SUBSIDIARY LEGISLATION 437.47

VETERINARY MEDICINAL PRODUCTS REGULATIONS

12th November, 2004

LEGAL NOTICE 469 of 2004, as amended by Legal Notices 82 of 2006, and 23 and 360 of 2009.

TITLE I

Title and scope. *Amended by: L.N. 82 of 2006.*

1. (1) The title of these regulations is the Veterinary Medicinal Products Regulations.

(2) The scope of these regulations is to implement the rules laid down under European Union Council Directive 2001/82/EEC on the European Community code relating to veterinary medicinal products.

(3) (*a*) These regulations shall apply to veterinary medicinal products, including pre-mixes for medicated feedingstuffs, intended to be placed on the market in Malta and prepared industrially or by a method involving an industrial process.

(*b*) In cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a "veterinary medicinal product" and within the definition of a product covered by other Community legislation, the provisions of these regulations shall apply.

(*c*) Notwithstanding paragraph (*a*), these regulations shall also apply to active substances used as starting materials to the extent set out in regulations 44, 44A, 45 and 72 and additionally to certain substances that may be used as veterinary medicinal products that have anabolic, anti-infectious, anti-parasitic, anti-inflammatory, hormonal or psychotropic properties to the extent set out in regulation 61.

Definitions. *Amended by: L.N. 82 of 2006.*

2. For the purposes of these regulations, the following terms shall have the following meanings -

(1) (*Deleted by L.N. 82 of 2006*).

(2) "Veterinary medicinal product" means:

(*a*) any substance or combination of substances presented as having properties for treating or preventing disease in animals; or

(*b*) any substance or combination of substances which may be used in or administered to animals with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

(3) (*Deleted by L.N. 82 of 2006*).

(4) "Substance" means any matter irrespective of origin which may be -

(*a*) human, e.g. human blood and human blood products;

(*b*) animal, e.g. micro organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products;

(*c*) vegetable, e.g. micro organisms, plants, parts of plants, vegetable secretions, extracts;

(*d*) chemical, e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis.

(5) "Premix for medicated feeding stuffs" means any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feedingstuffs.

(6) "Medicated feeding stuffs" means 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 veterinary medicinal product.

(7) "Immunological veterinary medicinal product" means 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" means any veterinary medicinal product prepared from substances 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 Member States. A homeopathic veterinary medicinal product may contain a number of principles.

(9) "Withdrawal period" means the period necessary between the last administration of the veterinary medicinal product to animals, under normal conditions of use and in accordance with the provisions of these regulations, and the production of foodstuffs from such animals, in order to protect public health by ensuring that such foodstuffs do not contain residues in quantities in excess of the maximum residue limits for active substances laid down pursuant to European Union Regulation (EEC) No 2377/90.

(10) "Adverse reaction" means a reaction to a veterinary medicinal product which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or to restore, correct or modify a physiological function.

(11) "Human adverse reaction" means a reaction which is noxious and unintended and which occurs in a human being following exposure to a veterinary medicine.

(12) "Serious adverse reaction" means an adverse reaction which results in death, is life-threatening, results in significant

disability or incapacity, is a congenital anomaly and, or birth defect, or which results in permanent or prolonged signs in the animals treated.

(13) "Unexpected adverse reaction" means 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" means the periodical reports containing the records referred to in regulation 68.

(15) "Post-marketing surveillance studies" means the pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying and investigating a safety hazard relating to an authorised veterinary medicinal product.

(16) "Off-label use" means the use of a veterinary medicinal product when such use 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" means 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 -

(*a*) the supply by a manufacturer of veterinary medicinal products manufactured by himself, or,

(*b*) retail supplies of veterinary medicinal products by persons entitled to carry out such supplies in accordance with regulation 59.

(17A)"Representative of the marketing authorisation holder" means the person, commonly known as local representative, designated by the marketing authorisation holder to represent him in Malta.

(18) "Agency" means the European Medicines Agency established by European Regulation (EC) No. 726/2004.

(19) "Risks relating to use of the product" means:

- any risk relating to the quality, safety and efficacy of the veterinary medicinal products as regards animal or human health;
- any risk of undesirable effects on the environment.

(20) "Committee for Veterinary Medicinal Products" hereinafter referred to as "the Committee" means part of the Agency set up to facilitate the adoption of common decisions on the authorisation of veterinary medicinal products on the basis of the scientific criteria of quality, safety and efficacy. This Committee shall be appointed in accordance with article 31 of European Union Council Directive 2001/82/EC.

(21) "Veterinary Services" means the competent authority within the territory of Malta as established under article 2 of the Veterinary Services Act. Cap. 437.

(22) "the Commission" means the European Commission.

(23) "the Community" means the European Community as established under the Treaty establishing the European Community.

(24) "Member State" means a State which is a Member of the European Community.

(25) "Third Country" means a State which is not a Member within the European Community.

(26) "Pharmacist" means a licensed professional as provided under the Health Care Professions Act. Cap. 464.

(27) "Risk/benefit balance" means an evaluation of the positive therapeutic effects of the veterinary medicinal product in relation to the risks as defined above.

(28) "Veterinary prescription" means any prescription for a veterinary medicinal product issued by a professional person qualified to do so in accordance with applicable national law.

(29) "Name of veterinary medicinal product" means the name, which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trademark or the name of the marketing authorisation holder.

(30) "Common name" means the international non-proprietary name recommended by the World Health Organisation, or, if one does not exist, the usual common name.

(31) "Strength" means the content of active substances, expressed quantitatively per dosage unit, per unit of volume or weight according to the dosage form.

(32) "Immediate packaging" means the container or any other form of packaging that is in direct contact with the medicinal product.

(33) "Outer packaging" means the packaging into which is placed the immediate packaging.

(34) "Labelling" means information on the immediate or outer packaging.

(35) "Package leaflet" means the leaflet containing information for the user that accompanies the medicinal product.

TITLE II

Applicability. *Substituted by: L.N. 82 of 2006.*

3. (1) These regulations shall not apply to:

(*a*) medicated feedingstuffs as defined in European Union Council Directive 90/167/EEC laying down the conditions governing the preparation, placing on the market and use of medicated feedingstuffs in the European Community;

(*b*) 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;

(*c*) veterinary medicinal products based on radio-active isotopes;

(*d*) any additives covered by European Union Council Directive 70/524/EEC concerning additives in feedingstuffs where they are incorporated in animal feedingstuffs and supplementary animal feedingstuffs in accordance with that Directive; and

(*e*) without prejudice to regulation 86, medicinal products for veterinary use intended for research and development trials.

However, medicated feedingstuffs referred to in paragraph (*a*) may be prepared only from pre-mixes that have been authorised under these regulations.

(2) Except for the provisions on the possession, prescription, dispensing and administration of veterinary medicinal products, these regulations shall not apply to:

(*a*) any medicinal product prepared in a pharmacy in accordance with a veterinary prescription for an individual animal or a small group of animals, commonly known as the magistral formula; and

(*b*) any medicinal product prepared in a pharmacy in accordance with the prescriptions of a Pharmacopoeia and intended to be supplied directly to the end-user, commonly known as the officinal formula.

Non-inactivated immunological veterinary medicinal products. *Amended by: L.N. 82 of 2006.*

4. (1) The territory of Malta may provide that these regulations 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.

(2) In the case of veterinary medicinal products intended solely for aquarium fish, cage birds, homing pigeons, terrarium animals, small rodents, and ferrets and rabbits kept exclusively as pets, Malta may permit exemptions from the provisions in regulations 5 to 8, provided that such products do not contain substances the use of which requires veterinary control and that all possible measures are taken to prevent unauthorised use of the products for other animals.

TITLE III

MARKETING

CHAPTER 1

Marketing authorisation

Marketing authorisation issued by the Veterinary Services. *Substituted by: L.N. 82 of 2006.*

5. (1) No veterinary medicinal product may be placed on the market of Malta unless a marketing authorisation has been granted by the Veterinary Services in accordance with these regulations or a marketing authorisation has been granted in accordance with European Union Regulation (EC) No 726/2004.

When a veterinary medicinal product has been granted an initial authorisation in accordance with the first paragraph, any additional species, strengths, pharmaceutical forms, administration

routes, presentations, as well as any variations and extensions, shall also be granted an authorisation in accordance with the first paragraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of regulation 13(1).

(2) The marketing authorisation holder shall be responsible for the marketing of the medicinal product. The designation of a representative shall not relieve the marketing authorisation holder of his legal responsibility.

Active substances in veterinary medicinal product. *Substituted by: L.N. 82 of 2006.*

6. (1) A veterinary medicinal product may not be the subject of a marketing authorisation for the purpose of administering it to one or more food-producing species unless the pharmacologically active substances which it contains appear in Annexes I, II or III to European Regulation (EEC) No 2377/90.

(2) If an amendment to the Annexes to Regulation (EEC) No 2377/90 so warrants, the marketing authorisation holder or, where appropriate, the Veterinary Services shall take all necessary measures to amend or revoke the marketing authorisation within sixty days of the date on which the amendment to the Annexes to that Regulation was published in the Official Journal of the European Union.

(3) By way of derogation from subregulation (1), a veterinary medicinal product containing pharmacologically active substances not included in Annexes I, II or III to European Regulation (EEC) No 2377/90 may be authorised for particular animals of the equidae family that have been declared, in accordance with European Commission Decision 93/623/EEC establishing the identification document (passport) accompanying registered equidae and European Commission Decision 2000/68/EC amending Decision 93/623/EEC and establishing the identification of equidae for breeding and production, as not being intended for slaughter for human consumption. Such veterinary medicinal products shall neither include active substances that appear in Annex IV to European Regulation (EEC) No 2377/90 nor be intended for use in the treatment of conditions, as detailed in the authorised Summary of Product Characteristics, for which a veterinary medicinal product is authorized for animals of the equidae family.

Authorisation of the marketing or administration to animals of veterinary medicinal products.

7. Where the health situation so requires, the Veterinary Services may authorise the marketing or administration to animals of veterinary medicinal products which have been authorised by another Member State in accordance with European Union Council Directive 2001/82/EC.

Serious disease epidemic. *Substituted by: L.N. 82 of 2006.*

8. (1) In the event of serious epizootic diseases, the Veterinary Services may provisionally allow the use of immunological veterinary medicinal products without a marketing authorisation, in the absence of a suitable medicinal product and after informing the European Commission of the detailed conditions of use.

(2) If an animal is being imported from, or exported to, a third

country and is thereby subject to specific binding health rules, the Veterinary Services may permit the use, for the animal in question, of an immunological veterinary medicinal product that is not covered by a marketing authorisation in Malta but is authorized under the legislation of the third country. The Veterinary Services shall take all appropriate measures concerning the supervision of the importation and the use of such immunological products.

Administration of veterinary medicinal product to animals.

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

Exception granted by the Veterinary Services. *Substituted by: L.N. 82 of 2006.*

10. (1) The Veterinary Services shall take the necessary measures to ensure that, if there is no authorised veterinary medicinal product in Malta for a condition affecting a non food-producing species, by way of exception, the veterinarian responsible may, under his/her direct personal responsibility and in particular to avoid causing unacceptable suffering, treat the animal concerned with:

(*a*) a veterinary medicinal product authorised in Malta under these regulations or under European Regulation (EC) No 726/2004 for use with another animal species, or for another condition in the same species; or

(*b*) if there is no product as referred to in paragraph (*a*) -

(i) either a medicinal product authorised for human use in Malta in accordance with European Directive 2001/83/EC of the European Parliament and of the European Council or under European Regulation (EC) No 726/2004,

(ii) or, in accordance with specific national measures, a veterinary medicinal product authorised in another Member State in accordance with these regulations for use in the same species or in another species for the condition in question or for another condition; or

(*c*) if there is no product as referred to in paragraph (*b*), and within the limits of the law of Malta, 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. The veterinarian may administer the medicinal product personally or allow another person to do so under the veterinarian's responsibility.

(2) By way of derogation from regulation 11, the provisions of subregulation (1) hereof shall also apply to the treatment by a veterinarian of an animal belonging to the equidae family provided that it has been declared, in accordance with European Commission Decisions 93/623/EEC and 2000/68/EC, as not being intended for slaughter for human consumption.

Records and further details to be kept by veterinarian. *Substituted by: L.N. 82 of 2006.*

11. (1) The Veterinary Services shall take the necessary measures to ensure that, if there is no authorised veterinary medicinal product in Malta for a condition affecting a food-producing species, by way of exception, the veterinarian responsible may, under his direct personal responsibility and in particular to avoid causing unacceptable suffering, treat the animals concerned on a particular holding with:

(*a*) a veterinary medicinal product authorised in Malta under these regulations or under European Regulation (EC) No 726/2004 for use with another animal species, or for another condition in the same species; or

(*b*) if there is no product as referred to in paragraph (*a*), either -

(i) a medicinal product for human use authorised in Malta in accordance with European Directive 2001/83/EC or under European Regulation (EC) No 726/2004, or

(ii) a veterinary medicinal product authorised in another Member State in accordance with these regulations for use in the same species or in another food-producing species for the condition in question or for another condition; or

(*c*) if there is no product as referred to in paragraph (*b*), and within the limits of the law of Malta, 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.

The veterinarian may administer the medicinal product personally or allow another person to do so under the veterinarian's responsibility.

(2) Subregulation (1) shall apply provided that pharmacologically active substances included in the medicinal product are listed in Annex I, II or III to European Regulation (EEC) No 2377/90, and that the veterinarian 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 for eggs,
- 7 days for milk,
- 28 days for meat from poultry and mammals including fat and offal,
- 500 degree-days for fish meat.

(3) With regard to homeopathic veterinary medicinal products in which active principles figure in Annex II to European Regulation (EEC) No 2377/90, the withdrawal period referred to in the second paragraph of subregulation (2) shall be reduced to zero.

(4) When a veterinarian has recourse to the provisions of subregulations (1) and (2), 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 doses administered, the duration of treatment and the withdrawal periods recommended, and shall make these records available for inspection by the Veterinary Services for a period of at least five years.

(5) Without prejudice to the other provisions of these regulations, Malta shall take all necessary measures concerning the import, distribution, dispensing of and information on the medicinal products which they permit for administration to food-producing animals in accordance with subregulation (1)(*b*)(ii).

Marketing authorisation for veterinary medicinal product. *Substituted by: L.N. 82 pf 2006.*

12. (1) For the purposes of obtaining a marketing authorisation in respect of a veterinary medicinal product, otherwise than under the procedure established by European Regulation (EC) No 726/2004, an application shall be lodged with the Veterinary Services.

In the case of veterinary medicinal products which are intended for one or more food-producing species but whose pharmacologically active substances have not yet been included, for the species in question, in Annexes I, II or III to European Regulation (EEC) No 2377/90, a marketing authorisation may not be applied for until after a valid application has been made for the establishment of maximum residue limits in accordance with that Regulation. At least six months shall elapse between a valid application for the establishment of maximum residue limits and an application for a marketing authorisation.

However, in the case of veterinary medicinal products referred to in regulation 6(3), a marketing authorisation may be applied for without a valid application in accordance with European Regulation (EEC) No 2377/90. All the scientific documentation necessary for the demonstration of the quality, safety and efficacy of the veterinary medicinal product, as provided for in subregulation (3), shall be submitted.

(2) A marketing authorisation may only be granted to an applicant established in the European Community.

(3) The application for marketing authorisation shall include all the administrative information and scientific documentation necessary for demonstrating the quality, safety and efficacy of the veterinary medicinal product in question. The file shall be submitted in accordance with the Schedule and shall contain, in particular, the following information:

(*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 veterinary medicinal product;

(*c*) qualitative and quantitative particulars of all the constituents of the veterinary medicinal product, including its international non-proprietary name (INN)

recommended by the WHO, where an INN exists, or its chemical name;

(*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*) reasons for any precautionary and safety measures to be taken when storing the veterinary medicinal product, administering it to animals and disposing of waste, together with an indication of potential risks that the veterinary medicinal product might pose to the environment, to human and animal health and to plants;

(*h*) indication of the withdrawal period in the case of medicinal products intended for food-producing species;

(*i*) description of the testing methods employed by the manufacturer;

(*j*) results of:

- pharmaceutical (physico-chemical, biological or microbiological) tests,
- safety tests and residue tests,
- pre-clinical and clinical trials;
- tests assessing the potential risks posed by the medicinal product for the environment. This impact shall be studied and consideration shall be given on a case-by-case basis to specific provisions seeking to limit it;

(*k*) a detailed description of the pharmacovigilance system and, where appropriate, the risk management system that the applicant will put in place;

(*l*) a summary in accordance with regulation 14 of the product characteristics, a mock-up of the immediate packaging and the outer packaging of the veterinary medicinal product, together with the package leaflet, in accordance with regulations 53 to 55;

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

(*n*) copies of any marketing authorisation 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 authorisation submitted in accordance with these regulations is under examination. Copies of the summary of the product characteristics proposed by

the applicant in accordance with regulation 14 or approved by the Veterinary Services in accordance with regulation 25 and copies of the package insert proposed, details of any decision to refuse authorisation, whether in the European Community or a third country and the reasons for that decision. All this information shall be updated on a regular basis;

(*o*) proof that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the European Community or in a third country;

(*p*) in the case of veterinary medicinal products intended for one or more food-producing species and containing one or more pharmacologically active substances not yet included, for the species in question, in Annexes I, II or III to European Regulation (EEC) No 2377/90, a document certifying that a valid application for the establishment of maximum residue limits has been submitted to the Agency in accordance with the aforementioned Regulation.

The documents and particulars relating to the results of the tests referred to in paragraph (*j*) shall be accompanied by detailed and critical summaries, drawn up as specified in regulation 15.

Derogation. *Substituted by: L.N. 82 of 2006.*

13. (1) By way of derogation from regulation 12(3)(*j*), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of the safety and residue tests or of the pre-clinical and clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under regulation 5 for not less than eight years in a Member State or the European Community.

A generic veterinary medicinal product authorized pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product.

The first subregulation shall also apply when the reference medicinal product was not authorised in the Member State in which the application for the generic medicinal product is submitted. In this case, the applicant shall indicate in the application the Member State in which the reference medicinal product is or has been authorised. At the request of the Veterinary Services, the competent authority of the other Member State shall transmit, within a period of one month, confirmation that the reference medicinal product is or has been authorized together with the full composition of the reference product and if necessary other relevant documentation. However, the ten-year period provided for in the second paragraph shall be extended to thirteen years in the case of veterinary medicinal products for fish or bees or other species designated in accordance with the procedure referred to in Article 89(2) of European Union Council Directive 2004/28 EC.

(2) For the purposes of this regulation:

(*a*) "reference medicinal product" shall mean a product authorised within the meaning of regulation 5 in accordance with the provisions of regulation 12;

(*b*) "generic medicinal product" shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and, or efficacy. In such cases, additional information intended to provide proof of the safety and, or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies neednot be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.

(3) In cases where the veterinary medicinal product does not fall under the definition of a generic medicinal product set out in subregulation (2)(*b*) or where bio-equivalence cannot be demonstrated through bioavailability studies or in the case of changes to the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration vis-à-vis the reference medicinal product, the results of the appropriate safety and residue tests and pre-clinical tests or clinical trials shall be provided.

(4) Where a biological veterinary medicinal product which is similar to a reference biological veterinary medicinal product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or in manufacturing processes of the biological veterinary medicinal product and the reference biological veterinary medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in the Schedule and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.

(5) In the case of veterinary medicinal products intended for one or more food-producing species and containing a new active substance that has not been authorised in the European Community by 30 April 2004 the ten-year period provided for in the second paragraph of subregulation (1) shall be extended by one year for each extension of the marketing authorisation to another food-

producing species, if it is authorised within the five years following the granting of the initial marketing authorisation.

This period shall not, however, exceed a total of thirteen years, for a marketing authorisation for four or more food-producing species.

The extension of the ten-year period to eleven, twelve, or thirteen years for a veterinary medicinal product intended for food-producing species shall be granted only if the marketing authorisation holder also originally applied for determination of the maximum residue limits established for the species covered by the authorisation.

(6) Conducting the necessary studies, tests and trials with a view to the application of subregulations (1) to (5) and the consequential practical requirements shall not be regarded as contrary to patent-related rights or to supplementary-protection certificates for medicinal products.

Derogation.
Added by:
L.N. 82 of 2006.

13A. (1) By way of derogation from regulation 12(3)(*j*), and without prejudice to the law on the protection of industrial and commercial property, the applicant shall not be required to provide the results of safety and residue tests or of pre-clinical tests or clinical trials if he can demonstrate that the active substances of the veterinary medicinal product have been in well-established veterinary use within the European Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in the Schedule. In that event, the applicant shall provide appropriate scientific literature.

(2) The assessment report published by the Agency following the evaluation of an application for the establishment of maximum residue limits in accordance with European Regulation (EEC) No 2377/90 may be used in an appropriate manner as literature, particularly for the safety tests.

(3) If an applicant makes use of scientific literature to obtain authorisation for a food-producing species, and submits, in respect of the same medicinal product and with a view to obtaining authorisation for another food-producing species, new residue studies in accordance with European Regulation (EEC) No 2377\90, together with further clinical trials, it shall not be permissible for a third party to use such studies or such trials pursuant to regulation 13, for a period of three years from the grant of the authorization for which they were carried out.

Active substances.
Added by:
L.N. 82 of 2006.

13B. In the case of veterinary medicinal products containing active substances used in the composition of authorized veterinary medicinal products but not hitherto used in combination for therapeutic purposes, the results of safety and residue tests, if necessary, and new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with regulation 12(3)(*j*), but it shall not be necessary to provide scientific references relating to each individual active substance.

Use of documentation. *Added by: L.N. 82 of 2006.*

13C. After the marketing authorisation has been granted, the marketing authorisation holder may allow use to be made of the pharmaceutical, safety and residues, pre-clinical and clinical documentation contained in the file for the veterinary medicinal product with a view to examining a subsequent application for a veterinary medicinal product having the same qualitative and quantitative composition in active substances and the same pharmaceutical form.

Derogation. *Added by: L.N. 82 of 2006.*

13D. By way of derogation from regulation 12(3)(*j*), and in exceptional circumstances with respect to immunological veterinary medicinal products, the applicant shall not be required to provide the results of certain field trials on the target species if these trials cannot be carried out for duly substantiated reasons, in particular on account of other European Community provisions.

Summary of product characteristics. *Substituted by: L.N. 82 of 2006.*

14. The summary of the product characteristics shall contain, in the order indicated below, the following information:

(1) name of the veterinary medicinal product followed by the strength and the pharmaceutical form;

(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;

(3) pharmaceutical form;

(4) clinical particulars:

(i) target species,

(ii) indications for use, specifying the target species,

(iii) contra-indications,

(iv) special warnings for each target species,

(v) special precautions for use, including special precautions to be taken by the person administering the medicinal product to the animals,

(vi) adverse reactions (frequency and seriousness),

(vii) use during pregnancy, lactation or lay,

(viii) interaction with other medicinal products and other forms of interaction,

(ix) amounts to be administered and administration route,

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

(xi) withdrawal periods for the various foodstuffs, including those for which the withdrawal period is zero;

(5) pharmacological properties:

(i) pharmacodynamic properties,

(ii) pharmacokinetic particulars;

(6) pharmaceutical particulars:

(i) list of excipients,

(ii) major incompatibilities,

(iii) shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,

(iv) special precautions for storage,

(v) nature and composition of immediate packaging,

(vi) special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products, if appropriate;

(7) marketing authorisation holder;

(8) marketing authorisation number(s);

(9) date of the first authorisation or date of renewal of the authorisation;

(10) date of revision of the text.

For authorisation under regulation 13, those parts of the summary of product characteristics of the reference medicinal product referring to indications or dosage forms which were still covered by patent law at the time when a generic medicine was marketed need not be included.

Necessary arrangements for documents to be drafted by experts. *Substituted by: L.N. 82 of 2006.*

15. (1) Applicants shall ensure that the detailed and critical summaries referred to in the second paragraph of regulation 12(3) are drafted and signed by persons with the requisite technical or professional qualifications, set out in a brief curriculum vitae, before being submitted to the Veterinary Services.

(2) Persons with the technical or professional qualifications referred to in subregulation (1) shall justify any use made of the scientific literature referred to in regulation 13A(1) in accordance with the conditions set out in the Schedule.

(3) A brief curriculum vitae of the persons referred to in subregulation (1) shall be appended to the detailed critical summaries.

CHAPTER 2

Particular provisions applicable to homeopathic veterinary medicinal products

Registration or authorisation of homeopathic veterinary medicinal products. *Substituted by: LN. 82 of 2006.*

16. (1) The Veterinary Services shall ensure that homeopathic veterinary medicinal products manufactured and placed on the market within the European Community are registered or authorised in accordance with regulations 17, 18 and 19, except where such veterinary medicinal products are covered by a registration or authorisation granted in accordance with national legislation on or before 31 December 1993. In the case of homeopathic medicinal products registered in accordance with regulation 17, regulation 32 and regulation 33(1) to (3) shall apply.

(2) The Veterinary Services shall establish a simplified registration procedure for the homeopathic veterinary medicinal

products referred to in regulation 17.

(3) By way of derogation from regulation 10, homeopathic veterinary medicinal products may be administered to non-food producing animals under the responsibility of a veterinarian.

(4) By way of derogation from regulation 11(1) and (2), Malta shall permit the administration of homeopathic veterinary medicinal products intended for food-producing species the active constituents of which appear in Annex II to European Regulation (EEC) No 2377/90 under the responsibility of a veterinarian. The Veterinary Services shall take appropriate measures to control the use of veterinary homeopathic medicinal products registered or authorised in another Member State in accordance with these regulations for use in the same species.

Homeopathic veterinary medicinal products which may be authorised. *Amended by: L.N. 82 of 2006.*

17. (1) Without prejudice to the provisions of European Regulation (EEC) No 2377/90 on the establishment of maximum residue limits of pharmacologically active substances intended for food-producing animals, only homeopathic veterinary medicinal products which satisfy all of the following conditions may be subject to a special, simplified registration procedure:

(*a*) they are administered by a route described in the European Pharmacopoeia or, in the absence thereof, by the Pharmacopoeias currently used officially in Malta;

(*b*) no specific therapeutic indication appears on the labelling of the veterinary medicinal product or in any information relating thereto;

(*c*) there is a sufficient degree of dilution to guarantee the safety of the medicinal product. In particular, the medicinal product shall not contain more than one part per 10 000 of the mother tincture.

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

Simplified application for registration. *Amended by: L.N. 82 of 2006.*

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:

(*a*) 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,

(*b*) dossier describing how any homeopathic stock has been obtained and is controlled, and justifying its 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,

(*c*) manufacturing and control file for each pharmaceutical form and a description of the method of dilution and potentisation,

(*d*) manufacturing authorisation for the medicinal products concerned,

(*e*) copies of any registrations or authorisations obtained for the same medicinal products in Member States,

(*f*) one or more mock-ups of the outer packaging and immediate packaging of the medicinal products to be registered,

(*g*) data concerning the stability of the medicinal product,

(*h*) proposed withdrawal period together with all requisite justification.

Other homeopathic veterinary medicinal products. *Substituted by: L.N. 82 of 2006.*

19. (1) Homeopathic veterinary medicinal products other than those referred to in regulation 17(1) shall be authorized in accordance with regulations 12, 13A, 13B, 13C, 13D and 14.

(2) Malta may introduce or retain on its territory specific rules for the safety tests and pre-clinical and clinical trials of homeopathic veterinary medicinal products intended for pet species and non-food-producing exotic species other than those referred to in regulation 17(1), in accordance with the principles and characteristics of homeopathy as practised in Malta. In this case, the Veterinary Services shall notify the European Commission of the specific rules in force.

Immunological homeopathic veterinary medicinal products.

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 authorisation

Procedure for authorisation to place a veterinary medicinal product on the market. *Substituted by: L.N. 82 of 2006.*

21. (1) The Veterinary Services shall take all appropriate measures to ensure that the procedure for granting a marketing authorisation for a veterinary medicinal product is completed within a maximum of two hundred and ten days days after the submission of a valid application.

Applications for marketing authorisations for the same veterinary medicinal product in two or more Member States, shall be submitted in accordance with regulations 31 to 43.

(2) Where Malta notes that another marketing authorisation application for the same medicinal product is being examined in another Member State, Malta shall decline to assess the application and shall advise the applicant that regulations 31 to 43 apply.

Authorisation to forward the assessment report. *Substituted by: L.N. 82 of 2006.*

22. Where the Veterinary Services is informed, in accordance with regulation 12(3)(*n*), that another Member State has authorised a veterinary medicinal product which is the subject of an application for authorisation in Malta, the Veterinary Services shall reject the application unless it was submitted in compliance with regulations 31 to 43.

Examination of application found under regulations 12 and 13. *Substituted by: L.N. 82 of 2006.*

23. In order to examine the application submitted pursuant to regulations 12 to 13D, the Veterinary Services -

(1) shall check that the documentation submitted in support of the application complies with regulations 12 to 13D and ascertain whether the conditions for the issue of the marketing authorisation have been fulfilled;

(2) may submit the medicinal product, its starting materials and if necessary intermediate products or other constituent materials for testing by an Official Medicines Control Laboratory or a laboratory that has designated for that purpose by the Veterinary Services, in order to ensure that the testing methods employed by the manufacturer and described in the application documents, in accordance with regulation 12(3)(*i*), are satisfactory;

(3) may similarly check, in particular through consultation of a national or European Community reference laboratory, that the analytical method used for detecting residues presented by the applicant for the purposes of regulation 12(3)(*j*), second indent is satisfactory;

(4) may, where appropriate, require the applicant to provide further information as regards the items listed in regulations 12, 13A, 13B, 13C and 13D. Where the Veterinary Services take this course of action, the time-limits specified in regulation 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.

Duties to be taken up by the Veterinary Services.

24. The territory of Malta shall take all appropriate measures to ensure that -

(*a*) the Veterinary Services ascertains 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 regulation 12(3)(*d*), and, or to carry out control tests in accordance with the methods described in the application documents under regulation 12(3)(*i*);

(*b*) the Veterinary Services may authorise 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 paragraph (*a*) carried out by

third parties; in such cases, checks by the Veterinary Services shall also be carried out in the establishments concerned.

Summary of the product characteristics. *Substituted by: L.N. 82 of 2006.*

25. (1) When granting a marketing authorisation, the Veterinary Services shall inform the holder of the summary of product characteristics that it has approved.

(2) The Veterinary Services shall take all necessary measures to ensure that information concerning the veterinary medicinal product, and in particular the labelling and package leaflet, is in conformity with the summary of product characteristics approved when the marketing authorisation was granted or subsequently.

(3) The Veterinary Services shall make the marketing authorisation publicly available without delay, together with the summary of product characteristics for each veterinary medicinal product that it has authorised.

(4) The Veterinary Services shall draw up an assessment report and comments on the file as regards the results of the pharmaceutical, safety and residue tests and the pre-clinical and 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.

The Veterinary Services shall make the assessment report and its reasons for the opinion publicly available without delay, after deleting any information of a commercially confidential nature.

Other particulars essential for safety or health protection. *Amended by: L.N. 82 of 2006.*

26. (1) The marketing authorisation may require the holder to indicate on the immediate packaging and, or the outer wrapping and the package leaflet, 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 regulation 12(3)(*j*) and in regulations 13 to 13D or from experience gained during the use of the veterinary medicinal product once it has been marketed.

(2) In exceptional circumstances, and following consultation with the applicant, the authorization may be granted subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the veterinary medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. Such authorisations may be granted only for objective, verifiable reasons. Continuation of the authorization shall be linked to the annual reassessment of such conditions.

Holder to take account of scientific and technical progress. *Amended by: L.N. 82 of 2006.*

27. (1) After a marketing authorisation has been issued, the holder must, in respect of the manufacturing methods and control methods provided for in regulation 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 Veterinary Services.

(2) The Veterinary Services may require the applicant or the marketing authorisation holder to provide sufficient quantities of the substances to enable controls to be made on the identification of the presence of residues of the veterinary medicinal products in question.

At the Veterinary Services' request, the marketing authorisation holder shall provide his technical expertise to facilitate the implementation of the analytical method for detecting residues of the veterinary medicinal products in the national reference laboratory designated under European Union Council Directive 96/23/EC on measures to monitor certain substances and residues thereof in live animals and animal products.

(3) The authorisation holder shall immediately supply the Veterinary Services with any new information that might entail the amendment of the particulars or documents referred to in regulations 12(3), 13, 13A, 13B and 14 or in the Schedule.

In particular, he shall immediately inform the Veterinary Services of any prohibition or restriction imposed by the competent authorities of any country in which the veterinary medicinal product is placed on the market and of any other new information which might influence the assessment of the benefits and risks of the veterinary medicinal product concerned.

In order to permit continuous assessment of the risk-benefit balance, the Veterinary Services may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable.

(4) (*Deleted by L.N. 82 of 2006*).

(5) The marketing authorisation holder shall immediately inform the Veterinary Services, with a view to authorisation, of any alteration which he proposes to make to the particulars or documents referred to in regulations 12 to 13D.

Holder to inform the Veterinary Services. *Added by: L.N. 82 of 2006.*

27A. After a marketing authorisation has been granted, the holder of the authorisation shall inform the Veterinary Services of the date of the actual placing on the market of the veterinary medicinal product in Malta, taking into account the various presentations authorised.

The holder shall also notify the Veterinary Services if the product ceases to be placed on the market of Malta, either temporarily or permanently. Such notification shall, otherwise than in exceptional circumstances, be made no less than two months before the interruption in the placing on the market of the product.

Upon request by the Veterinary Services, particularly in the context of pharmacovigilance, the marketing authorization holder shall provide the Veterinary Services with all data relating to the

volume of sales of the veterinary medicinal product, and any data in his possession relating to the volume of prescriptions.

Validity and renewal of authorisation. *Substituted by: L.N. 82 of 2006.*

28. (1) Without prejudice to subregulations (4) and (5), a marketing authorisation shall be valid for five years.

(2) The authorisation may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance.

To this end, the marketing authorisation holder shall submit a consolidated list of all documents submitted in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorisation ceases to be valid in accordance with subregulatioon (1). The Veterinary Services may require the applicant to submit the listed documents at any time.

(3) Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the Veterinary Services decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal in accordance with subregulation (2).

(4) Any authorisation that is not followed within three years of its granting by the actual placing on the market of the authorised veterinary medicinal product in Malta, shall cease to be valid.

(5) When an authorised veterinary medicinal product previously placed on the market in Malta is no longer actually present on Malta for a period of three consecutive years, the authorisation granted for that veterinary medicinal product shall cease to be valid.

(6) The Veterinary Services may, in exceptional circumstances, and on human or animal health grounds, grant exemptions from subregulations (4) and (5). Such exemptions shall be duly justified.

General legal liability of manufacturer.

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

Instances when the marketing authorisation shall be withheld. *Substituted by: L.N. 82 of 2006.*

30. The marketing authorisation shall be refused if the file submitted to the Veterinary Services does not comply with regulations 12 to 13D and regulation 15.

The authorisation shall also be refused if, after examination of the documents and particulars listed in regulations 12 and 13(1), it is clear that -

(*a*) the risk-benefit balance of the veterinary medicinal product is, under the authorised conditions of use, unfavourable; when the application concerns a veterinary medicinal product for zootechnical use, particular regard shall be had to the benefits for animal health and welfare and to consumer safety; or

(*b*) the product 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 labelling or the package leaflet proposed by the applicant does not comply with these regulations; or

(*f*) the veterinary medicinal product is offered for sale for a use prohibited under other European Union Community provisions.

However, when a European Union Community legislative framework is in the course of being adopted, the Veterinary Services may refuse authorisation for a veterinary medicinal product where such action is necessary for the protection of public health, consumer or animal health.

The applicant or marketing authorisation holder shall be responsible for the accuracy of documents and data submitted.

CHAPTER 4

Mutual recognition procedure and decentralized procedure

Substituted by: L.N. 82 of 2006.

Procedure before submitting an application for mutual recognition of marketing practices. *Substituted by: L.N. 82 of 2006.*

31. (1) With a view to the granting of a marketing authorization for a veterinary medicinal product in more than one Member State, the applicant shall submit an application based on an identical dossier in those Member States. The dossier shall contain all the administrative information and scientific and technical documentation described in regulations 12 to 14. The documents submitted shall include a list of Member States concerned by the application.

The applicant shall request one Member State to act as reference Member State and to prepare an assessment report in respect of the veterinary medicinal product in accordance with subregulation (2) or (3).

Where appropriate, the assessment report shall contain an evaluation for the purposes of regulation 13(5) or regulation 13A(3).

(2) If the veterinary medicinal product has already received a marketing authorisation at the time of application, the concerned Member States shall recognize the marketing authorisation granted by the reference Member State. To this end, the marketing authorization holder shall request the reference Member State either to prepare an assessment report in respect of the veterinary medicinal product or, if necessary, to update any existing assessment report. The reference Member State shall prepare or update the assessment report within ninety days of receipt of a valid application. The assessment report together with the approved summary of product characteristics, labelling and package leaflet shall be forwarded to the concerned Member States and the applicant.

(3) If the veterinary medicinal product has not received authorisation by the time of application, the applicant shall request the reference Member State to prepare a draft assessment report and drafts of the summary of product characteristics, labelling and package leaflet. The reference Member State shall prepare these drafts within one hundred and twenty days of the receipt of a valid application and shall send them to the concerned Member States and the applicant.

(4) Within ninety days after receipt of the documents referred to in subregulations (2) and (3), the Member States concerned shall approve the assessment report, the summary of product characteristics, the labelling and the package leaflet and inform the reference Member State accordingly. The reference Member State shall record the agreement of all parties, close the procedure and inform the applicant accordingly.

(5) Each Member State in which an application following paragraph 1 has been submitted shall adopt a decision in conformity with the approved assessment report, summary of product characteristics, labelling and package leaflet within thirty days after acknowledgement of the agreement.

Procedure by the Veterinary Services upon grounds for supposing that the marketing authorisation of the veterinary medicinal product concerned may present a risk to human health or animal health. *Substituted by: L.N. 82 of 2006.*

32. (1) If Malta cannot, within the period allowed in regulation 31(4), agree with the assessment report, summary of product characteristics, labelling and package leaflet on grounds of a potential serious risk to human or animal health or to the environment, a detailed statement of the reasons shall be provided to the reference Member State, the other Member States concerned and the applicant. The points of disagreement shall be referred without delay to the coordination group.

If a Member State to which an application has been submitted invokes the reasons referred to in regulation 64(1), it shall no longer be regarded as a Member State concerned by this Chapter.

(2) Within the co-ordination group, all Member States referred to in subregulation (1) shall use their best endeavours to reach agreement on the action to be taken. They shall provide the applicant with the opportunity to make his point of view known orally or in writing. If, within sixty days of the communication of the reasons for disagreement to the coordination group the Member States reach an agreement, the reference Member State shall record the agreement, close the procedure and inform the applicant accordingly. Regulation 31(5) shall apply in such cases.

(3) If within the period of sixty days the Member States fail to reach an agreement, the Agency shall be immediately informed with a view to application of the procedure laid down in Articles 36, 37 and 38 of European Union Council Directive 2004/28/EC. The Agency shall be provided with a detailed description of the matters on which agreement could not be reached and the reasons for the disagreement. The applicant shall be provided with a copy of such information.

(4) As soon as the applicant has been informed that the matter has been referred to the Agency, he shall forthwith forward to the

Agency a copy of the information and documents referred to in the first subparagraph of regulation 31(1).

(5) In the case referred to in subregulation (3), the Member States that have approved the assessment report, summary of product characteristics, labelling and package leaflet of the reference Member State may, on request by the applicant, grant a marketing authorisation for the veterinary medicinal product without waiting for the outcome of the procedure laid down in Article 36 of European Union Council Directive 2004/28/EC. In that case, the authorisation granted shall be without prejudice to the outcome of that procedure.

Several applications for marketing authorisation for a particular veterinary medicinal product. *Substituted by: L.N. 82 of 2006.*

33. If two or more applications submitted in accordance with regulations 12 to 14 have been made for marketing authorisation for a particular veterinary medicinal product and Member States have adopted divergent decisions concerning the authorisation of that veterinary medicinal product, or suspension or revocation of authorisation, a Member State, or the European Commission, or the marketing-authorisation holder may refer the matter to the Committee for Medicinal Products for Veterinary Use, hereinafter referred to as "the Committee", for the application of the procedure laid down in Articles 36, 37 and 38 of European Union Council Directive 2004/28/EC.

Situation when the matter has to be referred to the Committee before reaching a decision. *Substituted by: L.N. 82 of 2006.*

34. Malta or the European Commission or the applicant or marketing authorisation holder shall, in specific cases where the interests of the European Community are involved, refer the matter to the Committee for the application of the procedure laid down in Articles 36, 37 and 38 of European Union Council Directive 2004/28/EC before a decision is reached on a request for a marketing authorization or on the suspension or withdrawal of an authorisation, or on any other variations to the terms of a marketing authorisation which appear necessary, so as to take account in particular of the information collected in accordance with Title VII.

Malta or the European Commission shall clearly identify the question which is referred to the Committee for consideration and shall inform the applicant or the marketing authorisation holder.

Malta and the applicant or the marketing authorisation holder shall forward to the Committee all available information relating to the matter in question.

Necessity for variation of the terms of a marketing authorisation.

35. (1) Where the territory of Malta considers that the variation of the terms of a marketing authorisation 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, it shall forthwith refer the matter to the Agency for the application of the procedure laid down in articles 36, 37 and 38 of European Union Council Directive 2001/82.

(2) Without prejudice to the provisions of regulation 34(1), in exceptional cases, where urgent action is essential to protect human or animal health or the environment, until a definitive decision is

adopted, the territory of Malta may suspend the marketing and the use of the veterinary medicinal product concerned on its territory. It shall inform the European Commission and the other Member States no later than the following working day of the reasons for its action.

Application of articles 39 and 40 of European Union Council Directive 2001/82/EC.

36. Articles 39 and 40 of European Union Council Directive 2001/82/EC shall apply by analogy to veterinary medicinal products authorised by Member States following an opinion of the Committee given in accordance with previous regulations.

Non-application to homeopathic veterinary medicinal products. *Substituted by: L.N. 82 of 2006.*

37. Regulations 32(3), (4) and (5) and 33 to 34 shall not apply to the homeopathic veterinary medicinal products referred to in regulation 17.

Regulations 31 to 34 shall not apply to the homeopathic veterinary medicinal products referred to in regulation 19(2).

TITLE IV

MANUFACTURE AND IMPORTS

Authorisation of manufacturer of veterinary medicinal product. *Amended by: L.N. 82 of 2006.*

38. (1) The territory of Malta shall take all appropriate measures to ensure that the manufacture of veterinary medicinal products is subject to the holding of an authorisation. This manufacturing authorisation shall likewise be required for veterinary medicinal products intended for export.

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

However, such authorisation 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 authorised in the territory of Malta to carry out such processes.

(3) The authorisation referred to in subregulation (1) shall also be required for imports from third countries into the territory of Malta; this Title and regulation 75 shall apply to such imports in the same way as to manufacture.

The territory of Malta shall take all appropriate measures to ensure that veterinary medicinal products brought into the territory from a third country and destined for Member States are accompanied by a copy of the authorisation referred to in subregulation (1).

(4) Malta shall forward to the Agency a copy of the manufacturing authorisations referred to in subregulation (1). The Agency shall enter that information in the Community database referred to in Article 80(6) of European Union Council Directive 2004/28/EC.

Requirements for manufacturing authorisation.

39. In order to obtain the manufacturing authorisation, 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 territory of Malta lays down as regards both manufacture and control and the storage of products, in accordance with regulation 24;

(*c*) he shall have at his disposal the services of at least one qualified person within the meaning of regulation 45.

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

Accuracy of particulars.

40. (1) The Veterinary Services shall not issue the manufacturing authorisation until it has established the accuracy of the particulars supplied pursuant to regulation 39 by means of an inquiry carried out by its representatives.

(2) In order to ensure that the requirements referred to in regulation 39 are complied with, authorisation may be made conditional on the fulfilment of certain obligations imposed either when authorisation is granted or at a later date.

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

Time taken for the procedure to grant the authorisation.

41. The territory of Malta shall take all appropriate measures to ensure that the time taken for the procedure for granting the manufacturing authorisation does not exceed ninety days from the day on which the Veterinary Services receives the application.

Change in particulars.

42. If the holder of the manufacturing authorisation requests a change in any of the particulars referred to in regulation 39(*a*) and (*b*), the time taken for the procedure relating to this request shall not exceed thirty days. In exceptional cases, this period of time may be extended to ninety days.

Further information of applicant.

43. The Veterinary Services may require from the applicant further information concerning both the particulars supplied pursuant to regulation 39 and the qualified person referred to in regulation 45. Where the Veterinary Services exercise this right, application of the time limits referred to in regulations 41 and 42 shall be suspended until the additional data required have been supplied.

Obligations of holder.
Amended by: L.N. 82 of 2006.

44. The holder of a manufacturing authorisation shall at least be obliged to -

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

(*b*) dispose of the authorised veterinary medicinal products only in accordance with the legislation of the territory of Malta;

(*c*) give prior notice to the Veterinary Services of any changes which he may wish to make to any of the particulars supplied pursuant to regulation 39; the Veterinary Services shall, in any event, be immediately informed if the qualified person referred to in regulation 45 is replaced unexpectedly;

(*d*) allow the representatives of the Veterinary Services access to his premises at any time;

(*e*) enable the qualified person referred to in regulation 45 to carry out his duties, particularly by placing at his disposal all the necessary facilities;

(*f*) comply with the principles and the guidelines on good manufacturing practice for medicinal products and use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials;

(*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:

(i) date,

(ii) name of the veterinary medicinal product,

(iii) quantity supplied,

(iv) name and address of the recipient,

(v) batch number.

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

Starting materials. *Added by: L.N. 82 of 2006.*

44A. For the purposes of these regulations, manufacturing active substances for use as starting materials shall include the complete or partial manufacture or the import of an active substance used as a starting material, as defined in Part 2, Section C of the Schedule, and the various processes of dividing up, packaging or presentation prior to its incorporation in a veterinary medicinal product, including repackaging or re-labelling, such as carried out by a starting material distributor.

Services of a qualified person to be ensured by the holder of the manufacturing authorisation.

45. (1) The territory of Malta shall take all appropriate measures to ensure that the holder of the manufacturing authorisation has permanently and continuously at his disposal the services of at least one qualified person who fulfils the conditions laid down in regulation 46 and is responsible, in particular, for carrying out the duties specified in regulation 48.

(2) If such qualified person fulfils the conditions laid down in regulation 46, the holder of the authorisation may himself assume the responsibility referred to in subregulation (1).

Minimum conditions of qualification. *Amended by: L.N. 82 of 2006.*

46. (1) Malta shall ensure that the qualified person referred to in regulation 45 fulfils the conditions of qualification referred to in subregulations (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 recognised as equivalent by the territory of Malta, 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.

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

(*a*) experimental physics,

(*b*) general and inorganic chemistry,

(*c*) organic chemistry,

(*d*) analytical chemistry,

(*e*) pharmaceutical chemistry, including analysis of medicinal products,

(*f*) general and applied biochemistry (medical),

(*g*) physiology,

(*h*) microbiology,

(*i*) pharmacology,

(*j*) pharmaceutical technology,

(*k*) toxicology,

(*l*) 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 regulation 48.

Where certain diplomas, certificates or other evidence of formal qualifications mentioned in this subregulation do not fulfil the criteria laid down above, the Veterinary Services 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 authorised 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.

Person eligible to engage in the activities mentioned in regulation 45. *Amended by: L.N. 82 of 2006.*

47. (1) A person engaging, in Malta, in the activities of the person referred to in regulation 45(1) on the date on which these regulations became applicable, without complying with the provisions of regulation 46, shall be eligible to continue to engage in those activities within the Community.

(2) The holder of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course or a course recognised as equivalent by the territory of Malta in a scientific discipline allowing him to engage in the activities of the person referred to in regulation 45 in accordance with the laws of the territory of Malta, may, if he began his course prior to the date on which these regulations became applicable, be considered as qualified to carry out in the territory of Malta the duties of the person referred to in regulation 45, provided that he has previously engaged in the following activities for at least two years before the date on which these regulations became applicable in one or more undertakings with a manufacturing authorisation, 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 regulation 45 to ensure the quality of veterinary medicinal products.

If the person concerned has acquired the practical experience referred to in subregulation (1) before the date on which these regulations became applicable, a further one year's practical experience in accordance with the conditions referred to in subregulation (1) shall be completed by him immediately before he engages in such activities.

Responsibility of qualified person. *Amended by: L.N. 82 of 2006.*

48. (1) In the territory of Malta the qualified person referred to in regulation 45 is, without prejudice to his relationship with the holder of the manufacturing authorisation, responsible, in the context of the procedures referred to in regulation 49, for ensuring that -

(*a*) in the case of veterinary medicinal products manufactured within the territory of Malta, each batch of veterinary medicinal products has been manufactured and checked in compliance with the laws in force in the territory of Malta and in accordance with the requirements of the marketing authorisation;

(*b*) in the case of veterinary medicinal products coming from third countries, even if manufactured in the Community, each production batch imported has undergone in Malta a full qualitative analysis, a quantitative analysis of at least all the active substances, and all the other tests or controls necessary to ensure the quality of veterinary medicinal products

in accordance with the requirements of the marketing authorisation.

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 the territory of Malta, 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 European 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 European Community and to ensure that the controls referred to under subregulation (1)(*b*) 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 regulation; 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 Veterinary Services for at least five years.

Obligations of qualified persons to be fulfilled by appropriate administrative measures or following a professional code of conduct.

49. The territory of Malta the obligations of qualified persons referred to in regulation 45 are fulfilled, either by means of appropriate administrative measures or by making such persons subject to a professional code of conduct.

The Veterinary Services 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.

Applicability to homeopathic veterinary medicinal products.

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

TITLE V

LABELLING AND PACKAGE INSERT

Information regarding labelling and packages. *Amended by: L.N. 82 of 2006.*

51. (1) Except in the case of the medicinal products referred to in regulation 17(1), the Veterinary Services shall approve the immediate packaging and outer packaging of veterinary medicinal products. Packaging shall bear the following information, which shall conform with the particulars and documents provided pursuant to regulations 12 to 13D and the summary of product characteristics, and shall appear in legible characters:

(*a*) the name of the medicinal product, followed by its strength and pharmaceutical form. The common name shall appear if the medicinal product contains only one active substance and its name is an invented name;

(*b*) a statement of the active substances expressed qualitatively and quantitatively per unit or according

to the form of administration for a particular volume or weight, using the common names;

(*c*) manufacturer's batch number;

(*d*) marketing authorisation number;

(*e*) name or corporate name and permanent address or registered place of business of the marketing authorisation holder and, where appropriate, of the representative designated by the marketing authorization holder;

(*f*) the species of animal for which the veterinary medicinal product is intended; the method and, if necessary, the route of administration. Space shall be provided for the prescribed dose to be indicated;

(*g*) the withdrawal period for veterinary medicinal products to be administered to food-producing species, for all the species concerned and for the various foodstuffs concerned (meat and offal, eggs, milk, honey), including those for which the withdrawal period is zero;

(*h*) expiry date, in plain language;

(*i*) special storage precautions, if any;

(*j*) specific precautions relating to the disposal of unused medicinal products or waste derived from veterinary medicinal products, where appropriate, as well as a reference to any appropriate collection system in place;

(*k*) particulars required to be indicated pursuant to regulation 26(1), if any'

(*l*) the words "For animal treatment only" or, in the case of the medicinal products referred to in regulation 60, the words "For animal treatment only - to be supplied only on veterinary prescription".

(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 the Schedule, 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 subregulation (1)(*b*).

(4) The particulars mentioned in subregulation (1)(*f*) to (*l*) shall appear on the outer package and on the container of the medicinal products in the language of the territory of Malta being the country in which the product is placed on the market:

Provided that the language for the territory of Malta may be either Maltese or English or both.

(5) In the case of medicinal products that have been granted a marketing authorisation under European Regulation (EC) No 726/ 2004, Malta may permit or require that the outer packaging bear

additional information concerning distribution, possession, sale or any necessary precautions, provided that such information is not in infringement of Community law or the terms of the marketing authorisation, and is not promotional.

This additional information shall appear in a box with a blue border to separate it clearly from the information referred to in subregulation (1).

Information regarding ampoules. *Amended by: L.N. 82 of 2006.*

52. (1) As regards ampoules, the particulars listed in the first paragraph of regulation 51(1) shall be given on the outer package. On the immediate packaging, however, only the following particulars shall be necessary:

(*a*) name of veterinary medicinal product,

(*b*) quantity of the active substances,

(*c*) route of administration,

(*d*) manufacturer's batch number,

(*e*) date of expiry,

(*f*) the words "For animal treatment only".

(2) As regards small immediate packaging containing a single dose, other than ampoules, on which it is impossible to give the particulars mentioned in subregulation (1), the requirements of regulation 51(1), (2) and (3) shall apply only to the outer package.

(3) The particulars mentioned in subregulation (1)(*c*) and (*f*) shall appear on the outer package and on the immediate packaging of the medicinal products in the language or languages of the country in which they are placed on the market.

No outer package. *Substituted by: L.N. 82 of 2006.*

53. Where there is no outer package, all the particulars which should feature on such a package pursuant to regulations 51 and 52 shall be shown on the immediate packaging.

Inclusion of a package insert. *Amended by: L.N. 82 of 2006.*

54. (1) The inclusion of a package leaflet in the packaging of veterinary medicinal products shall be obligatory unless all the information required by this regulation can be conveyed on the immediate packaging and the outer packaging. Malta shall take all appropriate measures to ensure that the package leaflet relates solely to the veterinary medicinal product with which it is included. The package leaflet shall be written in terms that are comprehensible to the general public and in the official language or languages of Malta.

Subregulation (1) shall not prevent the package leaflet from being written in several languages, provided that the information given is identical in all the languages.

The Veterinary Services may exempt labels and package leaflets for specific veterinary medicinal products from the obligation for certain particulars to appear and for the leaflet to be in the official language or languages of Malta, when the product is intended to be administered only by a veterinarian.

(2) The Veterinary Services shall approve package leaflets. Leaflets shall contain at least the following information, in the

order indicated, which shall conform to the particulars and documents provided pursuant to regulations 12 to 13D and the approved summary of product characteristics:

(*a*) name or corporate name and permanent address or registered place of business of the marketing authorisation holder and of the manufacturer and, where appropriate, of the representative of the marketing authorization holder;

(*b*) name of the veterinary medicinal product followed by its strength and pharmaceutical form. The common name shall appear if the product contains only one active substance and its name is an invented name. Where the medicinal product is authorised according to the procedure provided for in regulations Articles 31 to 43 of European Union Council Directive 2004/ 28/EC under different names in Malta, a list of the names authorised in Malta;

(*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 regulation 26 (1), if any;

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

Suspension or withdrawal of marketing authorisation. *Substituted by: L.N. 82 of 2006.*

55. Where the provisions of this Title are not observed and a formal notice addressed to the person concerned has been ineffectual, the Veterinary Services may suspend or revoke the marketing authorisation.

Non-applicability of this Title.

56. The requirements of the territory of Malta 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.

Labelling of homeopathic veterinary medicinal product. *Amended by: L.N. 82 of 2006.*

57. (1) Without prejudice to subregulation (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 leaflet for the homeopathic veterinary medicinal products referred to in regulation 17(1) shall bear the following information and no other information:

(*a*) the scientific name of the stock or stocks followed by the degree of dilution, using the symbols of the Pharmacopoeia used in accordance with regulation 2(8). If the homeopathic veterinary medicinal product is composed of more than one stock, the labelling may mention an invented name in addition to the scientific names of the stocks,

(*b*) name and address of the marketing authorisation holder and, where appropriate, of the manufacturer,

(*c*) method of administration and, if necessary, route,

(*d*) expiry date, in clear terms (month, year),

(*e*) pharmaceutical form,

(*f*) contents of the sales presentation,

(*g*) special storage precautions, if any,

(*h*) target species,

(*i*) a special warning if necessary for the medicinal product,

(*j*) manufacturer's batch number,

(*k*) registration number.

TITLE VI

Substituted by: L.N. 82 of 2006.

POSSESSION, DISTRIBUTION AND DISPENSING OF VETERINARY MEDICINAL PRODUCTS

Wholesale distribution of veterinary medicinal product. *Amended by: L.N. 82 of 2006.*

58. (1) In the territory of Malta, the wholesale distribution of veterinary medicinal products is subject to the holding of an authorisation. The Veterinary Services shall take all appropriate measures to ensure that the time taken for the procedure for granting this authorisation does not exceed ninety days from the date on which it receives the application.

Supplies of small quantities of veterinary medicinal products from one retailer to another may be excluded from the scope of the definition of wholesale distribution under a decision to be laid down by the Veterinary Services.

(2) In order to obtain the authorisation 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 territory of Malta as regards the storage and handling of veterinary medicinal products:

Provided that for the purposes of this sub-regulation "technically competent staff" means responsible or qualified persons who shall be professionally responsible for the activity in question. Such person(s) must be in possession of qualifications as required by the Veterinary Services:

Provided further that, where more than one responsible or qualified person is nominated, the application will clearly specify the responsibilities of each respective person.

(3) The holder of the authorisation 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 Veterinary Services for a period of at least three years.

(3A) The holder of a distribution authorisation shall have an emergency plan guaranteeing the effective implementation of any recall operation ordered by the competent authorities or undertaken in cooperation with the manufacturer of the medicinal product in question or the holder of the marketing authorisation.

(4) The Veterinary Services 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 regulation 59, or to other persons who are lawfully permitted to receive veterinary medicinal products from wholesalers.

(5) Any distributor, not being the marketing authorization holder, who imports a product from another Member State shall notify the marketing authorization holder and the Veterinary Services to which the product will be imported of his intention to import it. In the case of products which have not been granted an authorisation pursuant to European Regulation (EC) No 726/2004, the notification to the Veterinary Services shall be without prejudice to additional procedures provided for in the legislation of Malta.

Persons who may conduct the retail supply of veterinary medicinal products. *Amended by: L.N. 82 of 2006.*

59. (1) In the territory of Malta, the retail supply of veterinary medicinal products is conducted only by persons who are licensed to carry out such operations by the legislation of the territory of Malta.

(2) Any person permitted under subregulation (1) to supply veterinary medicinal products shall be required to keep detailed records for veterinary medicinal products that may be supplied only on prescription, the following information being 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 in an appropriate register.

These records shall be available for inspection by the Veterinary Services for a period of five years.

(3) The Veterinary Services may permit the supply in Malta of veterinary medicinal products for food-producing animals for which a veterinary prescription is required by or under the supervision of a person registered for this purpose who provides guarantees with respect to qualifications, record-keeping and reporting in accordance with national law. The Veterinary Services shall notify the European Commission of relevant provisions of national law. This provision shall not apply to the supply of veterinary medicinal products for the oral or parenteral treatment of bacterial infections.

Prescription for dispensing products to the public. *Amended by: L.N. 82 of 2006.*

60. (1) Without prejudice to stricter European Community or national rules relating to dispensing veterinary medicinal products and serving to protect human and animal health, a veterinary 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 -

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

(ii) the restrictions on the use of veterinary medicinal products resulting from European Community legislation;

(*aa*) veterinary medicinal products for foodproducing animals.

However, Malta may grant exemptions from this requirement according to criteria established in accordance with the procedure referred to in Article 89(2) of European Union Council Directive 2004/28/EC;

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

(i) the target species,

(ii) the person administering the products to the animal,

(iii) 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*) official formula, within the meaning of Article 3(2)(b) of European Union Council Directive 2004/28/EC, intended for food-producing animals.

Malta shall take all necessary measures to ensure that, in the case of medicinal products supplied only on prescription, the quantity prescribed and supplied shall be restricted to the minimum amount required for the treatment or therapy concerned.

In addition, a prescription shall be required for new veterinary medicinal products containing an active substance that has been authorised for use in a veterinary medicinal product for fewer than five years.

(2) Veterinary medicinal products for food-producing animals may be exempted from the requirement to be dispensed only against veterinary prescription, if all of the following criteria are satisfied:

(*a*) the administration of veterinary medicinal products is restricted to formulations requiring no particular knowledge or skill in using the products;

(*b*) the veterinary medicinal product does not present a direct or indirect risk, even if administered incorrectly, to the animal or animals treated, to the person administering the product or to the environment;

(*c*) the summary of product characteristics of the veterinary medicinal product does not contain any warnings of potential serious side effects deriving from its correct use;

(*d*) neither the veterinary medicinal product nor any other product containing the same active substance has previously been the subject of frequent serious adverse reaction reporting;

(*e*) the summary of product characteristics does not refer to contra-indications related to other veterinary medicinal products commonly used without prescription;

(*f*) the veterinary medicinal product is not subject to special storage conditions;

(*g*) there is no risk for consumer safety as regards residues in food obtained from treated animals even where the veterinary medicinal products are used incorrectly;

(*h*) there is no risk to human or animal health as regards the development of resistance to antimicrobials or anthelmintic substances even where the veterinary medicinal products containing those substances are

used incorrectly.

Veterinary medicinal products that have anabolic, anti-infectious, anti-parasitic, anti-inflammatory, hormonal or psychotropic properties.

61. (1) In the territory of Malta, all necessary measures shall be taken to ensure that veterinary surgeons, qualified or responsible persons and pharmacists only, 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) The territory of Malta 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 sub-regulation (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 Veterinary Services for a period of at least three years.

(3) Any amendments to be made to the list of substances referred to in subregulation (1) shall be adopted in accordance with the procedure referred to in article 89 (2) of European Union Council Directive 2001/82/EC.

Obligations of owners or keepers of food-producing. *Amended by: L.N. 82 of 2006.*

62. Malta shall ensure that the owners or keepers of food-producing animals can provide proof of purchase, possession and administration of veterinary medicinal products to such animals for five years after their administration, including when the animal is slaughtered during the five-year period.

The territory of Malta may extend the scope of this obligation to other veterinary medicinal products.

In particular, the territory of Malta 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.

Administration of small quantities of readymade veterinary medicinal products. *Amended by: L.N. 82 of 2006.*

63. By way of derogation from regulation 9 and without prejudice to regulation 60, Malta shall ensure that veterinarians providing services in another Member State can take with them and administer to animals small quantities of veterinary medicinal products not exceeding daily requirements other than immunological veterinary medicinal products which are not authorised for use in the Member State in which the services are provided, provided that the following conditions are satisfied:

(*a*) the authorisation to place the product on the market provided for in regulations 5, 7 and 8 has been issued by the competent authority 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 authorised in accordance with regulations 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 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 authority 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.

Use of immunological veterinary medicinal products for the eradication or control of animal disease. *Amended by: L.N. 82 of 2006.*

64. (1) In the absence of specific European Community legislation concerning the use of immunological veterinary medicinal products for the eradication or control of animal disease, the territory of Malta 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 the 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 concerned.

Malta may also invoke the provisions of the first paragraph in order to withhold marketing authorisation in accordance with a decentralised procedure as provided for in Articles 31 to 43 of European Union Council Directive 2004/28/EC.

(2) The Veterinary Services shall inform the European Commission of all instances in which the provisions of sub-regulation (1) are applied.

TITLE VII

PHARMACOVIGILANCE

Suspected adverse reactions to veterinary medicinal products. *Amended by: L.N. 82 of 2006.*

65. (1) The territory of Malta shall take the appropriate measures to encourage the reporting to the Veterinary Services of suspected adverse reactions to veterinary medicinal products.

(2) Malta 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.

Participation in the veterinary pharmacovigilance system. *Amended by: L.N. 82 of 2006.*

66. In order to ensure the adoption of appropriate and harmonised regulatory decisions concerning the veterinary medicinal products authorised within the European Community, having regard to information obtained about suspected adverse reactions to veterinary medicinal products under normal conditions of use, Malta shall administer 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 relating 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.

Malta shall ensure that suitable information collected within this system is communicated to other Member States and the Agency. This information shall be recorded in the database referred to in point (k) of the second subparagraph of Article 57(1) of European Regulation (EC) No 726/2004 and shall be permanently accessible to all Member States and without delay to the public.

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 European Commission guidelines referred to in regulation 70(1), which may have an impact on the evaluation of their benefits and risks.

Management of funds.
Added by: L.N. 82 of 2006.

66A. The management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance shall be under the permanent control of the Veterinary Services in order to guarantee their independence.

Qualified person responsible for pharmacovigilance
Amended by: L.N. 82 of 2006.

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

That qualified person shall reside in the European Community and 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 European Community;

(*b*) the preparation for the Veterinary Services of the reports referred to in regulation 68, in such form as may be laid down by that authority, in accordance with the guidance referred to in regulation 70(1);

(*c*) ensuring that any request from the Veterinary Services 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 Veterinary Services, 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.

Detailed records of suspected adverse reactions.
Substituted by: L.N. 82 of 2006.

68. (1) The marketing authorisation holder shall maintain detailed records of all suspected adverse reactions occurring within the European Community or in a third country.

Save in exceptional circumstances, these reactions shall be communicated electronically in the form of a report in accordance with the guidelines referred to in regulation 70(1).

(2) The marketing authorisation holder shall record all suspected serious adverse reactions and human adverse reactions relating to the use of veterinary medicinal products that are brought to his attention, and report them promptly to the Veterinary Services, and no later than fifteen days following receipt of the information.

The marketing authorisation holder shall also record 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, and report them promptly to the Veterinary Services, and no later than fifteen days following receipt of the information.

(3) The marketing authorisation holder shall ensure that all suspected serious unexpected adverse reactions, human adverse reactions and any suspected transmission via a veterinary medicinal product of any infectious agent occurring on the territory of a third country are reported promptly in accordance with the guidelines referred to in regulation 70(1), so that they are available to the Agency and the competent authorities of the Member States in which the veterinary medicinal product is authorised, and no later than fifteen days following the receipt of the information.

(4) By way of derogation from subregulations (2) and (3), in the case of veterinary medicinal products which are covered by European Directive 87/22/EEC, have benefited from the authorisation procedures under Articles 31 and 32 of European Union Council Directive 2004/28/EC or have been the subject of the procedures provided for in Articles 36, 37 and 38 of European Union Council Directive 2004/28/EC, the marketing authorisation holder shall additionally ensure that all suspected serious adverse reactions and human adverse reactions occurring in the Community are reported in such a way so as to be accessible to the reference Member State or a competent authority designated as reference Member State. The reference Member State shall assume responsibility for the analysis and follow-up of any such adverse reactions.

(5) Unless other requirements have been laid down as a condition for the granting of the marketing authorisation or subsequently as indicated in the guidelines referred to in regulation 70(1), reports of all adverse reactions shall be submitted to the Veterinary Services in the form of a periodic safety update report, immediately upon request or at least every six months after authorisation until the placing on the market. Periodic safety update reports shall also be submitted immediately upon request or at least every six months during the first two years following the initial placing on the market, and once a year for the following two years. Thereafter, the reports shall be submitted at three-yearly intervals, or immediately upon request.

The periodic safety update reports shall include a scientific evaluation of the risk-benefit balance of the veterinary medicinal product.

(6) Following the granting of a marketing authorisation, the holder of such authorisation may request the amendment of the periods referred to in subregulation (5) in accordance with the procedure laid down by European Commission Regulation (EC) No 1084/2003.

(7) The holder of a marketing authorisation may not communicate information relating to pharmacovigilance concerns to the general public in relation to its authorized veterinary medicinal product without giving prior or simultaneous notification to the Veterinary Services.

In any case, the marketing authorisation holder shall ensure that such information is presented objectively and is not misleading.

Malta shall take the necessary measures to ensure that a marketing authorisation holder who fails to discharge these obligations is subject to effective, proportionate and dissuasive penalties.

Reports of suspected serious adverse reactions and human adverse reactions to be made available to the Agency and the Member States.

69. (1) Making use of the data-processing network set up by the Agency, in collaboration with the European Commission, the Veterinary Services shall ensure that reports of suspected serious adverse reactions and human adverse reactions, in accordance with the guidance referred to in regulation 70(1) and that have taken place on the territory are immediately made available to the Agency and the other Member States, and in any case within fifteen calendar days of their notification, at the latest.

(2) The Veterinary Services shall ensure that reports of suspected serious adverse reactions and human adverse reactions, that have taken place on the territory are immediately made available to the marketing authorisation holder, and in any case within fifteen calendar days of their notification at the latest.

Facilitation of exchange of information regarding pharmacovigilance

70. (1) In order to facilitate the exchange of information about pharmacovigilance within the territory of Malta and the Member States, the Veterinary Services, shall take due account of 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 drawn up by the European Commission in consultation with the Agency, Member States and the interested parties.

(2) For the interpretation of the definitions referred to in regulation 2(10) to (16) and principles outlined in this title, the marketing authorisation holder and the Veterinary Services shall refer to the detailed guidance referred to in subregulation (1).

Procedure upon the result of the evaluation. *Amended by: L.N. 82 of 2006.*

71. (1) Where, as a result of the evaluation of veterinary pharmacovigilance data, the Veterinary Services considers that a marketing authorisation should be suspended, withdrawn or varied to restrict the indications or availability, amend the posology, add a contra-indication or add a new precautionary measure, it shall forthwith inform the Agency, the Member States and the marketing authorisation holder.

(2) If urgent action is necessary for protecting human or animal health, Malta may suspend the marketing authorisation of a veterinary medicinal product, provided that the Agency, the Commission and the other Member States are informed on the following working day at the latest.

TITLE VIII

SUPERVISION AND SANCTIONS

Repeated inspections. *Amended by: L.N. 82 of 2006.*

72. (1) The Veterinary Services shall ensure, by means of repeated inspections and, if necessary, unannounced inspections, and where appropriate, by asking an Official Medicines Control Laboratory or a laboratory designated for that purpose to conduct

tests on samples, that the legal requirements relating to veterinary medicinal products are complied with.

The Veterinary Services may also carry out unannounced inspections at the premises of manufacturers of active substances used as starting materials for veterinary medicinal products, and of the premises of the marketing authorisation holder whenever it considers that there are grounds for suspecting non-compliance with the provisions of regulation Article 51 of European Union Council Directive 2004/28/EC. Such inspections may also be carried out at the request of another Member State, the Commission or the Agency.

In order to verify whether the data submitted in order to obtain a conformity certificate comply with the monographs of the European Pharmacopoeia, the standardization body for nomenclatures and quality norms within the meaning of the Convention relating to the elaboration of a European Pharmacopoeia (European Directorate for the Quality of Medicines) may ask the Commission or the Agency to request such an inspection when the starting material concerned is the subject of a European Pharmacopoeia monograph.

The Veterinary Services may carry out inspections of starting material manufacturers at the manufacturer's own request.

Such inspections shall be carried out by authorized representatives of the Veterinary Services who shall be empowered to -

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

(*b*) take samples including with a view to an independent analysis by an Official Medicines Control Laboratory or by a laboratory designated for that purpose by Malta;

(*c*) examine any documents relating to the object of the inspection, subject to the provisions in force in Malta placing restrictions on these powers with regard to the description of the manufacturing method;

(*d*) inspect the premises, records and documents of marketing authorisation holders or any firms performing the activities described in Title VII, and in particular regulations 67 and 68 thereof, on behalf of a marketing authorisation holder.

(2) The Veterinary Services shall take all appropriate measures to ensure that in the territory of Malta, the manufacturing processes used in the manufacture of immunological veterinary medicinal products are completely validated and batch-to-batch consistency is ensured.

(3) The authorised representatives of the Veterinary Services shall report after each of the inspections mentioned in subregulation (1) on whether the principles and guidelines on good

manufacturing practice referred to in Article 51 of European Union Council Directive 2004/28/EC or, where appropriate, the requirements set out in Title VII, are being complied with. The inspected manufacturer or market authorization holder shall be informed of the content of such reports.

(4) Without prejudice to any arrangements which may have been concluded between the European Community and a third country, Malta, the European Commission or the Agency may require a manufacturer established in a third country to undergo an inspection as referred to in subregulation (1).

(5) Within ninety days after an inspection as referred to in subregulation (1), a certificate of good manufacturing practice shall be issued to the manufacturer if the inspection established that the manufacturer in question is complying with the principles and guidelines on good manufacturing practice as provided for by Community law.

In the event of an inspection carried out at the request of the European Pharmacopoeia, a certificate of compliance with the monograph shall be issued, if appropriate.

(6) Malta shall enter the certificates of good manufacturing practice which they issue in a Community database managed by the Agency on behalf of the Community.

(7) If the outcome of the inspection as referred to in subregulation (1) is that the manufacturer does not comply with the principles and guidelines of good manufacturing practice as provided for by Community legislation, the information shall be entered in the Community database as referred to in subregulation (6).

Proof of the control tests which were carried out.

73. (1) The Veterinary Services shall take all appropriate measures to ensure that the marketing authorisation holder and, where appropriate, the holder of the manufacturing authorisation 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 authorisation.

(2) For the purposes of implementing subregulation (1), the Veterinary Services may require the marketing authorisation holder for immunological veterinary medicinal products to submit to them copies of all the control reports signed by the qualified person in accordance with regulation 48.

The marketing authorisation 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 Veterinary Services on request.

Samples to be submitted. *Substituted by: L.N. 82 of 2006.*

74. (1) Where it considers it necessary for reasons of human or animal health, the Veterinary Services may require the marketing authorisation holder for an immunological veterinary medicinal product to submit samples of batches of the bulk product and, or

veterinary medicinal product, for control by an Official Medicines Control Laboratory before the product is put into circulation.

(2) On request by the Veterinary Services, the marketing authorisation holder shall promptly supply the samples referred to in subregulation (1), together with the reports of the control referred to in regulation 73(2).

The Veterinary Services shall inform all the other Member States in which the veterinary medicinal product is authorised as well as the European Directorate for the Quality of Medicines of its intention to control batches or the batch in question.

(3) After studying the control reports referred to in regulation 73(2), the laboratory responsible for the control shall repeat, on the samples provided, all the tests carried out by the manufacturer on the finished product, in accordance with the relevant provisions shown in the dossier for marketing authorisation.

The list of tests to be repeated by the laboratory responsible for the control shall be restricted to justified tests, provided that all Member States concerned, and if appropriate the European Directorate for the Quality of Medicines, agree to this.

For immunological veterinary medicinal products authorized under European Regulation (EC) No 726/2004, the list of tests to be repeated by the control laboratory may be reduced only after agreement by the Agency.

(4) Malta shall recognise the results of the tests.

(5) Unless the European Commission is informed that a longer period is necessary to conduct the tests, the Veterinary Services shall ensure that this control is completed within sixty days of receipt of the samples.

The Veterinary Services shall notify the other Member States concerned, the European Directorate for the Quality of Medicines, the marketing authorisation holder and, if appropriate, the manufacturer, of the results of the tests within the same period of time.

If the Veterinary Services concludes that a batch of a veterinary medicinal product is not in conformity with the control report of the manufacturer or the specifications provided for in the marketing authorisation, it shall take all the necessary measures vis-a-vis the marketing authorisation holder and the manufacturer, where appropriate, and shall inform accordingly the other Member States in which the veterinary medicinal product is authorised.

Suspension or withdrawal of marketing authorisation. *Amended by: L.N. 82 of 2006.*

75. (1) The Veterinary Services shall suspend, revoke, withdraw or vary marketing authorisations when it is clear that:

(*a*) the risk-benefit assessment of the veterinary medicinal product is, under the authorized conditions of use, unfavourable, particular regard being had to the benefits for animal health and welfare and to consumer safety, when the authorisation concerns a veterinary medicinal product for zootechnical use;

(*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 provisions of the European Community;

(*f*) information given in the application documents pursuant to regulations 12 to 13D and 27 is incorrect;

(*g*) the control tests referred to in regulation 73(1) have not been carried out.

However, when a Community legislative framework is in the course of being adopted, the Veterinary Services may refuse authorisation for a veterinary medicinal product where such action is necessary for the protection of public health, consumer and animal health.

(2) Marketing authorisations may be suspended, revoked, withdrawn or varied when it is established that -

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

(*b*) any new information as referred to in regulation 27(3) has not been communicated to the Veterinary Services.

Regulations dealing with the prohibition or withdrawal of the supply of a veterinary medicinal product. *Amended by: L.N. 82 of 2006.*

76. (1) Without prejudice to regulation 75, in the territory of Malta, shall take the necessary measures to ensure that the supply of a veterinary medicinal product is prohibited and the medicinal product concerned is withdrawn from the market where -

(*a*) it is clear that the risk-benefit assessment of the veterinary medicinal product is, under the authorized conditions of use, unfavourable, particular regard being had to the benefits for animal health and welfare and to the safety and health benefits for the consumer, when the authorisation concerns a veterinary medicinal product for zootechnical use;

(*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 regulation 73(1) have not been carried out, or any other requirement or obligation relating to the grant of the manufacturing authorisation referred to in regulation 38(1) has not been complied with.

(2) The Veterinary Services may confine the prohibition on supply and withdrawal from the market solely to the contested production batches.

Suspension or withdrawal of the manufacturing authorisation. *Amended by: L.N. 82 of 2006.*

77. (1) The Veterinary Services shall suspend or withdraw the manufacturing authorisation for a category of preparations or for all preparations if any of the requirements laid down in regulation 39 are no longer met.

(2) The Veterinary Services may, in addition to the measures provided for in regulation 76, either suspend manufacture or imports of veterinary medicinal products from third countries or suspend or withdraw the manufacturing authorisation 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.

(3) The Veterinary Services shall prohibit the advertising to the general public of veterinary medicinal products that -

(*a*) in accordance with regulation 60, are available on veterinary prescription only; or

(*b*) contain psychotropic drugs or narcotics, such as those covered by the United Nations Conventions of 1961 and 1971.

Applicability of this Title.

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

Measures to be taken by the Veterinary Services.

79. (1) The Veterinary Services shall take appropriate measures to encourage veterinarians and other professionals concerned to report to it any adverse reaction of veterinary medicinal products.

(2) For the purposes of these regulations every licensed, registered farm in the territory of Malta shall nominate a veterinary surgeon responsible for animal health and animal welfare on the farm:

Provided that a register of the veterinary surgeons nominated by the licensed, registered farms shall be kept by the Veterinary Services.

(3) The person responsible for the farm may change veterinary surgeon upon informing the Veterinary Services within four days of such change:

Provided that in case of emergency the person responsible for the farm can ask for assistance from another veterinary surgeon.

TITLE IX

STANDING COMMITTEE

Changes to be made to the Schedule.

80. Any changes which are necessary in order to adapt the Schedule to take account of technical progress shall be adopted in accordance with the procedure referred to in article 89(2) of European Union Council Directive 2001/82/EC.

TITLE X

GENERAL PROVISIONS

Communication between competent authorities. *Substituted by: L.N. 82 of 2006.*

81. The Veterinary Services shall communicate the appropriate information to competent authorities in other Member States, particularly regarding compliance with the requirements adopted for the authorisations referred to in regulation 38, for the certificates referred to in regulation 72(5) or for authorization to place products on the market.

Upon reasoned request, the Veterinary Services shall forthwith communicate the reports referred to in regulation 72(3) to the competent authorities of another Member State.

The conclusions reached following an inspection as referred to in regulation 72(1) carried out by the inspectors of the Veterinary Services shall be valid for the European Community.

However, by way of exception, if Malta has not been able, for serious reasons of human or animal health, to accept the conclusions of an inspection as referred to in regulation 72(1), the Veterinary Services shall forthwith inform the Commission and the Agency.

When the European Commission is informed of such serious reasons, it may, after consulting the Veterinary Services, ask the inspector of the Veterinary Services to carry out a new inspection; the inspector may be accompanied by two other inspectors from Member States that are not parties to the disagreement.

Veterinary Services to inform Agency on decisions which grant or refuse marketing authorisation.

82. (1) The Veterinary Services shall take all appropriate measures to ensure that the Agency is informed immediately of decisions granting marketing authorisation and of all decisions refusing or withdrawing marketing authorisation, cancelling a decision refusing or withdrawing marketing authorisation, prohibiting supply or withdrawing a product from the market, together with the reasons on which such decisions are based.

(2) The marketing authorisation holder shall be obliged to notify the Veterinary Services 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. The Veterinary Services shall ensure that this information is brought to the attention of the Agency.

(3) The Veterinary Services shall ensure that appropriate information about actions taken pursuant to subregulations (1) and

(2) which may affect the protection of health in third countries is forthwith brought to the attention of the relevant international organisations, with a copy to the Agency.

Communication of information necessary to guarantee the quality and safety of homeopathic veterinary medicinal products.

83. The Veterinary Services shall communicate to the competent authorities of the other Member States all the information necessary to guarantee the quality and safety of homeopathic veterinary medicinal products manufactured and marketed within the territory of Malta, and in particular the information referred to in regulation 81 and 82.

Certification on the possession of a manufacturing authorisation.

84. (1) At the request of the manufacturer or exporter of veterinary medicinal products, or the authorities of an importing third country, the territory of Malta shall certify that such manufacturer is in possession of the manufacturing authorisation. When issuing such certificates, the Veterinary Services shall comply with the following conditions:

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

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

(2) Where the manufacturer is not in possession of an authorisation to place the product on the market, he shall provide the authorities responsible for establishing the certificate referred to in subregulation (1) with a declaration explaining why such authorisation is not available.

Decision taken by the Veterinary Services.
Amended by: L.N. 82 of 2006.

85. Any decision referred to in these regulations, taken by the Veterinary Services, may only be taken on the grounds set out in these regulations 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.

Decisions to grant or revoke a marketing authorization shall be made publicly available.

Foodstuffs taken from test animals.
Substituted by: L.N. 82 of 2006.

86. The Veterinary Services shall not permit foodstuffs for human consumption to be taken from test animals unless an appropriate withdrawal period has been established. The withdrawal period shall either -

(*a*) be at least as laid down in regulation 11(2) including, where appropriate, a safety factor reflecting the nature of the substance being tested; or

(*b*) if maximum residue limits have been established by the Community in accordance with Regulation (EEC) No 2377/90, ensure that this maximum limit will not

be exceeded in foodstuffs.

Collection. *Added by: L.N. 82 of 2006.*

87. The Veterinary Services shall ensure that appropriate Systems collection systems are in place for veterinary medicinal products that are unused or expired.

Substituted by:
L.N. 360 of 2009.

SCHEDULE

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

TABLE OF CONTENTS

1. General characteristics of the finished product
2. Identification and assay of active substance(s)
3. Identification and assay of excipient components
4. Safety tests

F. STABILITY TEST

1. Active substances(s)
2. Finished product

G. OTHER INFORMATION

PART 3: SAFETY AND RESIDUES TESTS

A. Safety tests

CHAPTER I: PERFORMANCE OF TESTS

1. Precise identification of the product and of its active substance(s)
2. Pharmacology

2.1. Pharmacodynamics

2.2. Pharmacokinetics

3. Toxicology

3.1. Single-dose toxicity

3.2. Repeat-dose toxicity

3.3. Tolerance in the target species

3.4. Reproductive toxicity including developmental toxicity

3.4.1. Study of the effects on reproduction

3.4.2. Study of developmental toxicity

3.5. Genotoxicity

3.6. Carcinogenicity

3.7. Exceptions

4. Other requirements

4.1. Special studies

4.2. Microbiological properties of residues

4.2.1. Potential effects on the human gut flora

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

4.3. Observations in humans

4.4. Development of resistance

5. User safety

6. Environmental risk assessment

6.1. Environmental risk assessment of veterinary medicinal products not containing or consisting of genetically modified organisms

6.2. Environmental risk assessment for veterinary medicinal products containing or consisting of genetically modified organisms

CHAPTER II: PRESENTATION OF PARTICULARS AND DOCUMENTS

B. Residue tests

CHAPTER I: PERFORMANCE OF TESTS

1. Introduction

2. Metabolism and residue kinetics

2.1. Pharmacokinetics (absorption, distribution, metabolism, excretion)

2.2. Depletion of residues

3. Residue analytical method

CHAPTER II: PRESENTATION OF PARTICULARS AND DOCUMENTS

1. Identification of the product

PART 4: PRE-CLINICAL AND CLINICAL TRIAL

CHAPTER I: PRE-CLINICAL REQUIREMENTS

A. Pharmacology

A.1. Pharmacodynamics

A.2. Development of resistance

A.3. Pharmacokinetics

B. Tolerance in the target animal species

CHAPTER II: CLINICAL REQUIREMENTS

1. General principles

2. Conduct of clinical trials

CHAPTER III: PARTICULARS AND DOCUMENTS

1. Results of pre-clinical trials

2. Results of clinical trials

TITLE II

REQUIREMENTS FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

PART 1: SUMMARY OF THE DOSSIER

A. ADMINISTRATIVE INFORMATION

B. SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

C. DETAILED AND CRITICAL SUMMARIES

PART 2: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL/ MICROBIOLOGICAL INFORMATION (QUALITY)

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

1. Qualitative particulars

2. "Usual terminology"

3. Quantitative particulars

4. Product development

B. DESCRIPTION OF MANUFACTURING METHOD
C. PRODUCTION AND CONTROL OF STARTING MATERIALS
1. Starting materials listed In Pharmacopoeias
2. Starting materials not listed in a pharmacopoeia
2.1. Starting materials of biological origin
2.2. Starting materials of non-biological origin
D. CONTROL TESTS DURING THE MANUFACTURING PROCESS
E. CONTROL TESTS ON THE FINISHED PRODUCT
1. General characteristics of the finished product
2. Identification of active substance(s)
3. Batch titre or potency
4. Identification and assay of adjuvants
5. Identification and assay of excipient components
6. Safety tests
7. Sterility and purity test
8. Residual humidity
9. Inactivation
F. BATCH TO BATCH CONSISTENCY
G. STABILITY TESTS
H. OTHER INFORMATION
PART 3: SAFETY TESTS
A. INTRODUCTION AND GENERAL REQUIREMENTS
B. LABORATORY TESTS
1. Safety of the administration of one dose
2. Safety of one administration of an overdose
3. Safety of the repeated administration of one dose
4. Examination of reproductive performance
5. Examination of immunological functions
6. Special requirements for live vaccines
6.1. Spread of the vaccine strain
6.2. Dissemination in the vaccinated animal
6.3. Reversion to virulence of attenuated vaccines
6.4. Biological properties of the vaccine strain
6.5. Recombination or genomic reassortment of strains
7. User safety
8. Study of residues
9. Interactions

INTRODUCTION AND GENERAL PRINCIPLES

1. The particulars and documents accompanying an application for marketing authorisation pursuant to regulations 12 to 13(1) shall be presented in accordance with the requirements set out in this Schedule and shall take into account the guidance published by the Commission in The rules governing medicinal products in the European Union, Volume 6 B, Notice to applicants, Veterinary medicinal

products, Presentation and Contents of the Dossier.

2. In assembling the dossier for application for marketing authorisation, applicants shall also take into account the current state of veterinary medicinal knowledge and the scientific guidelines relating to the quality, safety and efficacy of veterinary medicinal products published by the European Medicines Agency (Agency) and the other pharmaceutical Community guidelines published by the Commission in different volumes of The rules governing medicinal products in the European Union.

3. For veterinary medicinal products other than immunological veterinary medicinal products, with respect to the quality (pharmaceutical) part (physico-chemical, biological and microbiological tests) of the dossier, all relevant monographs including general monographs and the general chapters of the European Pharmacopoeia are applicable. For immunological veterinary medicinal products, with respect to the quality, safety and efficacy parts of the dossier, all relevant monographs including general monographs and the general chapters of the European Pharmacopoeia are applicable.

4. The manufacturing process shall comply with the requirements of Commission Directive 91/412/EEC* laying down the principles and guidelines for veterinary medicinal products and with the principles and guidelines on Good Manufacturing Practice (GMP), published by the Commission in The rules governing medicinal products in the European Union, Volume 4.

5. All information which is relevant to the evaluation of the veterinary 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.

6. Pharmacological, toxicological, residue and safety tests shall be carried out in conformity with the provisions related to Good Laboratory Practice (GLP) laid down in Directive 2004/10/EC of the European Parliament and of the Council† and Directive 2004/9/EC of the European Parliament and of the Council‡.

7. The Authority shall ensure that all experiments on animals are conducted in accordance with Council Directive 86/609/EEC§.

8. In order to monitor the risk/benefit assessment, any new information not in the original application and all pharmacovigilance information shall be submitted to the competent authority. After marketing authorisation has been granted, any change to the content of the dossier shall be submitted to the competent authorities in accordance with Commission Regulations (EC) No 1084/2003** or (EC) No 1085/2003†† for veterinary medicinal products authorised as defined in Article 1 of such regulations, respectively.

9. The environmental risk assessment connected with the release of veterinary medicinal products containing or consisting of Genetically Modified Organisms (GMOs) within the meaning of Article 2 of Directive 2001/18/EC of the European Parliament and of the Council‡‡ shall be provided in the dossier. The information shall be presented in accordance with the provisions of Directive 2001/18/EC and

*OJ L 228, 17.8.1991, p. 70.
†OJ L 50, 20.2.2004, p. 44.
‡OJ L 50, 20.2.2004, p. 28.
§OJ L 358, 18.12.1986, p. 1.
** OJ L 159, 27.6.2003, p. 1.
††OJ L 159, 27.6.2003, p. 24.
‡‡OJ L 106, 17.4.2001, p. 1.

Regulation (EC) No 726/2004 of the European Parliament and of the Council*, taking into account guidance documents published by the Commission.

10. In cases of applications for marketing authorisations for veterinary medicinal products indicated for animal species and indications representing smaller market sectors, a more flexible approach may be applicable. In such cases, relevant scientific guidelines and/or scientific advice should be taken into account.

This Schedule is divided in four titles:

Title I describes the standardised requirements for applications for veterinary medicinal products other than immunological veterinary medicinal products.

Title II describes the standardised requirements for applications for immunological veterinary medicinal products.

Title III describes specific types of marketing authorisation dossiers and requirements.

Title IV describes the dossier requirements for particular types of veterinary medicinal products.

TITLE I

REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS OTHER THAN IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

The following requirements shall apply to veterinary medicinal products other than immunological veterinary medicinal products, except where otherwise set out in Title III.

PART 1: SUMMARY OF THE DOSSIER

A. ADMINISTRATIVE INFORMATION

The veterinary medicinal product, which is the subject of the application, shall be identified by its name and by the name of the active substance(s), together with the strength, the pharmaceutical form, the route and method of administration (vide regulation 12) and a description of the final presentation of the product, including packaging, labelling and package leaflet (vide regulation 12).

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, testing and release (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 information shall be a document showing that the manufacturer is authorised to produce the veterinary medicinal products concerned, as defined in regulation 38, together with a list of countries in which authorisation has been granted, copies of all the summaries of product characteristics in accordance with regulation 14 as approved by the territory of Malta and a list of countries in which an application has been submitted or refused.

B. SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

*OJ L 136, 30.4.2004, p. 1.

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

A proposed labelling text for the immediate and outer packaging shall be provided in accordance with Title V of these regulations, together with a package leaflet where such is required pursuant to regulation 51 of these regulations. In addition the applicant shall provide one or more specimens or mock-ups of the final presentation(s) of the veterinary medicinal product in at least one of the official languages of the European Union; the mock-up may be provided in black and white and electronically where prior agreement from the competent authority has been obtained.

C. DETAILED AND CRITICAL SUMMARIES

In accordance with regulation 12(3), detailed and critical summaries shall be provided on the results of pharmaceutical (physico-chemical, biological or microbiological) tests, of the safety tests and residue tests, of the pre-clinical and clinical trials and of the tests assessing the potential risks posed by the veterinary medicinal product for the environment.

Each detailed and critical summary shall be prepared in the light of the state of scientific knowledge at the time of submission of the application. It shall contain an evaluation of the various tests and trials, which constitute the marketing authorisation dossier, and shall address all points relevant to the assessment of the quality, safety and efficacy of the veterinary medicinal product. It shall give detailed results of the tests and trials submitted and precise bibliographic references.

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

The detailed and critical summaries shall be signed and dated, and information about the author's educational background, training and occupational experience shall be attached. The professional relationship of the author with the applicant shall be declared.

Where the active substance has been included in a medicinal product for human use authorised in accordance with the requirements of Annex I to Directive 2001/83/EC of the European Parliament and of the Council* the overall quality summary provided for in Module 2, section 2.3 of that Annex may replace the summary regarding the documentation related to the active substance or the product, as appropriate.

Where the competent authority has publicly announced that the chemical, pharmaceutical and biological/microbiological information for the finished product may be included in the dossier in the Common Technical Document (CTD) format only, the detailed and critical summary on the results of pharmaceutical tests may be presented in the quality overall summary format.

In the case of application for an animal species or for indications representing smaller market sectors, the quality overall summary format may be used without prior agreement of the competent authorities.

PART 2: PHARMACEUTICAL (PHYSICO-CHEMICAL, BIOLOGICAL OR MICROBIOLOGICAL INFORMATION (QUALITY))

Basic principles and requirements

* OJ L 311, 28.11.2001, p. 67.

The particulars and documents which shall accompany the application for marketing authorisation pursuant to regulation 12 of these regulations shall be submitted in accordance with the requirements below.

The pharmaceutical (physico-chemical, biological or microbiological) data shall include for the active substance(s) and for the finished veterinary medicinal product information on the manufacturing process, the characterisation and properties, the quality control procedures and requirements, the stability as well as a description of the composition, the development and presentation of the veterinary medicinal product.

All monographs, including general monographs and general chapters of the European Pharmacopoeia, or failing that, of Malta are applicable.

All test procedures shall fulfil the criteria for analysis and control of the quality of the starting materials and the finished product and should take account of established guidance and requirements. The 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 Malta, this description may be replaced by a detailed reference to the pharmacopoeia in question.

Where relevant, chemical and biological reference material of the European Pharmacopoeia shall be used. If other reference preparations and standards are used, they shall be identified and described in detail.

In cases where the active substance has been included in a medicinal product for human use authorised in accordance with the requirements of Annex I to Directive 2001/83/EC the chemical, pharmaceutical and biological/microbiological information provided for in Module 3 of that Directive may replace the documentation related to the active substance or the finished product, as appropriate.

The chemical, pharmaceutical and biological/microbiological information for the active substance or the finished product may be included in the dossier in CTD format only where the competent authority has publicly announced this possibility.

In the case of any application for an animal species or for indications representing smaller market sectors the CTD format may be followed without prior agreement of the competent authorities.

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

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 constituents of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances,
- the constituents, intended to be ingested or otherwise administered to animals, of the outer covering of the veterinary medicinal products, such as capsules, gelatine capsules.

These particulars shall be supplemented by any relevant data concerning the immediate packaging and if relevant the secondary packaging 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 supplied with the medicinal product.

2. Usual terminology

The usual terminology to be used in describing the constituents of veterinary medicinal products means, notwithstanding the application of the other provisions of regulation 12(3)(*c*):

- in respect of constituents 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 constituents, the international non-proprietary name (INN) recommended by the World Health Organisation (WHO), which may be accompanied by another non-proprietary name, or, failing these, the exact scientific designation; constituents 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 by Council Directive 78/25/EEC*.

3. Quantitative particulars

3.1. In order to give "quantitative particulars" of all the active substances of the veterinary 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 Organisation, 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 by using where applicable the European Pharmacopoeia Units.

Whenever possible, biological activity per units of mass or volume shall be indicated. This information shall be supplemented:

- in respect of single-dose 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 veterinary medicinal products to be administered by drops, by the mass or units of biological activity of each active substance contained per drop or 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.

*OJ L 11, 14.1.1978, p. 18.

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 veterinary medicinal products containing an active substance which is the subject of an application for marketing authorisation 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 authorised veterinary medicinal products in Malta 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, immediate packaging, possible further packaging, outer packaging if relevant, the intended function of the excipients in the finished product and the method of manufacture of the finished product. This explanation shall be supported by scientific data on development pharmaceutics. The overage, with justification thereof, shall be stated. The microbiological characteristics (microbiological purity and antimicrobial activity) and usage instructions shall be proven to be appropriate for the intended use of the veterinary medicinal product as specified in the marketing authorisation application dossier.

B. DESCRIPTION OF THE MANUFACTURING METHOD

The name, address and responsibility of each manufacturer and each proposed production site or facility involved in manufacturing and testing shall be indicated.

The description of the manufacturing method accompanying the application for marketing authorisation pursuant to regulation 12(3)(d) hereof, 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 insofar as the pharmaceutical form makes this necessary; mention shall be made of any substances that may disappear in the course of manufacture; an overage shall be indicated and justified,
- a statement of the stages of manufacture at which sampling is carried out for in-process control tests and the limits applied, 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 and where appropriate a process validation scheme for production scale batches,
- for sterile products, where non-pharmacopoeial standard sterilisation conditions are used, details of the sterilisation processes and/or aseptic procedures used.

C. CONTROL OF STARTING MATERIALS

1. General requirements

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

The dossier shall include the specifications and information on the tests to be conducted for quality control of all batches of starting materials.

The routine tests carried out on each batch of starting materials must be as stated in the application for marketing authorisation. If tests other than those mentioned in a pharmacopoeia are used, this shall be justified by providing proof that the starting materials meet the quality requirements of that pharmacopoeia.

Where a Certificate of Suitability has been issued by the European Directorate for the Quality of Medicines and HealthCare for a starting material, active substance or excipient, this Certificate constitutes the reference to the relevant monograph of the European Pharmacopoeia.

Where a Certificate of Suitability is referred to, the manufacturer shall give an assurance in writing to the applicant that the manufacturing process has not been modified since the granting of the certificate of suitability by the European Directorate for the Quality of Medicines and HealthCare.

Certificates of Analysis shall be presented for the starting materials in order to demonstrate compliance with the defined specification.

1.1. Active substances

The name, address, and responsibility of each manufacturer and each proposed production site or facility involved in manufacturing and testing of an active substance shall be indicated.

For a well-defined active substance, the active substance manufacturer or the applicant may arrange for the following information to be supplied in a separate document directly to the competent authorities by the manufacturer of the active substance as an Active Substance Master File:

(*a*) a detailed description of the manufacturing process;

(*b*) a description of the quality control during manufacture;

(*c*) a description of the process validation.

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 veterinary 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 those documents and particulars shall also be supplied to the applicant where they concern the applicant’s part of the Active Substance Master File.

Additionally, information on the method of manufacture, on quality control and on impurities as well as evidence of the molecular structure shall be provided where a Certificate of Suitability for the active substance is not available:

1. Information on the manufacturing process shall include a description of the active substance manufacturing process that represents the applicant’s commitment for the manufacture of the active substance. All materials needed in order to manufacture the active substance(s) shall be listed, identifying where each material

is used in the process. Information on the quality and control of those materials shall be provided. Information demonstrating that materials meet standards which are appropriate for their intended use shall be provided.

2. Information on quality control shall contain tests (including acceptance criteria) carried out at every critical step, information on the quality and control of intermediates and process validation and/or evaluation studies as appropriate. It shall also contain validation data for the analytical methods applied to the active substance, where appropriate.

3. Information on impurities shall indicate predictable impurities together with the levels and nature of observed impurities. It shall also contain information on the safety of these impurities where relevant.

4. For biotechnological veterinary medicinal products, evidence of molecular structure shall include the schematic amino acid sequence and relative molecular mass.

1.1.1. Active substances listed in pharmacopoeias

The general and specific monographs of the European Pharmacopoeia shall be applicable to all active substances appearing in it.

Constituents fulfilling the requirements of the European Pharmacopoeia or the pharmacopoeia of one of the Member States shall be deemed to comply sufficiently with regulation 12(3). In this case the description of the analytical methods and procedures shall be replaced in each relevant section by an appropriate reference to the pharmacopoeia in question.

In cases where a specification contained in a monograph of the European Pharmacopoeia or in the national pharmacopoeia of Malta is insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the applicant, including limits for specific impurities with validated test procedures.

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

In the absence of a European Pharmacopoeia monograph for an active substance, and where the active substance is described in the pharmacopoeia of Malta, that monograph may be applied.

In cases where an active substance is described neither in the European Pharmacopoeia nor in the pharmacopoeia of Malta, compliance with the monograph of a third country pharmacopoeia may be accepted if its suitability is demonstrated; in such cases, the applicant shall submit a copy of the monograph accompanied by a translation where appropriate. Data to demonstrate the ability of the monograph to adequately control the quality of the active substance shall be presented.

1.1.2. Active substances 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 constituent, 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 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 each individual predictable impurity, 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*) tests and limits to control parameters relevant to the finished product, such as particle size and sterility shall be described and methods shall be validated where relevant;

(*f*) 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.

Those data shall demonstrate that the proposed set of test procedures is sufficient to control the quality of the active substance from the defined source.

1.1.3. 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 bioavailability of the veterinary medicinal product depends on them:

- crystalline form and solubility coefficients,
- particle size, where appropriate after pulverisation,
- state of hydration,
- oil/water coefficient of partition,
- pK/pH values.

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

1.2. Excipients

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

Excipients shall comply with the requirements of the appropriate European Pharmacopoeia monograph. Where such a monograph does not exist reference may be made to the pharmacopoeia of Malta. In the absence of such a monograph reference may be made to the pharmacopoeia of a third country. In this case the suitability of this monograph shall be demonstrated. Where appropriate, additional tests to control parameters such as particle size, sterility, residual solvents shall supplement the requirements of the monograph. In the absence of a pharmacopoeial monograph a specification shall be proposed and justified. The requirements for specifications as set out in section 1.1.2 (*a* to *e*) for the active substance shall be followed. The proposed methods and their supporting validation data shall be presented.

Colouring matters for inclusion in veterinary medicinal products shall satisfy the

requirements of Directive 78/25/EEC, except for certain veterinary medicinal products for topical use, such as insecticidal collars and ear tags, where the use of other colouring matters is justified.

Colouring matters shall meet the purity criteria as laid down in Commission Directive 95/45/EC*.

For novel excipients, that is to say excipient(s) used for the first time in a veterinary medicinal product or by a new route of administration, details of manufacture, characterisation, and controls, with cross references to supporting safety data, both clinical and non-clinical, shall be provided.

1.3. Container-closure systems

1.3.1. Active substance

Information on the container-closure system for the active substance shall be given.

The level of information required shall be determined by the physical state (liquid, solid) of the active substance.

1.3.2. Finished product

Information on the container-closure system for the finished product shall be given.

The level of information required shall be determined by the route of administration of the veterinary medicinal product and the physical state (liquid, solid) of the dosage form.

Packaging materials shall comply with the requirements of the appropriate European Pharmacopoeia monograph. Where such a monograph does not exist reference may be made to the pharmacopoeia of Malta. In the absence of such a monograph reference may be made to the Pharmacopoeia of a third country. In this case the suitability of this monograph shall be demonstrated.

In the absence of a pharmacopoeial monograph, a specification shall be proposed and justified for the packaging material.

Scientific data on the choice and suitability of the packaging material shall be presented.

For novel packaging materials in contact with the product, information on their composition, manufacture and safety shall be presented.

Specifications and, if appropriate, performance data shall be presented for any dosing or administration device supplied with the veterinary medicinal product.

1.4. Substances of biological origin

Where source materials such as microorganisms, 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.

*OJ L 226, 22.9.1995, p. 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.

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

When starting materials of animal or human origin are used, the measures used to ensure freedom from potentially pathogenic agents shall be described.

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

Documentation shall be supplied to demonstrate that the seed materials, cell seeds, batches of serum and other material originating from animal species relevant for the transmission of TSE comply with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*, as well as with the corresponding monograph of the European Pharmacopoeia. Certificates of Suitability issued by the European Directorate for the Quality of Medicines and HealthCare, with reference to the relevant monograph of the European Pharmacopoeia, may be used to demonstrate compliance.

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

The dossier 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 veterinary 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.

Where an intermediate product may be stored prior to further processing or primary assembly, a shelf life for the intermediate product shall be defined on the basis of the data resulting from stability studies.

E. TESTS ON THE FINISHED PRODUCT

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 sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time.

The application for marketing authorisation 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 dossier 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 relevant monographs and general chapters of the European

*OJ C 24, 28.1.2004, p. 6.

Pharmacopoeia, or failing that, of Malta, shall be applicable to all products defined therein.

If test procedures and limits other than those mentioned in the relevant monographs and general chapters of the European Pharmacopoeia, or failing this, in the pharmacopoeia of Malta are used, this shall be justified by providing proof 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. 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. 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 Malta; 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, unless otherwise justified. Those studies shall also be carried out where administration is by another means if the competent Authority concerned consider this necessary.

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 shall propose and justify maximum acceptable deviation limits in the active substance content of the finished product up to the end of the proposed shelf life.

In certain 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 simplified technique may not be extended to the characterisation of the substances concerned. It 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 degradation occurs during manufacture of the finished product, the maximum acceptable levels of individual and total degradation products immediately following manufacture shall be indicated.

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 or where the stability data show that the assay of the active substance declines on storage, 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 characterisation and/or assay of the degradation products.

3. Identification and assay of excipient components

An identification test and an upper and lower limit test shall be obligatory for each individual antimicrobiological preservative and for any excipient that is liable to affect the bioavailability of the active substance, unless the bioavailability is guaranteed by other appropriate tests. An identification test and an upper limit test shall be obligatory for any antioxidant and for any excipient liable to adversely affect physiological functions, with a lower limit test also included for antioxidants at time of release.

4. Safety tests

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

F. STABILITY TEST

1. Active substances(s)

A retest period and storage conditions for the active substance shall be specified except in the case where the active substance is the subject of a monograph in the European Pharmacopoeia and the manufacturer of the finished product fully retests the active substance immediately before its use in the manufacture of the finished product.

Stability data shall be presented to support the defined retest period and storage conditions. The type of stability studies conducted, protocols used, the analytical procedures used and their validation together with the detailed results shall be presented. The stability commitment with a summary of the protocol shall be provided.

However, where a Certificate of Suitability for the active substance from the proposed source is available and specifies a retest period and storage conditions, stability data for the active substance from that source are not required.

2. Finished product

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.

The type of stability studies conducted, protocols used, the analytical procedures used and their validation together with the detailed results shall be presented.

Where a finished product requires reconstitution or dilution prior to administration, details of the proposed shelf life and specification for the

reconstituted/diluted product are required, supported by relevant stability data.

In the case of multi-dose containers, where relevant, stability data shall be presented to justify a shelf life for the product after it has been broached for the first time and an in-use specification shall be defined.

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

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

The maximum acceptable level of individual and total 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 are concerned.

The stability commitment with a summary of the protocol shall be provided.

G. OTHER INFORMATION

Information relating to the quality of the veterinary medicinal product not covered in the previous sections may be included in the dossier.

For medicated premixes (products intended for incorporation into medicated feedingstuffs), information shall be provided on inclusion rates, instructions for incorporation, homogeneity in-feed, compatibility/suitable feedingstuffs, stability in-feed, and the proposed in-feed shelf life. A specification for the medicated feedingstuffs, manufactured using these pre-mixes in accordance with the recommended instructions for use shall also be provided.

PART 3: SAFETY AND RESIDUES TESTS

The particulars and documents which shall accompany the application for marketing authorisation pursuant to the second and fourth indents of regulation 12(3) shall be submitted in accordance with the requirements below.

A. Safety tests

CHAPTER I: PERFORMANCE OF TESTS

The safety documentation shall show:

(*a*) the potential toxicity of the veterinary 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;

(*b*) 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;

(*c*) the potential risks which may result from the exposure of human beings to the veterinary medicinal product, for example during its administration to the animal;

(*d*) the potential risks for the environment resulting from the use of the

veterinary 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, information shall be provided regarding 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. Precise identification of the product and of its active substance(s)
   - international non-proprietary name (INN),
   - International Union of Pure and Applied Chemistry Name (IUPAC),
   - Chemical Abstract Service (CAS) number,
   - therapeutic, pharmacological and chemical classification,
   - synonyms and abbreviations,
   - structural formula,
   - molecular formula,
   - molecular weight,
   - degree of impurity,
   - qualitative and quantitative composition of impurities,
   - description of physical properties,
   - melting point,
   - boiling point,
   - vapour pressure,
   - solubility in water and organic solvents expressed in g/l, with indication of temperature,
   - density,
   - spectra of refraction, rotation, etc,
   - formulation of the product.
2. Pharmacology

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

However, pharmacological studies may also assist in the understanding of toxicological phenomena. Moreover, where a veterinary 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 veterinary 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.

2.1. Pharmacodynamics

Information on the mechanism of action of the active substance(s) shall be provided, together with information on primary and secondary pharmacodynamic effects in order to assist in the understanding of any adverse effects in the animal studies.

2.2. Pharmacokinetics

Data on the fate of the active substance and its metabolites in the species used in the toxicological studies shall be provided, covering absorption, distribution, metabolism and excretion (ADME). The data shall be related to the dose/effect findings in the pharmacological and toxicological studies, to determine adequate exposure. Comparison with the pharmacokinetic data obtained in the studies on the target species, Part 4, Chapter I, Section A.2, shall be included in Part 4 in order to determine the relevance of the results obtained in the toxicology studies for the toxicity to the target species.

3. Toxicology

The documentation on toxicology shall follow the guidance published by the Agency on the general approach to testing and guidance on particular studies. This guidance includes:

1. basic tests required for all new veterinary medicinal products for use in food-producing animals in order to assess the safety of any residues present in food for human consumption;
2. additional tests that may be required depending on specific toxicological concerns such as those associated with the structure, class, and mode of action of the active substance(s);
3. special tests which might assist in the interpretation of data obtained in the basic or additional tests.

The studies shall be conducted with the active substance(s), not with the formulated product. Where studies of the formulated product are required, this is specified in the text below.

3.1. Single-dose toxicity

Single-dose toxicity studies may 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.

The studies to be carried out shall be selected with a view to providing information on user safety, e.g. if substantial exposure by inhalation or dermal contact of the user of the veterinary medicinal product is anticipated, those routes of exposure shall be studied.

3.2. Repeat-dose toxicity

Repeat-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 pharmacologically active substances or veterinary medicinal

products intended solely for use in non-food-producing animals, a repeat-dose toxicity study in one species of experimental animal shall 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 shall 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 veterinary medicinal products intended for use in food-producing animals, repeat-dose (90 day) toxicity testing shall be performed in a rodent and a non-rodent species in order to identify target organs and toxicological endpoints and identify the appropriate species and the dose levels to be used in chronic toxicity testing, if appropriate.

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 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 these regulations, the repeat-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

A summary shall be provided of any signs of intolerance which have been observed during studies conducted, usually with the final formulation, 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 shall be identified. Details of any unexpected physiological changes shall also be provided. The full reports of these studies shall be included in Part 4.

3.4. Reproductive toxicity including developmental toxicity

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 veterinary medicinal products or substance under investigation.

In the case of pharmacologically active substances or veterinary medicinal products intended for use in food-producing animals, the study of the effects on reproduction shall be performed in the form of a multi-generation reproduction study, designed to detect any effect on mammalian reproduction. These include effects on male and female fertility, mating, conception, implantation, ability to maintain pregnancy to term, parturition, lactation, survival, growth and development of the offspring from birth through to weaning, sexual maturity and the subsequent reproductive function of the offspring as adults. 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.

3.4.2. Study of developmental toxicity

In the case of pharmacologically active substances or veterinary medicinal products intended for use in food-producing animals, tests on developmental toxicity shall be performed. These tests shall be designed to detect any adverse effects on the pregnant female and development of the embryo and foetus consequent to exposure of the female from implantation through gestation to the day before predicted birth. Such adverse effects include enhanced toxicity relative to that observed in non-pregnant females, embryo-foetal death, altered foetal growth, and structural changes to the foetus. A developmental toxicity test in the rat is required. Depending on the results, a study in a second species may have to be performed, in accordance with established guidance.

In the case of pharmacologically active substances or veterinary medicinal products not intended for use in food producing animals, a study of developmental toxicity shall be performed in at least one species, which may be the target species, if the product is intended for use in female animals which may be used for breeding.

However, where the use of the veterinary medicinal product would result in significant exposure to users, standard developmental toxicity studies shall be performed.

3.5. Genotoxicity

Tests for genotoxic potential shall be performed to reveal changes which a substance may cause in the genetic material of cells. Any substance intended to be included in a veterinary medicinal product for the first time must be assessed for genotoxic properties.

A standard battery of *in vitro* and *in vivo* genotoxicity tests in accordance with established guidance shall usually be carried out on the active substance(s). In some cases, it may also be necessary to test one or more metabolites that occur as residues in foodstuffs.

3.6. Carcinogenicity

The decision on whether carcinogenicity testing is required shall take into account the results of genotoxicity tests, structure-activity relationships and the findings in systemic toxicity tests that may be relevant to neoplastic lesions in longer term studies.

Any known species specificity of the mechanism of toxicity shall be considered, as well as any differences in metabolism between the test species, target animal species, and human beings.

Where carcinogenicity testing is necessary, generally a two-year rat study and an 18-month mouse study are required. With appropriate scientific justification, carcinogenicity studies may be carried out in one rodent species, preferably the rat.

3.7. Exceptions

Where a veterinary medicinal product is intended for topical use, systemic absorption shall be investigated in the target animal species. 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 intended conditions of use laid down, oral ingestion of the veterinary medicinal product by the animal is to be expected, or

- under the intended conditions of use laid down, exposure of the user of the veterinary medicinal product by other routes than the dermal route is to be expected, or
- the active substance or metabolites may enter foodstuffs obtained from the treated animal.

4. Other requirements

4.1. Special studies

For particular groups of substances or if the effects observed during repeated dose studies in animals include changes indicative of e.g. immunotoxicity, neurotoxicity - or, endocrine dysfunction, further testing shall be required, e.g. sensitisation studies or delayed neurotoxicity tests. Depending on the nature of the product, it may be necessary to conduct additional studies to assess the underlying mechanism of the toxic effect or the irritation potential. Such studies shall usually be conducted with the final formulation.

The state of scientific knowledge and established guidance 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 potential microbiological risk presented by residues of antimicrobial compounds for the human intestinal flora shall be investigated in accordance with established guidance.

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 microbiologically active residues may interfere in technological processes in the industrial processing of foodstuff.

4.3. Observations in humans

Information shall be provided showing whether the pharmacologically active substances of the veterinary medicinal product are used as medicinal products in human therapy; if this is so, a compilation shall be made of all the effects observed (including adverse reactions) in humans and of their cause, to the extent that they may be important for the assessment of the safety of the veterinary medicinal product, where appropriate including results from published studies; where constituents of the veterinary medicinal products are themselves not used or are no longer used as medicinal products in human therapy, the reasons shall be stated.

4.4. Development of resistance

Data on the potential emergence of resistant bacteria of relevance for human health are necessary in the case of veterinary medicinal products. The mechanism of the development of such resistance is particularly important in this regard. Where necessary, measures to limit resistance development from the intended use of the veterinary medicinal product shall be proposed.

Resistance relevant for clinical use of the product shall be addressed in accordance with Part 4. Where relevant, cross reference shall be made to the data set out in Part 4.

5. User safety

This section shall include a discussion of the effects found in the preceding sections and relate this to the type and extent of human exposure to the product with a view to formulating appropriate user warnings and other risk management

measures.

6. Environmental risk assessment

6.1. Environmental risk assessment of veterinary medicinal products not containing or consisting of genetically modified organisms

An environmental risk assessment shall be performed to assess the potential harmful effects, which the use of the veterinary medicinal product may cause to the environment and to identify the risk of such effects. The assessment shall also identify any precautionary measures which may be necessary to reduce such risk.

This assessment shall normally be conducted in two phases. The first phase of the assessment shall always be performed. The details of the assessment shall be provided in accordance with accepted guidance. It shall indicate the potential exposure of the environment to the product and the level of risk associated with any such exposure taking into account in particular the following items:

- the target animal species, and the proposed pattern of use,
- 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 excreta,
- the disposal of unused veterinary medicinal product or other waste product.

In the second phase, further specific investigation of the fate and effects of the product on particular ecosystems shall be conducted, in accordance with established guidance. 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 substance(s) concerned, including metabolites in case of an identified risk, which has been obtained during the conduct of the other tests and trials required by these regulations, shall be taken into consideration.

6.2. Environmental risk assessment for veterinary medicinal products containing or consisting of genetically modified organisms.

In the case of a veterinary medicinal product containing or consisting of genetically modified organisms the application shall also be accompanied by the documents required under Article 2 and Part C of Directive 2001/18/EC.

CHAPTER II: PRESENTATION OF PARTICULARS AND DOCUMENTS

The dossier of safety tests shall include the following:

- an index of all studies included in the dossier,
- a statement confirming that all data known by the applicant at the time of submission, whether favourable or unfavourable, are included,
- a justification for the omission of any type of study,
- an explanation of the inclusion of an alternative type of study,
- a discussion of the contribution that any study that pre-dates studies performed in line with good laboratory practice (GLP) according to Directive 2004/10/EC can make to the overall risk assessment.

Each study report shall include:

- a copy of the study plan (protocol),

- a statement of compliance with good laboratory practice, where applicable,
- a description of the methods, apparatus and materials used,
- a description and justification of the test system,
- a description of the results obtained, in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author,
- a statistical analysis of the results where appropriate,
- a discussion of the results, with comment on observed and no-observed-effect levels, and on any unusual findings,
- a detailed description and a thorough discussion of the results of the study of the safety profile of the active substance, and its relevance for the evaluation of potential risks presented by residues to humans.

B. Residue tests

CHAPTER I: PERFORMANCE OF TESTS

1. Introduction

For the purposes of this Schedule, the definitions of Council Regulation (EEC) No 2377/90* shall apply.

The purpose of studying the depletion of residues from the edible tissues or of eggs, milk and honey derived from treated animals is to determine under what conditions and to what extent residues may persist in foodstuffs produced from these animals.

In addition, the studies shall enable the determination of a withdrawal period.

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 edible tissues of the treated animal or in milk, eggs and/or honey obtained therefrom;
2. that in order to prevent any risk to the health of the consumer of foodstuffs from 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 the analytical method(s) used in the residues depletion study are sufficiently validated to provide the necessary reassurance that the residues data submitted are suitable as the basis for a withdrawal period.

2. Metabolism and residue kinetics

2.1. Pharmacokinetics (absorption, distribution, metabolism, excretion)

The following characteristics shall be described:

- specificity,
- accuracy,
- precision,
- limit of detection,

*OJ C 24, 28.1.2004, p. 6.

- limit of quantification,
- practicability and applicability under normal laboratory conditions,
- susceptibility to interference,
- stability of incurred residues.

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.

The analytical method shall be presented in an internationally agreed format.

CHAPTER II: PRESENTATION OF PARTICULARS AND DOCUMENTS

1. Identification of the product

An identification of the veterinary medicinal product(s) used in the testing shall be provided, including:

- composition,
- the physical and chemical (potency and purity) test results for the relevant batch(es),
- batch identification
- relationship to the final product,
- specific activity and radio-purity of labelled substances,
- position of labelled atoms in the molecule.

The dossier of residue tests shall include:

- an index of all studies included in the dossier,
- a statement confirming that all data known by the applicant at the time of submission, whether favourable or unfavourable, are included,
- a justification for the omission of any type of study,
- an explanation of the inclusion of an alternative type of study,
- a discussion of the contribution that any study that pre-dates GLP can make to the overall risk assessment,
- a withdrawal period proposal.

Each study report shall include:

- a copy of the study plan (protocol),
- a statement of compliance with good laboratory practice, where applicable,
- a description of the methods, apparatus and materials used,
- a description of the results obtained, in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author,
- a statistical analysis of the results where appropriate,
- a discussion of the results,
- an objective discussion of the results obtained, 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.

PART 4: PRE-CLINICAL AND CLINICAL TRIAL

The particulars and documents, which shall accompany applications for marketing authorisations in terms of regulation 12(3)(*j*) shall be submitted in accordance with the requirements below.

CHAPTER I: PRE-CLINICAL REQUIREMENTS

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

A. Pharmacology

46

A.1. Pharmacodynamics

The pharmacodynamic effects of the active substance(s) included in the veterinary medicinal product shall be characterised.

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, an overall pharmacological assessment of the active substance shall be provided, with special reference to the possibility of secondary pharmacological effects. In general, the effects on the main body functions shall be investigated.

Any effect of the other characteristics of the products (such as the route of administration or formulation) on the pharmacological activity of the active substance shall be investigated.

The investigations shall be intensified where the recommended dose approaches a dose likely 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.

Fixed 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 new active substance, the latter shall have been previously studied in depth.

A.2. Development of resistance

Where relevant, data on the potential emergence of resistant organisms of clinical relevance are necessary for veterinary medicinal products. The mechanism of the development of such resistance is particularly important in this regard. Measures to

limit resistance development from the intended use of the veterinary medicinal product shall be proposed by the applicant.

Where relevant, cross reference shall be made to data set out in Part 3.

A.3. Pharmacokinetics

Basic pharmacokinetic data concerning a new active substance are required in the context of assessment of the clinical safety and efficacy of the veterinary medicinal product.

The objectives of pharmacokinetic studies in the target animal species can be divided into three main areas:

(i) descriptive pharmacokinetics leading to the determination of basic parameters.;

(ii) use of these parameters to investigate the relationships between dosage regimen, plasma and tissue concentration over time and pharmacological, therapeutic or toxic effects;

(iii) where appropriate, to compare the kinetics between different target species and to explore possible species differences having an impact on target animal safety and efficacy of the veterinary medicinal product.

In the target animal species, pharmacokinetic studies are, as a rule, necessary as a complement to the pharmacodynamic studies to support the establishment of effective dosage regimens (route and site of administration, dose, dosing interval, number of administrations, etc.). Additional pharmacokinetic studies may be required to establish dosage regimens according to certain population variables.

Where pharmacokinetic studies have been submitted under Part 3 cross reference to such studies may be made.

In the case of new combinations of known substances which have been investigated in accordance with the provisions of these regulations, 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.

Appropriate bioavailability studies shall be undertaken to establish bioequivalence:

- when comparing a reformulated veterinary medicinal product with the existing one,
- where necessary for the comparison of a new method or route of administration with an established one.

B. Tolerance in the target animal species

The local and systemic tolerance of the veterinary medicinal product shall be investigated in the target animal species. The purpose of these studies is to characterise signs of intolerance and to establish an adequate margin of safety using the recommended route(s) of administration. This may be achieved by increasing the therapeutic dose and/or the duration of treatment. The report on the trials shall contain details of all expected pharmacological effects and all adverse reactions.

CHAPTER II: CLINICAL REQUIREMENTS

1. General principles

The purpose of clinical trials is to demonstrate or substantiate the effect of the veterinary medicinal product after administration at the proposed dosage regimen via

the proposed route of administration and to specify its indications and contra-indications according to species, age, breed and sex, its directions for use as well as any adverse reactions which it may have.

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

Unless justified, clinical trials shall be carried out with control animals (controlled clinical trials). The efficacy results obtained should be compared with those from the target animal species that have received a veterinary medicinal product authorised in the Community for the same indications for use in the same target animal species, or a placebo or no treatment. All the results obtained, whether positive or negative, shall be reported.

Established statistical principles shall be used in protocol design, analysis and evaluation of clinical trials, unless justified.

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

1. the yield of animal produce,
2. the quality of animal produce (organoleptic, nutritional, hygienic and technological qualities),
3. nutritional efficiency and growth of target animal species,
4. general health status of the target animal species.

2. Conduct of clinical trials

All veterinary clinical trials shall be conducted in accordance with a detailed trial protocol.

Clinical field trials shall be conducted in accordance with established principles of good clinical practice, unless otherwise justified.

Before the commencement of any field 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 field trial is conducted with a blind design, the provisions of regulations 55, 56 and 57 shall apply respectively to the labelling of formulations intended for use in veterinary field trials. In all cases, the words "for veterinary field trial use only" shall appear prominently and indelibly upon the labelling.

CHAPTER III: PARTICULARS AND DOCUMENTS

The dossier on efficacy shall include all pre-clinical and clinical documentation and/or results of trials, whether favourable or unfavourable to the veterinary medicinal products, in order to enable an objective overall assessment of the risk/benefit balance of the product.

1. Results of pre-clinical trials

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

(*a*) tests demonstrating pharmacological actions;

(*b*) tests demonstrating the pharmacodynamic mechanisms underlying the therapeutic effect;

(*c*) tests demonstrating the main pharmacokinetic profile;

(*d*) tests demonstrating target animal safety;

(*e*) tests investigating resistance.

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 efficacy and safety of the veterinary medicinal product.

Total or partial omission of any of these data shall be justified.

2. Results of clinical trials

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 clinical trial protocol giving a description of the methods used, including methods of randomisation 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 animal management and feeding, stating the composition of the feed and the nature and quantity of any feed additives;

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

(*f*) diagnosis and means used to make it;

(*g*) clinical signs, if possible according to conventional criteria;

(*h*) precise identification of the formulation of the veterinary medicinal product used in the clinical trial and the physical and chemical test results for the relevant batch(es);

(*i*) dosage of the veterinary 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 other veterinary medicinal products 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 any interactions observed;

(*l*) all results of the clinical trials, fully describing the results based on the efficacy criteria and end points specified in the clinical trial protocol

and including the results of the statistical analyses, if appropriate;

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

(*n*) effect on animals' performance if appropriate;

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

(*p*) a conclusion on the safety and efficacy in each individual case or, summarised in terms of frequencies or other appropriate variables where specific mass treatment is concerned.

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

The marketing authorisation 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 authorised.

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

(*a*) the number of control and test 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, or
- received a placebo, or
- received another veterinary medicinal product authorised in the Community for the same indication for use in the same target animal species, or
- received the same 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 animal performance, if appropriate;

(*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.

Finally, the investigator shall draw general conclusions on the efficacy and safety of the veterinary medicinal product under the proposed conditions of use, and in particular any information relating to indications and contraindications, dosage and average duration of treatment and where, appropriate, any interactions observed with other veterinary medicinal products or feed additives as well as any special precautions to be taken during treatment and the clinical symptoms of overdosage, when observed.

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.

TITLE II

REQUIREMENTS FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Without prejudice to specific requirements laid down by Community legislation for the control and eradication of specific infectious animal diseases, the following requirements shall apply to immunological veterinary medicinal products, except when the products are intended for use in some species or with specific indications as defined in Title III and in relevant guidelines.

PART 1: SUMMARY OF THE DOSSIER

A. ADMINISTRATIVE INFORMATION

The immunological 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 biological activity, potency or titre, the pharmaceutical form, the route and method if appropriate of administration and a description of the final presentation of the product, including packaging, labelling and leaflet. Diluents may be packed together with the vaccine vials or separately.

Information on diluents needed for making the final vaccine preparation shall be included in the dossier. An immunological veterinary medicinal product is regarded as one product even when more than one diluent is required so that different preparations of the final product can be prepared, which may be for administration by different routes or methods of administration.

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 and control (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 information shall be copies of a document showing that the manufacturer is authorised to produce immunological veterinary medicinal products, as defined in regulation 38 of these regulations. Moreover, the list of organisms handled at the production site shall be given.

The applicant shall submit a list of countries in which authorisation has been granted, and a list of countries in which an application has been submitted or refused.

B. SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

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

A proposed labelling text for the immediate and outer packaging shall be provided in accordance with Title V of these regulations, together with a package leaflet where one is required pursuant to regulation 51. In addition the applicant shall provide one or more specimens or mock-ups of the final presentation(s) of the veterinary medicinal product in at least one of the official languages of the European Union; the mock-up may be provided in black and white and electronically where prior agreement from the competent authority has been obtained.

C. DETAILED AND CRITICAL SUMMARIES

Each detailed and critical summary referred to in regulation 12(3)(*l*) shall be prepared in the light of the state of scientific knowledge at the time of submission of the application. It shall contain an evaluation of the various tests and trials, which constitute the marketing authorisation dossier and shall address all points relevant to the assessment of the quality, safety and efficacy of the immunological veterinary medicinal product. It shall give the detailed results of the tests and trials submitted and precise bibliographic references.

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

The detailed and critical summaries shall be signed and dated, and information about the author's educational background, training and occupational experience shall be attached. The professional relationship of the author with the applicant shall be declared.

PART 2: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL/ MICROBIOLOGICAL INFORMATION (QUALITY)

All test procedures shall fulfil the necessary criteria for analysis and control of the quality of the starting materials and the finished product and shall be validated procedures. The results of the validation studies shall be provided. 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 Malta, this description may be replaced by a detailed reference to the pharmacopoeia in question.

Where available, chemical and biological reference material of the European Pharmacopoeia shall be used. If other reference preparations and standards are used, they shall be identified and described in detail.

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

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. If the device is not delivered together with the immunological veterinary medicinal product, relevant information about the device shall be provided, where necessary for the assessment of the product.

2. "Usual terminology"

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 regulation 12(3)(*c*):

- in respect of substances which appear in the European Pharmacopoeia or, failing this, in the 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 Organisation, 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. Product development

An explanation shall be provided with regard to the composition, components and containers, supported by scientific data on product development. The overage, with justification thereof, shall be stated.

B. DESCRIPTION OF MANUFACTURING METHOD

The description of the manufacturing method accompanying the application for marketing authorisation pursuant to regulation 12(3), 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 production of the antigen and 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; the validation of key stages in the production process shall be demonstrated and the validation of the production process as a whole shall be demonstrated with provision of results of three consecutive batches produced using the method described,

- in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity and consistency of each batch of the finished product,
- listing of all the substances at the appropriate steps where they are used, including those which cannot be recovered in the course of manufacturing,
- the details of the blending, with the quantitative particulars of all the substances used,
- a statement of the stages of manufacture at which sampling is carried out for control tests during production.

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 consisting of several components used for production of the active substance shall be regarded as one starting material. Nevertheless, the qualitative and quantitative composition of the any culture media shall be presented in so far as the authorities consider that this information is relevant to the quality of the finished product and any risks that might be posed. If materials of animal origin are used for preparation of these culture media, the animal species and the tissue used have to be included.

The dossier shall include the specifications, information on the tests to be conducted for the quality control of all batches of starting materials and results for a batch for all 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 starting materials 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 regulation 12(3) hereof. In this case the description of the analytical methods may be replaced by a detailed reference to the pharmacopoeia in question.

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 authorisation. 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 pharmacopoeia of Malta might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the applicant for marketing authorisation. The alleged insufficiency shall be reported to the authorities responsible for the pharmacopoeia in question.

In cases where a starting material is described neither in the European Pharmacopoeia nor in the pharmacopoeia of Malta, 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.

When starting materials of animal origin are used, they shall comply with the relevant monographs including general monographs and general chapters of the European Pharmacopoeia. The tests and controls conducted shall be appropriate to the starting material.

The applicant shall supply documentation to demonstrate that the starting materials and the manufacturing of the veterinary medical product is in comply with the requirements of the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, as well as with the requirements of the corresponding monograph of the European Pharmacopoeia. Certificates of Suitability issued by the European Directorate for the Quality of Medicines and HealthCare, with reference to the relevant monograph of the European Pharmacopoeia, may be used to demonstrate compliance.

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 seeds. 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 and defined pools of source materials shall be used.

The origin, including geographical region, 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 seeds and raw serum for anti-serum production shall be tested for identity and extraneous 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 controls during production,
- details of any tests for contamination carried out on each batch of the substance.

If the presence of extraneous 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 extraneous agents shall be demonstrated.

When cell seeds 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.

Documentation shall be supplied to demonstrate that the seed materials, cell seeds, batches of serum and other material originating from animal species relevant for the transmission of TSE comply with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, as well as with the corresponding monograph of the European Pharmacopoeia. Certificates of Suitability issued by the European Directorate for the Quality of Medicines and HealthCare, with reference to the relevant monograph of the European Pharmacopoeia, can be used to demonstrate compliance.

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,
- any special precautions which may be necessary during storage of the starting material and, if necessary, its storage life shall be given.

D. CONTROL TESTS DURING THE MANUFACTURING PROCESS

1. The dossier shall include particulars relating to the control tests, which are carried out on intermediate products with a view to verifying the consistency of the manufacturing process and the final product.

2. For inactivated or detoxified vaccines, inactivation or detoxification shall be tested during each production run as soon as possible after the end of the inactivation or detoxification process and after neutralisation if this occurs, but before the next step of production.

E. CONTROL TESTS ON THE FINISHED PRODUCT

For all tests, the description of the techniques for analysing the finished product shall be set out in sufficiently precise detail for quality assessment.

The dossier 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 pharmacopoeia of Malta, 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 authorisation 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.

Where available, chemical and biological reference material of the European Pharmacopoeia shall be used. If other reference preparations and standards are used, they shall be identified and described in detail.

1. General characteristics of the finished product

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

2. Identification of active substance(s)

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

3. Batch titre or potency

A quantification of the active substance shall be carried out on each batch to show that each batch will contain the appropriate potency or titre to ensure its safety and efficacy.

4. Identification and assay of adjuvants

Insofar as testing procedures are available, the quantity and nature of the adjuvant and its components shall be verified on the finished product.

5. Identification and assay of excipient components

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

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.

6. Safety tests

Apart from the results of tests submitted in accordance with Part 3 of this Title (Safety Tests), particulars of the batch 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. Routine application of the batch safety test may be waived in the interests of animal welfare when a sufficient number of consecutive production batches have been produced and been found to comply with the test.

7. Sterility and purity test

Appropriate tests to demonstrate the absence of contamination by extraneous 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. If fewer tests than required by the relevant European Pharmacopoeia are routinely employed for each batch, the tests carried out shall be critical to the compliance with the monograph. Proof must be supplied that the immunological veterinary medicinal product would meet the requirements, if fully tested according to the monograph.

8. Residual humidity

Each batch of lyophilised product shall be tested for residual humidity.

9. Inactivation

For inactivated vaccines, a test to verify inactivation shall be carried out on the product in the final container unless it has been conducted at a late stage in-process.

F. BATCH-TO-BATCH CONSISTENCY

In order to ensure that quality of the product is consistent from batch to batch and

to demonstrate conformity with specifications a full protocol of three consecutive batches giving the results for all tests performed during production and on the finished product shall be provided.

G. STABILITY TESTS

The particulars and documents accompanying the application for marketing authorisation pursuant to regulation 12(3) hereof 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 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 or is administered in drinking water, 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.

Stability data obtained from combined products may be used as preliminary data for derivative products containing one or more of the same components.

The proposed in-use shelf life shall be justified.

The efficacy of any preservative system shall be demonstrated.

Information on the efficacy of preservatives in other similar immunological veterinary medicinal products from the same manufacturer may be sufficient.

H. OTHER INFORMATION

Information relating to the quality of the immunological veterinary medicinal product not covered by the previous sections may be included in the dossier.

PART 3: SAFETY TESTS

A. INTRODUCTION AND GENERAL REQUIREMENTS

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.

The safety studies shall be carried out in the target species. The dose to be used shall be the quantity of the product to be recommended for use and the batch used for safety testing shall be taken from a batch or batches produced according to the manufacturing process described in Part 2 of the application.

In the case of an immunological veterinary medicinal products containing a live organism, the dose to be used in the laboratory tests described in Sections B.1 and B.2 shall be the quantity of the product containing the maximum titre. If necessary

the concentration of the antigen may be adjusted to achieve the required dose. For inactivated vaccines the dose to be used shall be that quantity recommended for use containing the maximum antigen content unless justified.

The safety documentation shall be used for assessment of the potential risks which may result from the exposure of human beings to the veterinary medicinal product, for example during its administration to the animal.

B. 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.

This study may be part of the repeated dose study required under point 3 or omitted if the results of the overdose study required under point 2 have revealed no signs of systemic or local reactions.

2. Safety of one administration of an overdose

Only live immunological veterinary medicinal products require overdose testing.

An overdose of the immunological veterinary medicinal product shall be administered by each recommended route(s) of administration to animals of the most sensitive categories of the target species, unless the selection of the most sensitive of several similar routes is justified. In the case of immunological veterinary medicinal products administered by injection, the doses and route(s) of administration shall be chosen to take account of the maximum volume, which can be administered at any one single injection site. The animals shall be observed and examined for at least 14 days after administration for signs of systemic and local reactions. Other criteria shall be recorded, such as rectal temperature and performance measurements.

Where appropriate, these studies shall include detailed post-mortem macroscopic and microscopic examinations of the injection site if this has not been done under point 1.

3. Safety of the repeated administration of one dose

In the case of immunological veterinary medicinal products to be administered more than once, as part of the basic vaccination scheme, a study of the repeated administration of one dose shall 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 (such as certain breeds, age groups), using each 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 the most sensitive route 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 points 1, 2, 3 or of the field studies provided for in Section C.

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 animal 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 as appropriate. 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 zoonoses within the meaning of Directive 2003/99/EC of the European Parliament and of the Council* to be used for food producing animals, these studies must shall take particularly into account the persistence of the organism at the injection site.

6.3. Reversion to virulence of attenuated vaccines

Reversion to virulence shall be investigated with the master seed. If the master seed is not available in sufficient quantity the lowest passage seed used for the production shall be examined. Use of another passage option shall be justified. The initial vaccination shall be carried out using the route of administration most likely to lead to reversion to virulence. Serial passages shall be made in target animals through five groups of animals, unless there is justification to make more passages or the organism disappears from the test animals sooner. Where the organism fails to replicate adequately, as many passages as possible shall be carried out in the target species.

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. User safety

* OJ L 325, 12.12.2003, p. 31.

This section shall include a discussion of the effects found in the preceding sections, which shall relate those effects to the type and extent of human exposure to the product with a view to formulating appropriate user warnings and other risk management measures.

8. 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.

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.

9. Interactions

If there is a compatibility statement with other veterinary immunological products in the summary of product characteristics the safety of the association shall be investigated. Any other known interactions with veterinary medicinal products shall be described.

C. FIELD STUDIES

Unless justified, results from laboratory studies shall be supplemented with data from field studies, using batches according to the manufacturing process described in the marketing authorisation application. Both safety and efficacy may be investigated in the same field studies.

D. ENVIRONMENTAL RISK ASSESSMENT

The purpose of the environmental risk assessment 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.

This assessment shall normally be conducted in two phases. The first phase of the assessment shall always be performed. The details of the assessment shall be provided in accordance with established guidance. It shall indicate the potential exposure of the environment to the product and the level of risk associated with any such exposure, taking into account in particular the following items:

- the target animal species and the proposed pattern of use,
- the method of administration, in particular the likely extent to which the product will enter directly into the environmental system,
- the possible excretion of the product, its active substances into the environment by treated animals, persistence in such excreta,
- the disposal of unused or waste product.

In the case of live vaccine strains which may be zoonotic, the risk to humans shall be assessed.

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 risk(s) that the veterinary medicinal product might pose to the environment. Where necessary, further investigations on the impact of the product (soil, water, air, aquatic systems, non-target organisms) shall be carried out.

E. ASSESSMENT REQUIRED FOR VETERINARY MEDICINAL PRODUCTS CONTAINING OR CONSISTING OF GENETICALLY MODIFIED ORGANISMS

In the case of veterinary medicinal products containing or consisting of genetically modified organisms the application shall also be accompanied by the documents required under Article 2 and Part C of Directive 2001/18/EC.

PART 4: EFFICACY TESTS

CHAPTER I

1. General principles

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 authorisation.

2. Performance of trials

All efficacy trials shall be conducted in accordance with a fully considered detailed 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 organisation, conduct, data collection, documentation and verification of efficacy trials shall be required.

Field trials shall be conducted in accordance with established principles of good clinical practice, unless otherwise justified.

Before the commencement of any field 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 field trial is conducted with a blind design, the provisions of regulations 55, 56 and 57 shall apply by analogy to the labelling of formulations intended for use in veterinary field trials. In all cases, the words "for veterinary field trial use only" shall appear prominently and indelibly upon the labelling.

CHAPTER II

A. General requirements

1. The choice of antigens or 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 unless this is not justified for animal welfare reasons and efficacy can be otherwise demonstrated.

In general, these laboratory trials 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 controlled trials, carried out at the request of the competent authorities. The investigator shall demonstrate the validity of all the techniques involved.

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 target animal 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, if appropriate. Unless justified, the onset and duration of immunity shall be established and 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 veterinary immunological product to the efficacy of the scheme as a whole shall be demonstrated.

6. The dose to be used shall be the quantity of the product to be recommended for use and the batch used for efficacy testing shall be taken from a batch or batches produced according to the manufacturing process described in Part 2 of the application.

7. If there is a compatibility statement with other immunological products in the summary of product characteristics, the efficacy of the association shall be investigated. Any other known interactions with any other veterinary medicinal products shall be described. Concurrent or simultaneous use may be allowed if supported by appropriate studies.

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

9. For vaccines intended to allow a distinction between vaccinated and infected animals (marker vaccines), where the efficacy claim is reliant on *in vitro* diagnostic tests, sufficient data on the diagnostic tests shall be provided to allow adequate assessment of the claims related to the marker properties.

B. 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. Insofar as possible, the conditions under which the challenge is carried out shall mimic the natural conditions for infection. Details of the challenge strain and its relevance shall be provided.

For live vaccines, batches containing the minimum titre or potency shall be used unless justified. For other products, batches containing the minimum active content shall be used unless otherwise justified.

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.

C. Field trials

1. Unless justified, results from laboratory trials shall be supplemented with data from field trials, using batches representative of the manufacturing process described in the marketing authorisation application. Both safety and efficacy may be investigated in the same field study.

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

PART 5: PARTICULARS AND DOCUMENTS

A. INTRODUCTION

The dossier of the safety and efficacy studies shall include an introduction defining the subject and indicating the tests which have been carried out in compliance with Parts 3 and 4 as well as a summary, with detailed references to the published literature. This summary 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. Omission of any tests or trials listed 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 or breed 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 and a justification of the statistical methods used;
4. in the case of control animals, whether they received a placebo or no treatment;
5. in the case of treated animals and where appropriate, whether they received the test product or another product authorised in the Community;
6. 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;
7. the nature, frequency and duration of observed adverse reactions;
8. the number of animals withdrawn prematurely from the studies and reasons for such withdrawal;
9. a statistical analysis of the results, where such is called for by the test programme, and variance within the data;
10. occurrence and course of any intercurrent disease;
11. all details concerning veterinary medicinal products (other than the product under study), the administration of which was necessary during the course of the study;
12. 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, identity code that can be linked to the 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. effects on the animals' 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 veterinary 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.

PART 6: BIBLIOGRAPHICAL REFERENCES

The bibliographical references cited in the summary mentioned under Part 1 shall be listed in detail and copies shall be provided.

TITLE III

REQUIREMENTS FOR SPECIFIC MARKETING AUTHORISATION APPLICATIONS

1. Generic veterinary medicinal products

Applications based on regulation 13 hereof (generic veterinary medicinal products) shall contain the data referred to in Parts 1 and 2 of Title I of this Schedule together with an environmental risk assessment and data demonstrating that the product has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product and data showing bio-equivalence with the reference medicinal product. If the reference veterinary medicinal product is a biological medicinal product, the documentation requirements in Section 2 for similar biological veterinary medicinal products shall be fulfilled.

For generic veterinary medicinal products the detailed and critical summaries on safety and efficacy shall particularly focus on the following elements:

- the grounds for claiming essential similarity,
- a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed together with an evaluation of these impurities,
- an evaluation of the bio-equivalence studies or a justification as to why studies were not performed with reference to established guidance,
- if applicable, additional data in order to demonstrate the equivalence of safety and efficacy properties of different salts, esters or derivatives of an authorised active substance shall be provided by the applicant; those data shall include evidence that there is no change in the pharmacokinetic or pharmacodynamic properties of the therapeutic moiety and/or in toxicity, which could influence the safety/efficacy profile.

Every claim in the summary of product characteristics not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non-clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.

For generic veterinary medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes, the following additional data shall be provided:

- evidence to demonstrate equivalent or differing depletion of residues from the administration site, which may be substantiated by appropriate residue depletion studies,
- evidence to demonstrate target animal tolerance at the administration site, which may be substantiated by appropriate target animal tolerance studies.

2. Similar biological veterinary medicinal products

In accordance with regulation 13(4), where a biological veterinary medicinal product which is similar to a reference biological veterinary medicinal product does not meet the conditions in the definition of generic medicinal product, information to be supplied shall not be limited to Parts 1 and 2 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bioavailability data. In such cases, additional data shall be provided, in particular on the safety and efficacy of the product.

- The type and amount of additional data (i.e. toxicological and other

safety studies and appropriate clinical studies) shall be determined on a case-by-case basis in accordance with relevant scientific guidelines.

- Due to the diversity of biological veterinary medicinal products, the competent authority shall determine the necessary studies foreseen in Parts 3 and 4, taking into account the specific characteristic of each individual biological veterinary medicinal product.

The general principles to be applied shall be addressed in guideline which shall be adopted by the Agency, taking into account the characteristics of the concerned biological veterinary medicinal product. If the reference biological veterinary medicinal product has more than one indication, the efficacy and safety of the biological veterinary medicinal product claimed to be similar shall be justified or, if necessary, demonstrated separately for each of the claimed indications.

3. Well-established veterinary use

For veterinary medicinal products the active substance(s) of which has/have been in "well-established veterinary use" as referred to in regulation 13A(1), with recognised efficacy and an acceptable level of safety, the following specific rules shall apply.

The applicant shall submit Parts 1 and 2 as described in Title I of this Schedule.

For Parts 3 and 4, a detailed scientific bibliography shall address all aspects of the safety and efficacy.

The following specific rules shall apply in order to demonstrate the well-established veterinary use:

3.1. The following factors shall be taken into account in order to establish a well-established veterinary medicinal use of constituents of veterinary medicinal products:

(*a*) the time over which an active substance has been used;

(*b*) quantitative aspects of the use of the active substance;

(*c*) the degree of scientific interest in the use of the active substance (reflected in the published scientific literature);

(*d*) the coherence of scientific assessments.

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 veterinary use of a constituent of a medicinal product shall not be less than ten years from the first systematic and documented use of that substance as a veterinary medicinal product in the Community.

3.2. The documentation submitted by the applicant shall cover all aspects of the safety and/or efficacy assessment of the product for the proposed indication in the target species using the proposed route of administration and dosage regimen. It must include or refer to a review of the relevant literature, taking into account pre- and post-marketing 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, shall be communicated. With respect to the provisions on well-established veterinary use, it is in particular necessary to clarify that bibliographic reference to other sources of evidence (post-marketing studies, epidemiological studies etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.

3.3. Particular attention must be paid to any missing information and justification must be given as to why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking.

3.4. The detailed and critical summaries regarding safety and efficacy must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether or not the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences.

3.5. Post-marketing experience with other products containing the same constituents is of particular importance and applicants shall put a special emphasis on this issue.

4. Combination veterinary medicinal products

For applications based on regulation 13B of these regulations, a dossier containing Parts 1, 2, 3 and 4 shall be provided for the combination veterinary medicinal product. It shall not be necessary to provide studies on the safety and efficacy of each active substance. It shall nevertheless be possible to include information on the individual substances in the application for a fixed combination. The submission of data on each individual active substance, in conjunction with the required user safety studies, residues depletion studies and clinical studies on the fixed combination product, may be considered a suitable justification for omitting data on the combination product, based on animal welfare grounds and unnecessary testing on animals, unless there is suspected interaction leading to added toxicity. Where applicable, information regarding the manufacturing sites and the safety evaluation of adventitious agents shall be provided.

5. Informed consent applications

Applications based on regulation 13C hereof shall contain the data described in Part 1 of Title 1 of this Schedule, provided that the marketing authorisation holder for the original veterinary medicinal product has given the applicant his consent to refer to the content of Parts 2, 3 and 4 of the dossier of that product. In this case, there is no need to submit quality, safety and efficacy detailed and critical summaries.

6. Documentation for applications in exceptional circumstances

A marketing authorisation may be granted subject to certain specific obligations requiring the applicant to introduce specific procedures, in particular concerning the safety and efficacy of the veterinary medicinal product, when, as provided for in regulation 26(2) of these regulations, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use.

The identification of essential requirements for all applications mentioned in this section should be subject to guidelines which shall be adopted by the Agency.

7. Mixed marketing authorisation applications

Mixed marketing authorisation applications are applications where Part(s) 3 and/or 4 of the dossier consist of safety and efficacy studies carried out by the applicant as well as bibliographical references. All other part(s) are in accordance with the structure described in Part I of Title I of this Schedule. The competent authority shall accept the proposed format presented by the applicant on a case-by-case basis.

TITLE IV

REQUIREMENTS FOR MARKETING AUTHORISATION APPLICATIONS

FOR PARTICULAR VETERINARY MEDICINAL PRODUCTS

This part lays down specific requirements for identified veterinary medicinal products related to the nature of the active substances contained therein.

1. IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

A. VACCINE ANTIGEN MASTER FILE

For particular immunological veterinary medicinal products and by derogation from the provisions of Title II, Part 2 Section C on active substances, the concept of a Vaccine Antigen Master File is introduced.

For the purpose of this Schedule, a Vaccine Antigen Master File means a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information on quality concerning each of the active substances, which are part of this veterinary medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.

Scientific guidelines for the submission and evaluation of a vaccine antigen master file shall be adopted by the Agency. The procedure for the submission and evaluation of a vaccine antigen master file shall follow the guidance published by the Commission in The rules governing medicinal products in the European Union, Volume 6B, Notice to Applicants.

B. MULTI-STRAIN DOSSIER

For certain immunological veterinary medicinal products (foot-and-mouth disease, avian influenza and bluetongue) and by derogation from the provisions of Title II, Part 2 Section C on active substances the concept of the use of a multi-strain dossier is introduced.

A multi-strain dossier means a single dossier containing the relevant data for a unique and thorough scientific assessment of the different options of strains/combinations of strains permitting the authorisation of vaccines against antigenically variable viruses.

Scientific guidelines for the submission and evaluation of multi-strain dossiers shall be adopted by the Agency. The procedure for the submission and evaluation of multi-strain dossiers shall follow the guidance published by the Commission in The rules governing medicinal products in the European Union, Volume 6B, Notice to Applicants.

2. HOMEOPATHIC VETERINARY MEDICINAL PRODUCTS

This section sets out specific provisions on the application of Title I, Parts 2 and 3 to homeopathic veterinary medicinal products as defined in regulation 2(8).

Part 2

The provisions of Part 2 shall apply to the documents submitted in accordance with regulation 18 in the simplified registration of homeopathic veterinary medicinal products referred to in regulation 17(1) as well as to the documents for authorisation of other homeopathic veterinary medicinal products referred to in regulation 19(1) with the following modifications.

(*a*) Terminology

The Latin name of the homeopathic stock described in the marketing authorisation application dossier shall be in accordance with the Latin title of the European Pharmacopoeia or, in absence thereof, of an official pharmacopoeia of Malta. Where relevant the traditional name(s) used in each Member State shall be provided.

(*b*) Control of starting materials

The particulars and documents on the starting materials, i.e. all of the materials used including raw materials and intermediates up to the final dilution to be incorporated into the finished homeopathic veterinary medicinal product, accompanying the application shall be supplemented by additional data on the homeopathic stock.

The general quality requirements shall apply to all of the starting and raw materials as well as intermediate steps of the manufacturing process up to the final dilution to be incorporated into the finished homeopathic product. Where a toxic component is present, this should be controlled if possible in the final dilution. However, if this is not possible because of the high dilution, the toxic component shall normally be controlled at an earlier stage. Every step of the manufacturing process from the starting materials up to the final dilution to be incorporated into the finished product must be fully described.

In case dilutions are involved, these dilution steps shall be done in accordance with the homeopathic manufacturing methods laid down in the relevant monograph of the European Pharmacopoeia or, in absence thereof, in an official pharmacopoeia of Malta.

(*c*) Control tests on the finished medicinal product

The general quality requirements shall apply to the homeopathic finished veterinary medicinal products. Any exception shall be duly justified by the applicant.

Identification and assay of all the toxicologically relevant constituents shall be carried out. If it can be justified that identification and/or an assay on all the toxicologically relevant constituents is not possible e.g. due to their dilution in the finished medicinal product the quality shall be demonstrated by complete validation of the manufacturing and dilution process.

(*d*) Stability tests

The stability of the finished product shall be demonstrated. Stability data from the homeopathic stocks are generally transferable to dilutions/potentisations obtained thereof. If no identification or assay of the active substance is possible due to the degree of dilution, stability data of the pharmaceutical form may be considered.

Part 3

The provisions of Part 3 shall apply to the simplified registration of homeopathic veterinary medicinal products referred to in regulation 17(1) with the following specification, without prejudice to the provisions of Regulation (EEC) No 2377/90 for substances included in the homeopathic stocks intended for administration to food-producing animal species.

Any missing information must be justified, e.g. justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking.