products in respect of which special precautions must be taken by the veterinarian in order to avoid any unnecessary risk to:

— the target species,

— the person administering the products to the animal,

— the consumer of foodstuffs obtained from the treated animal,

— the environment;

(c) those products intended for treatments or pathological processes which require a precise prior diagnosis or the use of which may cause effects which impede or interfere with subsequent diagnostic or therapeutic measures;

(d) magistral formulae intended for animals.

In addition, a prescription shall be required for new veterinary medicinal products containing an active substance which has been authorized for use in a veterinary medicinal product for less than five years unless, having regard to the information and particulars provided by the applicant, or experience acquired in the practical use of the veterinary medicinal product, the competent authorities are satisfied that none of the criteria referred to in (a) to (d) of the first paragraph apply.

Article 68

1. Member States shall take all measures necessary to ensure that only persons empowered under their national legislation in force possess or have under their control veterinary medicinal products or substances which may be used as veterinary medicinal products that have anabolic, anti-infectious, anti-parasitic, anti-inflammatory, hormonal or psychotropic properties.

2. Member States shall maintain a register of manufacturers and dealers permitted to be in possession of active substances which may be used in the manufacture of veterinary medicinal products having the properties referred to in paragraph 1.

Such persons must maintain detailed records of all dealings in substances which may be used in the manufacture of veterinary medicinal products and keep these records available for inspection by the competent authorities for a period of at least three years.

3. Any amendments to be made to the list of substances referred to in paragraph 1 shall be adopted in accordance with the procedure referred to in Article 89(2).

Article 69

Member States shall ensure that the owners or keepers of food-producing animals can provide proof of purchase, possession and administration of veterinary medicinal products containing the substances set out in Article 68; Member States may extend the scope of this obligation to other veterinary medicinal products.

In particular, Member States may require the maintenance of a record giving at least the following information:

(a) date;

(b) name of the veterinary medicinal product;

(c) quantity;

(d) name and address of the supplier of the medicinal product;

(e) identification of the animals treated.

Article 70

Notwithstanding Articles 9 and 67, Member States shall ensure that veterinarians providing services in another Member State can take with them and administer to animals small quantities of ready-made veterinary medicinal products not exceeding daily requirements other than immunological veterinary medicinal products which are not authorized for use in the Member State in which the services are provided (hereinafter: host Member State), providing that the following conditions are satisfied:

(a) the authorization to place the product on the market provided for in Articles 5, 7 and 8 has been issued by the competent authorities of the Member State in which the veterinarian is established;

(b) the veterinary medicinal products are transported by the veterinarian in the original manufacturer's packaging;

(c) the veterinary medicinal products intended for administration to food-producing animals have the same qualitative and quantitative composition in terms of active substances as the medicinal products authorized in accordance with Articles 5, 7 and 8 in the host Member State;

(d) the veterinarian providing services in another Member State acquaints himself with the good veterinary practices applied in that Member State and ensures that the withdrawal period specified on the labelling of the veterinary medicinal product concerned is complied with, unless he could reasonably be expected to know that a longer withdrawal period should be specified to comply with these good veterinary practices;

(e) the veterinarian shall not furnish any veterinary medicinal product to the owner or keeper of the animals treated in the host Member State unless this is permissible on the basis of the rules of the host Member State; in this case he shall, however, supply only in relation to animals under his care and only the minimum quantities of veterinary medicinal product necessary to complete the treatment of animals concerned on that occasion;

(f) the veterinarian shall be required to keep detailed records of the animals treated, the diagnosis, the veterinary medicinal products administered, the dosage administered, the duration of treatment and the withdrawal period applied. These records shall be available for inspection by the competent authorities of the host Member State for a period of at least three years;

(g) the overall range and quantity of veterinary medicinal products carried by the veterinarian shall not exceed that generally required for the daily needs of good veterinary practice.

Article 71

1. In the absence of specific Community legislation concerning the use of immunological veterinary medicinal products for the eradication or control of animal disease, a Member State may, in accordance with its national legislation, prohibit the manufacture, import, possession, sale, supply and/or use of immunological veterinary medicinal products on the whole or part of its territory if it is established that:

(a) the administration of the product to animals will interfere with the implementation of a national programme for the diagnosis, control or eradication of animal disease, or will cause difficulties in certifying the absence of contamination in live animals or in foodstuffs or other products obtained from treated animals;

(b) the disease to which the product is intended to confer immunity is largely absent from the territory in question.

2. The competent authorities of the Member States shall inform the Commission of all instances in which the provisions of paragraph 1 are applied.

TITLE VII

PHARMACOVIGILANCE

Article 72

1. Member States shall take all appropriate measures to encourage the reporting to the competent authorities of suspected adverse reactions to veterinary medicinal products.

2. The Member States may impose specific requirements on veterinary practitioners and other health care professionals in respect of the reporting of suspected serious or unexpected adverse reactions and human adverse reactions, in particular where such reporting is a condition of the marketing authorization.

Article 73

In order to ensure the adoption of appropriate regulatory decisions concerning the veterinary medicinal products authorised within the Community, having regard to information obtained about suspected adverse reactions to veterinary medicinal products under normal conditions of use, the Member States shall establish a veterinary pharmacovigilance system. This system shall be used to collect information useful in the surveillance of veterinary medicinal products, with particular reference to adverse reactions in animals and in human beings related to the use of veterinary medicinal products, and to evaluate such information scientifically.

Such information shall be collated with available data on the sale and prescription of veterinary medicinal products.

This system also takes into account any available information related to the lack of expected efficacy, off-label use, investigations of the validity of the withdrawal period and on potential environmental problems, arising from the use of the product, interpreted in accordance with the Commission guidelines referred to in Article 77(1), which may have an impact on the evaluation of their benefits and risks.

Article 74

The marketing authorization holder shall have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance.

That qualified person shall be responsible for the following:

(a) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the company, including its representatives, is collected and collated in order to be accessible at least at one point within the Community;

(b) the preparation for the competent authorities of the reports referred to in Article 75, in such form as may be laid down by those authorities, in accordance with the guidance referred to in Article 77(1);

(c) ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a veterinary medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the veterinary medicinal product concerned;

(d) the provision to the competent authorities, of any other information relevant to the evaluation of the benefits and risks afforded by a veterinary medicinal product, including appropriate information on post-marketing surveillance studies.

Article 75

1. The marketing authorization holder shall be required to maintain detailed records of all suspected adverse reactions occurring either in the Community or in a third country.

2. The marketing authorization holder shall be required to record and to report all suspected serious adverse reactions and human adverse reactions related to the use of veterinary medicinal products, of which he can reasonably be expected to have knowledge, or which are brought to his attention, immediately to the competent authority of the Member State in whose territory the incident occurred, and in no case later than 15 calendar days following the receipt of the information.

3. The marketing authorization holder shall ensure that the suspected serious and unexpected adverse reactions and human adverse reactions, occurring in the territory of a third country, are reported immediately in accordance with the guidance referred to in Article 77(1), so that they are available to the Agency and to the competent authorities in the Member State(s) where the veterinary medicinal product is authorized, and in no case later than 15 calendar days following the receipt of the information.

4. In the case of veterinary medicinal products which have been considered within the scope of Directive 87/22/EEC, or which have benefited from the procedures of mutual recognition under Articles 21, 22 and 32(4) of this Directive and veterinary medicinal products for which there has been a referral to the procedures under Articles 36, 37 and 38 of this Directive, the marketing authorisation holder shall additionally ensure that all suspected serious adverse reactions and human adverse reactions, occurring in the Community, are reported in the format and at intervals to be agreed with the reference Member State or a competent authority designated as reference Member State, in such a way so as to be accessible to the reference Member State.

5. Unless other requirements have been laid down as condition of the granting of authorization, records of all adverse reactions shall be submitted to the competent authorities in the form of a periodic safety update report, either immediately upon request or periodically as follows: six monthly for the first two years after authorization, annually for the subsequent two years, and at the same time of the first

renewal. Thereafter, the periodic safety update reports shall be submitted at five-yearly intervals together with the application for renewal of the authorization. The periodic safety update report shall include a scientific evaluation of the benefits and risks afforded by the veterinary medicinal product.

6. Following the granting of a marketing authorization, the marketing authorization holder may request the amendment of the periods referred to in this Article according to the procedure laid down by the Commission Regulation (EC) No 541/95 ([1]), if applicable.

Article 76

1. The Agency, in collaboration with the Member States and the Commission shall set up a data-processing network to facilitate the exchange of pharmacovigilance information regarding medicinal products marketed in the Community.

2. Making use of the network foreseen in the first paragraph, Member States shall ensure that reports of suspected serious adverse reactions and human adverse reactions, in accordance with the guidance referred to in Article 77(1), that have taken place on their territory are immediately made available to the Agency and the other Member States, and in any case within 15 calendar days of their notification, at the latest.

3. The Member States shall ensure that reports of suspected serious adverse reactions and human adverse reactions, that have taken place on their territory are immediately made available to the marketing authorisation holder, and in any case within 15 calendar days of their notification at the latest.

Article 77

1. In order to facilitate the exchange of information about pharmacovigilance within the Community, the Commission, in consultation with the Agency, Member States and the interested parties, shall draw up guidance on the collection, verification and presentation of adverse reaction reports, including technical requirements for electronic exchange of veterinary pharmacovigilance information in accordance with internationally agreed terminology.

This guidance shall be published in Volume 9 of the Rules governing medicinal products in the European Community and shall take account of international harmonisation work carried out in the field of pharmacovigilance.

2. For the interpretation of the definitions referred to in Article 1 points 10 to 16 and principles outlined in this title, the marketing authorisation holder and the competent authorities shall refer to the detailed guidance referred to in paragraph 1.

([1]) OJ L 55, 11.3.1995, p. 7. Regulation amended by Regulation (EC) No 1146/98 (OJ L 159, 3.6.1998, p. 31).

Article 78

1. Where, as a result of the evaluation of veterinary pharmacovigilance data, a Member State considers that a marketing authorization should be suspended, withdrawn or varied to restrict the indications or availability, amend the posology, add a contraindication or add a new precautionary measure, it shall forthwith inform the Agency, the other Member States and the marketing authorization holder.

2. In case of urgency, the Member State concerned may suspend the marketing authorization of a veterinary medicinal product, provided the Agency, the Commission and the other Member States are informed at the latest on the following working day.

Article 79

Any amendments which may be necessary to update the provisions of Articles 72 to 78 to take account of scientific and technical progress shall be adopted in accordance with the procedure referred to in Article 89(2).

TITLE VIII

SUPERVISION AND SANCTIONS

Article 80

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

Such inspections shall be carried out by authorized representatives of the competent authority who shall be empowered to:

(a) inspect manufacturing or trading establishments and any laboratories entrusted by the holder of the manufacturing authorization, with the task of carrying out control tests pursuant to Article 24;

(b) take samples;

(c) examine any documents relating to the object of the inspection, subject to current provisions in the Member States from 9 October 1981 which place restrictions on these powers with regard to the description of the manufacturing method.

2. Member States shall take all appropriate measures to ensure that the manufacturing processess used in the manufacture of immunological veterinary medicinal products are completely validated and batch-to-batch consistency is ensured.

3. The officials representing the competent authority shall report after each of the inspections mentioned in the first paragraph on whether the manufacturer complies with the principles and guidelines of good manufacturing practice referred to in Article 51. The inspected manufacturer shall be informed of the content of such reports.

Article 81

1. Member States shall take all appropriate measures to ensure that the marketing authorization holder and, where appropriate, the holder of the manufacturing authorization furnish proof of the control tests carried out on the veterinary medical product and/or on the constituents and intermediate products of the manufacturing process, in accordance with the methods laid down for the purposes of marketing authorization.

2. For the purposes of implementing paragraph 1, Member States may require the marketing authorization holder for immunological veterinary medicinal products to submit to the competent authorities copies of all the control reports signed by the qualified person in accordance with Article 55.

The marketing authorization holder for immunological veterinary medicinal products shall ensure that an adequate number of representative samples of each batch of veterinary medical products is held in stock at least up to the expiry date, and provide samples promptly to the competent authorities on request.

Article 82

1. Where it considers it necessary, a Member State may require the marketing authorization holder for immunological products to submit samples from the batches of the bulk and/or medical product for examination by a State laboratory or an approved laboratory before entry into circulation.

In the case of a batch manufactured in another Member State, examined by the competent authority of another Member State and declared to be in conformity with national specifications, such a control may be carried out only after the control reports of the batch in question have been examined, after the Commission has been informed, and where the difference in veterinary conditions between the two Member States concerned justifies it.

2. Except where the Commission has been informed that a longer period is necessary to complete the analyses, Member States shall ensure that any such examination is completed within 60 days of receipt of the samples. The marketing authorization holder shall be notified of the results of the examination within the same time-limit.

3. Before 1 January 1992, the Member States shall notify the Commission of the immunological veterinary medicinal products subject to compulsory official control before being placed on the market.

Article 83

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

(a) the veterinary medicinal product proves to be harmful under the conditions of use stated at the time of application for authorization or subsequently;

(b) the veterinary medicinal product does not have any therapeutic effect on the species of animal for which the treatment is intended;

(c) its qualitative and quantitative composition is not as stated;

(d) the recommended withdrawal period is inadequate to ensure that foodstuffs obtained from the treated animal do not contain residues which might constitute a health hazard to the consumer;

(e) the veterinary medicinal product is offered for sale for a use which is prohibited by other community provisions.

However, pending Community rules, the competent authorities may refuse to grant authorization for a veterinary medicinal product where such action is necessary for the protection of public, consumer or animal health;

(f) the information given in the application documents pursuant to Article 12, 13(1) and 27 is incorrect;

(g) the control tests referred to in Article 81(1) have not been carried out;

(h) the obligation referred to in Article 26(2) has not been fulfilled.

2. Authorization may be suspended, or withdrawn where it is established that:

(a) the particulars supporting the application, as provided for in Articles 12 and 13(1), have not been amended in accordance with Article 27(1) and (5);

(b) any new information as referred to in Article 27(3) has not been communicated to the competent authorities.

Article 84

1. Without prejudice to Article 83, Member States shall take all necessary measures to ensure that supply of a veterinary medicinal product is prohibited and that the medicinal product concerned is withdrawn form the market where:

(a) it is clear that the veterinary medicinal product is harmful under the conditions of use stated at the time of the application for authorization or subsequently, pursuant to Article 27(5);

(b) the veterinary medicinal product has no therapeutic effect on the species of animal for which the treatment was intended;

(c) the qualitative and quantitative composition of the veterinary medicinal product is not as stated;

(d) the recommended withdrawal period is inadequate to ensure that foodstuffs obtained from the treated animal do not contain residues which might constitute a health hazard to the consumer;

(e) the control tests referred to in Article 81(1) have not been carried out, or any other requirement or obligation relating to the grant of the manufacturing authorization referred to in Article 44(1) has not been complied with.

2. The competent authority may confine the prohibition on supply and withdrawal from the market solely to the contested production batches.

Article 85

1. The competent authority of a Member State shall suspend or withdraw the manufacturing authorization for a category of preparations or for all preparations if any of the requirements laid down in Article 45 are no longer met.

2. The competent authority of a Member State may, in addition to the measures provided for in Article 84, either suspend manufacture or imports of veterinary medicinal products from third countries or suspend or withdraw the manufacturing authorization for a category of preparations or for all preparations in the event of non-compliance with the provisions regarding manufacture or imports from third countries.

Article 86

The provisions of this Title shall apply to homeopathic veterinary medicinal products.

Article 87

Member States shall take appropriate measures to encourage veterinarians and other professionals concerned to report to the competent authorities any adverse reaction of veterinary medicinal products.

TITLE IX

STANDING COMMITTEE

Article 88

Any changes which are necessary in order to adapt Annex I to take account of technical progress shall be adopted in accordance with the procedure referred to in Article 89(2).

Article 89

1. The Commission shall be assisted by a Standing Committee on Veterinary Medicinal Products for the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Veterinary Medicinal Products Sector, (hereinafter referred to as the 'Standing Committee'.

2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period provided for in Article 5(6) of Decision 1999/468/EC shall be set at three months.

3. The Standing Committee shall adopt its rules of procedure.

TITLE X

GENERAL PROVISIONS

Article 90

Member States shall take all measures necessary to ensure that the competent authorities concerned communicate the appropriate information to each other, in particular regarding compliance with the requirements adopted for manufacturing authorization, or for authorization to place products on the market.

Upon reasoned request, Member States shall forthwith communicate the reports referred to in Article 80(3) to the competent authorities of another Member State. If, after considering the reports, the Member State receiving the reports considers that it cannot accept the conclusions reached by the competent authority of the Member State in which the report was established, it shall inform the competent authorities concerned of its reasons and may request further information. The Member States concerned shall attempt to reach agreement. If necessary, in the event of serious differences of opinion, one of the Member States concerned shall inform the Commission.

Article 91

1. Each Member State shall take all appropriate measures to ensure that the Agency is informed immediately of decisions granting marketing authorization and of all decisions refusing or withdrawing 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.

2. The marketing authorization holder shall be obliged to notify the Member States forthwith of any action taken by him to suspend the marketing of a veterinary medicinal product or to withdraw a product from the market, together with the reasons for such action if it concerns the effectiveness of the veterinary medicinal product or the protection of public health. Member States shall ensure that this information is brought to the attention of the Agency.

3. Member States shall ensure that appropriate information about actions taken pursuant to paragraphs 1 and 2 which may affect the protection of health in third countries is

forthwith brought to the attention of the relevant international organizations, with a copy to the Agency.

Article 92

Member States shall communicate to each other all the information necessary to guarantee the quality and safety of homeopathic veterinary medicinal products manufactured and marketed within the Community, and in particular the information referred to in Articles 90 and 91.

Article 93

1. At the request of the manufacturer or exporter of veterinary medicinal products, or the authorities of an importing third country, Member States shall certify that such manufacturer is in possession of the manufacturing authorization. When issuing such certificates, Member States shall comply with the following conditions:

(a) they shall have regard to the prevailing administrative arrangements of the World Health Organization;

(b) for veterinary medicinal products intended for export which are already authorized in their territory, they shall supply the summary of the product characteristics as approved in accordance with Article 25 or, in the absence thereof, an equivalent document.

2. Where the manufacturer is not in possession of an authorization to place the product on the market, he shall provide the authorities responsible for establishing the certificate referred to in the first paragraph with a declaration explaining why such authorization is not available.

Article 94

Any decision referred to in this Directive, taken by the competent authorities of the Member States, may only be taken on the grounds set out in this Directive and shall state in detail the reasons on which it is based.

Such a decision 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 allowed for seeking such remedies.

Marketing authorizations and revocations of such authorizations shall be published by each Member State in its official gazette.

Article 95

The Member States shall not permit foodstuffs for human consumption to be taken from test animals unless maximum residue limits have been established by the Community in accordance with the provisions of Regulation (EEC) No 2377/90 and an appropriate withdrawal period has been established to ensure that this maximum limit will not be exceeded in the foodstuffs.

TITLE XI

FINAL MEASURES

Article 96

Directives 81/851/EEC, 81/852/EEC, 90/677/EEC and 92/74/EEC referred to in Annex II, Part A are repealed, without prejudice to the obligations of the Member States in respect of the deadline for transposition laid down in Annex II, Part B.

The reference made to the said Repealed Directives shall be construed as references to this Directive and should be read in accordance with the correlation table set out in Annex III.

Article 97

This Directive enters into force on the 20th day following that of its publication in the *Official Journal of the European Communities*.

Article 98

This Directive is addressed to the Member States.

Done at Brussels, 6 November 2001.

For the European Parliament	*For the Council*
The President	*The President*
N. FONTAINE	D. REYNDERS

ANNEX I

REQUIREMENTS AND ANALYTICAL PROTOCOL, SAFETY TESTS, PRE-CLINICAL AND CLINICAL FOR TESTS OF VETERINARY MEDICINAL PRODUCTS

INTRODUCTION

The particulars and documents accompanying an application for marketing authorization pursuant to Articles 12 and 13(1) shall be presented in accordance with the requirements set out in this Annex and taking account of the guidance contained in the 'Notice to applicants for marketing authorizations for veterinary medicinal products in the Member States of the European Community', published by the Commission in *The rules governing medicinal products in the European Community*, volume V: *Veterinary Medicinal Products*.

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

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

Member States ensure that all experiments on animals are conducted in accordance with Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes ([1]).

The provisions of Title I of this Annex shall apply to veterinary medicinal products other than immunological veterinary medicinal products.

The provisions of Title II of this Annex shall apply to immunological veterinary medicinal products.

TITLE I

Requirements for veterinary medicinal products other than immunological veterinary medicinal products

PART 1

Summary of the dossier

A. ADMINISTRATIVE DATA

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

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

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

Annexed to the administrative data shall be a document showing that the manufacturer is authorized to produce the veterinary medicinal products concerned, as defined in Article 44, together with a list of countries in which authorization has been granted, copies of all the summaries of product characteristics in accordance with Article 14 as approved by Member States and a list of countries in which an application has been submitted.

B. SUMMARY OF PRODUCT CHARACTERISTICS

The applicant shall propose a summary of the product characteristics, in accordance with Article 14 of this Directive.

([1]) OJ L 358, 18.12.1986, p. 1.

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

C. EXPERT REPORTS

In accordance with Article 15(2) and (3), expert reports must be provided on the analytical documentation, the pharmacotoxicological documentation, the residues documentation and the clinical documentation.

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

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

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

PART 2

Analytical (physico-chemical, biological or microbiological) tests of veterinary medicinal products other than immunological veterinary medicinal products

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

All the test procedure(s) shall be described in sufficiently precise detail so as to be reproducible in control tests, carried out at the request of the competent authority; any special apparatus and equipment which may be used shall be described in adequate detail, possibly accompanied by a diagram. The formulae of the laboratory reagents shall be supplemented, if necessary, by the method of preparation. In the case of test procedures included in the *European Pharmacopoeia* or the pharmacopoeia of a Member State, this description may be replaced by a detailed reference to the pharmacopoeia in question.

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

The particulars and documents which must accompany applications for marketing authorization, pursuant to Article 12(3)(c), shall be submitted in accordance with the following requirements.

1. **Qualitative particulars**

'Qualitative particulars' of all the constituents of the medicinal product shall mean the designation or description of:

— the active substance(s),

— the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc,

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

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

2. The 'usual terminology', to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions of Article 12(3)(c):

— in respect of substances which appear in the *European Pharmacopoeia* or, failing this, in the national pharmacopoeia of one of the Member States, the main title at the head of the monograph in question, with reference to the pharmacopoeia concerned,

— in respect of other substances, the international non-proprietary name recommended by the World Health Organization (WHO), which may be accompanied by another non-proprietary name, or, failing these, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,

— in respect of colouring matter, designation by the 'E' code assigned to them in Council Directive 78/25/EEC of 12 December 1977 on the approximation of the rules of the Member States concerning the colouring matters authorized for use in medicinal products [1].

3. **Quantitative particulars**

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

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

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

This information shall be supplemented:

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

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

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

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

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

4. **Development pharmaceutics**

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

B. DESCRIPTION OF THE MANUFACTURING METHOD

The description of the manufacturing method accompanying the application for marketing authorization pursuant to Article 12(3)(d), shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.

For this purpose it shall include at least:

— mention of the various stages of manufacture, so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced an adverse change in the constituents,

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

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

[1] OJ L 11, 14.1.1978, p. 18. Directive as last amended by the 1985 Act of Accession.

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

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

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

C. CONTROL OF STARTING MATERIALS

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

In the case of:

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

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

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

The particulars and documents accompanying the application for marketing authorization pursuant to Article 12(3)(i) and (j) and Article 13(1), shall include the results of the tests, including batch analyses particularly for active substances, relating to quality control of all the constituents used. These shall be submitted in accordance with the following provisions.

1.1. *Starting materials listed in pharmacopoeias*

The monographs of the *European Pharmacopoeia* shall be applicable to all substances appearing in it.

In respect of other substances, each Member State may require observance of its own national pharmacopoeia with regard to products manufactured in its territory.

Constituents fulfilling the requirements of the *European Pharmacopoeia* or the pharmacopoeia of one of the Member States shall be deemed to comply sufficiently with Article 12(3)(i). In this case the description of the analytical methods may be replaced by a detailed reference to the pharmacopoeia in question.

However, where a starting material in the *European Pharmacopoeia* or in the pharmacopoeia of a Member State has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described.

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

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

In cases where a specification contained in a monograph of the *European Pharmacopoeia* or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorization holder.

The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorization holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.

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

1.2. *Starting materials not in a pharmacopoeia*

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

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

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

(c) methods of identification may be described in the form of complete techniques as used for production of the substance, and in the form of tests which ought to be carried out as a routine matter;

(d) purity tests shall be described in relation to the sum total of predictable impurities, especially those which may have a harmful effect, and, if necessary, those which, having regard to the combination of substances to which the application refers, might adversely affect the stability of the medicinal product or distort analytical results;

(e) with regard to complex substances of plant or animal origin, a distinction must be made between the case where multiple pharmacological effects render chemical, physical or biological control of the principal components necessary, and the case of substances containing one or more groups of principles having similar activity, in respect of which an overall method of assay may be accepted;

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

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

1.3. *Physico-chemical characteristics liable to affect bioavailability*

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

— crystalline form and solubility coefficients,

— particle size, where appropriate after pulverization,

— state of solvation,

— oil/water coefficient of partition ([1]).

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

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

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

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

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

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

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

D. SPECIFIC MEASURES CONCERNING THE PREVENTION OF THE TRANSMISSION OF ANIMAL SPONGIFORM ENCEPHALOPATHIES

The applicant must demonstrate that the veterinary medical product is manufactured in accordance with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via veterinary medicinal products and its updates, published by the European Commission in Volume 7 of its publication 'The rules governing medicinal products in the European Community'.

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

The particulars and documents accompanying an application for marketing authorization, pursuant to Article 12(3)(i) and (j) and also Article 13(1), shall include particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the technical characteristics and the production process.

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

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

F. TESTS ON THE FINISHED PRODUCT

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

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

The particulars and documents accompanying the application for marketing authorization pursuant to Article 12(3)(i) and (j) and also Article 13(1), shall include particulars relating to control tests on the finished product at release. They shall be submitted in accordance with the following requirements.

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

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

1.1. *General characteristics of the finished product*

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

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

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

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

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

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

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

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

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

Where the particulars given in section B show that a significant overage of an active substance is employed in the manufacture of the medicinal product, the description of the control tests on the finished product shall include, where appropriate, the chemical and, if necessary, the toxico-pharmacological investigation of the changes that this substance has undergone, and possibly the characterization and/or assay of the degradation products.

1.3. *Identification and assay of excipient components*

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

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

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

1.4. *Safety tests*

Apart from the toxico-pharmacological tests submitted with the application for marketing authorization, particulars of safety tests, such as sterility, bacterial endotoxin, pyrogenicity and local tolerance in animals shall be included in the analytical particulars wherever such tests must be undertaken as a matter of routine in order to verify the quality of the product.

G. STABILITY TEST

The particulars and documents accompanying the application for marketing authorization pursuant to Article 12(3)(f) and (i) shall be submitted in accordance with the following requirements.

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

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

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

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

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

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

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

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

PART 3

Safety and residues testing

The particulars and documents which shall accompany the application for marketing authorization pursuant to Articles 12(3)(j) and 13(1) shall be submitted in accordance with the requirements below.

Member States shall ensure that the tests are carried out in accordance with the provisions relating to good laboratory practice laid down by Council Directive 87/18/EEC of 18 December 1986 on the harmonization of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances ([1]) and Council Directive 88/320/EEC of 9 June 1988 on the inspection and verification of good laboratory practice (GLP) ([2]).

A. SAFETY TESTING

Chapter I

Performance of tests

1. **Introduction**

The safety documentation shall show:

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

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

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

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

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

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

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

([1]) OJ L 15, 17.1.1987, p. 29. Directive as last amended by Commission Directive 1999/11/EC (OJ L 77, 23.3.1999, p. 8).
([2]) OJ L 145, 11.6.1988, p. 35. Directive as last amended by Commission Decision 1999/12/EC (OJ L 77, 23.3.1999, p. 22).

2. **Pharmacology**

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

However, pharmacological studies may also assist in the understanding of toxicological phenomena. Moreover, where a medicinal product produces pharmacological effects in the absence of a toxic response, or at doses lower than those required to elicit toxicity, these pharmacological effects shall be taken into account during the evaluation of the safety of the medicinal product.

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

3. **Toxicology**

3.1. *Single-dose toxicity*

Single-dose toxicity studies can be used to predict:

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

— the possible effects of accidental administration to humans,

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

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

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

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

3.2. *Repeated-dose toxicity*

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

In the case of substances or medicinal products intended solely for use in non food-producing animals, a repeated dose toxicity study in one species of experimental animal will normally be sufficient. This study may be replaced by a study conducted in the target animal. The frequency and route of administration, and the duration of the study should be chosen having regard to the proposed conditions of clinical use. The investigator shall give his reasons for the extent and duration of the trials and the dosages chosen.

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

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

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

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

3.3. *Tolerance in the target species*

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

3.4. *Reproductive toxicity including teratogenicity*

3.4.1. Study of the effects on reproduction

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

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

Evaluation of the effects on reproduction shall be based upon fertility, pregnancy and maternal behaviour; the suckling, growth and development of the F1 offspring from conception to maturity; the development of the F2 offspring to weaning.

3.4.2. Study of embryotoxic/fetotoxic effects including teratogenecity

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

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

3.5. *Mutagenicity*

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

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

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

3.6. *Carcinogenicity*

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

— which have a close chemical analogy with known carcinogens,

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

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

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

3.7. *Exceptions*

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

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

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

4. **Other requirements**

4.1. *Immunotoxicity*

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

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

4.2. *Microbiological properties of residues*

4.2.1. Potential effects on the human gut flora

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

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

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

4.3. *Observations in humans*

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

5. **Ecotoxicity**

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

5.2. An assessment of ecotoxicity shall be compulsory for any application for marketing authorization for a veterinary medicinal product other than applications submitted in accordance with Articles 12(3)(j) and 13(1).

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

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

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

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

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

— the disposal of unused or waste product.

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

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

— fate and behaviour in soil,

— fate and behaviour in water and air,

— effects on aquatic organisms,

— effects on other non-target organisms.

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

Chapter II

Presentation of particulars and documents

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

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

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

— international non-proprietary name (INN),

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

— Chemical Abstract Service (CAS) number,

— therapeutical and pharmacological classification,

— synonyms and abbreviations,

— structural formula,

— molecular formula,

— molecular weight,

— degree of impurity,

— qualitative and quantitative composition of impurities,

([1]) OJ 196, 16.8.1967, p. 1. Directive as last amended by Commission Directive 2000/33/EC (OJ L 136, 8.6.2000, p. 90).

— description of physical properties,

— melting point,

— boiling point,

— vapour pressure,

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

— density,

— spectra of refraction, rotation, etc;

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

(d) all the results obtained, whether favourable or unfavourable. The original data should be described in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author. By way of explanation, the results may be accompanied by illustrations;

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

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

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

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

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

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

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

B. RESIDUE TESTING

Chapter I

Performance of tests

1. **Introduction**

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

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

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

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

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

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

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

2. **Metabolism and residue kinetics**

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

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

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

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

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

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

2.2. *Depletion of residues*

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

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

3. **Routine analytical method for the detection of residues**

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

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

The following characteristics shall be described:

— specificity,

— accuracy, including sensitivity,

— precision,

— limit of detection,

— limit of quantitation,

— practicability and applicability under normal laboratory conditions,

— susceptibility to interference.

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

Chapter II

Presentation of particulars and documents

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

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

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

— composition,

— purity,

— batch identification,

— relationship to the final product,

— specific activity and radio-purity of labelled substances,

— position of labelled atoms in the molecule;

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

(d) all the results obtained, whether favourable or unfavourable. The original data should be described in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author. The results may be accompanied by illustrations;

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

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

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

PART 4

Pre-clinical and clinical testing

The particulars and documents which shall accompany applications for marketing authorizations pursuant to Articles 12(3)(j) and 13(1) shall be submitted in accordance with the provisions of this Part.

Chapter I

Pre-clinical requirements

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

A. PHARMACOLOGY

A.1. ***Pharmacodynamics***

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

First, the mechanism of action and the pharmacological effects on which the recommended application in practice is based shall be adequately described. The results shall be expressed in quantitative terms (using, for example, dose-effect curves, time-effect curves, etc.) and, wherever possible, in comparison with a substance the activity of which is well known. Where a higher efficacy is being claimed for an active substance, the difference shall be demonstrated and shown to be statistically significant.

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

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

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

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

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

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

A.2. ***Pharmacokinetics***

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

Pharmacokinetic objectives can be divided into two main areas:

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

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

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

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

A.2.1. **Bioavailability/bioequivalence**

Appropriate bioavailability studies shall be undertaken to establish bioequivalence:

— when comparing a reformulated medicinal product with the existing one,

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

— in all cases referred to in Article 13(1).

B. TOLERANCE IN THE TARGET SPECIES OF ANIMAL

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

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

C. RESISTANCE

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

Chapter II

Clinical requirements

1. **General principles**

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

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

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

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

— the yield of animal produce,

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

— nutritional efficiency and growth of animal,

— the general status of health of the animal.

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

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

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

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

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

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

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

2. **Performance of trials**

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

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

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

Unless the trial is conducted with a blind design, the provisions of Articles 58, 59 and 60 concerning the labelling of veterinary medicinal products shall apply by analogy to the labelling of formulations intended for use in veterinary clinical trials. In all cases, the words 'for veterinary clinical trial use only' shall appear prominently and indelibly upon the labelling.

Chapter III

Particulars and documents

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

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

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

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

(a) tests demonstrating pharmacological actions;

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

(c) tests demonstrating the main pharmacokinetic processes.

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

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

(a) a summary;

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

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

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

Total or partial omission of these data must be explained.

2.1. *Records of clinical observations*

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

The particulars supplied shall take the following form:

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

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

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

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

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

(f) diagnosis and means used to make it;

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

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

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

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

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

(l) all results of the clinical trials (including unfavourable or negative results) with a full statement of the clinical observations and the results of the objective tests of activity (laboratory analyses, physiological tests), required to evaluate the application; the techniques used must be specified, and the significance of any variations in the results explained (e.g. variance in method, variance between individuals or the effects of the medication); demonstration of the pharmacodynamic effect in animals shall not in itself suffice to justify conclusions concerning any therapeutic effect;

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

(n) effect of animals' performance (e.g. egg-laying, milk production and reproductive function);

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

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

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

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

2.2. *Summary and conclusions of clinical observations*

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

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

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

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

— received no treatment;

— received a placebo;

— received another authorized medicinal product of known effect;

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

(d) the frequency of observed adverse reactions;

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

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

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

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

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

3. **Concluding expert report**

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

TITLE II

Requirements for immunological veterinary medicinal products

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

PART 5

Summary of the dossier

A. ADMINISTRATIVE DATA

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

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

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

Annexed to the administrative data shall be copies of a document showing that the manufacturer is authorized to produce immunological veterinary medicinal products, as defined in Article 44 (with a brief description of the production site). Moreover, the list of organisms handled at the production site shall be given.

The applicant shall submit a list of countries in which authorization has been granted, copies of all the summaries of product characteristics in accordance with Article 14 as approved by Member States and a list of countries in which an application has been submitted.

B. SUMMARY OF PRODUCT CHARACTERISTICS

The applicant shall propose a summary of the product characteristics, in accordance with Article 14.

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

C. EXPERT REPORTS

In accordance with Article 15(2) and (3) expert reports must be provided on all aspects of the documentation.

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

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

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

PART 6

Analytical (physico-chemical, biological or microbiological) tests of immunological veterinary medicinal products

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

All the test procedure(s) shall be described in sufficiently precise detail so as to be reproducible in control tests, carried out at the request of the competent authority; any special apparatus and equipment which may be used shall be described in adequate detail, possibly accompanied by a diagram. The formulae of the laboratory reagents shall be supplemented, if necessary, by the manufacturing method. In the case of test procedures included in the *European Pharmacopoeia* or the pharmacopoeia of a Member State, this description may be replaced by a detailed reference to the pharmacopoeia in question.

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

The particulars and documents which must accompany applications for marketing authorization, pursuant to Article 12(3)(c), shall be submitted in accordance with the following requirements.

1. **Qualitative particulars**

'Qualitative particulars' of all the constituents of the immunological veterinary medicinal product shall mean the designation or description of:

— the active substance(s),

— the constituents of the adjuvants,

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

— the constituents of the pharmaceutical form administered to animals.

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

2. The 'usual terminology', to be used in describing the constituents of immunological veterinary medicinal products, shall mean, notwithstanding the application of the other provisions of Article 12(3)(c):

— in respect of substances which appear in the *European Pharmacopoeia* or, failing this, in the national pharmacopoeia of one of the Member States, the main title of the monograph in question, which will be obligatory for all such substances, with reference to the pharmacopoeia concerned,

— in respect of other substances, the international non-proprietary name recommended by the World Health Organization, which may be accompanied by another non-proprietary name or, failing these, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,

— in respect of colouring matter, designation by the 'E' code assigned to them in Directive 78/25/EEC.

3. **Quantitative particulars**

In order to give the 'quantitative particulars' of the active substances of an immunological veterinary medicinal product, it is necessary to specify whenever possible the number of organisms, the specific protein content, the mass, the number of International Units (IU) or units of biological activity, either per dosage-unit or volume, and with regard to the adjuvant and to the constituents of the excipients, the mass or the volume of each of them, with due allowance for the details provided in section B.

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

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

4. **Development pharmaceutics**

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

B. DESCRIPTION OF MANUFACTURING METHOD OF THE FINISHED PRODUCT

The description of the manufacturing method accompanying the application for marketing authorization pursuant to Article 12(3)(d), shall be drafted in such a way as to give an adequate description of the nature of the operations employed.

For this purpose the description shall include at least:

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

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

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

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

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

C. PRODUCTION AND CONTROL OF STARTING MATERIALS

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

In the case of:

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

or

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

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

The particulars and documents accompanying the application for marketing authorization pursuant to Article 12(3)(i) and (j) and Article 13(1) shall include the results of the tests relating to quality control of all the components used and shall be submitted in accordance with the following provisions.

1. **Starting materials listed in pharmacopoeias**

The monographs of the *European Pharmacopoeia* shall be applicable to all substances appearing in it.

In respect of other substances, each Member State may require observance of its own national pharmacopoeia with regard to products manufactured in its territory.

Components fulfilling the requirements of the *European Pharmacopoeia* or the pharmacopoeia of one of the Member States shall be deemed to comply sufficiently with Article 12(3)(i). In this case the description of the analytical methods may be replaced by a detailed reference to the pharmacopoeia in question.

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

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

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

In cases where a specification or other provisions contained in a monograph of the *European Pharmacopoeia* or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the applicant for marketing authorization.

The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The applicant for marketing authorization shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.

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

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

2.1. *Starting materials of biological origin*

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

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

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

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

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

— details of the source of the materials,

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

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

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

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

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

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

2.2. *Starting materials of non-biological origin*

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

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

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

— the function of the starting material,

— methods of identification,

— purity shall be described in relation to the sum total of predictable impurities, especially those which may have a harmful effect and, if necessary, those which, having regard to the combination of substances to which the application refers, may adversely effect the stability of the medicinal product or distort analytical results. A brief description shall be provided of the tests undertaken to establish the purity of each batch of the starting material,

— any special precautions which may be necessary during storage of the starting material and, if necessary, its storage life shall be given.

D. SPECIFIC MEASURES CONCERNING THE PREVENTION OF THE TRANSMISSION OF ANIMAL SPONGIFORM ENCEPHALOPATHIES

The applicant must demonstrate that the veterinary medical product is manufactured in accordance with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via veterinary medicinal products and its updates, published by the European Commission in Volume 7 of its publication 'The rules governing medicinal products in the European Community'.

E. CONTROL TESTS DURING PRODUCTION

1. The particulars and documents accompanying an application for marketing authorization, pursuant to Article 12(3)(i) and (j) and Article 13(1), shall include particulars relating to the control tests which are carried out on intermediate products with a view to verifying the consistency of the production process and the final product.

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

F. CONTROL TESTS ON THE FINISHED PRODUCT

The particulars and documents accompanying the application for marketing authorization pursuant to Article 12(3)(i) and (j) and Article 13(1), shall include particulars relating to control tests on the finished product. Where appropriate monographs exist, if test procedures and limits other than those mentioned in the monographs of the *European Pharmacopoeia*, or failing this, in the national pharmacopoeia of a Member State, are used, proof must be supplied that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned. The application for marketing authorization shall list those tests which are carried out on representative samples of each batch of finished product. The frequency of the tests which are not carried out on each batch shall be stated. Release limits shall be indicated.

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

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

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

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

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

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

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

In certain exceptional cases where assay of active substances which are very numerous or present in very low amounts would necessitate an intricate investigation difficult to carry out in respect of each production batch, the assay of one or more active substances in the finished product may be omitted, on the express condition that such assays are made at intermediate stages as late as possible in the production process. This relaxation may not be extended to the characterization of the substances concerned. This simplified technique shall be supplemented by a method of quantitative evaluation, enabling the competent authority to verify that the immunological veterinary medicinal product is in accordance with its formula after it has been placed on the market.

3. **Identification and assay of adjuvants**

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

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

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

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

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

5. **Safety tests**

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

6. **Sterility and purity test**

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

7. **Inactivation**

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

8. **Residual humidity**

Each batch of lyophilised product shall be tested for residual humidity.

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

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

G. STABILITY TESTS

The particulars and documents accompanying the application for marketing authorization pursuant to Article 12(3)(f) and (i) shall be submitted in accordance with the following requirements.

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

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

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

Where a finished product requires reconstitution prior to administration, details of the proposed shelf-life are required for the product reconstituted as recommended. Data in support of the proposed shelf-life for the reconstituted product shall be submitted.

PART 7

Safety testing

A. INTRODUCTION

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

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

2. The particulars and documents which shall accompany the application for marketing authorization pursuant to Article 12(3)(j) and 13(1) shall be submitted in accordance with the requirements of section B.

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

B. GENERAL REQUIREMENTS

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

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

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

C. LABORATORY TESTS

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

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

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

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

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

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

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

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

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

4. **Examination of reproductive performance**

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

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

5. **Examination of immunological functions**

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

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

6.1. *Spread of the vaccine strain*

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

6.2. *Dissemination in the vaccinated animal*

Faeces, urine, milk, eggs, oral, nasal and other secretions shall be tested for the presence of the organism. Moreover, studies may be required of the dissemination of the vaccine strain in the body, with particular attention being paid to the predilection sites for replication of the organism. In the case of live vaccines for well established zoonotic diseases for food producing animals, these studies must be undertaken.

6.3. *Reversion to virulence of attenuated vaccines*

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

6.4. *Biological properties of the vaccine strain*

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

6.5. *Recombination or genomic reassortment of strains*

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

7. **Study of residues**

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

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

8. **Interactions**

Any known interactions with other products shall be indicated.

D. FIELD STUDIES

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

E. ECOTOXICITY

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

An assessment of ecotoxicity shall be compulsory for any application for marketing authorization for an immunological veterinary medicinal product other than applications submitted in accordance with Article 12(3)(j) and 13(1).

This assessment shall normally be conducted in two phases.

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

— the target species and the proposed pattern of use (e.g. mass medication or individual animal medication),

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

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

— the disposal of unused or waste product.

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

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

PART 8

Efficacy trials

A. INTRODUCTION

1. The purpose of the trials described in this Part is to demonstrate or to confirm the efficacy of the immunological veterinary medicinal product. All claims made by the applicant with regard to the properties, effects and use of the product, shall be fully supported by results of specific trials contained in the application for marketing authorization.

2. The particulars and documents which shall accompany applications for marketing authorizations pursuant to Article 12(3)(j) and 13(1) shall be submitted in accordance with the provisions below.

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

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

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

5. Unless the trial is conducted with a blind design, the provisions of Articles 58, 59 and 60 shall apply by analogy to the labelling of formulations intended for use in veterinary clinical trials. In all cases, the words 'for veterinary clinical trial use only' shall appear prominently and indelibly upon the labelling.

B. GENERAL REQUIREMENTS

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

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

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

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

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

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

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

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

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

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

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

C. LABORATORY TRIALS

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

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

D. FIELD TRIALS

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

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

PART 9

Particulars and documents concerning safety testing and efficacy trials of immunological veterinary medicinal products

A. INTRODUCTION

As in any scientific work, the dossier of safety and efficacy studies shall include an introduction defining the subject and indicating the tests which have been carried out in compliance with Parts 7 and 8, as well as a summary, with references to the published literature. Omission of any tests or trials listed in Parts 7 and 8 shall be indicated and discussed.

B. LABORATORY STUDIES

The following shall be provided for all studies:

1. a summary;

2. the name of the body having carried out the studies;

3. a detailed experimental protocol giving a description of the methods, apparatus and materials used, details such as species, breed or strain of animals, categories of animals, where they were obtained, their identification and number, the conditions under which they were housed and fed (stating inter alia whether they were free from any specified pathogens and/or specified antibodies, the nature and quantity of any additives contained in the feed), dose, route, schedule and dates of administration, a description of the statistical methods used;

4. in the case of control animals, whether they received a placebo or no treatment;

5. all general and individual observations and results obtained (with averages and standard deviations), whether favourable or unfavourable. The data shall be described in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author. The raw data shall be presented in tabular form. By way of explanation and illustration, the results may be accompanied by reproductions of recordings, photomicrographs, etc.;

6. the nature, frequency and duration of observed side-effects;

7. the number of animals withdrawn prematurely from the studies and reasons for such withdrawal;

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

9. occurrence and course of any intercurrent disease;

10. all details concerning medicinal products (other than the product under study), the administration of which was necessary during the course of the study;

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

C. FIELD STUDIES

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

1. a summary;

2. name, address, function and qualifications of the investigator in charge;

3. place and date of administration, name and address of the owner of the animal(s);

4. details of the trial protocol, giving a description of the methods, apparatus and materials used, details such as the route of administration, the schedule of administration, the dose, the categories of animals, the duration of observation, the serological response and other investigations carried out on the animals after administration;

5. in the case of control animals, whether they received a placebo or no treatment;

6. identification of the treated and control animals (collective or individual, as appropriate), such as species, breeds or strains, age, weight, sex, physiological status;

7. a brief description of the method of rearing and feeding, stating the nature and quantity of any additives contained in the feed;

8. all the particulars on observations, performances and results (with averages and standard deviation); individual data shall be indicated when tests and measurements on individuals have been carried out;

9. all observations and results of the studies, whether favourable or unfavourable, with a full statement of the observations and the results of the objective tests of activity required to evaluate the product; the techniques used must be specified and the significance of any variations in the results explained;

10. effect on the animals' performances (e.g. egg laying, milk production, reproductive performance);

11. the number of animals withdrawn prematurely from the studies and reasons for such withdrawal;

12. the nature, frequency and duration of observed adverse reactions;

13. occurrence and course of any intercurrent disease;

14. all details concerning medicinal products (other than the product under study) which have been administered either prior to or concurrently with the test product or during the observation period; details of any interactions observed;

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

D. GENERAL CONCLUSIONS

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

E. BIBLIOGRAPHICAL REFERENCES

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

ANNEX II

PART A

Repealed Directives and their successive amendments
(referred to by Article 96)

Council Directive 81/851/EEC (OJ L 317, 6.11.1981, p. 1)
Council Directive 90/676/EEC (OJ L 373, 31.12.1990, p. 15)
Council Directive 90/677/EEC (OJ L 373, 31.12.1990, p. 26)
Council Directive 92/74/EEC (OJ L 297, 13.10.1992, p. 12)
Council Directive 93/40/EEC (OJ L 214, 24.8.1993, p. 31)
Commission Directive 2000/37/EC (OJ L 139, 10.6.2000, p. 25)

Council Directive 81/852/EEC (OJ L 317, 6.11.1981, p. 16)
Council Directive 87/20/EEC (OJ L 15, 17.1.1987, p. 34)
Council Directive 92/18/EEC (OJ L 97, 10.4.1992, p. 1)
Council Directive 93/40/EEC
Commission Directive 1999/104/EC (OJ L 3, 6.1.2000, p. 18)

PART B

Time-limits for transposition into national law
(referred to by Article 96)

Directive	Deadline for transposition
Directive 81/851/EEC	9 October 1983
Directive 81/852/EEC	9 October 1983
Directive 87/20/EEC	1 July 1987
Directive 90/676/EEC	1 January 1992
Directive 90/677/EEC	20 March 1993
Directive 92/18/EEC	1 April 1993
Directive 92/74/EEC	31 December 1993
Directive 93/40/EEC	1 January 1995
	1 January 1998 (Art. 1.7)
Directive 1999/104/EC	1 January 2000
Directive 2000/37/EC	5 December 2001

ANNEX III

CORRELATION TABLE

This Directive	Dir. 65/65/EEC	Dir. 81/851/EEC	Dir. 81/852/EEC	Dir. 90/677/EEC	Dir. 92/74/EEC
Art. 1 points 1 and 2	Art. 1 points 1 and 2	Art. 1(1)			
Art. 1 point 3		Art. 1(2), 2nd indent			
Art. 1 point 4	Art. 1, point 3	Art. 1(1)			
Art. 1 points 5 and 6		Art. 1(2), 3rd and 4th indents			
Art. 1 point 7				Art. 1(2)	
Art. 1 point 8					Art. 1
Art. 1 point 9		Art. 5, 3rd subparagraph, point 8			
Art. 1 points 10 to 16		Art.42b, 1st subparagraph			
Art. 1 point 17		Art. 50a(1), 2nd subparagraph			
Art. 1 point 18		Art.16(1)			
Art. 1 point 19		Art. 18(1), footnote			
Art. 2		Art. 2(1)			
Art. 3 point 1, 1st subparagraph		Art. 2(2), 1st indent			
Art. 3 point 1, 2nd subparagraph		Art. 2(3)			
Art. 3 point 2				Art. 1(3)	
Art. 3 points 3 and 4	Art. 1 points 4 and 5 and Art. 2(3)	Art. 1(1)			
Art. 3 point 5		Art. 2(2), 3rd indent			
Art. 3 point 6		Art. 1 point 4			
Art. 4(1)				Art. 1(4)	
Art. 4(2)		Art. 3			
Art. 5		Art. 4(1), 1st subparagraph			

This Directive	Dir. 65/65/EEC	Dir. 81/851/EEC	Dir. 81/852/EEC	Dir. 90/677/EEC	Dir. 92/74/EEC
Art. 6		Art. 4(2), 1st subparagraph			
Art. 7		Art. 4(1), 2nd subparagraph			
Art. 8		Art. 4(1), 3rd subparagraph			
Art. 9		Art. 4(3), 1st subparagraph			
Art. 10(1) and (2), 1st and 2nd subparagraphs		Art. 4(4), 1st and 2nd subparagraphs			
Art. 10(2), 3rd subparagraph					Art. 2(1), 2nd subparagraph
Art. 11		Art. 4(4), 3rd subparagraph			
Art. 12(1)		Art. 5, 1st subparagraph			
Art. 12(2)		Art. 5, 2nd subparagraph			
Art. 12(3)(a) to (i)		Art. 5, 3rd subparagraph, points 1 to 9	Art. 1, 1st subparagraph		
Art. 12(3)(j)		Art. 5, 3rd subparagraph, point 10, 1st subparagraph			
Art. 12(3)(k) to (n)		Art. 5, 3rd subparagraph, points 11 to 14			
Art. 13(1)		Art. 5, 3rd subparagraph, point 10, 2nd subparagraph			
Art. 13(2)			Art. 1, 2nd subparagraph		
Art. 14		Art. 5a			
Art. 15(1)		Art. 6			
Art. 15(2) and (3)		Art. 7			
Art. 16					Art. 6
Art. 17(1)					Art. 7(1)
Art. 17(2)					Art. 7(3)
Art. 17(3)					Art. 4, 2nd subparagraph
Art. 18					Art. 8
Art. 19					Art. 9
Art. 20 first paragraph					Art. 2(3)

Art. 20 second paragraph					Art. 9
Art. 21		Art. 8			
Art. 22		Art. 8a			
Art. 23		Art. 9			
Art. 24		Art. 10			
Art. 25		Art. 5b			
Art. 26(1) and (2)		Art. 12			
Art. 26(3)		Art. 15(2)			
Art. 27(1)		Art. 14(1), 1st subparagraph			
Art. 27(2)		Art. 14(1), 2nd subparagraph			
Art. 27(3)		Art. 14(2)			
Art. 27(4) and (5)		Art. 14(3) and (4)			
Art. 28		Art. 15(1)			
Art. 29		Art. 13			
Art. 30		Art. 11			
Art. 31(1)		Art. 16(1)			
Art. 31(2)		Art. 16(2)	Art. 2		
Art. 31(3)		Art. 16(3)			
Art. 32(1)		Art. 17(3)			
Art. 32(2)		Art. 17(1)			
Art. 32(3)		Art. 17(2)			
Art. 32(4)		Art. 17(4)			
Art. 33		Art. 18			
Art. 34		Art. 19			
Art. 35		Art. 20			
Art. 36		Art. 21			
Art. 37		Art. 22(1)			

This Directive	Dir. 65/65/EEC	Dir. 81/851/EEC	Dir. 81/852/EEC	Dir. 90/677/EEC	Dir. 92/74/EEC
Art. 38		Art. 22(2), (3) and (4)			
Art. 39		Art. 23			
Art. 40		Art. 23a			
Art. 41		Art. 23b			
Art. 42		Art. 23c			
Art. 43		Art. 22(5)			
Art. 44		Art. 24			
Art. 45		Art. 25			
Art. 46		Art. 26			
Art. 47		Art. 28(1)			
Art. 48		Art. 28(2)			
Art. 49		Art. 28(3)			
Art. 50		Art. 27			
Art. 51		Art. 27a			
Art. 52		Art. 29			
Art. 53		Art. 31			
Art. 54		Art. 32			
Art. 55(1)		Art. 30(1), 1st and 2nd subparagraphs			
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This Directive	Dir. 65/65/EEC	Dir. 81/851/EEC	Dir. 81/852/EEC	Dir. 90/677/EEC	Dir. 92/74/EEC
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Art. 80(3)		Art. 34, 3rd subparagraph			
Art. 81(1)		Art. 35			
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DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 6 November 2001

on the Community code relating to medicinal products for human use

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission;

Having regard to the opinion of the Economic and Social Committee ([1]),

Acting in accordance with the procedure laid down in Article 251 of the Treaty ([2]),

Whereas:

(1) Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products ([3]), Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products ([4]), Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products ([5]), Council Directive 89/342/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens ([6]), Council Directive 89/343/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for radiopharmaceuticals ([7]), Council Directive 89/381/EEC of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products and laying down special provisions for proprietary medicinal products derived from human blood or human plasma ([8]), Council Directive 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use ([9]), Council Directive 92/26/EEC of 31 March 1992 concerning the classification for the supply of medicinal products for human use ([10]), Council Directive 92/27/EEC of 31 March 1992 on the labelling of medicinal products for human use and on package leaflets ([11]), Council Directive 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use ([12]), Council Directive 92/73/EEC of 22 September 1992 widening the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products and laying down additional provisions on homeopathic medicinal products ([13]) have been frequently and substantially amended. In the interests of clarity and rationality, the said Directives should therefore be codified by assembling them in a single text.

(2) The essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health.

(3) However, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community.

(4) Trade in medicinal products within the Community is hindered by disparities between certain national provisions, in particular between provisions relating to medicinal products (excluding substances or combinations of substances which are foods, animal feeding-stuffs or toilet preparations), and such disparities directly affect the functioning of the internal market.

(5) Such hindrances must accordingly be removed; whereas this entails approximation of the relevant provisions.

(6) In order to reduce the disparities which remain, rules should be laid down on the control of medicinal products and the duties incumbent upon the Member States' competent authorities should be specified with a view to ensuring compliance with legal requirements.

([1]) OJ C 368, 20.12.1999, p. 3.
([2]) Opinion of the European Parliament of 3 July 2001 (not yet published in the Official Journal) and Council Decision of 27 September 2001.
([3]) OJ 22, 9.2.1965, p. 369/65. Directive as last amended by Directive 93/39/EEC (OJ L 214, 24.8.1993, p. 22).
([4]) OJ L 147, 9.6.1975, p. 1. Directive as last amended by Commission Directive 1999/83/EC (OJ L 243, 15.9.1999, p. 9).
([5]) OJ L 147, 9.6.1975, p. 13. Directive as last amended by Commission Directive 2000/38/EC (OJ L 139, 10.6.2000, p. 28).
([6]) OJ L 142, 25.5.1989, p. 14.
([7]) OJ L 142, 25.5.1989, p. 16.
([8]) OJ L 181, 28.6.1989, p. 44.
([9]) OJ L 113, 30.4.1992, p. 1.
([10]) OJ L 113, 30.4.1992, p. 5.
([11]) OJ L 113, 30.4.1992, p. 8.
([12]) OJ L 113, 30.4.1992, p. 13.
([13]) OJ L 297, 13.10.1992, p. 8.

(7) The concepts of harmfulness and therapeutic efficacy 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. The particulars and documents which must accompany an application for marketing authorization for a medicinal product demonstrate that potential risks are outweighed by the therapeutic efficacy of the product.

(8) Standards and protocols for the performance of tests and trials on medicinal products are an effective means of control of these products and hence of protecting public health and can facilitate the movement of these products by laying down uniform rules applicable to tests and trials, the compilation of dossiers and the examination of applications.

(9) Experience has shown that it is advisable to stipulate more precisely the cases in which the results of toxicological and pharmacological tests or clinical trials do not have to be provided with a view to obtaining authorization for a medicinal product which is essentially similar to an authorized product, while ensuring that innovative firms are not placed at a disadvantage.

(10) However, there are reasons of public policy for not conducting repetitive tests on humans or animals without over-riding cause.

(11) The adoption of the same standards and protocols by all the Member States will enable the competent authorities to arrive at their decisions on the basis of uniform tests and by reference to uniform criteria and will therefore help to avoid differences in evaluation.

(12) With the exception of those medicinal products which are subject to the centralized Community authorization procedure established by Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products [1] a marketing authorization for a medicinal product granted by a competent authority in one Member State ought to be recognized by the competent authorities of the other Member States unless there are serious grounds for supposing that the authorization of the medicinal product concerned may present a risk to public health. In the event of a disagreement between Member States about the quality, the safety or the efficacy of a medicinal product, a scientific evaluation of the matter should be undertaken according to a Community standard, leading to a single decision on the area of disagreement binding on the Member States concerned. Whereas this decision should be adopted by a rapid procedure ensuring close cooperation between the Commission and the Member States.

(13) For this purpose, a Committee for Proprietary Medicinal Products should be set up attached to the European Agency for the Evaluation of Medicinal Products established in the abovementioned Regulation (EEC) No 2309/93.

(14) This Directive represents an important step towards achievement of the objective of the free movement of medicinal products. Further measures may abolish any remaining barriers to the free movement of proprietary medicinal products will be necessary in the light of experience gained, particularly in the abovementioned Committee for Proprietary Medicinal Products.

(15) In order better to protect public health and avoid any unnecessary duplication of effort during the examination of application for a marketing authorization for medicinal products, Member States should systematically prepare assessment reports in respect of each medicinal product which is authorized by them, and exchange the reports upon request. Furthermore, a Member State should be able to suspend the examination of an application for authorization to place a medicinal product on the market which is currently under active consideration in another Member State with a view to recognizing the decision reached by the latter Member State.

(16) Following the establishment of the internal market, specific controls to guarantee the quality of medicinal products imported from third countries can be waived only if appropriate arrangements have been made by the Community to ensure that the necessary controls are carried out in the exporting country.

(17) It is necessary to adopt specific provisions for immunological medicinal products, homeopathic medicinal products, radiopharmaceuticals, and medicinal products based on human blood or human plasma.

(18) Any rules governing radiopharmaceuticals must take into account the provisions of Council Directive 84/466/Euratom of 3 September 1984 laying down basic measures for the radiation protection of persons undergoing medical examination or treatment [2]. Account should also be taken of Council Directive 80/836/Euratom of 15 July 1980 amending the Directives laying down the basic safety standards for the health protection of the general public and workers

[1] OJ L 214, 24.8.1993, p. 1. Regulation as amended by Commission Regulation (EC) No 649/98 (OJ L 88, 24.3.1998, p. 7).

[2] OJ L 265, 5.10.1984, p. 1. Directive repealed with effect from 13 May 2000 by Directive 97/43/Euratom (OJ L 180, 9.7.1997, p. 22).

against the dangers of ionizing radiation [1], the objective of which is to prevent the exposure of workers or patients to excessive or unnecessarily high levels of ionizing radiation, and in particular of Article 5c thereof, which requires prior authorization for the addition of radioactive substances to medicinal products as well as for the importation of such medicinal products.

(19) The Community entirely supports the efforts of the Council of Europe to promote voluntary unpaid blood and plasma donation to attain self-sufficiency throughout the Community in the supply of blood products, and to ensure respect for ethical principles in trade in therapeutic substances of human origin.

(20) The rules designed to guarantee the quality, safety and efficacy of medicinal products derived from human blood or human plasma must be applied in the same manner to both public and private establishments, and to blood and plasma imported from third countries.

(21) Having regard to the particular characteristics of these homeopathic medicinal products, such as the very low level of active principles they contain and the difficulty of applying to them the conventional statistical methods relating to clinical trials, it is desirable to provide a special, simplified registration procedure for those homeopathic medicinal products which are placed on the market without therapeutic indications in a pharmaceutical form and dosage which do not present a risk for the patient.

(22) The anthroposophic medicinal products described in an official pharmacopoeia and prepared by a homeopathic method are to be treated, as regards registration and marketing authorization, in the same way as homeopathic medicinal products.

(23) It is desirable in the first instance to provide users of these homeopathic medicinal products with a very clear indication of their homeopathic character and with sufficient guarantees of their quality and safety.

(24) The rules relating to the manufacture, control and inspection of homeopathic medicinal products must be harmonized to permit the circulation throughout the Community of medicinal products which are safe and of good quality.

(25) The usual rules governing the authorization to market medicinal products should be applied to homeopathic medicinal products placed on the market with therapeutic indications or in a form which may present risks which must be balanced against the desired therapeutic effect. In particular, those Member States which have a homeopathic tradition should be able to apply particular rules for the evaluation of the results of tests and trials intended to establish the safety and efficacy of these medicinal products provided that they notify them to the Commission.

(26) In order to facilitate the movement of medicinal products and to prevent the controls carried out in one Member State from being repeated in another, minimum requirements should be laid down for manufacture and imports coming from third countries and for the grant of the authorization relating thereto.

(27) It should be ensured that, in the Member States, the supervision and control of the manufacture of medicinal products is carried out by a person who fulfils minimum conditions of qualification.

(28) Before an authorization to market an immunological medicinal product or derived from human blood or human plasma can be granted, the manufacturer must demonstrate his ability to attain batch-to-batch consistency. Before an authorization to market a medicinal product derived from human blood or human plasma can be granted, the manufacturer must also demonstrate the absence of specific viral contamination, to the extent that the state of technology permits.

(29) The conditions governing the supply of medicinal products to the public should be harmonized.

(30) In this connection persons moving around within the Community have the right to carry a reasonable quantity of medicinal products lawfully obtained for their personal use. It must also be possible for a person established in one Member State to receive from another Member State a reasonable quantity of medicinal products intended for his personal use.

(31) In addition, by virtue of Regulation (EC) No 2309/93, certain medicinal products are the subject of a Community marketing authorization. In this context, the classification for the supply of medicinal products covered by a Community marketing authorization needs to be established. It is therefore important to set the criteria on the basis of which Community decisions will be taken.

(32) It is therefore appropriate, as an initial step, to harmonize the basic principles applicable to the classification for the supply of medicinal products in the Community or in the Member State concerned, while taking as a starting point the principles already established on this subject by the Council of Europe as well as the work of harmonization completed within the framework of the United Nations, concerning narcotic and psychotropic substances.

[1] OJ L 246, 17.9.1980, p. 1. Directive as amended by Directive 84/467/Euratom (OJ L 265, 5.10.1984, p. 4), repealed with effect from 13 May 2000 by Directive 96/29/Euratom (OJ L 314, 4.12.1996, p. 20).

(33) The provisions dealing with the classification of medicinal products for the purpose of supply do not infringe the national social security arrangements for reimbursement or payment for medicinal products on prescription.

(34) Many operations involving the wholesale distribution of medicinal products for human use may cover several Member States simultaneously.

(35) It is necessary to exercise control over the entire chain of distribution of medicinal products, from their manufacture or import into the Community through to supply to the public, so as to guarantee that such products are stored, transported and handled in suitable conditions. The requirements which must be adopted for this purpose will considerably facilitate the withdrawal of defective products from the market and allow more effective efforts against counterfeit products.

(36) Any person involved in the wholesale distribution of medicinal products should be in possession of a special authorization. Pharmacists and persons authorized to supply medicinal products to the public, and who confine themselves to this activity, should be exempt from obtaining this authorization. It is however necessary, in order to control the complete chain of distribution of medicinal products, that pharmacists and persons authorized to supply medicinal products to the public keep records showing transactions in products received.

(37) Authorization must be subject to certain essential conditions and it is the responsibility of the Member State concerned to ensure that such conditions are met; whereas each Member State must recognize authorizations granted by other Member States.

(38) Certain Member States impose on wholesalers who supply medicinal products to pharmacists and on persons authorized to supply medicinal products to the public certain public service obligations. Those Member States must be able to continue to impose those obligations on wholesalers established within their territory. They must also be able to impose them on wholesalers in other Member States on condition that they do not impose any obligation more stringent than those which they impose on their own wholesalers and provided that such obligations may be regarded as warranted on grounds of public health protection and are proportionate in relation to the objective of such protection.

(39) Rules should be laid down as to how the labelling and package leaflets are to be presented.

(40) The provisions governing the information supplied to users should provide a high degree of consumer protection, in order that medicinal products may be used correctly on the basis of full and comprehensible information.

(41) The marketing of medicinal products whose labelling and package leaflets comply with this Directive should not be prohibited or impeded on grounds connected with the labelling or package leaflet.

(42) This Directive is without prejudice to the application of measures adopted pursuant to Council Directive 84/450/EEC of 10 September 1984 relating to the approximation of the laws, regulations and administrative provisions of the Member States concerning misleading advertising [1].

(43) All Member States have adopted further specific measures concerning the advertising of medicinal products. There are disparities between these measures. These disparities are likely to have an impact on the functioning of the internal market, since advertising disseminated in one Member State is likely to have effects in other Member States.

(44) Council Directive 89/552/EEC of 3 October 1989 on the coordination of certain provisions laid down by law, regulation or administrative action in Member States concerning the pursuit of television broadcasting activities [2] prohibits the television advertising of medicinal products which are available only on medical prescription in the Member State within whose jurisdiction the television broadcaster is located. This principle should be made of general application by extending it to other media.

(45) Advertising to the general public, even of non-prescription medicinal products, could affect public health, were it to be excessive and ill-considered. Advertising of medicinal products to the general public, where it is permitted, ought therefore to satisfy certain essential criteria which ought to be defined.

(46) Furthermore, distribution of samples free of charge to the general public for promotional ends must be prohibited.

(47) The advertising of medicinal products to persons qualified to prescribe or supply them contributes to the information available to such persons. Nevertheless, this advertising should be subject to strict conditions and effective monitoring, referring in particular to the work carried out within the framework of the Council of Europe.

(48) Advertising of medicinal products should be subject to effective, adequate monitoring. Reference in this regard should be made to the monitoring mechanisms set up by Directive 84/450/EEC.

(49) Medical sales representatives have an important role in the promotion of medicinal products. Therefore, certain obligations should be imposed upon them, in particular the obligation to supply the person visited with a summary of product characteristics.

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[1] OJ L 250, 19.9.1984, p. 17. Directive as amended by Directive 97/55/EC (OJ L 290, 23.10.1997, p. 18).

[2] OJ L 298, 17.10.1989, p. 23. Directive as amended by Directive 97/36/EC (OJ L 202, 30.7.1997, p. 60).

(50) Persons qualified to prescribe medicinal products must be able to carry out these functions objectively without being influenced by direct or indirect financial inducements.

(51) It should be possible within certain restrictive conditions to provide samples of medicinal products free of charge to persons qualified to prescribe or supply them so that they can familiarize themselves with new products and acquire experience in dealing with them.

(52) Persons qualified to prescribe or supply medicinal products must have access to a neutral, objective source of information about products available on the market. Whereas it is nevertheless for the Member States to take all measures necessary to this end, in the light of their own particular situation.

(53) Each undertaking which manufactures or imports medicinal products should set up a mechanism to ensure that all information supplied about a medicinal product conforms with the approved conditions of use.

(54) In order to ensure the continued safety of medicinal products in use, it is necessary to ensure that pharmacovigilance systems in the Community are continually adapted to take account of scientific and technical progress.

(55) It is necessary to take account of changes arising as a result of international harmonisation of definitions, terminology and technological developments in the field of pharmacovigilance.

(56) The increasing use of electronic networks for communication of information on adverse reactions to medicinal products marketed in the Community is intended to allow competent authorities to share the information at the same time.

(57) It is the interest of the Community to ensure that the pharmacovigilance systems for centrally authorised medicinal products and those authorised by other procedures are consistent.

(58) Holders of marketing authorisations should be proactively responsible for on-going pharmacovigilance of the medicinal products they place on the market.

(59) The measures necessary for the implementation of this Directive should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission ([1]).

([1]) OJ L 184, 17.7.1999, p. 23.

(60) The Commission should be empowered to adopt any necessary changes to Annex I in order to take into account scientific and technical progress.

(61) This Directive should be without prejudice to the obligations of the Member States concerning the time-limits for transposition of the Directives set out in Annex II, Part B.

HAVE ADOPTED THIS DIRECTIVE:

TITLE I

DEFINITIONS

Article 1

For the purposes of this Directive, the following terms shall bear the following meanings:

1. *Proprietary medicinal product:*

   Any ready-prepared medicinal product placed on the market under a special name and in a special pack.

2. *Medicinal product:*

   Any substance or combination of substances presented for treating or preventing disease in human beings.

   Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product.

3. *Substance:*

   Any matter irrespective of origin which may be:

   — human, e.g.

     human blood and human blood products;

   — animal, e.g.

     micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products;

   — vegetable, e.g.

     micro-organisms, plants, parts of plants, vegetable secretions, extracts;

   — chemical, e.g.

     elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis.

4. *Immunological medicinal product:*

Any medicinal product consisting of vaccines, toxins, serums or allergen products:

(a) vaccines, toxins and serums shall cover in particular:

(i) agents used to produce active immunity, such as cholera vaccine, BCG, polio vaccines, smallpox vaccine;

(ii) agents used to diagnose the state of immunity, including in particular tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin;

(iii) agents used to produce passive immunity, such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin;

(b) 'allergen product' shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent.

5. *Homeopathic medicinal product:*

Any medicinal product prepared from products, substances or compositions called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in absence thereof, by the pharmacopoeias currently used officially in the Member States.

A homeopathic medicinal product may also contain a number of principles.

6. *Radiopharmaceutical:*

Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

7. *Radionuclide generator:*

Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical.

8. *Radionuclide kit:*

Any preparation to be reconsitituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration.

9. *Radionuclide precursor:*

Any other radionuclide produced for the radio-labelling of another substance prior to administration.

10. *Medicinal products derived from human blood or human plasma:*

Medicinal products based on blood constitutents which are prepared industrially by public or private establishments, such medicinal products including, in particular, albumin, coagulating factors and immunoglobulins of human origin.

11. *Adverse reaction:*

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

12. *Serious adverse reaction:*

An adverse reaction which results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

13. *Unexpected adverse reaction:*

An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics.

14. *Periodic safety update reports:*

The periodical reports containing the records referred to in Article 104.

15. *Post-authorisation safety study:*

A pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product.

16. *Abuse of medicinal products:*

Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effets.

17. *Wholesale distribution of medicinal products:*

All activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public. Such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorized or entitled to supply medicinal products to the public in the Member State concerned.

18. *Public service obligation:*

The obligation placed on wholesalers to guarantee permanently an adequate range of medicinal products to meet the requirements of a specific geographical area and to deliver the supplies requested within a very short time over the whole of the area in question.

19. *Medicinal Prescription:*

Any medicinal prescription issued by a professional person qualified to do so.

20. *Name of the medicinal product:*

The name given to a medicinal product, which may be either an invented name or a common or scientific name, together with a trade mark or the name of the manufacturer; the invented name shall not be liable to confusion with the common name.

21. *Common name:*

The international non-proprietary name recommended by the World Health Organization, or, if one does not exist, the usual common name.

22. *Strength of the medicinal product:*

The content of the active substances expressed quantitatively per dosage unit, per unit of volume or weight according to the dosage form.

23. *Immediate packaging:*

The container or other form of packaging immediately in contact with the medicinal product.

24. *Outer packaging:*

The packaging into which is placed the immediate packaging.

25. *Labelling:*

Information on the immediate or outer packaging.

26. *Package leaflet:*

A leaflet containing information for the user which accompanies the medicinal product.

27. *Agency:*

The European Agency for the Evaluation of Medicinal Products established by Regulation (EEC) No 2309/93.

28. *Risk to public health:*

All risks with regard to the quality, safety and efficacy of the medicinal product.

TITLE II

SCOPE

Article 2

The provisions of this Directive shall apply to industrially produced medicinal products for human use intended to be placed on the market in Member States.

Article 3

This Directive shall not apply to:

1. Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).

2. Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the official formula).

3. Medicinal products intended for research and development trials.

4. Intermediate products intended for further processing by an authorized manufacturer.

5. Any radionuclides in the form of sealed sources.

6. Whole blood, plasma or blood cells of human origin.

Article 4

1. Nothing in this Directive shall in any way derogate from the Community rules for the radiation protection of persons undergoing medical examination or treatment, or from the Community rules laying down the basic safety standards for the health protection of the general public and workers against the dangers of ionizing radiation.

2. This Directive shall be without prejudice to Council Decision 86/346/EEC of 25 June 1986 accepting on behalf of the Community the European Agreement on the Exchange of Therapeutic Substances of Human Origin ([1]).

3. The provisions of this Directive shall not affect the powers of the Member States' authorities either as regards the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes, on the basis of health, economic and social conditions.

4. This Directive shall not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products as contraceptives or abortifacients. The Member States shall communicate the national legislation concerned to the Commission.

Article 5

A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients on his direct personal responsibility.

TITLE III

PLACING ON THE MARKET

CHAPTER 1

Marketing authorization

Article 6

1. No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive or an authorization has been granted in accordance with Regulation (EEC) No 2309/93.

2. The authorisation referred to in paragraph 1 shall also be required for radionuclide generators, radionuclide kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals.

Article 7

A marketing authorization shall not be required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorized, according to national legislation, to use such medicinal products in an approved health care establishment exclusively from authorized radionuclide generators, radionuclide kits or radionuclide precursors in accordance with the manufacturer's instructions.

Article 8

1. In order to obtain an authorization to place a medicinal product on the market regardless of the procedure established by Regulation (EEC) No 2309/93, an application shall be made to the competent authority of the Member State concerned.

2. A marketing authorization may only be granted to an applicant established in the Community.

3. The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:

(a) Name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer.

(b) Name of the medicinal product.

(c) Qualitative and quantitative particulars of all the constituents of the medicinal product in usual terminology, but excluding empirical chemical formulae, with mention of the international non-proprietary name recommended by the World Health Organization where such name exists.

(d) Description of the manufacturing method.

(e) Therapeutic indications, contra-indications and adverse reactions.

(f) Posology, pharmaceutical form, method and route of administration and expected shelf life.

(g) If applicable, reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of any potential risks presented by the medicinal product for the environment.

(h) Description of the control methods employed by the manufacturer (qualitative and quantitative analysis of the constituents and of the finished product, special tests, e.g. sterility tests, tests for the presence of pyrogenic substances, the presence of heavy metals, stability tests, biological and toxicity tests, controls carried out at an intermediate stage of the manufacturing process).

(i) Results of:

— physico-chemical, biological or microbiological tests,

— toxicological and pharmacological tests,

— clinical trials.

([1]) OJ L 207, 30.7.1986, p. 1.

(j) A summary, in accordance with Article 11, of the product characteristics, one or more specimens or mock-ups of the outer packaging and the immediate packaging of the medicinal product, together with a package leaflet.

(k) A document showing that the manufacturer is authorised in his own country to produce medicinal products.

(l) Copies of any authorisation obtained in another Member State or in a third country to place the medicinal product on the market, together with a list of those Member States in which an application for authorisation submitted in accordance with this Directive is under examination. Copies of the summary of the product characteristics proposed by the applicant in accordance with Article 11 or approved by the competent authorities of the Member State in accordance with Article 21. Copies of the package leaflet proposed in accordance with Article 59 or approved by the competent authorities of the Member State in accordance with Article 61. Details of any decision to refuse authorization, whether in the Community or in a third country, and the reasons for such a decision.

This information shall be updated on a regular basis.

Article 9

In addition to the requirements set out in Articles 8 and 10(1), an application for authorization to market a radionuclide generator shall also contain the following information and particulars:

— a general description of the system together with a detailed description of the components of the system which may affect the composition or quality of the daughter nucleid preparation,

— qualitative and quantitative particulars of the eluate or the sublimate.

Article 10

1. In derogation of Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property:

(a) The applicant shall not be required to provide the results of toxicological and pharmacological tests or the results of clinical trials if he can demonstrate:

(i) either that the medicinal product is essentially similar to a medicinal product authorized in the Member State concerned by the application and that the holder of the marketing authorization for the original medicinal product has consented to the toxicological, pharmacological and/or clinical references contained in the file on the original medicinal product being used for the purpose of examining the application in question;

(ii) or that the constituent or constituents of the medicinal product have a well established medicinal use, with recognized efficacy and an acceptable level of safety, by means of a detailed scientific bibliography;

(iii) or that the medicinal product is essentially similar to a medicinal product which has been authorized within the Community, in accordance with Community provisions in force, for not less than six years and is marketed in the Member State for which the application is made. This period shall be extended to 10 years in the case of high-technology medicinal products having been authorised according to the procedure laid down in Article 2(5) of Council Directive 87/22/EEC ([1]). Furthermore, a Member State may also extend this period to 10 years by a single Decision covering all the medicinal products marketed on its territory where it considers this necessary in the interest of public health. Member States are at liberty not to apply the six-year period beyond the date of expiry of a patent protecting the original medicinal product.

However, where the medicinal product is intended for a different therapeutic use from that of the other medicinal products marketed or is to be administered by different routes or in different doses, the results of appropriate toxicological and pharmacological tests and/or of appropriate clinical trials must be provided.

(b) In the case of new medicinal products containing known constituents not hitherto used in combination for therapeutic purposes, the results of toxicological and pharmacological tests and of clinical trials relating to that combination must be provided, but it shall not be necessary to provide references relating to each individual constituent.

2. Annex I shall apply by analogy where, pursuant to point (ii) of paragraph 1, (a), bibliographic references to published data are submitted.

Article 11

The summary of the product characteristics shall contain the following information:

1. Name of the medicinal product.

2. Qualitative and quantitative composition in terms of the active substances and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product. The usual common name or chemical description shall be used.

([1]) OJ L 15, 17.1.1987, p. 38. Directive repealed by Directive 93/41/EEC (OJ L 214, 24.8.1993, p. 40).

3. Pharmaceutical form.

4. Pharmacological properties and, in so far as this information is useful for therapeutic purposes, pharmacokinetic particulars.

5. Clinical particulars:

5.1. therapeutic indications,

5.2. contra-indications,

5.3. adverse reactions (frequency and seriousness),

5.4. special precautions for use and, in the case of immunological medicinal products, any special precautions to be taken by persons handling such products and administering them to patients, together with any precautions to be taken by the patient,

5.5. use during pregnancy and lactation,

5.6. interaction with other medicaments and other forms of interaction,

5.7. posology and method of administration for adults and, where necessary, for children,

5.8. overdose (symptoms, emergency procedures, antidotes),

5.9. special warnings,

5.10. effects on ability to drive and to use machines.

6. Pharmaceutical particulars:

6.1. major incompatibilities,

6.2. shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,

6.3. special precautions for storage,

6.4. nature and contents of the immediate packaging,

6.5. special precautions for disposal of unused medicinal products or waste materials derived from such medicinal products, if appropriate.

7. Name or corporate name and permanent address of the marketing authorization holder.

8. For radiopharmaceuticals, full details of internal radiation dosimetry.

9. For radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform with its specifications.

Article 12

1. Member States shall take all appropriate measures to ensure that the documents and particulars listed in Article 8(3)(h) and (i), and Article 10(1)(a)(ii) are drawn up by experts with the necessary technical or professional qualifications before they are submitted to the competent authorities. These documents and particulars shall be signed by the experts.

2. The duties of the experts according to their respective qualifications shall be:

(a) to perform tasks falling within their respective disciplines (analysis, pharmacology and similar experimental sciences, clinical trials) and to describe objectively the results obtained (qualitatively and quantitatively);

(b) to describe their observations in accordance with Annex I, and to state, in particular:

— in the case of the analyst, whether the medicinal product is consistent with the declared composition, giving any substantiation of the control methods employed by the manufacturer;

— in the case of the pharmacologist or the specialist with similar experimental competence, the toxicity of the medicinal product and the pharmacological properties observed;

— in the case of the clinician, whether he has been able to ascertain effects on persons treated with the medicinal product which correspond to the particulars given by the applicant in accordance with Articles 8 and 10, whether the patient tolerates the medicinal product well, the posology the clinician advises and any contra-indications and adverse reactions;

(c) where applicable, to state the grounds for using the bibliography mentioned in point (a)(ii) of Article 10(1).

3. Detailed reports by the experts shall form part of the particulars accompanying the application which the applicant submits to the competent authorities.

CHAPTER 2

Specific provisions applicable to homeopathic medicinal products

Article 13

1. Member States shall ensure that homeopathic medicinal products manufactured and placed on the market within the

Community are registered or authorized in accordance with Articles 14, 15 and 16, except where the products are covered by a registration or authorization which was granted under national law on or before 31 December 1993 (and whether or not that registration or authorization has been renewed after that date). Each Member State shall take due account of registrations and authorizations previously granted by another Member State.

2. A Member State may refrain from establishing a special, simplified registration procedure for the homeopathic medicinal products referred to in Article 14. A Member State shall inform the Commission accordingly. The Member State concerned shall allow the use in its territory of homeopathic medicinal products registered by other Member States in accordance with Articles 14 and 15.

Article 14

1. Only homeopathic medicinal products which satisfy all of the following conditions may be subject to a special, simplified registration procedure:

— they are administered orally or externally,

— no specific therapeutic indication appears on the labelling of the medicinal product or in any information relating thereto,

— there is a sufficient degree of dilution to guarantee the safety of the medicinal product; in particular, the medicinal product may not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription.

At the time of registration, Member States shall determine the classification for the dispensing of the medicinal product.

2. The criteria and rules of procedure provided for in Article 4(4), Article 17(1) and Articles 22 to 26, 112, 116 and 125 shall apply by analogy to the special, simplified registration procedure for homeopathic medicinal products, with the exception of the proof of therapeutic efficacy.

3. The proof of therapeutic efficacy shall not be required for homeopathic medicinal products registered in accordance with paragraph 1 of this Article, or, where appropriate, admitted in accordance with Article 13(2).

Article 15

An application for special, simplified registration may cover a series of medicinal products derived from the same homeopathic stock or stocks. The following documents shall be included with the application in order to demonstrate, in particular, the pharmaceutical quality and the batch-to-batch homogeneity of the products concerned:

— scientific name or other name given in a pharmacopoeia of the homeopathic stock or stocks, together with a statement of the various routes of administration, pharmaceutical forms and degree of dilution to be registered,

— dossier describing how the homeopathic stock or stocks is/are obtained and controlled, and justifying its/their homeopathic nature, on the basis of an adequate bibliography,

— manufacturing and control file for each pharmaceutical form and a description of the method of dilution and potentization,

— manufacturing authorization for the medicinal product concerned,

— copies of any registrations or authorizations obtained for the same medicinal product in other Member States,

— one or more specimens or mock-ups of the outer packaging and the immediate packaging of the medicinal products to be registered,

— data concerning the stability of the medicinal product.

Article 16

1. Homeopathic medicinal products other than those referred to in Article 14(1) shall be authorized and labelled in accordance with Articles 8, 10 and 11.

2. A Member State may introduce or retain in its territory specific rules for the toxicological and pharmacological tests and clinical trials of homeopathic medicinal products other than those referred to in Article 14(1) in accordance with the principles and characteristics of homeopathy as practised in that Member State.

In this case, the Member State concerned shall notify the Commission of the specific rules in force.

3. Title IX shall apply to homeopathic medicinal products, with the exception of those referred to in Article 14(1).

CHAPTER 3

Procedures relevant to the marketing authorization

Article 17

1. Member States shall take all appropriate measures to ensure that the procedure for granting an authorization to place a medicinal product on the market is completed within 210 days of the submission of a valid application.

2. Where a Member State notes that an application for authorization is already under active examination in another Member State in respect of that medicinal product, the Member State concerned may decide to suspend the detailed examination of the application in order to await the assessment report prepared by the other Member State in accordance with Article 21(4).

The Member State concerned shall inform the other Member State and the applicant of its decision to suspend detailed examination of the application in question. As soon as it has completed the examination of the application and reached a decision, the other Member State shall forward a copy of its assessment report to the Member State concerned.

Article 18

Where a Member State is informed in accordance with Article 8(3)(l) that another Member State has authorized a medicinal product which is the subject of an application for authorization in the Member State concerned, that Member State shall forthwith request the authorities of the Member State which has granted the authorization to forward to it the assessment report referred to in Article 21(4).

Within 90 days of the receipt of the assessment report, the Member State concerned shall either recognize the decision of the first Member State and the summary of the product characteristics as approved by it or, if it considers that there are grounds for supposing that the authorization of the medicinal product concerned may present a risk to public health, it shall apply the procedures set out in Articles 29 to 34.

Article 19

In order to examine the application submitted in accordance with Articles 8 and 10(1), the competent authority of the Member State:

1. must verify whether the particulars submitted in support of the application comply with the said Articles 8 and 10(1) and examine whether the conditions for issuing an authorization to place medicinal products on the market (marketing authorization) are complied with.

2. may submit the medicinal product, its starting materials and, if need be, its intermediate products or other constituent materials, for testing by a State laboratory or by a laboratory designated for that purpose in order to ensure that the control methods employed by the manufacturer and described in the particulars accompanying the application in accordance with Article 8(3)(h) are satisfactory.

3. may, where appropriate, require the applicant to supplement the particulars accompanying the application in respect of the items listed in the Articles 8(3) and 10(1). Where the competent authority avails itself of this option, the time limits laid down in Article 17 shall be suspended until such time as the supplementary information required has been provided. Likewise, these time limits shall be suspended for the time allowed the applicant, where appropriate, for giving oral or written explanation.

Article 20

Member States shall take all appropriate measures to ensure that:

(a) the competent authorities verify that manufacturers and importers of medicinal products coming from third countries are able to carry out manufacture in compliance with the particulars supplied pursuant to Article 8(3)(d), and/or to carry out controls according to the methods described in the particulars accompanying the application in accordance with Article 8(3)(h);

(b) the competent authorities may allow manufacturers and importers of medicinal products coming from third countries, in exceptional and justifiable cases, to have certain stages of manufacture and/or certain of the controls referred to in (a) carried out by third parties; in such cases, the verifications by the competent authorities shall also be made in the establishment designated.

Article 21

1. When the marketing authorization is issued, the holder shall be informed, by the competent authorities of the Member State concerned, of the summary of the product characteristics as approved by it.

2. The competent authorities shall take all necessary measures to ensure that the information given in the summary is in conformity with that accepted when the marketing authorization is issued or subsequently.

3. The competent authorities shall forward to the Agency a copy of the authorization together with the summary of the product characteristics.

4. The competent authorities shall draw up an assessment report and comments on the dossier as regards the results of the analytical and pharmacotoxicological tests and the clinical trials of the medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is of importance for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

Article 22

In exceptional circumstances, and following consultation with the applicant, an authorization may be granted subject to certain specific obligations, including:

— the carrying out of further studies following the granting of authorization,

— the notification of adverse reactions to the medicinal product.

These exceptional decisions may be adopted only for objective and verifiable reasons and shall be based on one of the causes referred to in Part 4 (G) of Annex I.

Article 23

After an authorization has been issued, the authorization holder must, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h), take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

These changes shall be subject to the approval of the competent authority of the Member State concerned.

Article 24

Authorization shall be valid for five years and shall be renewable for five-year periods, on application by the holder at least three months before the expiry date and after consideration by the competent authority of a dossier containing in particular details of the data on pharmacovigilance and other information relevant to the monitoring of the medicinal product.

Article 25

Authorization shall not affect the civil and criminal liability of the manufacturer and, where applicable, of the marketing authorization holder.

Article 26

The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles 8 and 10(1), it proves that:

(a) the medicinal product is harmful in the normal conditions of use, or

(b) that its therapeutic efficacy is lacking or is insufficiently substantiated by the applicant, or

(c) that its qualitative and quantitative composition is not as declared.

Authorisation shall likewise be refused if the particulars and documents submitted in support of the application do not comply with Articles 8 and 10(1).

CHAPTER 4

Mutual recognition of authorizations

Article 27

1. In order to facilitate the adoption of common decisions by Member States on the authorization of medicinal products on the basis of the scientific criteria of quality, safety and efficacy, and to achieve thereby the free movement of medicinal products within the Community, a Committee for Proprietary Medicinal Products, hereinafter referred to as 'the Committee', is hereby set up. The Committee shall be part of the Agency.

2. In addition to the other responsibilities conferred upon it by Community law, the Committee shall examine any question relating to the granting, variation, suspension or withdrawal of marketing authorization which is submitted to it in accordance with this Directive.

3. The Committee shall draw up its own Rules of Prodecure.

Article 28

1. Before submitting the application for recognition of a marketing authorization, the holder of the authorization shall inform the Member State which granted the authorization on which the application is based (hereinafter 'reference Member State'), that an application is to be made in accordance with this Directive and shall notify it of any additions to the original dossier; that Member State may require the applicant to provide it with all the particulars and documents necessary to enable it to check that the dossiers filed are identical.

In addition the holder of the authorization shall request the reference Member State to prepare an assessment report in respect of the medicinal product concerned, or, if necessary, to update any existing assessment report. That Member State shall prepare the assessment report, or update it, within 90 days of the receipt of the request.

At the same time as the application is submitted in accordance with paragraph 2, the reference Member State shall forward the assessment report to the Member State or Member States concerned by the application.

2. In order to obtain the recognition according to the procedures laid down in this Chapter in one or more of the Member States of a marketing authorization issued by a Member State, the holder of the authorization shall submit an application to the competent authorities of the Member State or Member States concerned, together with the information and particulars referred to in Articles 8, 10(1) and 11. He shall testify that the dossier is identical to that accepted by the reference Member State, or shall identify any additions or amendments it may contain. In the latter case, he shall certify that the summary of the product characteristics proposed by him in accordance with Article 11 is identical to that accepted by the reference Member State in accordance with Article 21. Moreover, he shall certify that all the dossiers filed as part of the procedure are identical.

3. The holder of the marketing authorization shall communicate the application to the Agency, inform it of the Member States concerned and of the dates of submission of the application and send it a copy of the authorization granted by the reference Member State. He shall also send the Agency copies of any such authorization which may have been granted by the other Member States in respect of the medicinal product concerned, and shall indicate whether any application for authorization is currently under consideration in any Member State.

4. Save in the exceptional case provided for in Article 29(1), each Member State shall recognize the marketing authorization granted by the reference Member State within 90 days of receipt of the application and the assessment report. It shall inform the reference Member State which granted the initial authorization, the other Member States concerned by the application, the Agency, and the marketing authorization holder.

Article 29

1. Where a Member State considers that there are grounds for supposing that the marketing authorization of the medicinal product concerned may present a risk to public health, it shall forthwith inform the applicant, the reference Member State which granted the initial authorization, any other Member States concerned by the application and the Agency. The Member State shall state its reasons in detail and shall indicate what action may be necessary to correct any defect in the application.

2. All the Member States concerned shall use their best endeavours to reach agreement on the action to be taken in respect of the application. They shall provide the applicant with the opportunity to make his point of view known orally or in writing. However, if the Member States have not reached agreement within the time limit referred to in Article 28(4) they shall forthwith refer the matter to the Agency with regard to the Committee's reference for the application of the procedure laid down in Article 32.

3. Within the time limit referred to in Article 28(4), the Member States concerned shall provide the Committee with a detailed statement of the matters on which they have been unable to reach agreement and the reasons for their disagreement. The applicant shall be provided with a copy of this information.

4. As soon as he is informed that the matter has been referred to the Committee, the applicant shall forthwith forward to the Committee a copy of the information and particulars referred to in Article 28(2).

Article 30

If several applications submitted in accordance with Articles 8, 10(1) and Article 11 have been made for marketing authorization for a particular medicinal product, and Member States have adopted divergent decisions concerning the authorization of the medicinal product or its suspension or withdrawal, a Member State, or the Commission, or the marketing authorization holder may refer the matter to the Committee for application of the procedure laid down in Article 32.

The Member State concerned, the marketing authorization holder or the Commission shall clearly identify the question which is referred to the Committee for consideration and, where appropriate, shall inform the holder.

The Member State and the marketing authorization holder shall forward to the Committee all available information relating to the matter in question.

Article 31

The Member States or the Commission or the applicant or holder of the marketing authorization may, in specific cases where the interests of the Community are involved, refer the matter to the Committee for the application of the procedure laid down in Article 32 before reaching a decision on a request for a marketing authorization or on the suspension or withdrawal of an authorization, or on any other variation to the terms of a marketing authorization which appears necessary, in particular to take account of the information collected in accordance with Title IX.

The Member State concerned or the Commission shall clearly identify the question which is referred to the Committee for consideration and shall inform the marketing authorization holder.

The Member States and the marketing authorization holder shall forward to the Committee all available information relating to the matter in question.

Article 32

1. When reference is made to the procedure described in this Article, the Committee shall consider the matter concerned and issue a reasoned opinion within 90 days of the date on which the matter was referred to it.

However, in cases submitted to the Committee in accordance with Articles 30 and 31, this period may be extended by 90 days.

In case of urgency, on a proposal from its Chairman, the Committee may agree to a shorter deadline.

2. In order to consider the matter, the Committee may appoint one of its members to act as rapporteur. The Committee may also appoint individual experts to advise it on specific questions. When appointing experts, the Committee shall define their tasks and specify the time-limit for the completion of these tasks.

3. In the cases referred to in Articles 29 and 30, before issuing its opinion, the Committee shall provide the marketing authorization holder with an opportunity to present written or oral explanations.

In the case referred to in Article 31, the marketing authorization holder may be asked to explain himself orally or in writing.

If it considers it appropriate, the Committee may invite any other person to provide information relating to the matter before it.

The Committee may suspend the time limit referred to in paragraph 1 in order to allow the marketing authorization holder to prepare explanations.

4. The Agency shall forthwith inform the marketing authorization holder where the opinion of the Committee is that:

— the application does not satisfy the criteria for authorization, or

— the summary of the product characteristics proposed by the applicant in accordance with Article 11 should be amended, or

— the authorization should be granted subject to conditions, with regard to conditions considered essential for the safe and effective use of the medicinal product including pharmacovigilance, or

— a marketing authorization should be suspended, varied or withdrawn.

Within 15 days of the receipt of the opinion, the marketing authorization holder may notify the Agency in writing of his intention to appeal. In that case, he shall forward the detailed grounds for appeal to the Agency within 60 days of receipt of the opinion. Within 60 days of receipt of the grounds for appeal, the Committee shall consider whether its opinion should be revised, and the conclusions reached on the appeal shall be annexed to the assessment report referred to in paragraph 5.

5. Within 30 days of its adoption, the Agency shall forward the final opinion of the Committee to the Member States, the Commission and the marketing authorization holder together with a report describing the assessment of the medicinal product and stating the reasons for its conclusions.

In the event of an opinion in favour of granting or maintaining an authorization to place the medicinal product concerned on the market, the following documents shall be annexed to the opinion.

(a) a draft summary of the product characteristics, as referred to in Article 11;

(b) any conditions affecting the authorization within the meaning of paragraph 4.

Article 33

Within 30 days of the receipt of the opinion, the Commission shall prepare a draft of the decision to be taken in respect of the application, taking into account Community law.

In the event of a draft decision which envisages the granting of marketing authorization, the documents referred to in Article 32(5)(a) and (b) shall be annexed.

Where, exceptionally, the draft decision is not in accordance with the opinion of the Agency, the Commission shall also annex a detailed explanation of the reasons for the differences.

The draft decision shall be forwarded to the Member States and the applicant.

Article 34

1. A final decision on the application shall be adopted in accordance with the procedure referred to in Article 121(2).

2. The rules of procedure of the Standing Committee established by Article 121(1) shall be adjusted to take account of the tasks incumbent upon it in accordance with this Chapter.

These adjustments shall involve the following:

— except in cases referred to in the third paragraph of Article 33, the opinion of the Standing Committee shall be obtained in writing,

— each Member State is allowed at least 28 days to forward written observations on the draft decision to the Commission,

— each Member State is able to require in writing that the draft decision be discussed by the Standing Committee, giving its reasons in detail.

Where, in the opinion of the Commission, the written observations of a Member State raise important new questions of a scientific or technical nature which have not been addressed in the opinion of the Agency, the Chairman shall suspend the procedure and refer the application back to the Agency for further consideration.

The provisions necessary for the implementation of this paragraph shall be adopted by the Commission in accordance with the procedure referred to in Article 121(2).

3. A decision as referred to in paragraph 1 shall be addressed to the Member States concerned by the matter and reported to the marketing authorization holder. The Member States shall either grant or withdraw marketing authorization, or vary the terms of a marketing authorization as necessary to comply with the decision within 30 days of its notification. They shall inform the Commission and the Agency thereof.

Article 35

1. Any application by the marketing authorization holder to vary a marketing authorization which has been granted in accordance with the provisions of this Chapter shall be submitted to all the Member States which have previously authorized the medicinal product concerned.

The Commission shall, in consultation with the Agency, adopt appropriate arrangements for the examination of variations to the terms of a marketing authorization.

These arrangements shall include a notification system or administration procedures concerning minor variations and define precisely the concept of 'a minor variation'.

These arrangements shall be adopted by the Commission in the form of an implementing Regulation in accordance with the procedure referred to in Article 121(2).

2. In case of arbitration submitted to the Commission, the procedure laid down in Articles 32, 33 and 34 shall apply by analogy to variations made to marketing authorizations.

Article 36

1. Where a Member State considers that the variation of a marketing authorization which has been granted in accordance with the provisions of this Chapter or its suspension or withdrawal is necessary for the protection of public health, the Member State concerned shall forthwith refer the matter to the Agency for the application of the procedures laid down in Articles 32, 33 and 34.

2. Without prejudice to the provisions of Article 31, in exceptional cases, where urgent action is essential to protect public health, until a definitive decision is adopted a Member State may suspend the marketing and the use of the medicinal product concerned on its territory. It shall inform the Commission and the other Member States no later than the following working day of the reasons for its action.

Article 37

Articles 35 and 36 shall apply by analogy to medicinal products authorized by Member States following an opinion of the Committee given in accordance with Article 4 of Directive 87/22/EEC before 1 January 1995.

Article 38

1. The Agency shall publish an annual report on the operation of the procedures laid down in this Chapter and shall forward that report to the European Parliament and the Council for information.

2. By 1 January 2001, the Commission shall publish a detailed review of the operation of the procedures laid down in this Chapter and shall propose any amendments which may be necessary to improve these procedures.

The Council shall decide, under the conditions provided for in the Treaty, on the Commission proposal within one year of its submission.

Article 39

The provisions referred to in Articles 27 to 34 shall not apply to the homeopathic medicinal products referred to in Article 16(2).

TITLE IV

MANUFACTURE AND IMPORTATION

Article 40

1. Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorization. This manufacturing authorization shall be required nothwithstanding that the medicinal products manufactured are intended for export.

2. The authorization referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation.

However, such authorization shall not be required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorized in the Member States to carry out such processes.

3. Authorization referred to in paragraph 1 shall also be required for imports coming from third countries into a Member State; this Title and Article 118 shall have corresponding application to such imports as they have to manufacture.

Article 41

In order to obtain the manufacturing authorization, the applicant shall meet at least the following requirements:

(a) specify the medicinal products and pharmaceutical forms which are to be manufactured or imported and also the place where they are to be manufactured and/or controlled;

(b) have at his disposal, for the manufacture or import of the above, suitable and sufficient premises, technical equipment and control facilities complying with the legal requirements which the Member State concerned lays down as regards both manufacture and control and the storage of medicinal products, in accordance with Article 20;

(c) have at his disposal the services of at least one qualified person within the meaning of Article 48.

The applicant shall provide particulars in support of the above in his application.

Article 42

1. The competent authority of the Member State shall issue the manufacturing authorization only after having made sure of the accuracy of the particulars supplied pursuant to Article 41, by means of an inquiry carried out by its agents.

2. In order to ensure that the requirements referred to in Article 41 are complied with, authorization may be made conditional on the carrying out of certain obligations imposed either when authorization is granted or at a later date.

3. The authorization shall apply only to the premises specified in the application and to the medicinal products and pharmaceutical forms specified in that same application.

Article 43

The Member States shall take all appropriate measures to ensure that the time taken for the procedure for granting the manufacturing authorization does not exceed 90 days from the day on which the competent authority receives the application.

Article 44

If the holder of the manufacturing authorization requests a change in any of the particulars referred to in points (a) and (b) of the first paragraph of Article 41, the time taken for the procedure relating to this request shall not exceed 30 days. In exceptional cases this period of time may be extended to 90 days.

Article 45

The competent authority of the Member State may require from the applicant further information concerning the particulars supplied pursuant to Article 41 and concerning the qualified person referred to in Article 48; where the competent authority concerned exercises this right, application of the time-limits referred to in Article 43 and 44 shall be suspended until the additional data required have been supplied.

Article 46

The holder of a manufacturing authorization shall at least be obliged:

(a) to have at his disposal the services of staff who comply with the legal requirements existing in the Member State concerned both as regards manufacture and controls;

(b) to dispose of the authorized medicinal products only in accordance with the legislation of the Member States concerned;

(c) to give prior notice to the competent authority of any changes he may wish to make to any of the particulars supplied pursuant to Article 41; the competent authority shall, in any event, be immediately informed if the qualified person referred to in Article 48 is replaced unexpectedly;

(d) to allow the agents of the competent authority of the Member State concerned access to his premises at any time;

(e) to enable the qualified person referred to in Article 48 to carry out his duties, for example by placing at his disposal all the necessary facilities;

(f) to comply with the principles and guidelines of good manufacturing practice for medicinal products as laid down by Community law.

Article 47

The principles and guidelines of good manufacturing practices for medicinal products referred to in Article 46(f) shall be adopted in the form of a directive, in accordance with the procedure referred to in Article 121(2).

Detailed guidelines in line with those principles will be published by the Commission and revised necessary to take account of technical and scientific progress.

Article 48

1. Member States shall take all appropriate measures to ensure that the holder of the manufacturing authorization has permanently and continuously at his disposal the services of at least one qualified person, in accordance with the conditions laid down in Article 49, responsible in particular for carrying out the duties specified in Article 51.

2. If he personally fulfils the conditions laid down in Article 49, the holder of the authorization may himself assume the responsibility referred to in paragraph 1.

Article 49

1. Member States shall ensure that the qualified person referred to in Article 48 fulfils the minimum conditions of qualification set out in paragraphs 2 and 3.

2. A qualified person shall be in possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course of study, or a course recognized as equivalent by the Member State concerned, extending over a period of at least four years of theoretical and practical study in one of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology.

However, the minimum duration of the university course may be three and a half years where the course is followed by a period of theoretical and practical training of a minimum duration of one year and including a training period of at least six months in a pharmacy open to the public, corroborated by an examination at university level.

Where two university courses or two courses recognized by the State as equivalent co-exist in a Member State and where one of these extends over four years and the other over three years, the three-year course leading to a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course or its recognized equivalent shall be considered to fulfil the condition of duration referred to in the second subparagraph in so far as the diplomas, certificates or other evidence of formal qualifications awarded on completion of both courses are recognized as equivalent by the State in question.

The course shall include theoretical and practical study bearing upon at least the following basic subjects:

— Applied physics

— General and inorganic chemistry

— Organic chemistry

— Analytical chemistry

— Pharmaceutical chemistry, including analysis of medicinal products

— General and applied biochemistry (medical)

— Physiology

— Microbiology

— Pharmacology

— Pharmaceutical technology

— Toxicology

— Pharmacognosy (study of the composition and effects of the natural active substances of plant and animal origin).

Studies in these subjects should be so balanced as to enable the person concerned to fulfil the obligations specified in Article 51.

In so far as certain diplomas, certificates or other evidence of formal qualifications mentioned in the first subparagraph do not fulfil the criteria laid down in this paragraph, the competent authority of the Member State shall ensure that the person concerned provides evidence of adequate knowledge of the subjects involved.

3. The qualified person shall have acquired practical experience over at least two years, in one or more undertakings which are authorized to manufacture medicinal products, in the activities of qualitative analysis of medicinal products, of quantitative analysis of active substances and of the testing and checking necessary to ensure the quality of medicinal products.

The duration of practical experience may be reduced by one year where a university course lasts for at least five years and by a year and a half where the course lasts for at least six years.

Article 50

1. A person engaging in the activities of the person referred to in Article 48 from the time of the application of Directive 75/319/EEC, in a Member State without complying with the provisions of Article 49 shall be eligible to continue to engage in those activities in the State concerned.

2. The holder of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course — or a course recognized as equivalent by the Member State concerned — in a scientific discipline allowing him to engage in the activities of the person referred to in Article 48 in accordance with the laws of that State may — if he began his course prior to 21 May 1975 — be considered as qualified to carry out in that State the duties of the person referred to in Article 48 provided that he has previously engaged in the following activities for at least two years before 21 May 1985 following notification of this directive in one or more undertakings authorized to manufacture: production supervision and/or qualitative and quantitative analysis of active substances, and the necessary testing and checking under the direct authority of the person referred to in Article 48 to ensure the quality of the medicinal products.

If the person concerned has acquired the practical experience referred to in the first subparagraph before 21 May 1965, a further one year's practical experience in accordance with the conditions referred to in the first subparagraph will be required to be completed immediately before he engages in such activities.

Article 51

1. Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 48, without prejudice to his relationship with the holder of the manufacturing authorization, is responsible, in the context of the procedures referred to in Article 52, for securing:

(a) in the case of medicinal products manufactured within the Member States concerned, that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorization;

(b) in the case of medicinal products coming from third countries, that each production batch has undergone in the importing Member State a full qualitative analysis, a quantitative analysis of at least all the active constituents and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorization.

The batches of medicinal products which have undergone such controls in a Member State shall be exempt from the controls if they are marketed in another Member State, accompanied by the control reports signed by the qualified person.

2. In the case of medicinal products imported from a third country, where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the Community, and to ensure that the controls referred to under point (b) of the first subparagraph of paragraph 1 have been carried out in the exporting country, the qualified person may be relieved of responsibility for carrying out those controls.

3. In all cases and particularly where the medicinal products are released for sale, the qualified person must certify in a register or equivalent document provided for that purpose, that each production batch satisfies the provisions of this Article; the said register or equivalent document must be kept

up to date as operations are carried out and must remain at the disposal of the agents of the competent authority for the period specified in the provisions of the Member State concerned and in any event for at least five years.

Article 52

Member States shall ensure that the duties of qualified persons referred to in Article 48 are fulfilled, either by means of appropriate administrative measures or by making such persons subject to a professional code of conduct.

Member States may provide for the temporary suspension of such a person upon the commencement of administrative or disciplinary procedures against him for failure to fulfil his obligations.

Article 53

The provisions of this Title shall also apply to homeopathic medicinal products.

TITLE V

LABELLING AND PACKAGE LEAFLET

Article 54

The following particulars shall appear on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging:

(a) the name of the medicinal product followed by the common name where the product contains only one active substance and if its name is an invented name; where a medicinal product is available in several pharmaceutical forms and/or several strengths, the pharmaceutical form and/or the strength (baby, child or adult as appropriate) must be included in the name of the medicinal product;

(b) a statement of the active substances expressed qualitatively and quantitatively per dosage unit or according to the form of administration for a given volume or weight, using their common names;

(c) the pharmaceutical form and the contents by weight, by volume or by number of doses of the product;

(d) a list of those excipients known to have a recognized action or effect and included in the guidelines published pursuant to Article 65. However, if the product is injectable, or a topical or eye preparation, all excipients must be stated;

(e) the method and, if necessary, the route of administration;

(f) a special warning that the medicinal product must be stored out of reach of children;

(g) a special warning, if this is necessary for the medicinal product;

(h) the expiry date in clear terms (month/year);

(i) special storage precautions, if any;

(j) special precautions for disposal of unused medicinal products or waste materials from medicinal products, if appropriate;

(k) the name and address of the holder of the authorization for placing the medicinal product on the market;

(l) the number of the authorization for placing the medicinal product on the market;

(m) the manufacturer's batch number;

(n) in the case of self-medication, instructions on the use of the medicinal products.

Article 55

1. The particulars laid down in Articles 54 and 62 shall appear on immediate packagings other than those referred to in paragraphs 2 and 3.

2. The following particulars at least shall appear on immediate packagings which take the form of blister packs and are placed in an outer packaging that complies with the requirements laid down in Articles 54 and 62.

— the name of the medicinal product as laid down in Article 54(a),

— the name of the holder of the authorization for placing the product on the market,

— the expiry date,

— the batch number.

3. The following particulars at least shall appear on small immediate packaging units on which the particulars laid down in Articles 54 and 62 cannot be displayed:

— the name of the medicinal product and, if necessary, the strength and the route of administration,

— the method of administration,

— the expiry date,

— the batch number,

— the contents by weight, by volume or by unit.

Article 56

The particulars referred to in Articles 54, 55 and 62 shall be easily legible, clearly comprehensible and indelible.

Article 57

Notwithstanding Article 60, Member States may require the use of certain forms of labelling of the medicinal product making it possible to ascertain:

— the price of the medicinal product,

— the reimbursement conditions of social security organizations,

— the legal status for supply to the patient, in accordance with Title VI,

— identification and authenticity.

Article 58

The inclusion in the packaging of all medicinal products of a package leaflet shall be obligatory unless all the information required by Articles 59 and 62 is directly conveyed on the outer packaging or on the immediate packaging.

Article 59

1. The package leaflet shall be drawn up in accordance with the summary of the product characteristics; it shall include, in the following order:

(a) for the identification of the medicinal product:

— the name of the medicinal product, followed by the common name if the product contains only one active substance and if its name is an invented name; where a medicinal product is available in several pharmaceutical forms and/or several strengths, the pharmaceutical form and/or the strength (for example, baby, child, adult) must be included in the name of the medicinal product,

— a full statement of the active substances and excipients expressed qualitatively and a statement of the active substances expressed quantitatively, using their common names, in the case of each presentation of the medicinal product,

— the pharmaceutical form and the contents by weight, by volume or by number of doses of the product, in the case of each presentation of the product,

— the pharmaco-therapeutic group, or type of activity in terms easily comprehensible for the patient,

— the name and address of the holder of the authorization for placing the medicinal product on the market and of the manufacturer;

(b) the therapeutic indications;

(c) list of information which is necessary before taking the medicinal product:

— contra-indications,

— appropriate precautions for use,

— forms of interaction with other medicinal products and other forms of interaction

(e.g. alcohol, tobacco, foodstuffs) which may affect the action of the medicinal product,

— special warnings;

this list must:

— take into account the particular condition of certain categories of users (e.g. children, pregnant or breastfeeding women, the elderly, persons with specific pathological conditions),

— mention, if appropriate, potential effects on the ability to drive vehicles or to operate machinery,

— detail those excipients, knowledge of which is important for the safe and effective use of the medicinal product and included in the guidelines published pursuant to Article 65;

(d) the necessary and usual instructions for proper use, in particular:

— the dosage,

— the method and, if necessary, route of administration,

— the frequency of administration, specifying if necessary, the appropriate time at which the medicinal product may or must be administered,

and, as appropriate, depending on the nature of the product:

— the duration of treatment, where it should be limited,

— the action to be taken in the case of an overdose (e.g., symptoms, emergency procedures),

— the course of action to take when one or more doses have not been taken,

— indication, if necessary, of the risk of withdrawal effects;

(e) a description of the undesirable effects which can occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case; the patient should be expressly invited to communicate any

undesirable effect which is not mentioned in the leaflet to his doctor or to his pharmacist;

(f) a reference to the expiry date indicated on the label, with:

— a warning against using the product after this date,

— where appropriate, special storage precautions,

— if necessary, a warning against certain visible signs of deterioration;

(g) the date on which the package leaflet was last revised.

2. Notwithstanding paragraph 1(b), the authority competent may decide that certain therapeutic indications shall not be mentioned in the package leaflet, where the dissemination of such information might have serious disadvantages for the patient.

Article 60

Member States may not prohibit or impede the placing on the market of medicinal products within their territory on grounds connected with labelling or the package leaflet where these comply with the requirements of this Title.

Article 61

1. One or more specimens or mock-ups of the outer packaging and the immediate packaging of a medicinal product, together with the draft package leaflet, shall be submitted to the authorities competent for authorizing marketing when the marketing authorization is requested.

2. The competent authority shall refuse the marketing authorization if the labelling or the package leaflet do not comply with the provisions of this Title or if they are not in accordance with the particulars listed in the summary of product characteristics.

3. All proposed changes to an aspect of the labelling or the package leaflet covered by this Title and not connected with the summary of product characteristics shall be submitted to the authorities competent for authorizing marketing. If the competent authorities have not opposed a proposed change within 90 days following the introduction of the request, the applicant may put the change into effect.

4. The fact that the competent authority do not refuse a marketing authorization pursuant to paragraph 2 or a change to the labelling or the package leaflet pursuant to paragraph 3 does not alter the general legal liability of the manufacturer or as appropriate the marketing authorization holder.

Article 62

The outer packaging and the package leaflet may include symbols or pictograms designed to clarify certain information mentioned in Articles 54 and 59(1) and other information compatible with the summary of the product characteristics which is useful for health education, to the exclusion of any element of a promotional nature.

Article 63

1. The particulars for labelling listed in Articles 54, 59 and 62 shall appear in the official language or languages of the Member State where the product is placed on the market.

The first subparagraph shall not prevent these particulars from being indicated in several languages, provided that the same particulars appear in all the languages used.

2. The package leaflet must be written in clear and understandable terms for the users and be clearly legible in the official language or languages of the Member State where the medicinal product is placed on the market.

The first subparagraph shall not prevent the package leaflet being printed in several languages, provided that the same information is given in all the languages used.

3. The competent authorities may exempt labels and package leaflets for specific medicinal products from the obligation that certain particulars shall appear and that the leaflet must be in the official language or languages of the Member State where the product is placed on the market, when the product is not intended to be delivered to the patient for self-administration.

Article 64

Where the provisions of this Title are not complied with, and a notice served on the person concerned has remained without effect, the competent authorities of the Member States may suspend the marketing authorization, until the labelling and the package leaflet of the medicinal product in question have been made to comply with the requirements of this Title.

Article 65

As necessary, the Commission shall publish guidelines concerning in particular:

— the formulation of certain special warnings for certain categories of medicinal products,

— the particular information needs relating to self-medication,

— the legibility of particulars on the labelling and package leaflet,

— methods for the identification and authentication of medicinal products,

— the list of excipients which must feature on the labelling of medicinal products and the way these excipients must be indicated.

These guidelines shall be adopted in the form of a Directive, in accordance with the procedure referred to in Article 121(2).

Article 66

1. The outer carton and the container of medicinal products containing radionuclides shall be labelled in accordance with the regulations for the safe transport of radioactive materials laid down by the International Atomic Energy Agency. Moreover, the labelling shall comply with the provisions set out in paragraphs 2 and 3.

2. The label on the shielding shall include the particulars mentioned in Article 54. In addition, the labelling on the shielding shall explain in full, the codings used on the vial and shall indicate, where necessary, for a given time and date, the amount of radioactivity per dose or per vial and the number of capsules, or, for liquids, the number of millilitres in the container.

3. The vial shall be labelled with the following information:

— the name or code of the medicinal product, including the name or chemical symbol of the radionuclide,

— the batch identification and expiry date,

— the international symbol for radioactivity,

— the name of the manufacturer,

— the amount of radioactivity as specified in paragraph 2.

Article 67

The competent authority shall ensure that a detailed instruction leaflet is enclosed with the packaging of radiopharmaceuticals, radionuclide generators, radionuclide kits or radionuclide precursors. The text of this leaflet shall be established in accordance with the provisions of Article 59. In addition, the leaflet shall include any precautions to be taken by the user and the patient during the preparation and administration of the medicinal product and special precautions for the disposal of the packaging and its unused contents.

Article 68

Without prejudice to the provisions of Article 69, homeopathic medicinal products shall be labelled in accordance with the provisions of this title and shall be identified by a reference on their labels, in clear and legible form, to their homeopathic nature.

Article 69

1. In addition to the clear mention of the words 'homeopathic medicinal product', the labelling and, where appropriate, the package insert for the medicinal products referred to in Article 14(1) shall bear the following, and no other, information:

— the scientific name of the stock or stocks followed by the degree of dilution, making use of the symbols of the pharmacopoeia used in accordance with Article 1(5),

— name and address of the registration holder and, where appropriate, of the manufacturer,

— method of administration and, if necessary, route,

— expiry date, in clear terms (month, year),

— pharmaceutical form,

— contents of the sales presentation,

— special storage precautions, if any,

— a special warning if necessary for the medicinal product,

— manufacturer's batch number,

— registration number,

— 'homeopathic medicinal product without approved therapeutic indications',

— a warning advising the user to consult a doctor if the symptoms persist during the use of the medicinal product.

2. Notwithstanding paragraph 1, Member States may require the use of certain types of labelling in order to show:

— the price of the medicinal product,

— the conditions for refunds by social security bodies.

TITLE VI

CLASSIFICATION OF MEDICINAL PRODUCTS

Article 70

1. When a marketing authorization is granted, the competent authorities shall specify the classification of the medicinal product into:

— a medicinal product subject to medical prescription,

— a medicinal product not subject to medical prescription.

To this end, the criteria laid down in Article 71(1) shall apply.

2. The competent authorities may fix sub-categories for medicinal products which are available on medical prescription only. In that case, they shall refer to the following classification:

(a) medicinal products on renewable or non-renewable medical prescription;

(b) medicinal products subject to special medical prescription;

(c) medicinal products on restricted medical prescription, reserved for use in certain specialized areas.

Article 71

1. Medicinal products shall be subject to medical prescription where they:

— are likely to present a danger either directly or indirectly, even when used correctly, if utilized without medical supervision, or

— are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health, or

— contain substances or preparations thereof, the activity and/or adverse reactions of which require further investigation, or

— are normally prescribed by a doctor to be administered parenterally.

2. Where Member States provide for the sub-category of medicinal products subject to special medical prescription, they shall take account of the following factors:

— the medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions of 1961 and 1971, or

— the medicinal product is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes, or

— the medicinal product contains a substance which, by reason of its novelty or properties, could be considered as belonging to the group envisaged in the second indent as a precautionary measure.

3. Where Member States provide for the sub-category of medicinal products subject to restricted prescription, they shall take account of the following factors:

— the medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment,

— the medicinal product is used in the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere, or

— the medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring a prescription drawn up as required by a specialist and special supervision throughout the treatment.

4. A competent authority may waive application of paragraphs 1, 2 and 3 having regard to:

(a) the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form, certain types of packaging; and/or

(b) other circumstances of use which it has specified.

5. If a competent authority does not designate medicinal products into sub-categories referred to in Article 70(2), it shall nevertheless take into account the criteria referred to in paragraphs 2 and 3 of this Article in determining whether any medicinal product shall be classified as a prescription-only medicine.

Article 72

Medicinal products not subject to prescription shall be those which do not meet the criteria listed in Article 71.

Article 73

The competent authorities shall draw up a list of the medicinal products subject, on their territory, to medical prescription, specifying, if necessary, the category of classification. They shall update this list annually.

Article 74

On the occasion of the five-yearly renewal of the marketing authorization or when new facts are brought to their notice, the competent authorities shall examine and, as appropriate, amend the classification of a medicinal product, by applying the criteria listed in Article 71.

Article 75

Each year, Member States shall communicate to the Commission and to the other Member States, the changes that have been made to the list referred to in Article 73.

TITLE VII

WHOLESALE DISTRIBUTION OF MEDICINAL PRODUCTS

Article 76

Without prejudice to Article 6, Member States shall take all appropriate action to ensure that only medicinal products in respect of which a marketing authorization has been granted in accordance with Community law are distributed on their territory.

Article 77

1. Member States shall take all appropriate measures to ensure that the wholesale distribution of medicinal products is subject to the possession of an authorization to engage in activity as a wholesaler in medicinal products, stating the place for which it is valid.

2. Where persons authorized or entitled to supply medicinal products to the public may also, under national law, engage in wholesale business, such persons shall be subject to the authorization provided for in paragraph 1.

3. Possession of a manufacturing authorization shall include authorization to distribute by wholesale the medicinal products covered by that authorization. Possession of an authorization to engage in activity as a wholesaler in medicinal products shall not give dispensation from the obligation to possess a manufacturing authorization and to comply with the conditions set out in that respect, even where the manufacturing or import business is secondary.

4. At the request of the Commission or any Member State, Member States shall supply all appropriate information concerning the individual authorizations which they have granted under paragraph 1.

5. Checks on the persons authorized to engage in the activity of wholesaler in medicinal products and the inspection of their premises, shall be carried out under the responsibility of the Member State which granted the authorization.

6. The Member State which granted the authorization referred to in paragraph 1 shall suspend or revoke that authorization if the conditions of authorization cease to be met. It shall forthwith inform the other Member States and the Commission thereof.

7. Should a Member State consider that, in respect of a person holding an authorization granted by another Member State under the terms of paragraph 1, the conditions of authorization are not, or are no longer met, it shall forthwith inform the Commission and the other Member State involved. The latter shall take the measures necessary and shall inform the Commission and the first Member State of the decisions taken and the reasons for those decisions.

Article 78

Member States shall ensure that the time taken for the procedure for examining the application for the distribution authorization does not exceed 90 days from the day on which the competent authority of the Member State concerned receives the application.

The competent authority may, if need be, require the applicant to supply all necessary information concerning the conditions of authorization. Where the authority exercises this option, the period laid down in the first paragraph shall be suspended until the requisite additional data have been supplied.

Article 79

In order to obtain the distribution authorization, applicants must fulfil the following minimum requirements:

(a) they must have suitable and adequate premises, installations and equipment, so as to ensure proper conservation and distribution of the medicinal products;

(b) they must have staff, and in particular, a qualified person designated as responsible, meeting the conditions provided for by the legislation of the Member State concerned;

(c) they must undertake to fulfil the obligations incumbent on them under the terms of Article 80.

Article 80

Holders of the distribution authorization must fulfil the following minimum requirements:

(a) they must make the premises, installations and equipment referred to in Article 79(a) accessible at all times to the persons responsible for inspecting them;

(b) they must obtain their supplies of medicinal products only from persons who are themselves in possession of the distribution authorization or who are exempt from obtaining such authorization under the terms of Article 77(3);

(c) they must supply medicinal products only to persons who are themselves in possession of the distribution authorization or who are authorized or entitled to supply medicinal products to the public in the Member State concerned;

(d) they must have an emergency plan which ensures effective implementation of any recall from the market ordered by the competent authorities or carried out in cooperation with the manufacturer or marketing authorization holder for the medicinal product concerned;

(e) they must keep records either in the form of purchase/sales invoices, or on computer, or in any other form, giving for any transaction in medicinal products received or dispatched at least the following information:

— date,

— name of the medicinal product,

— quantity received or supplied,

— name and address of the supplier or consignee, as appropriate;

(f) they must keep the records referred to under (e) available to the competent authorities, for inspection purposes, for a period of five years;

(g) they must comply with the principles and guidelines of good distribution practice for medicinal products as laid down in Article 84.

Article 81

With regard to the supply of medicinal products to pharmacists and persons authorized or entitled to supply medicinal products to the public, Member States shall not impose upon the holder of a distribution authorization which has been granted by another Member State, any obligation, in particular public service obligations, more stringent than those they impose on persons whom they have themselves authorized to engage in equivalent activities.

The said obligations should, moreover, be justified, in keeping with the Treaty, on grounds of public health protection and be proportionate in relation to the objective of such protection.

Article 82

For all supplies of medicinal products to a person authorized or entitled to supply medicinal products to the public in the Member State concerned, the authorized wholesaler must enclose a document that makes it possible to ascertain:

— the date,

— the name and pharmaceutical form of the medicinal product,

— the quantity supplied,

— the name and address of the supplier and consignor.

Member States shall take all appropriate measures to ensure that persons authorized or entitled to supply medicinal products to the public are able to provide information that makes it possible to trace the distribution path of every medicinal product.

Article 83

The provisions of this Title shall not prevent the application of more stringent requirements laid down by Member States in respect of the wholesale distribution of:

— narcotic or psychotropic substances within their territory,

— medicinal products derived from blood,

— immunological medicinal products,

— radiopharmaceuticals.

Article 84

The Commission shall publish guidelines on good distribution practice. To this end, it shall consult the Committee for Proprietary Medicinal Products and the Pharmaceutical Committee established by Council Decision 75/320/EEC ([1]).

Article 85

The provisions of this Title shall apply to homeopathic medicinal products, with the exception of those referred to in Article 14(1).

TITLE VIII

ADVERTISING

Article 86

1. For the purposes of this Title, 'advertising of medicinal products' shall include any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products; it shall include in particular:

— the advertising of medicinal products to the general public,

— advertising of medicinal products to persons qualified to prescribe or supply them,

— visits by medical sales representatives to persons qualified to prescribe medicinal products,

— the supply of samples,

([1]) OJ L 187, 9.6.1975, p. 23.

— the provision of inducements to prescribe or supply medicinal products by the gift, offer or promise of any benefit or bonus, whether in money or in kind, except when their intrinsic value is minimal,

— sponsorship of promotional meetings attended by persons qualified to prescribe or supply medicinal products,

— sponsorship of scientific congresses attended by persons qualified to prescribe or supply medicinal products and in particular payment of their travelling and accommodation expenses in connection therewith.

2. The following are not covered by this Title:

— the labelling and the accompanying package leaflets, which are subject to the provisions of Title V,

— correspondence, possibly accompanied by material of a non-promotional nature, needed to answer a specific question about a particular medicinal product,

— factual, informative announcements and reference material relating, for example, to pack changes, adverse-reaction warnings as part of general drug precautions, trade catalogues and price lists, provided they include no product claims,

— statements relating to human health or diseases, provided there is no reference, even indirect, to medicinal products.

Article 87

1. Member States shall prohibit any advertising of a medicinal product in respect of which a marketing authorization has not been granted in accordance with Community law.

2. All parts of the advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics.

3. The advertising of a medicinal product:

— shall encourage the rational use of the medicinal product, by presenting it objectively and without exaggerating its properties,

— shall not be misleading.

Article 88

1. Member States shall prohibit the advertising to the general public of medicinal products which:

— are available on medical prescription only, in accordance with Title VI,

— contain psychotropic or narcotic substances, such as the United Nations Conventions of 1961 and 1971,

— may not be advertised to the general public in accordance with the second subparagraph of paragraph 2.

2. Medicinal products may be advertised to the general public which, by virtue of their composition and purpose, are intended and designed for use without the intervention of a medical practitioner for diagnostic purposes or for the prescription or monitoring of treatment, with the advice of the pharmacist, if necessary.

Member States shall prohibit the mentioning in advertising to the general public of therapeutic indications such as:

— tuberculosis,

— sexually transmitted diseases,

— other serious infectious diseases,

— cancer and other tumoral diseases,

— chronic insomnia,

— diabetes and other metabolic illnesses.

3. Member States shall be able to ban, on their territory, advertising to the general public of medicinal products the cost of which may be reimbursed.

4. The prohibition referred to in paragraph 1 shall not apply to vaccination campaigns carried out by the industry and approved by the competent authorities of the Member States.

5. The prohibition referred to in paragraph 1 shall apply without prejudice to Article 14 of Directive 89/552/EEC.

6. Member States shall prohibit the direct distribution of medicinal products to the public by the industry for promotional purposes; they may, however, authorize such distribution in special cases for other purposes.

Article 89

1. Without prejudice to Article 88, all advertising to the general public of a medicinal product shall:

(a) be set out in such a way that it is clear that the message is an advertisement and that the product is clearly identified as a medicinal product;

(b) include the following minimum information:

— the name of the medicinal product, as well as the common name if the medicinal product contains only one active substance,

— the information necessary for correct use of the medicinal product,

— an express, legible invitation to read carefully the instructions on the package leaflet or on the outer packaging, as the case may be.

2. Member States may decide that the advertising of a medicinal product to the general public may, notwithstanding paragraph 1, include only the name of the medicinal product if it is intended solely as a reminder.

Article 90

The advertising of a medicinal product to the general public shall not contain any material which:

(a) gives the impression that a medical consultation or surgical operation is unnecessary, in particular by offering a diagnosis or by suggesting treatment by mail;

(b) suggests that the effects of taking the medicine are guaranteed, are unaccompanied by adverse reactions or are better than, or equivalent to, those of another treatment or medicinal product;

(c) suggests that the health of the subject can be enhanced by taking the medicine;

(d) suggests that the health of the subject could be affected by not taking the medicine; this prohibition shall not apply to the vaccination campaigns referred to in Article 88(4);

(e) is directed exclusively or principally at children;

(f) refers to a recommendation by scientists, health professionals or persons who are neither of the foregoing but who, because of their celebrity, could encourage the consumption of medicinal products;

(g) suggests that the medicinal product is a foodstuff, cosmetic or other consumer product;

(h) suggests that the safety or efficacy of the medicinal product is due to the fact that it is natural;

(i) could, by a description or detailed representation of a case history, lead to erroneous self-diagnosis;

(j) refers, in improper, alarming or misleading terms, to claims of recovery;

(k) uses, in improper, alarming or misleading terms, pictorial representations of changes in the human body caused by disease or injury, or of the action of a medicinal product on the human body or parts thereof;

(l) mentions that the medicinal product has been granted a marketing authorization.

Article 91

1. Any advertising of a medicinal product to persons qualified to prescribe or supply such products shall include:

— essential information compatible with the summary of product characteristics;

— the supply classification of the medicinal product.

Member States may also require such advertising to include the selling price or indicative price of the various presentations and the conditions for reimbursement by social security bodies.

2. Member States may decide that the advertising of a medicinal product to persons qualified to prescribe or supply such products may, notwithstanding paragraph 1, include only the name of the medicinal product, if it is intended solely as a reminder.

Article 92

1. Any documentation relating to a medicinal product which is transmitted as part of the promotion of that product to persons qualified to prescribe or supply it shall include, as a minimum, the particulars listed in Article 91(1) and shall state the date on which it was drawn up or last revised.

2. All the information contained in the documentation referred to in paragraph 1 shall be accurate, up-to-date, verifiable and sufficiently complete to enable the recipient to form his or her own opinion of the therapeutic value of the medicinal product concerned.

3. Quotations as well as tables and other illustrative matter taken from medical journals or other scientific works for use in the documentation referred to in paragraph 1 shall be faithfully reproduced and the precise sources indicated.

Article 93

1. Medical sales representatives shall be given adequate training by the firm which employs them and shall have sufficient scientific knowledge to be able to provide information which is precise and as complete as possible about the medicinal products which they promote.

2. During each visit, medical sales representatives shall give the persons visited, or have available for them, summaries of the product characteristics of each medicinal product they present together, if the legislation of the Member State so permits, with details of the price and conditions for reimbursement referred to in Article 91(1).

3. Medical sales representatives shall transmit to the scientific service referred to in Article 98(1) any information about the use of the medicinal products they advertise, with particular reference to any adverse reactions reported to them by the persons they visit.

Article 94

1. Where medicinal products are being promoted to persons qualified to prescribe or supply them, no gifts, pecuniary advantages or benefits in kind may be supplied, offered or promised to such persons unless they are inexpensive and relevant to the practice of medicine or pharmacy.

2. Hospitality at sales promotion shall always be reasonable in level and secondary to the main purpose of the meeting and must not be extended to other than health professionals.

3. Persons qualified to prescribe or supply medicinal products shall not solicit or accept any inducement prohibited under paragraph 1 or contrary to paragraph 2.

4. Existing measures or trade practices in Member States relating to prices, margins and discounts shall not be affected by paragraphs 1, 2 and 3.

Article 95

The provisions of Article 94(1) shall not prevent hospitality being offered, directly or indirectly, at events for purely professional and scientific purposes; such hospitality shall always be reasonable in level and remain subordinate to the main scientific objective of the meeting; it must not be extended to persons other than health professionals.

Article 96

1. Free samples shall be provided on an exceptional basis only to persons qualified to prescribe them and on the following conditions:

(a) the number of samples for each medicinal product each year on prescription shall be limited;

(b) any supply of samples shall be in response to a written request, signed and dated, from the prescribing agent;

(c) those supplying samples shall maintain an adequate system of control and accountability;

(d) each sample shall be identical with the smallest presentation on the market;

(e) each sample shall be marked 'free medical sample — not for sale' or shall show some other wording having the same meaning;

(f) each sample shall be accompanied by a copy of the summary of product characteristics;

(g) no samples of medicinal products containing psychotropic or narcotic substances within the meaning of international conventions, such as the United Nations Conventions of 1961 and 1971, may be supplied.

2. Member States may also place further restrictions on the distribution of samples of certain medicinal products.

Article 97

1. Member States shall ensure that there are adequate and effective methods to monitor the advertising of medicinal products. Such methods, which may be based on a system of prior vetting, shall in any event include legal provisions under which persons or organizations regarded under national law as having a legitimate interest in prohibiting any advertisement inconsistent with this Title, may take legal action against such advertisement, or bring such advertisement before an administrative authority competent either to decide on complaints or to initiate appropriate legal proceedings.

2. Under the legal provisions referred to in paragraph 1, Member States shall confer upon the courts or administrative authorities powers enabling them, in cases where they deem such measures to be necessary, taking into account all the interests involved, and in particular the public interest:

— to order the cessation of, or to institute appropriate legal proceedings for an order for the cessation of, misleading advertising, or

— if misleading advertising has not yet been published but publication is imminent, to order the prohibition of, or to institute appropriate legal proceedings for an order for the prohibition of, such publication,

even without proof of actual loss or damage or of intention or negligence on the part of the advertiser.

3. Member States shall make provision for the measures referred to in the second subparagraph to be taken under an accelerated procedure, either with interim effect or with definitive effect.

It shall be for each Member State to decide which of the two options set out in the first subparagraph to select.

4. Member States may confer upon the courts or administrative authorities powers enabling them, with a view to eliminating the continuing effects of misleading advertising the cessation of which has been ordered by a final decision:

— to require publication of that decision in full or in part and in such form as they deem adequate,

— to require in addition the publication of a corrective statement.

5. Paragraphs 1 to 4 shall not exclude the voluntary control of advertising of medicinal products by self-regulatory bodies and recourse to such bodies, if proceedings before such bodies are possible in addition to the judicial or administrative proceedings referred to in paragraph 1.

Article 98

1. The marketing authorization holder shall establish, within his undertaking, a scientific service in charge of information about the medicinal products which he places on the market.

2. The marketing authorization holder shall:

— keep available for, or communicate to, the authorities or bodies responsible for monitoring advertising of medicinal products, a sample of all advertisements emanating from his undertaking together with a statement indicating the persons to whom it is addressed, the method of dissemination and the date of first dissemination,

— ensure that advertising of medicinal products by his undertaking conforms to the requirements of this Title,

— verify that medical sales representatives employed by his undertaking have been adequately trained and fulfill the obligations imposed upon them by Article 93(2) and (3),

— supply the authorities or bodies responsible for monitoring advertising of medicinal products with the information and assistance they require to carry out their responsibilities,

— ensure that the decisions taken by the authorities or bodies responsible for monitoring advertising of medicinal products are immediately and fully complied with.

Article 99

Member States shall take the appropriate measures to ensure that the provisions of this Title are applied and shall determine in particular what penalties shall be imposed should the provisions adopted in the execution of Title be infringed.

Article 100

Advertising of the homeopathic medicinal products referred to in Article 13(2) and Article 14(1) shall be subject to the provisions of this Title with the exception of Article 87(1).

However, only the information specified in Article 69(1) may be used in the advertising of such medicinal products.

Moreover, each Member State may prohibit in its territory any advertising of the homeopathic medicinal products referred to in Article 13(2) and Article 14(1).

TITLE IX

PHARMACOVIGILANCE

Article 101

The Member States shall take all appropriate measures to encourage doctors and other health care professionals to report suspected adverse reactions to the competent authorities.

The Member States may impose specific requirements on doctors and other health care professionals, in respect of the reporting of suspected serious or unexpected adverse reactions, in particular where such reporting is a condition of the marketing authorization.

Article 102

In order to ensure the adoption of appropriate regulatory decisions concerning the medicinal products authorized within the Community, having regard to information obtained about adverse reactions to medicinal products under normal conditions of use, the Member States shall establish a pharmacovigilance system. This system shall be used to collect information useful in the surveillance of medicinal products, with particular reference to adverse reactions in human beings, and to evaluate such information scientifically.

Such information shall be collated with data on consumption of medicinal products.

This system shall also take into account any available information on misuse and abuse of medicinal products which may have an impact on the evaluation of their benefits and risks.

Article 103

The marketing authorization holder shall have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance.

That qualified person shall be responsible for the following:

(a) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the company, and to medical representatives, is collected and collated in order to be accessible at least at one point within the Community;

(b) the preparation for the competent authorities of the reports referred to in Article 104, in such form as may be laid down by those authorities, in accordance with the guidance referred to in Article 106(1);

(c) ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned;

(d) the provision to the competent authorities, of any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on post-authorization safety studies.

Article 104

1. The marketing authorization holder shall be required to maintain detailed records of all suspected adverse reactions occurring either in the Community or in a third country.

2. The marketing authorization holder shall be required to record and to report all suspected serious adverse reactions which are brought to his attention by a health care professional immediately to the competent authority of the Member State in whose territory the incident occurred, and in no case later than 15 calendar days following the receipt of the information.

3. The marketing authorization holder shall be required to record and report all other suspected serious adverse reactions which meet the reporting criteria in accordance with the guidance referred to in Article 106(1) of which he can reasonably be expected to have knowledge immediately to the competent authority of the Member State in whose territory the incident occurred, and in no case later than 15 calendar days following the receipt of the information.

4. The marketing authorization holder shall ensure that all suspected serious and unexpected adverse reactions occurring in the territory of a third country and brought to his attention by a health care professional are reported immediately in accordance with the guidance referred to in Article 106(1), so that they are available to the Agency and to the competent authorities of the Member States where the medicinal product is authorised, and in no case later than 15 calendar days following the receipt of the information.

5. In the case of medicinal products which have been considered within the scope of Directive 87/22/EEC, or which have benefited from the procedures of mutual recognition foreseen in Articles 17 and 18 of this Directive, Article 28(4) of this Directive, and medicinal products for which there has been a referral to the procedures foreseen by Articles 32, 33 and 34 of this Directive, the marketing authorisation holder shall additionally ensure that all suspected serious adverse reactions occurring in the Community are reported in the format and at intervals to be agreed with the reference Member State, or a competent authority acting as the reference Member State, in such a way so as to be accessible to the reference Member State.

6. Unless other requirements have been laid down as a condition of the granting of authorisation, or subsequently as indicated in the guidance referred to in Article 106(1), records of all adverse reactions shall be submitted to the competent authorities in the form of a periodic safety update report, either immediately upon request or periodically as follows: six monthly for the first two years after authorisation, annually for the subsequent two years, and at the time of the first renewal. Thereafter the periodic safety update reports shall be submitted at five-yearly intervals together with the application for renewal of the authorisation. The periodic safety update reports shall include a scientific evaluation of the benefit and risks afforded by the medicinal products.

7. Following the granting of a marketing authorisation, the marketing authorisation holder may request the amendment of the periods referred to in this article according to the procedure laid down by Commission Regulation (EC) No 541/95 [1].

Article 105

1. The Agency, in collaboration with the Member States and the Commission shall set up a data-processing network to facilitate the exchange of pharmacovigilance information regarding medicinal products marketed in the Community intended to allow all competent authorities to share the information at the same time.

2. Making use of the network foreseen in paragraph 1, Member States shall ensure that reports of suspected serious adverse reactions that have taken place on their territory are immediately made available to the Agency and the other Member States, and in any case within 15 calendar days of their notification, at the latest.

3. The Member States shall ensure that reports of suspected serious adverse reactions that have taken place on their territory are immediately made available to the marketing authorisation holder, and in any case within 15 calendar days of their notification, at the latest.

[1] OJ L 55, 11.3.1995, p. 7. Regulation amended by Regulation (EC) No 1146/98 (OJ L 159, 3.6.1998, p. 31).

Article 106

1. In order to facilitate the exchange of information about pharmacovigilance within the Community, the Commission, in consultation with the Agency, Member States and interested parties, shall draw up guidance on the collection, verification and presentation of adverse reaction reports, including technical requirements for electronic exchange of pharmacovigilance information in accordance with internationally agreed formats and shall publish a reference to an internationally agreed medical terminology.

This guidance shall be published in Volume 9 of The rules governing medicinal products in the European Community and shall take account of international harmonisation work carried out in the field of pharmacovigilance.

2. For the interpretation of the definitions referred to in Article 1 points 11 to 16 and the principles outlined in this Title, the marketing authorisation holder and the competent authorities shall refer to the guidance referred to in paragraph 1.

Article 107

1. Where, as a result of the evaluation of pharmacovigilance data, a Member State considers that a marketing authorisation should be suspended, withdrawn or varied in accordance with the guidance referred to in Article 106(1), it shall forthwith inform the Agency, the other Member States and the marketing authorisation holder.

2. In case of urgency, the Member State concerned may suspend the marketing authorisation of a medicinal product, provided the Agency, the Commission and the other Member States are informed at the latest on the following working day.

Article 108

Any amendments which may be necessary to update provisions of Articles 101 to 107 to take account of scientific and technical progress shall be adopted in accordance with the procedure referred to in Article 121(2).

TITLE X

SPECIAL PROVISIONS ON MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD AND PLASMA

Article 109

1. In respect of the use of human blood or human plasma as a starting material for the manufacture of medicinal products, Member States shall take the necessary measures to prevent the transmission of infectious diseases. In so far as this is covered by the amendments referred to in Article 121(1), as well as the application of the monographs of the European Pharmacopoeia regarding blood and plasma, these measures shall comprise those recommended by the Council of Europe and the World Health Organization, particularly with reference to the selection and testing of blood and plasma donors.

2. Member States shall take the necessary measures to ensure that human blood and human plasma donors and donation centres are always clearly identifiable.

3. All the safety guarantees referred to in paragraphs 1 and 2 must also be given by importers of human blood or human plasma from third countries.

Article 110

Member States shall take the necessary measures to promote Community self-sufficiency in human blood or human plasma. For this purpose, they shall encourage the voluntary unpaid donation of blood and plasma and shall take the necessary measures to develop the production and use of products derived from human blood or human plasma coming from voluntary unpaid donations. They shall notify the Commission of such measures.

TITLE XI

SUPERVISION AND SANCTIONS

Article 111

1. The competent authority of the Member State concerned shall ensure, by means of repeated inspections, that the legal requirements governing medicinal products are complied with.

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

(a) inspect manufacturing or commercial establishments and any laboratories entrusted by the holder of the manufacturing authorization with the task of carrying out checks pursuant to Article 20;

(b) take samples;

(c) examine any documents relating to the object of the inspection, subject to the provisions in force in the Member States on 21 May 1975 and which place restrictions on these powers with regard to the descriptions of the method of preparation.

2. Member States shall take all appropriate steps to ensure that the manufacturing processes used in the manufacture of immunological products are properly validated and attain batch-to-batch consistency.

3. After every inspection as referred to in paragraph 1, the officials representing the competent authority shall report on whether the manufacturer complies with the principles and

guidelines of good manufacturing practice laid down in Article 47. The content of such reports shall be communicated to the manufacturer who has to undergo the inspection.

Article 112

Member States shall take all appropriate measures to ensure that the holder of the marketing authorization for a medicinal product and, where appropriate, the holder of the manufacturing authorization, furnish proof of the controls carried out on the medicinal product and/or the ingredients and of the controls carried out at an intermediate stage of the manufacturing process, in accordance with the methods laid down in Article 8(3)(h).

Article 113

For the purpose of implementing Article 112, Member States may require manufacturers of immunological products to submit to a competent authority copies of all the control reports signed by the qualified person in accordance with Article 51.

Article 114

1. Where it considers it necessary in the interests of public health, a Member State may require the holder of an authorization for marketing:

— live vaccines,

— immunological medicinal products used in the primary immunization of infants or of other groups at risk,

— immunological medicinal products used in public health immunization programmes,

— new immunological medicinal products or immunological medicinal products manufactured using new or altered kinds of technology or new for a particular manufacturer, during a transitional period normally specified in the marketing authorization,

to submit samples from each batch of the bulk and/or the medicinal product for examination by a State laboratory or a laboratory designated for that purpose before release on to the market unless, in the case of a batch manufactured in another Member State, the competent authority of that Member State has previously examined the batch in question and declared it to be in conformity with the approved specifications. Member States shall ensure that any such examination is completed within 60 days of the receipt of the samples.

2. Where, in the interests of public health, the laws of a Member State so provide, the competent authorities may require the marketing authorization holder for medicinal products derived from human blood or human plasma to submit samples from each batch of the bulk and/or the medicinal product for testing by a State laboratory or a laboratory designated for that purpose before being released into free circulation, unless the competent authorities of another Member State have previously examined the batch in question and declared it to be in conformity with the approved specifications. Member States shall ensure that any such examination is completed within 60 days of the receipt of the samples.

Article 115

Member States shall take all necessary measures to ensure that the manufacturing and purifying processes used in the preparation of medicinal products derived from human blood or human plasma are properly validated, attain batch-to-batch consistency and guarantee, insofar as the state of technology permits, the absence of specific viral contamination. To this end manufacturers shall notify the competent authorities of the method used to reduce or eliminate pathogenic viruses liable to be transmitted by medicinal products derived from human blood or human plasma. The competent authority may submit samples of the bulk and/or the medicinal product for testing by a State laboratory or a laboratory designated for that purpose, either during the examination of the application pursuant to Article 19, or after a marketing authorization has been granted.

Article 116

The competent authorities of the Member States shall suspend or revoke an authorization to place a medicinal product on the market where that product proves to be harmful in the normal conditions of use, or where its therapeutic efficacy is lacking, or where its qualitative and quantitative composition is not as declared. Therapeutic efficacy is lacking when it is established that therapeutic results cannot be obtained with the medicinal product.

An authorization shall also be suspended or revoked where the particulars supporting the application as provided for in Articles 8, 10(1) and 11 are incorrect or have not been amended in accordance with Article 23, or where the controls referred to in Article 112 have not been carried out.

Article 117

1. Notwithstanding the measures provided for in Article 116, Member States shall take all appropriate measures to ensure that the supply of the medicinal product shall be prohibited and the medicinal product withdrawn from the market if:

(a) the medicinal product proves to be harmful under normal conditions of use, or

(b) it is lacking in therapeutic efficacy, or

(c) its qualitative and quantitative composition is not as declared, or

(d) the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorization has not been fulfilled.

2. The competent authority may limit the prohibition to supply the product, or its withdrawal from the market, to those batches which are the subject of dispute.

Article 118

1. The competent authority shall suspend or revoke the marketing authorization for a category of preparations or all preparations where any one of the requirements laid down in Article 41 is no longer met.

2. In addition to the measures specified in Article 117, the competent authority may suspend manufacture or imports of medicinal products coming from third countries, or suspend or revoke the manufacturing authorization for a category of preparations or all preparations where Articles 42, 46, 51 and 112 are not complied with.

Article 119

The provisions of this Title shall apply to homeopathic medicinal products, subject to the provisions of Article 14(3).

TITLE XII

STANDING COMMITTEE

Article 120

Any changes which are necessary in order to adapt Annex I to take account of scientific and technical progress shall be adopted in accordance with the procedure referred to in Article 121(2).

Article 121

1. The Commission shall be assisted by a Standing Committee on Medicinal Products for Human Use on the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Medicinal Products Sector, (hereinafter referred to as the 'Standing Committee').

2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to Article 8 thereof.

The period provided for in Article 5(6) of Decision 1999/468/EC shall be set at three months.

3. The Standing Committee shall adopt its rules of procedure.

TITLE XIII

GENERAL PROVISIONS

Article 122

Member States shall take all appropriate measures to ensure that the competent authorities concerned communicate to each other such information as is appropriate to guarantee that the requirements for the manufacturing authorizations or marketing authorizations are fulfilled.

Upon reasoned request, Member States shall forthwith communicate the reports referred to in Article 111(3) to the competent authorities of another Member State. If, after considering the reports, the Member State receiving the reports considers that it cannot accept the conclusions reached by the competent authorities of the Member State in which the report was established, it shall inform the competent authorities concerned of its reasons and may request further information. The Member States concerned shall use their best endeavours to reach agreement. If necessary, in the case of serious differences of opinion, the Commission shall be informed by one of the Member States concerned.

Article 123

1. Each Member State shall take all the appropriate measures to ensure that decisions authorizing marketing, refusing or revoking a marketing authorization, cancelling a decision refusing or revoking a 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 Agency forthwith.

2. The marketing authorization holder shall be obliged to notify the Member States concerned forthwith of any action taken by him to suspend the marketing of a medicinal product or to withdraw a medicinal product from the market, together with the reasons for such action if the latter concerns the efficacy of the medicinal product or the protection of public health. Member States shall ensure that this information is brought to the attention of the Agency.

3. Member States shall ensure that appropriate information about action taken pursuant to paragraphs 1 and 2 which may affect the protection of public health in third countries is forthwith brought to the attention of the World Health Organization, with a copy to the Agency.

4. The Commission shall publish annually a list of the medicinal products which are prohibited in the Community.

Article 124

Member States shall communicate to each other all the information necessary to guarantee the quality and safety of homeopathic medicinal products manufactured and marketed within the Community, and in particular the information referred to in Articles 122 and 123.

Article 125

Every decision referred to in this Directive which is taken by the competent authority of a Member State shall state in detail the reasons on which it is based.

Such decision shall be notified to the party concerned, together with information as to the redress available to him under the laws in force and of the time-limit allowed for access to such redress.

Marketing authorizations, and decisions to revoke such authorizations, shall be published by each Member State in the appropriate official publication.

Article 126

An authorization to market a medicinal product shall not be refused, suspended or revoked except on the grounds set out in this Directive.

No decision concerning suspension of manufacture or of importation of medicinal products coming from third countries, prohibition of supply or withdrawal from the market of a medicinal product may be taken except on the grounds set out in Articles 117 and 118.

Article 127

1. At the request of the manufacturer, the exporter or the authorities of an importing third country, Member States shall certify that a manufacturer of medicinal products is in possession of the manufacturing authorization. When issuing such certificates Member States shall comply with the following conditions:

(a) they shall have regard to the prevailing administrative arrangements of the World Health Organization;

(b) for medicinal products intended for export which are already authorized on their territory, they shall supply the summary of the product characteristics as approved in accordance with Article 21.

2. When the manufacturer is not in possession of a marketing authorization he shall provide the authorities responsible for establishing the certificate referred to in paragraph 1, with a declaration explaining why no marketing authorization is available.

TITLE XIV

FINAL PROVISIONS

Article 128

Directives 65/65/EEC, 75/318/EEC, 75/319/EEC, 89/342/EEC, 89/343/EEC, 89/381/EEC, 92/25/EEC, 92/26/EEC, 92/27/EEC, 92/28/EEC and 92/73/EEC, amended by the Directives referred to in Annex II, Part A, are repealed, without prejudice to the obligations of the Member States concerning the time-limits for implementation set out in Annex II, Part B.

References to the repealed Directives shall be construed as references to this Directive and shall be read in accordance with the correlation table in Annex III.

Article 129

This Directive shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Communities*.

Article 130

This Directive is addressed to the Member States.

Done at Brussels, 6 November 2001.

For the European Parliament	*For the Council*
The President	*The President*
N. FONTAINE	D. REYNDERS

ANNEX I

ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS

INTRODUCTION

The particulars and documents accompanying an application for marketing authorization pursuant to Articles 8 and 10(1) shall be presented in four parts, in accordance with the requirements set out in this Annex and taking account of the guidance published by the Commission in *The rules governing medicinal products in the European Community*,Volume II: *Notice to applicants for marketing authorizations for medicinal products for human use in the Member States of the European Community*.

In assembling the dossier for application for marketing authorization, applicants shall take into account the Community guidelines relating to the quality, safety and efficacy of medicinal products published by the Commission in *The rules governing medicinal products in the European Community*, Volume III and its supplements: *Guidelines on the quality, safety and efficacy of medicinal products for human use*.

All information which is relevant to the evaluation of the medicinal product concerned shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned pharmacotoxicological or clinical test or trial relating to the medicinal product. Moreover, in order to monitor the benefit/risk assessment after marketing authorization has been granted, any change to the data in the dossier, any new information not in the original application and all pharmacovigilance reports, shall be submitted to the competent authorities.

The general sections of this Annex give the requirements for all categories of medicinal products; they are supplemented by sections containing additional special requirements for radiopharmaceuticals and for biological medicinal products, such as immunological medicinal products derived from human blood or plasma. The additional special requirements for biological medicinal products are also applicable to medicinal products obtained through processes mentioned in Part A and the first indent of Part B of the Annex to Regulation (EEC) No 2309/93.

Member States shall also ensure that all tests on animals are conducted in accordance with Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulation and administrative provisions of the Member States regarding the protection of animals for experimental and other scientific purposes ([1]).

PART I

SUMMARY OF THE DOSSIER

A. Administrative data

The medicinal product which is the subject of the application shall be identified by name and name of the active substance(s), together with the pharmaceutical form, the method of administration, the strength and the final presentation, including packaging.

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

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

Annexed to the administrative data shall be copies of the manufacturing authorization as defined in Article 40, together with a list of countries in which authorization has been granted, copies of all the summaries of product characteristics in accordance with Article 11 as approved by Member States and a list of countries in which an application has been submitted.

B. Summary of product characteristics

The applicant shall propose a summary of the product characteristics, in accordance with Article 11.

([1]) OJ L 358, 18.12.1986, p.1.

In addition the applicant shall provide samples or mock-ups of the packaging, labels and package leaflets for the medicinal product concerned.

C. **Expert reports**

In accordance with Article 12(2), expert reports must be provided on the chemical, pharmaceutical and biological documentation, the pharmacotoxicological documentation and the clinical documentation respectively.

The expert report shall consist of a critical evaluation of the quality of the medicinal product and the investigations carried out on animals and human beings and bring out all the data relevant for evaluation. It shall be worded so as to enable the reader to obtain a good understanding of the properties, quality, the proposed specifications and control methods, the safety, the efficacy, the advantages and disadvantages of the medicinal product.

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

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

PART 2

CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL TESTING OF MEDICINAL PRODUCTS

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

All the test procedure(s) shall be described in sufficiently precise detail so as to be reproducible in control tests, carried out at the request of the competent authority; any special apparatus and equipment which may be used shall be described in adequate detail, possibly accompanied by a diagram. The formulae of the laboratory reagents shall be supplemented, if necessary, by the manufacturing method. In the case of test procedures included in the *European Pharmacopoeia* or the pharmacopoeia of a Member State, this description may be replaced by a detailed reference to the pharmacopoeia in question.

A. **Qualitative and quantitative particulars of the constituents**

The particulars and documents which must accompany applications for marketing authorization, pursuant to point 3 of Article 8(3)(c) shall be submitted in accordance with the following requirements.

1. *Qualitative particulars*

1.1. 'Qualitative particulars' of all the constituents of the medicinal product shall mean the designation or description of:

— the active substance(s),

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

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

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

1.2. In the context of a radiopharmaceutical kit, which is to be radiolabelled after supply by the manufacturer, the active substance is considered to be that part of the formulation which is intended to carry or bind the radionuclide. Details of the source of the radionuclide shall be stated. In addition, any compounds essential for the radiolabelling shall be stated.

In a generator, both mother and daughter radionuclides are to be considered as active substances.

2. The 'usual terminology', to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions in Article 8(3)(c):

— in respect of substances which appear in the *European Pharmacopoeia* or, failing this, in the national pharmacopoeia of one of the Member States, the main title at the head of the monograph in question, with reference to the pharmacopoeia concerned,

— in respect of other substances, the international non-proprietary name recommended by the World Health Organization, which may be accompanied by another non-proprietary name, or, failing these, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,

— in respect of colouring matter, designation by the 'E' code assigned to them in Council Directive 78/25/EEC of 12 December 1977 on the approximation of the rules of the Member States concerning the colouring matters authorized for use in medicinal products ([1]).

3. *Quantitative particulars*

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

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

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

This information shall be supplemented:

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

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

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

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

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

3.4. For allergen products, the quantitative particulars shall be expressed by units of biological activity, except for well defined allergen products for which the concentration may be expressed by mass/unit of volume.

3.5. The requirement to express the content of active substances in terms of the mass of active entities, as in point 3.3. above, may not apply to radiopharmaceuticals. For radionuclides, radioactivity shall be expressed in becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated.

4. *Development pharmaceutics*

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

([1]) OJ L 11, 14.1.1978, p. 18. Directive as last amended by the 1985 Act of Accession.

4.2. For radiopharmaceuticals, this should include a consideration of chemical/radiochemical purity and its relationship to biodistribution.

B. **Description of manufacturing method**

1. The description of the manufacturing method accompanying the application for marketing authorization pursuant to Article 8(3)(d), shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.

For this purpose it shall include at least:

— mention of the various stages of manufacture, so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced an adverse change in the constituents,

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

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

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

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

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

2. For radiopharmaceutical kits, the description of the manufacturing method shall also include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product.

For radionuclides, the nuclear reactions involved shall be discussed.

C. **Controls of starting materials**

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

In the case of:

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

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

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

The particulars and documents accompanying the application for marketing authorization pursuant to Article 8(3)(h) and (i) and 10(1), shall include the results of the tests, including batch analyses particularly for active substances, relating to quality control of all the constituents used. These shall be submitted in accordance with the following provisions.

1.1. Starting materials listed in pharmacopoeias

The monographs of the *European Pharmacopoeia* shall be applicable to all substances appearing in it.

In respect of other substances, each Member State may require observance of its own national pharmacopoeia with regard to products manufactured in its territory.

Constituents fulfilling the requirements of the *European Pharmacopoeia* or the pharmacopoeia of one of the Member States shall be deemed to comply sufficiently with Article 8(3)(h). In this case the description of the analytical methods may be replaced by a detailed reference to the pharmacopoeia in question.

However, where a starting material in the *European Pharmacopoeia* or in the pharmacopoeia of a Member State has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described.

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

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

In cases where a specification contained in a monograph of the *European Pharmacopoeia* or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorization holder.

The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorization holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.

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

1.2. Starting materials not in a pharmacopoeia

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

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

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

(c) methods of identification may be described in the form of complete techniques as used for production of the substance, and in the form of tests which ought to be carried out as a routine matter;

(d) purity tests shall be described in relation to the sum total of predictable impurities, especially those which may have a harmful effect, and, if necessary, those which, having regard to the combination of substances to which the application refers, might adversely affect the stability of the medicinal product or distort analytical results;

(e) with regard to complex substances of plant or animal/human origin, a distinction must be made between the case where multiple pharmacological effects render chemical, physical or biological control of the principal constituents necessary, and the case of substances containing one or more groups of principles having similar activity, in respect of which an overall method of assay may be accepted;

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

(g) for radionuclides, the nature of the radionuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be given;

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

1.3. Physico-chemical characteristics liable to effect bio-availability

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

— crystalline form and solubility coefficients,

— particle size, where appropriate after pulverization,

— state of solvation,

— oil/water coefficient of partition ([1]).

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

2. For biological medicinal products, such as immunological medicinal products and medicinal products derived from human blood or plasma, the requirements of this paragraph shall apply.

For the purposes of this paragraph, starting materials shall mean any substance used in the manufacture of the medicinal product; this includes the constituents of the medicinal product, and, if necessary, of its container, as referred to in paragraph A, point 1 above, as well as source materials such as microorganisms, tissues of either plant or animal origin, cells or fluids (including blood) of human or animal origin, and biotechnological cell constructs. The origin and history of starting materials shall be described and documented.

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

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

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

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

2.3. Whenever possible, vaccine production shall be based on a seed lot system and on established cell banks; for serums, defined pools of starting materials shall be used.

For bacterial and viral vaccines, the characteristics of the infectious agent shall be demonstrated on the seed. In addition, for live vaccines, the stability of the attenuation characteristics shall be demonstrated on the seed; if this proof is not sufficient, the attenuation characteristics shall also be demonstrated at the production stage.

2.4. For allergen products, the specifications and control methods for the source materials shall be described in as much detail as possible. The description shall include particulars concerning collection, pretreatment and storage.

2.5. For medicinal products derived from human blood or plasma, the origin and the criteria and procedures for collection, transportation and storage of the source material shall be described and documented.

Defined pools of source material shall be used.

3. For radiopharmaceuticals, starting materials include irradiation target materials.

D. **Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies**

The applicant must demonstrate that the medicinal product is manufactured in accordance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in Volume 3 of its publication *The rules governing medicinal products in the European Community*.

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

E. **Control tests carried out at intermediate stages of the manufacturing process**

1. The particulars and documents accompanying an application for marketing authorization, pursuant to Article 8(3)(h) and (i) and Article 10, paragraph 1 of this Directive, shall include particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the technical characteristics and the production process.

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

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

2. For biological medicinal products, such as immunological medicinal products and medicinal products derived from human blood or plasma, the procedures and the criteria of acceptability published as recommendations of the WHO (*Requirements for Biological Substances*) shall serve as guidelines for all controls of production stages which are not specified in the *European Pharmacopoeia*, or falling this, in the national pharmacopoeia of a Member State.

For inactivated or detoxified vaccines, effective inactivation or detoxification shall be verified during each production run, unless this control is dependent upon a test for which the availability of susceptible animals is limited. In this case, the test shall be carried out until consistency of production and correlation with appropriate in process controls have been established and thereafter compensated by appropriate in-process controls.

3. For modified or adsorbed allergen products, the products shall be qualitatively and quantitatively characterized at an intermediate stage, as late as possible in the manufacturing process.

F. **Control tests on the finished product**

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

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

The particulars and documents accompanying the application for marketing authorization pursuant to Article 8(3)(h) and (i) and Article 10(1) of this Directive, shall include particulars relating to control tests on the finished product at release. They shall be submitted in accordance with the following requirements.

The provisions of the monographs for pharmaceutical forms, immunosera, vaccines and radiopharmaceutical preparations of the *European Pharmacopoeia* or failing that, of a Member State, shall be applicable to all products defined therein. For all controls of biological medicinal products such as immunological medicinal products and medicinal products derived from human blood or plasma which are not specified in the *European Pharmacopoeia* or failing this, in the pharmacopoeia of a Member State, the procedures and the criteria of acceptability published as recommendations in the WHO (*Requirements for Biological Substances*) shall serve as guidelines.

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

1.1. General characteristics of the finished product

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

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

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

1.2. Identification and assay of active substance(s)

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

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

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

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

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

Where the particulars given in section B show that a significant overage of an active substance is employed in the manufacture of the medicinal product, the description of the control tests on the finished product shall include, where appropriate, the chemical and, if necessary, the toxico-pharmacological investigation of the changes that this substance has undergone, and possibly the characterization and/or assay of the degradation products.

1.3. Identification and assay of excipient constituents

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

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

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

1.4. Safety tests

1. Apart from the pharmacotoxicological tests submitted with the application for marketing authorization, particulars of safety tests, such as sterility, bacterial endotoxin, pyrogenicity and local tolerance in animals shall be included in the analytical particulars wherever such tests must be undertaken as a matter of routine in order to verify the quality of the product.

2. For all controls of biological medicinal products, such as immunological medicinal products and medicinal products derived from human blood or plasma, which are not specified in the *European Pharmacopoeia*, or failing this, in the national pharmacopoeia of a Member State, the procedures and the criteria of acceptability published as recommendations in the World Health Organization (*Requirements for Biological Substances*) shall serve as guidelines.

3. For radiopharmaceuticals, radionuclidic purity, radiochemical purity and specific activity shall be described. For content of radioactivity, the deviation from that stated on the label should not exceed ± 10 %.

For generators, details on the testing for mother and daughter radionuclides are required. For generator-eluates, tests for mother radionuclides and for other components of the generator system shall be provided.

For kits, the specifications of the finished product shall include tests on performance of products after radiolabelling. Appropriate controls on radiochemical and radionuclidic purity of the radiolabelled compound shall be included. Any material essential for radiolabelling shall be identified and assayed.

G. **Stability tests**

1. The particulars and documents accompanying the application for marketing authorization pursuant to Article 8(3)(g) and (h) shall be submitted in accordance with the following requirements.

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

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

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

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

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

2. Where for biological medicinal products, such as immunological medicinal products and medicinal products derived from human blood or plasma, stability tests cannot be carried out on the finished products, it is acceptable to carry out stability indicating tests at an intermediate stage of production as late as possible in the manufacturing process. In addition, there should be an evaluation of the stability of the finished product using other secondary tests.

3. For radiopharmaceuticals, information on stability shall be given for radionuclide generators, radionuclide kits and radiolabelled products. The stability during use of radiopharmaceuticals in multi-dose vials shall be documented.

PART 3

TOXICOLOGICAL AND PHARMACOLOGICAL TESTS

I. **Introduction**

1. The particulars and documents accompanying the application for marketing authorization pursuant to Articles 8(3)(i) and 10(1) shall be given in accordance with the requirements below.

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

The toxicological and pharmacological tests must show:

(a) the potential toxicity of the product and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human beings; these should be evaluated in relation to the pathological condition concerned;

([1]) OJ L 15, 17.1.1987, p. 29.
([2]) OJ L 145, 11.6.1988, p. 35. Directive as amended by Directive 90/18/EEC (OJ L 11, 13.1.1990, p. 37).

(b) the pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in human beings. All results must be reliable and of general applicability. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results.

Additionally, it is necessary for clinicians to be given information about the therapeutic potential of the product.

2. Where a medicinal product is intended for topical use, systemic absorption must be investigated, due account also being taken of the possible use of the product on broken skin and absorption through other relevant surfaces. Only if it is proved that systemic absorption under these conditions is negligible may repeated dose systemic toxicity tests, foetal toxicity tests and studies of reproductive function be omitted.

If, however, systemic absorption is demonstrated during therapeutic experimentation, toxicity tests shall be carried out on animals, including where necessary, foetal toxicity tests.

In all cases, tests of local tolerance after repeated application shall be carried out with particular care and include histological examinations; the possibility of sensitization shall be investigated and any carcinogenic potential investigated in the cases referred to in Section II E of this Part.

3. For biological medicinal products such as immunological medicinal products and medicinal products derived from human blood or plasma, the requirements of this Part may have to be adapted for individual products; therefore the testing programme carried out shall be justified by the applicant.

In establishing the testing programme, the following shall be taken into consideration:

— all tests requiring repeated administration of the product shall be designed to take account of the possible induction of, and interference by, antibodies;

— examination of reproductive function, of embryo/foetal and perinatal toxicity, of mutagenic potential and of carcinogenic potential shall be considered. Where components other than the active substance(s) are incriminated, validation of their removal may replace the study.

4. For radiopharmaceuticals, it is appreciated that toxicity may be associated with a radiation dose. In diagnosis, this is a consequence of the use of radiopharmaceuticals; in therapy, it is the wanted property. The evaluation of safety and efficacy of radiopharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects. Organ/tissue exposure to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognized system by a particular route of administration.

5. The toxicology and pharmacokinetics of an excipient used for the first time in the pharmaceutical field shall be investigated.

6. Where there is a possibility of significant degradation during storage of the medicinal product, the toxicology of degradation products must be considered.

II. *PERFORMANCE OF TESTS*

A. **Toxicity**

1. *Single dose toxicity*

An acute test is a qualitative and quantitative study of the toxic reactions which may result from a single administration of the active substance or substances contained in the medicinal product, in the proportions and physico-chemical state in which they are present in the actual product.

The acute toxicity test must be carried out in two or more mammalian species of known strain unless a single species can be justified. At least two different routes of administration shall normally be used, one being identical with or similar to that proposed for use in human beings and the other ensuring systemic exposure to the substance.

This study will cover the signs observed, including local reactions. The period during which the test animals are observed shall be fixed by the investigator as being adequate to reveal tissue or organ damage or recovery, usually for a period of 14 days but not less than 7 days, but without exposing the animals to prolonged suffering.

Animals dying during the observation period should be subject to autopsy as also should all animals surviving to the end of the observation period. Histopathological examinations should be considered on any organ showing macroscopic changes at autopsy. The maximum amount of information should be obtained from the animals used in the study.

The single dose toxicity tests should be conducted in such a way that signs of acute toxicity are revealed and the mode of death assessed as far as reasonably possible. In suitable species, a quantitative evaluation of the approximate lethal dose and information on the dose effect relationship should be obtained, but a high level of precision is not required.

These studies may give some indication of the likely effects of acute overdosage in man and may be useful for the design of toxicity studies requiring repeated dosing on the suitable animal species.

In the case of active substances in combination, the study must be carried out in such a way as to check whether or not there is enhancement of toxicity or if novel toxic effects occur.

2. *Repeated dose toxicity (sub-acute or chronic toxicity)*

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

Generally, it is desirable that two tests be performed: one short-term, lasting two to four weeks, the other long-term. The duration of the latter shall depend on the conditions of clinical use. Its purpose shall be to determine by experiment the non-toxic dose range of the product and normally it shall last three to six months.

In respect of medicinal products to be administered once only to humans, a single test lasting two to four weeks shall be performed.

If however, having regard to the proposed duration of use in human beings, the investigator sees fit to carry out experiments of greater or lesser duration than indicated above, he must give adequate reasons for doing so.

Reasons should also be given for the dosages chosen.

Repeated dose toxicity tests shall be carried out on two species of mammals one of which must be a non-rodent. The choice of route(s) of administration employed shall depend on the intended therapeutic use and the possibilities of systemic absorption. The method and frequency of dosage 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 product to be determined.

Wherever possible, and always in experiments on small rodents, the design of the experiment and the control procedures must be suited to the scale of the problem being tackled and enable fiducial limits to be determined.

The evaluation of the toxic effects shall be based on observation of behaviour, growth, haematological and biochemical tests, especially those relating to the excretory mechanism, 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.

In the case of new combinations of known substances that have been investigated in accordance with the provisions of this Directive, the chronic long-term tests may, except where acute and sub-acute toxicity tests have demonstrated potentiation or novel toxic effects, be suitably modified by the investigator who shall submit his reasons for such modification.

B. **Examination of reproductive function**

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

C. **Embryo/foetal and perinatal toxicity**

This investigation comprises a demonstration of the toxic and especially the teratogenic effects observed in the issue of conception when the medicinal product under investigation has been administered to the female during pregnancy.

Although up to the present these tests have had only a limited predictive value in regard to the application of the results to human beings, they are thought to provide important information where the results show effects such as resorptions and other anomalies.

Omission of these tests, either because the medicinal product will not normally be used by women capable of child-bearing or for other reasons, must be adequately justified.

Embryo/foetal toxicity studies shall normally be conducted on two mammalian species, one of which should be other than a rodent. Peri- and postnatal studies shall be conducted in at least one species. Where metabolism of a medicinal product in a particular species is known to be similar to that in man, it is desirable to include this species. Also, it is desirable that one of the species is the same as in the repeated dose toxicity studies.

The details of the test (number of animals, amounts administered, timing of administration 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.

D. **Mutagenic potential**

The purpose of the study of mutagenic potential is to reveal the changes which a substance may cause in the genetic material of individuals or cells and which have the effect of making successors permanently and hereditarily different from their predecessors. This study is obligatory for any new substance.

The number and types of results and the criteria for their evaluation shall depend on the state of scientific knowledge at the time when the application is lodged.

E. **Carcinogenic potential**

Tests to reveal carcinogenic effects shall normally be required:

(a) in respect of substances having a close chemical analogy with known carcinogenic or cocarcinogenic compounds;

(b) in respect of substances which have given rise to suspicious changes during the long-term toxicological tests;

(c) in respect of substances which have given rise to suspicious results in the mutagenic-potential tests or in other short-term carcinogenicity tests.

Such tests may also be required in respect of substances to be included in medicinal products likely to be administered regularly over a prolonged period of a patient's life.

The state of scientific knowledge at the time when the application is lodged shall be taken into account when determining the details of the tests.

F. **Pharmacodynamics**

This heading covers the variations caused by the medicinal product in the functions of the physiological systems, whether these functions are normal or experimentally modified.

This study shall follow two distinct lines of approach.

Firstly, the actions on which the recommended application in therapeutic practice is based shall be adequately described. The results shall be expressed in quantitative terms using, (e.g. dose-effect curves, time-effect curves etc.), and wherever possible, compared with data relating to a substance whose activity is known. Where a higher therapeutic potency is being claimed for a substance, the difference shall be demonstrated and shown to be statistically significant.

Secondly, the investigator shall provide a general pharmacological characterization of the substance, with special reference to adverse reactions. In general, the main functions of the physiological systems should be investigated. The depth of this investigation must be increased as the doses liable to produce adverse reactions approach those producing the main effect for which the substance is being proposed.

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 validity. The experimental results shall be set out clearly and, when relevant to the test, their statistical significance quoted.

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

Tests on combinations of active substances may be prompted either by pharmacological premisses or by indications of therapeutic effect.

In the first case, the pharmacodynamic study shall demonstrate those interactions which might make the combination of value in therapeutic use.

In the second case, where scientific justification for the combination is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and the importance of any collateral effects shall at least be investigated.

If a combination includes a novel active substance, the latter must previously have been studied in depth.

G. **Pharmacokinetics**

Pharmacokinetics means the study of the fate of the active substance within the organism, and covers the study of the absorption, distribution, biotransformation and excretion of the substance.

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

Information on distribution and elimination (i.e. biotransformation and excretion) shall be necessary in all cases where such data are indispensable to determine the dosage for humans, and in respect of chemotherapeutic substances (antibiotics, etc.) and substances whose use depends on their non-pharmacodynamic effects (e.g. numerous diagnostic agents, etc.).

Pharmacokinetic investigation of pharmacologically active substances is necessary.

In the case of new combinations of known substances which have been investigated in accordance with the provisions of this Directive, pharmacokinetic studies may not be required, if the toxicity tests and therapeutic experimentation justify their omission.

H. **Local tolerance**

The purpose of local tolerance studies is to ascertain whether medicinal products (both active substances and excipients) are tolerated at sites in the body which may come into contact with the medicinal product as a result of its administration in clinical use. The testing strategy shall be such that any mechanical effects of administration or purely physico-chemical actions of the product can be distinguished from toxicological or pharmacodynamic ones.

I. **Well-established medicinal use**

For the purpose of demonstrating, pursuant to Article 10(1)(a)(ii), that the component(s) of a medicinal product have a well established use, with an acceptable level of safety, the following specific rules shall apply:

(a) Factors which have to be taken into account in order to establish a 'well established medicinal use' of components of medicinal products are the time over which a substance has been used, quantitative aspects of the use of the substance, the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments. Therefore different periods of time may be necessary for establishing 'well established use' of different substances. In any case, however, the period of time required for establishing a 'well established medicinal use' of a component of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community.

(b) The documentation submitted by the applicant should cover all aspects of the safety assessment and must include or refer to a review of the relevant literature, taking into account pre- and postmarketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, should be communicated.

(c) Particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking.

(d) The Expert report must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgment must be made whether the product studied can be considered as similar to the product which will be granted a marketing authorisation in spite of the existing differences.

(e) Post-marketing experience with other products containing the same components is of particular importance and applicants should put a special emphasis on this issue.

PART 4

CLINICAL DOCUMENTATION

The particulars and documents accompanying applications for marketing authorizations pursuant to Articles 8(3)(i) and 10(1) of this Directive shall be submitted in accordance with the provisions below.

A clinical trial is any systematic study of medicinal products in human subjects whether in patients or non-patient volunteers in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or study their absorption, distribution, metabolism and excretion in order to ascertain the efficacy and safety of the products.

Evaluation of the application for marketing authorization shall be based on clinical trials including clinical pharmacological trials designed to determine the efficacy and safety of the product under normal conditions of use, having regard to the therapeutic indications for use in human beings. Therapeutic advantages must outweigh potential risks.

A. **General requirements**

The clinical particulars to be provided pursuant to Articles 8(3)(i) and 10(1) must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorization. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.

Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of Part 3 of this Annex. The investigator must acquaint himself with the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide him at least with the investigator's brochure, consisting of all the relevant information known prior to the onset of a clinical trial including chemical, pharmaceutical and biological data, toxicological, pharmacokinetic and pharmacodynamic data in animals and the results of earlier clinical trials, with adequate data to justify the nature, scale and duration of the proposed trial; the complete pharmacological and toxicological reports shall be provided on request. For materials of human or animal origin, all available means shall be employed to ensure safety from transmission of infectious agents prior to the commencement of the trial.

B. **Conduct of trials**

1. *Good clinical practice*

1.1. All phases of clinical investigation, including bioavailability and bioequivalence studies, shall be designed, implemented and reported in accordance with good clinical practice.

1.2. All clinical trials shall be carried out in accordance with the ethical principles laid down in the current revision of the Declaration of Helsinki. In principle, the freely given informed consent of each trial subject shall be obtained and documented.

The trial protocol (including statistical design), the technical application and documentation shall be submitted by the sponsor and/or investigator for an opinion to the relevant ethics committee. The trials shall not begin before the opinion of this committee has been received in writing.

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

1.4. In the case of radiopharmaceuticals, clinical trials shall be carried out under the responsibility of a medical doctor authorized to use radionuclides for medical purposes.

2. *Archiving*

The marketing authorization holder shall make arrangements for archiving of documentation.

(a) The investigator shall arrange for the retention of the patient identification codes for at least 15 years after the completion or discontinuation of the trial.

(b) Patient files and other source data shall be kept for the maximum period of time permitted by the hospital, institution or private practice.

(c) The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the product is authorized. These procedures shall include:

— the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product, the reference medicinal product and/or the placebo used,

— standard operating procedures,

— all written opinions on the protocol and procedures,

— the investigator's brochure,

— case report forms on each trial subject,

— final report,

— audit certificate(s), if available.

(d) The final report shall be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorized.

Any change of ownership of the data shall be documented.

All data and documents shall be made available if requested by relevant authorities.

C. **Presentation of results**

1. The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made:

— the protocol, including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational medicinal product used,

— audit certificate(s), if available,

— the list of investigator(s), and each investigator shall give his name, address, appointments, qualifications and clinical duties, state where the trial was carried out and assemble the information in respect of each patient individually, including case report forms on each trial subject,

— final report signed by the investigator and for multicentre trials, by all the investigators or the coordinating (principal) investigator.

2. The particulars of clinical trials referred to above shall be forwarded to the competent authorities. However, in agreement with the competent authorities, the applicant may omit part of this information. Complete documentation shall be provided forthwith upon request.

3. The clinical observations shall be summarized for each trial indicating:

   (a) the number and sex of patients treated;

   (b) the selection and age-distribution of the groups of patients being investigated and the comparative tests;

   (c) the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal;

   (d) where controlled trials were carried out under the above conditions, whether the control group:

      — received no treatment,

      — received a placebo,

      — received another medicinal product of known effect,

      — received treatment other than therapy using medicinal products;

   (e) the frequency of observed adverse reactions;

   (f) details concerning patients who may be at increased risk, e.g. elderly people, children, women during pregnancy or menstruation, or whose physiological or pathological condition requires special consideration;

   (g) parameters or evaluation criteria of efficacy and the results in terms of these parameters;

   (h) a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.

4. The investigator shall, in his conclusions on the experimental evidence, express an opinion on the safety of the product under normal conditions of use, its tolerance, its efficacy and any useful information relating to indications and contra-indications, dosage and average duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of overdosage. In reporting the results of a multi-centre study, the principal investigator shall, in his conclusions, express an opinion on the safety and efficacy of the investigational medicinal product on behalf of all centres.

5. In addition, the investigator shall always indicate his observations on:

   (a) any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;

   (b) any interactions that have been observed with other medicinal products administered concomitantly;

   (c) the criteria determining exclusion of certain patients from the trials;

   (d) any deaths which occurred during the trial or within the follow-up period.

6. Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and efficacy of the combination.

7. Total or partial omission of data must be explained. Should unexpected results occur during the course of the trials, further preclinical toxicological and pharmacological tests must be undertaken and reviewed.

   If the medicinal product is intended for long-term administration, particulars shall be given of any modification of the pharmacological action following repeated administration, as well as the establishment of long-term dosage.

D. **Clinical pharmacology**

1. *Pharmacodynamics*

   The pharmacodynamic action correlated to the efficacy shall be demonstrated including:

   — the dose-response relationship and its time course,

   — justification for the dosage and conditions of administration,

   — the mode of action, if possible.

The pharmacodynamic action not related to efficacy shall be described.

The demonstration of pharmacodynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect.

2. *Pharmacokinetics*

The following pharmacokinetic characteristics shall be described:

— absorption (rate and extent),

— distribution,

— metabolism,

— excretion.

Clinically significant features including the implication of the kinetic data for the dosage regimen especially for patients at risk, and differences between man and animal species used in the preclinical studies, shall be described.

3. *Interactions*

If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

If pharmacodynamic/pharmacokinetic interactions exist between the substance and other medical products or substances like alcohol, caffeine, tobacco or nicotine, likely to be taken simultaneously, or if such interactions are likely, they should be described and discussed; particularly from the point of view of clinical relevance and the relationship to the statement concerning interactions in the summary of product characteristics presented in accordance with Article 11 point 5.6.

E. **Bioavailability/bioequivalence**

The assessment of bioavailability must be undertaken in all cases where it is necessary, e.g. where the therapeutic dose is near the toxic dose or where the previous tests have revealed anomalies which may be related to pharmacodynamic properties, such as variable absorption.

In addition, an assessment of bioavailability shall be undertaken where necessary to demonstrate bioequivalence for the medicinal products referred to in Article 10(1)(a).

F. **Clinical efficacy and safety**

1. In general, clinical trials shall be done as 'controlled clinical trials' and if possible, randomized; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.

As far as possible, and particularly in trials where the effect of the product cannot be objectively measured, steps shall be taken to avoid bias, including methods of randomization and blinding.

2. The protocol of the trial must include a thorough description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomization, shall be documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.

3. Clinical statements concerning the efficacy or safety of a medicinal product under normal conditions of use which are not scientifically substantiated cannot be accepted as valid evidence.

4. The value of data on the efficacy and safety of a medicinal product under normal conditions of use will be very greatly enhanced if such data come from several competent investigators working independently.

5. For vaccines and serums, the immunological status and age of the trial population and the local epidemiology are of critical importance and shall be monitored during the trial and fully described.

   For live attenuated vaccines, clinical trials shall be so designed as to reveal potential transmission of the immunizing agent from vaccinated to non-vaccinated subjects. If transmission is possible, the genotypic and phenotypic stability of the immunizing agent shall be studied.

   For vaccines and allergen products, follow-up studies shall include appropriate immunological tests, and where applicable, antibody assays.

6. The pertinence of the different trials to the assessment of safety and the validity of methods of evaluation shall be discussed in the expert report.

7. All adverse events including abnormal laboratory values shall be presented individually and discussed, especially:

   — in terms of overall adverse experience, and

   — as a function of the nature, seriousness and causality of effects.

8. A critical assessment of relative safety, taking into account adverse reactions, shall be made in relation to:

   — the disease to be treated,

   — other therapeutic approaches,

   — particular characteristics in sub-groups of patients,

   — preclinical data on toxicology and pharmacology.

9. Recommendations shall be made for the conditions of use, with the intention of reducing the incidence of adverse reactions.

G. **Documentation for applications in exceptional circumstances**

When, in respect of particular therapeutic indications, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

— the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or

— in the present state of scientific knowledge, comprehensive information cannot be provided, or

— it would be contrary to generally accepted principles of medical ethics to collect such information,

marketing authorization may be granted on the following conditions:

(a) the applicant completes on identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile,

(b) the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and for a radiopharmaceutical, by an authorized person,

(c) the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

H. **Post-marketing experience**

1. If the medicinal product is already authorized in other countries, information shall be given in respect of adverse drug reactions of the medicinal product concerned and medicinal products containing the same active substance(s), in relation to the usage rates if possible. Information from worldwide studies relevant to the safety of the medicinal product shall be included.

   For this purpose, an adverse drug reaction is a reaction which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function.

2. In the case of vaccines already authorized in other countries, information on the monitoring of vaccinated subjects to evaluate the prevalence of the disease in question as compared to nonvaccinated subjects shall be submitted, when available.

3. For allergen products, response in periods of increased antigen exposure shall be identified.

I. **Well-established medicinal use**

For the purpose of demonstrating, pursuant to Article 10(1)(a)(ii), that the component(s) of a medicinal product have a well established use, with recognised efficacy, the following specific rules shall apply:

(a) Factors which have to be taken into account in order to establish a 'well established medicinal use' of components of medicinal products are the time over which a substance has been used, quantitative aspects of the use of the substance, the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments. Therefore different periods of time may be necessary for establishing 'well established use' of different substances. In any case, however, the period of time required for establishing a 'well established medicinal use' of a component of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community.

(b) The documentation submitted by the applicant should cover all aspects of the efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and postmarketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, should be communicated.

(c) Particular attention must be paid to any missing information and justification must be given why demonstration of efficacy can be supported although some studies are lacking.

(d) The Expert report must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgment must be made whether the product studied can be considered as similar to the product which will be granted a marketing authorisation in spite of the existing differences.

(e) Post-marketing experience with other products containing the same components is of particular importance and applicants should put a special emphasis on this issue.

ANNEX II

PART A

Repealed Directives, with their successive amendments (referred to by Article 128)

Council Directive 65/65/EEC (OJ 22, 9. 2. 1965, p. 369/65)
- Council Directive 66/454/EEC (OJ 144, 5. 8. 1966, p. 2658/66)
- Council Directive 75/319/EEC (OJ L 147, 9. 6. 1975, p. 13)
- Council Directive 83/570/EEC (OJ L 332, 28. 11. 1983, p. 1)
- Council Directive 87/21/EEC (OJ L 15, 17. 1. 1987, p. 36)
- Council Directive 89/341/EEC (OJ L 142, 25. 5. 1989, p. 11)
- Council Directive 92/27/EEC (OJ L 113, 30. 4. 1992, p. 8)
- Council Directive 93/39/EEC (OJ L 214, 24. 8. 1993, p. 22)

Council Directive 75/318/EEC (OJ L 147, 9. 6. 1975, p. 1)
- Council Directive 83/570/EEC
- Council Directive 87/19/EEC (OJ L 15, 17. 1. 1987, p. 31)
- Council Directive 89/341/EEC
- Commission Directive 91/507/EEC (OJ L 270, 26. 9. 1991, p. 32)
- Council Directive 93/39/EEC
- Commission Directive 1999/82/EC (OJ L 243, 15. 9. 1999, p. 7)
- Commission Directive 1999/83/EC (OJ L 243, 15. 9. 1999, p. 9)

Council Directive 75/319/EEC
- Council Directive 78/420/EEC (OJ L 123, 11. 5. 1978, p. 26)
- Council Directive 83/570/EEC
- Council Directive 89/341/EEC
- Council Directive 92/27/EEC
- Council Directive 93/39/EEC
- Commission Directive 2000/38/EC (OJ L 139, 10. 6. 2000, p. 28)

Council Directive 89/342/EEC (OJ L 142, 25. 5. 1989, p. 14)

Council Directive 89/343/EEC (OJ L 142, 25. 5. 1989, p. 16)

Council Directive 89/381/EEC (OJ L 181, 28. 6. 1989, p. 44)

Council Directive 92/25/EEC (OJ L 113, 30. 4. 1992, p. 1)

Council Directive 92/26/EEC (OJ L 113, 30. 4. 1992, p. 5)

Council Directive 92/27/EEC

Council Directive 92/28/EEC (OJ L 113, 30. 4. 1992, p. 13)

Council Directive 92/73/EEC (OJ L 297, 13. 10. 1992, p. 8)

PART B

Time-limits for transposition into national law (referred to by Article 128)

Directive	Deadline for transposition
Directive 65/65/EEC	31 December 1966
Directive 66/454/EEC	—
Directive 75/318/EEC	21 November 1976
Directive 75/319/EEC	21 November 1976
Directive 78/420/EEC	—
Directive 83/570/EEC	31 October 1985
Directive 87/19/EEC	1 July 1987
Directive 87/21/EEC	1 July 1987
	1 January 1992 ([1])
Directive 89/341/EEC	1 January 1992
Directive 89/342/EEC	1 January 1992
Directive 89/343/EEC	1 January 1992
Directive 89/381/EEC	1 January 1992
Directive 91/507/EEC	1 January 1992 ([2])
	1 January 1995 ([3])
Directive 92/25/EEC	1 January 1993
Directive 92/26/EEC	1 January 1993
Directive 92/27/EEC	1 January 1993
Directive 92/28/EEC	1 January 1993
Directive 92/73/EEC	31 December 1993
Directive 93/39/EEC	1 January 1995 ([4])
	1 January 1998 ([5])
Directive 1999/82/EC	1 January 2000
Directive 1999/83/EC	1 March 2000
Directive 2000/38/EC	5 December 2001

([1]) Deadline for transposition applicable to Greece, Spain and Portugal.
([2]) Except Section A, point 3.3 in Part II of the Annex.
([3]) Deadline for transposition applicable to Section A, point 3.3 in Part II of the Annex.
([4]) Except with regard to Article 1(6).
([5]) Deadline for transposition applicable to Article 1(7).

ANNEX III

CORRELATION TABLE

This Dir.	65/65/EEC	75/318/EEC	75/319/EEC	89/342/EEC	89/343/EEC	89/381/EEC	92/25/EEC	92/26/EEC	92/27/EEC	92/28/EEC	92/73/EEC
Art. 1(1) to (3)	Art. 1(1) to (3)										
Art. 1(4)			Annex	Art. 1(1) and (2)							
Art. 1(5)											Art. 1
Art. 1(6) to (9)					Art. 1(2)						
Art. 1(10)						Art. 1(1)					
Art. 1(11) to (16)			Art. 29b, 1st paragraph								
Art. 1(17) and (18)							Art. 1(2)				
Art. 1(19)								Art. 1(2), 2nd sentence			
Art. 1(20) to (26)									Art. 1(2)		
Art. 1(27)			Art. 8(1)								
Art. 1(28)			Art. 10(1)								
Art. 2	Art. 2(1)										
Art. 3(1) and (2)	Art. 1(4) and (5) Art 2(3), 1st indent										
Art. 3(3) and (4)	Art.2(3), 2nd and 3rd indents										
Art. 3(5)					Art. 1(1)						
Art. 3(6)						Art. 1(2)					
Art. 4(1)					Art. 1(3)						
Art. 4(2)						Art. 1(3)					

Art. 4(3)	Art. 3, 2nd subparagraph										
Art. 4(4)	Art. 6										
Art. 5	Art. 2(4)										
Art. 6(1)	Art. 3(1)										
Art. 6(2)					Art. 2, 1st sentence						
Art. 7					Art. 2, 2nd sentence						
Art. 8(1) and (2)	Art. 4(1) and (2)										
Art. 8(3)(a) to (e)	Art. 4, 3rd para., points 1 to 5	Art. 1, 1st paragraph									
Art. 8(3)(f) to (i)	Art. 4, 3rd para., points 6 to 8.1										
Art. 8(3)(j) to (l)	Art. 4, 3rd para., points 9 to 11										
Art. 9					Art. 3						
Art. 10(1)	Art. 4, 3rd paragraph, point 8.2										
Art. 10(2)		Art. 1, 2nd paragraph									
Art. 11, points 1 to 5.3	Art. 4a, points 1 to 5.3										
Art. 11, point 5.4	Art. 4a, point 5.4			Art. 3							
Art. 11, points 5.5 to 6.4	Art. 4a, points 5.5 to 6.4										
Art. 11, point 6.5	Art. 4a, point 6.6										
Art. 11, point 7	Art. 4a, point 6.5										
Art. 11, points 8 to 9					Art. 4						
Art. 12(1)			Art. 1								

This Dir.	65/65/EEC	75/318/EEC	75/319/EEC	89/342/EEC	89/343/EEC	89/381/EEC	92/25/EEC	92/26/EEC	92/27/EEC	92/28/EEC	92/73/EEC
Art. 12(2) and (3)			Art. 2								
Art. 13											Art. 6(1) and (2)
Art. 14(1) and (2)											Art. 7(1) and (4)
Art. 14(3)											Art. 4, 2nd paragraph
Art. 15											Art. 8
Art. 16											Art. 9
Art. 17	Art. 7										
Art. 18	Art. 7a										
Art. 19			Art. 4								
Art. 20			Art. 5								
Art. 21	Art. 4b										
Art. 22	Art. 10(2)										
Art. 23	Art. 9a										
Art. 24	Art. 10(1)										
Art. 25	Art. 9										
Art. 26	Art. 5										
Art. 27			Art. 8								
Art. 28(1)			Art. 9(3)								
Art. 28(2)			Art. 9(1)								
Art. 28(3)			Art. 9(2)								
Art. 28(4)			Art. 9(4)								
Art. 29			Art. 10								
Art. 30			Art. 11								
Art. 31			Art. 12								
Art. 32			Art. 13								
Art. 33			Art. 14(1)								
Art. 34			Art. 14(2) to (4)								
Art. 35			Art. 15								

Art. 36			Art. 15a								
Art. 37			Art. 15b								
Art. 38			Art. 15c								
Art. 39			Art. 14(5)								
Art. 40			Art. 16								
Art. 41			Art. 17								
Art. 42			Art. 18								
Art. 43			Art. 20(1)								
Art. 44			Art. 20(2)								
Art. 45			Art. 20(3)								
Art. 46			Art. 19								
Art. 47			Art. 19a								
Art. 48			Art. 21								
Art. 49			Art. 23								
Art. 50			Art. 24								
Art. 51(1) and (2)			Art. 22(1)								
Art. 51(3)			Art. 22(2)								
Art. 52			Art. 25								
Art. 53											Art. 3
Art. 54									Art. 2(1)		
Art. 55									Art. 3		
Art. 56									Art. 4(1)		
Art. 57									Art. 5(2)		
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Art. 59									Art. 7(1) and (2)		
Art. 60									Art. 5(1) and Art. 9		
Art. 61									Art. 10(1) to (4)		
Art. 62									Art. 2(2) and Art. 7(3)		

This Dir.	65/65/EEC	75/318/EEC	75/319/EEC	89/342/EEC	89/343/EEC	89/381/EEC	92/25/EEC	92/26/EEC	92/27/EEC	92/28/EEC	92/73/EEC
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Art. 63(2)									Art. 8		
Art. 63(3)									Art. 10(5)		
Art. 64									Art. 11(1)		
Art. 65									Art. 12		
Art. 66					Art. 5						
Art. 67					Art. 6(1)						
Art. 68											Art. 2(2)
Art. 69											Art. 7(2) and (3)
Art. 70								Art. 2			
Art. 71								Art. 3			
Art. 72								Art. 4			
Art. 73								Art. 5(1)			
Art. 74								Art. 5(2)			
Art. 75								Art. 6(2)			
Art. 76							Art. 2				
Art. 77							Art. 3				
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Art. 79							Art. 5				
Art. 80							Art. 6				
Art. 81							Art. 7				
Art. 82							Art. 8				
Art. 83							Art. 9				
Art. 84							Art. 10				
Art. 85											Art. 9
Art. 86										Art. 1(3) and (4)	
Art. 87										Art. 2	
Art. 88										Art. 3(1) to (6)	

Art. 89										Art. 4	
Art. 90										Art. 5	
Art. 91										Art. 6	
Art. 92										Art. 7	
Art. 93										Art. 8	
Art. 94										Art. 9	
Art. 95										Art. 10	
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Art. 97(1) to (4)										Art. 12(1) and (2)	
Art. 97(5)										Art. 12(4)	
Art. 98										Art. 13	
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Art. 100											Art. 6(3)
Art. 101			Art. 29e								
Art. 102			Art. 29a								
Art. 103			Art. 29c								
Art. 104			Art. 29d								
Art. 105			Art. 29f								
Art. 106(1)			Art. 29g								
Art. 106(2)			Art. 29b, 2nd paragraph								
Art. 107			Art. 29h								
Art. 108			Art. 29i								
Art. 109						Art. 3(1) to (3)					
Art. 110						Art. 3(4)					
Art. 111(1)			Art. 26, 1st and 2nd paragraph								
Art. 111(2)				Art. 4(1)							
Art. 111(3)			Art. 26, 3rd paragraph								

This Dir.	65/65/EEC	75/318/EEC	75/319/EEC	89/342/EEC	89/343/EEC	89/381/EEC	92/25/EEC	92/26/EEC	92/27/EEC	92/28/EEC	92/73/EEC
Art. 112	Art. 8		Art. 27								
Art. 113				Art. 4(2)		Art. 4(2)					
Art. 114(1)				Art. 4(3)							
Art. 114(2)						Art. 4(3)					
Art. 115						Art. 4(1)					
Art. 116	Art. 11										
Art. 117			Art. 28								
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Art. 121		Art. 2b	Art. 37a								
Art. 122			Art. 30								
Art. 123			Art. 33								
Art. 124											Art. 5
Art. 125	Art. 12		Art. 31				Art. 4(2)		Art. 11(2)	Art. 12(3)	
Art. 126, 1st paragraph	Art. 21										
Art. 126, 2nd paragraph			Art. 32								
Art. 127			Art. 28a								
Art. 128	—	—	—	—	—	—	—	—	—	—	—
Art. 129	—	—	—	—	—	—	—	—	—	—	—
Art. 130	—	—	—	—	—	—	—	—	—	—	—
Annex I		Annex									
Annex II	—	—	—	—	—	—	—	—	—	—	—
Annex III	—	—	—	—	—	—	—	—	—	—	—