Pursuant to Article 9, paragraph 5, Article 11, paragraph 5, Article 23, paragraph 5, Article 24, paragraph 5, Article 25, paragraph 2, Article 27, paragraph 3, Article 30, paragraph 3, Article 32, paragraph 4, Article 33, paragraph 5, Article 35, paragraph 2, Article 40, paragraph 7, Article 48, paragraph 5, Article 52, paragraph 5, Article 56, paragraph 8, Article 55, paragraph 8, Article 62, paragraph 9, Article 64, paragraph 3 and Article 67, paragraph 3 of the Act on Veterinary Medicinal Products (Official Gazette 84/08), the Minister of Agriculture, Fisheries and Rural Development hereby issues the

ORDINANCE

ON VETERINARY MEDICINAL PRODUCTS[1]

Title I
SCOPE OF APPLICATION

Article 1

This Ordinance lays down the procedure for issuing authorisations for marketing of veterinary medicinal products and manufacture of veterinary medicinal products, labelling of veterinary medicinal products, wholesale and retail sale of veterinary medicinal products, pharmacovigilance, surveillance of veterinary medicinal products and testing and quality control of veterinary medicinal products.

Article 2

1) This Ordinance shall apply to veterinary medicinal products, including pre-mixes for medicated feeedingstuffs, intended to be placed on the market, and prepared industrially or by a method involving an industrial process.

2) 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 special legislation, the provisions of this Ordinance shall apply.

3) Notwithstanding paragraph 1 of this Article, this Ordinance shall also apply to active substances used as starting materials to the extent set out in Articles 46, 47 and 75 of this Ordinance, 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 Article 64 of this Ordinance.

Article 3

1) This Ordinance shall not apply to:

(a) medicated feedingstuffs, as defined in the Ordinance on the conditions governing the preparation, placing on the market and use of medicated feedingstuffs (Official Gazette 101/05)[2];

(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 the Ordinance on additives for use in animal nutrition (Official Gazette 09/07) and the Ordinance on the circulation of feed materials and compound feedingstuffs (Official Gazette 112/08)[3], where they are incorporated in animal feedingstuffs and supplementary animal feedingstuffs in accordance with the above mentioned ordinances;

(e) without prejudice to Article 88 of this Ordinance medicinal products for veterinary use intended for research and development trials.

2) Medicated feedingstuffs referred to in paragraph 1, item (a) of this Article may be prepared only from pre-mixes that have been authorised under this Ordinance.

3) Except for the provisions on the possession, prescription, dispensing and administration of veterinary medicinal products, this Ordinance 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.

Title II
DEFINITIONS

Article 4

For the purposes of this Ordinance, definitions from Article 2, items 12, 14, 16 to 18, 22 to 25, 27 to 30, 33, 40, and 44 to 54 of the Act on Veterinary Medicinal Products (Official Gazette 84/08) shall apply, as well as the following definitions:

1. *Post-marketing surveillance study* – 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;

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

– the supply by a manufacturer of veterinary medicinal products manufactured by himself;

– retail supplies of veterinary medicinal products by persons entitled to carry out such supplies in accordance with Article 62 of this Ordinance;

3. *Representative of a marketing authorisation holder* – the person, commonly known as local representative, designated by the marketing authorisation holder to represent him in the Republic of Croatia;

4. *Reference medicinal product* – a product authorised within the meaning of Article 5 of this Ordinance, and in accordance with Article 12 of this Ordinance;

5. *Generic veterinary medicinal products* – a veterinary medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference veterinary medicinal product, and whose bioequivalence with the reference veterinary 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 need not 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;

6. *Competent authority* – the Ministry of Agriculture, Fisheries and Rural Development;

7. *Third country* – a country that is not a Member State of the European Union.

Title III
MARKETING

Chapter 1
MARKETING AUTHORISATION

Article 5

1) No veterinary medicinal product may be placed on the market unless a marketing authorisation has been granted in accordance with Article 9, paragraph 1, items 1 and 2 of the Act on Veterinary Medicinal Products.

2) When a veterinary medicinal product has been granted an initial authorisation in accordance with paragraph 1 of this Article, 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 paragraph 1 of this Article o 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 Article 13, paragraph 1 of this Ordinance.

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

Article 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 of the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin (Official Gazette75/08)[4].

2) If an amendment to the Annex to the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin5 so warrants, the marketing authorisation holder or, where appropriate, the competent authorities shall take all necessary measures to amend or revoke the marketing authorisation within 60 days of the date on which the amendment was published.

3) By way of derogation from the provision of paragraph 1 of this Article, a veterinary medicinal product containing pharmacologically active substances not included in Annexes I, II or III of the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin6, authorised for particular animals of the equidae family that are not intended for slaughter for human consumption in accordance with the Ordinance on identification and registration of equidae (Official Gazette 74/07)[5]7 and a special regulation[6]8. Such veterinary medicinal product shall neither include active substances that appear in Annex IV to the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin [7]9, 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 authorised for animals of the equidae family.

Article 7

Where the health situation so requires, the competent authority may, in accordance with the provisions of this Ordinance, authorise the marketing or administration to animals of veterinary medicinal products which have been authorised by a member state of the European Union (hereinafter: Member State).

Article 8

1) In the event of serious disease epidemic, the competent authority may provisionally allow the use of immunological veterinary medicinal products without an authorisation for placing on the market, in the absence of a suitable medicinal product.

2) In case of acting in accordance with paragraph 1 of this Article, the competent authority shall notify in advance the European Commission on detailed conditions for use.

3) If an animal is being imported from, or exported to, a third country and is thereby subject to specific binding health rules, the competent authority may permit the use, for the animal in question, of an immunological veterinary medicinal product that is not covered by a marketing authorisation in the Republic of Croatia, but is authorised under the legislation of

the third country. The competent authority shall take all appropriate measures concerning the supervision of the importation and the use of such immunological products.

Article 9

No veterinary medicinal product may be administered to animals unless the marketing authorisation has been issued, following notification or authorisation, in accordance with rules in force, except for the tests carried out for the purpose of issuing the marketing authorisation referred to in Article 12, paragraph 4, item (j) of this Ordinance.

Article 10

1) If there is no authorised veterinary medicinal product in the Republic of Croatia for a condition affecting a non food-producing species, by way of exception, the competent authority may, under the direct personal responsibility of a veterinarian and in particular to avoid causing unacceptable suffering, approve treating the animal concerned with:

(a) a veterinary medicinal product authorised in the Member State concerned for use with another animal species, or for another condition in the same species; or

(b) if it is not possible to act in accordance with item (a) of this paragraph:

– a medicinal product authorised for human use in accordance with the Ordinance on the procedure and the manner of issuing marketing authorisations for medicinal products (Official Gazette 113/08)[8]10 or in accordance with a special regulation [9]11, or

– of a veterinary medicinal product authorised in the Member State for use with another animal species, or for another condition in the same species; or

(c) if it is not possible to act in accordance with item (b) of this paragraph, and in accordance with the rules in force, of a veterinary medicinal product prepared extemporaneously by a person authorised to do so, in accordance with the terms of a veterinary prescription.

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

3) By way of derogation from Article 11 of this Ordinance, the provisions of paragraph 1 of this Article shall also apply to the treatment by a veterinarian of an animal belonging to the equidae family provided that it has been declared as not being intended for slaughter for human consumption in accordance with the Ordinance on identification and registration of equidae (Official Gazette 74/07)[10]12 and a special regulation[11]13.

Article 11

1) By way of exception, if in the Republic of Croatia there is no authorised medicinal product for a condition affecting a food-producing species, by way of exception, the competent authority may, under the direct personal responsibility of a veterinarian and in particular to avoid causing unacceptable suffering, approve treating the animal concerned with:

(a) a veterinary medicinal product authorised in accordance with provisions of this Ordinance or in accordance with a special regulation14 for use with another animal species, or for another condition in the same species; or

(b) if it is not possible to act in accordance with item (a) of this paragraph:

– of a medicinal product for human use authorised in accordance with the Ordinance on the procedure and the manner of issuing marketing authorisations for medicinal products [12]15 or in accordance with a special regulation [13]16, or

– of a veterinary medicinal product authorised in the Member State for use in the same or another animal species, or for another condition in the same species; or

(c) if it is not possible to act in accordance with item (b) of this paragraph, and in accordance with the rules in force, a veterinary medicinal product prepared extemporaneously by a person authorised to do so, in accordance with the terms of a veterinary prescription.

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

3) Paragraph 1 of this Article shall apply provided that pharmacologically active principles included in the medicinal product are listed in Annex I, II or III of the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin [14]17, and that the veterinarian specifies an appropriate withdrawal period.

4) 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 of poultry and mammals, including fat and offal

– 500 degree-days for fish meat.

5) With regard to homeopathic veterinary medicinal products in which active principles figure in Annex II to the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin [15]18, the withdrawal period referred to paragraph 4 of this Article shall be reduced to zero.

6) When a veterinarian has recourse to the provisions of 1 to 4 of this Article, 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 dose administered,

– the duration of treatment, and

– the withdrawal periods recommended.

7) These records shall be made available for inspection by the competent authorities for a period of at least five years.

8) Without prejudice to the other provisions of this Ordinance, the competent authority shall take all necessary measures concerning the import, distribution, dispensing of and information on the medicinal products in accordance with paragraph 1, item (b), the second indent of this Article.

9) For issuing authorisations referred to in Article 10, paragraph 1 of this Ordinance and paragraph 1 of this Article the competent authority may ask an opinion of the Commission for Veterinary Medical Products and additional documentation of importance for the evaluation of the quality, safety or efficacy of the veterinary medicinal product concerned.

Article 12

1) The application for marketing authorisation shall be submitted to the competent authority, except in case of acting in accordance with a special regulation[16]19.

2) 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, Annex I, II or III of the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin [17]20, 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 the above mentioned Ordinance. At least six months shall elapse between a valid application for the establishment of maximum residue limits and an application for a marketing authorisation.

3) However, in the case of veterinary medicinal products referred to in paragraph 2 of this Article, for veterinary medicinal products referred to in Article 6, paragraph 3 of this Ordinance, a marketing authorisation may be applied for without a valid application for determination of maximum residue limits in accordance with the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin [18]21. In that case, all scientific documentation necessary for the demonstration of the quality, safety or efficacy of the veterinary medicinal product concerned shall be submitted in accordance with paragraph 4 of this Article.

4) 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 Annex to this Ordinance 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 the veterinary medicinal product;

(c) qualitative and quantitative particulars of all the constituents of the veterinary medicinal product, including its international nonproprietary name (hereinafter: INN*)* recommended by the World Health Organisation, 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) explanations of the precautionary and safety measures to be taken when the product is stored, when it is administered to animals and when waste therefrom is disposed of, together with an indication of any potential risks the medicinal product might pose to the environment and the health of humans, animals or plants;

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

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

(j) results of:

– pharmacological (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 Article 18 of this Ordinance, 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 Articles 54 to 57 of this Ordinance;

(m) a document showing that the manufacturer is authorised 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 this Ordinance[19]*, is under examination. Copies of the summary of the product characteristics proposed by the applicant in accordance with Article 18 of this Ordinance or approved by the competent authority of the Member State in accordance with Article 29 of this Ordinance[20]** and copies of the package insert proposed, details of any decision to refuse authorisation, whether in the 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 Republic of Croatia, in the European Union 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 of the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin[21]22, a document certifying that a valid application for the establishment of maximum residue limits has been submitted in accordance with the abovementioned Ordinance.

5) The documents and particulars relating to the results of the tests referred to in paragraph 4, item (j) of this Article, shall be accompanied by detailed and critical summaries, drawn up as specified in Article 19 of this Ordinance.

Article 13

1) By way of derogation from Article 12, paragraph 4, item (j), the first indent of this Ordinance 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 in the Republic of Croatia or the European Union is or has been authorised pursuant to Article 5 of this Ordinance, for not less eight years.

2) A generic veterinary medicinal product shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product. The ten-year period may be extended to 13 years in case of veterinary medicinal products intended for fish or bees or other species of animals.

3) Paragraph 1 of this Article shall also apply when the application for the generic veterinary medicinal product is submitted and the reference medicinal product was not authorised in the Republic of Croatia. In this case, the applicant shall indicate in the application the Member State in which the reference medicinal product is or has been authorised.

4) The competent authority shall request from the competent authority of the Member State the confirmation that the reference medicinal product is or has been authorised, together with the full composition of the reference product and if necessary other relevant documentation.

5) In cases where the veterinary medicinal product does not fall under the definition of a generic medicinal product set out in paragraph 4, item 5 of this Ordinance, 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.

6) 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 Annex to this Ordinance and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.

7) 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 before entry into force of this Ordinance, the ten-year period provided for in paragraph 2 of this Article 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 13 years, for a marketing authorisation for four or more food-producing species.

The extension of the ten-year period to 11, 12, or 13 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.

8) Conducting the necessary studies, tests and trials with a view to the application of paragraphs 1 to 7 of this Article, shall not be regarded as contrary to patent-related rights or to supplementary-protection certificates for medicinal products.

Article 14

1) By way of derogation from Article 12, paragraph 4, item (j), the first indent of this Ordinance 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 Union for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex to this Ordinance. In that event, the applicant shall provide appropriate scientific literature.

2) The assessment report published by EMEA, following the evaluation of an application for the establishment of maximum residue limits in accordance with the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin[22]*** may be

used in an appropriate manner as literature from paragraph 1 of this Article, 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 the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin [23]23 together with further clinical trials, it shall not be permissible for a third party to use such studies or such trials pursuant to Article 13 of this Ordinance for a period of three years from the grant of the authorisation for which they were carried out.

Article 15

In the case of veterinary medicinal products containing active substances used in the composition of authorised 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 Article 12, paragraph 4, item (j), the first indent of this Ordinance, but it shall not be necessary to provide scientific references relating to each individual active substance.

Article 16

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.

Article 17

By way of derogation from Article 12, paragraph 4, item (j), the first indent of this Ordinance 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 special regulations.

Article 18

1) 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:

4.1. target species,

4.2. indications for use, specifying the target species,

4.3. contra-indications,

4.4. special warnings for each target species,

4.5. special precautions for use, including special precautions to be taken by the person administering the medicinal product to the animals,

4.6. adverse reactions (frequency and seriousness),

4.7. use during pregnancy and lactation or lay,

4.8. interaction with other medicinal products and other forms of interaction,

4.9. amounts to be administered and administration route,

4.10. overdose (symptoms, emergency procedures, antidotes) (if necessary),

4.11. withdrawal periods for the various foodstuffs, including those for which the withdrawal period is zero;

5. pharmacological particulars:

5.1. pharmacodynamic properties,

5.2. pharmacokinetic particulars;

6. pharmaceutical particulars:

6.1. list of excipients,

6.2. major incompatibilities,

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

6.4. special precautions for storage,

6.5. nature and contents of immediate packaging,

6.6. special precautions for the disposal of unused medicinal product 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.

2) For authorisation under Article 13 of this Ordinance those parts of the summary of product characteristics of the reference medicinal product referring to indications or dosage forms which were still covered by a special patent protection regulation need not be included.

Article 19

1) Applicants shall ensure that the detailed and critical summaries referred to in Article 12, paragraph 5 of this Ordinance, 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 competent authorities,

2) Persons with the technical or professional qualifications referred to in paragraph 1 of this Article shall justify any use made of the scientific literature referred to in Article 14, paragraph 1 of this Ordinance, in accordance with the conditions set out in Annex to this Ordinance.

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

Chapter 2
PARTICULAR PROVISIONS APPLICABLE TO HOMEOPATHIC VETERINARY MEDICINAL PRODUCTS

Article 20

1) Homeopathic veterinary medicinal products manufactured and placed on the market shall be registered or authorised in accordance with the provisions of Articles 21 to 23 of this Ordinance. In the case of homeopathic medicinal products registered in accordance with Article 21 of this Ordinance, Article 36 and Article 37, paragraph 1 and 2 of this Ordinance shall apply.

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

3) By way of derogation from Article 11, paragraph 1 to 5 of this Ordinance, homeopathic veterinary medicinal products may be administered to food producing species the active constituents of which appear in Annex II of the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin [24] under the responsibility of a veterinarian.

4) The competent authority shall take appropriate measures to control the use of veterinary homeopathic medicinal products registered or authorised in Member States in accordance with the provisions of this Ordinance[25]*, for use in the same species.

Article 21

1) Without prejudice to the provisions of the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin 25, only homeopathic veterinary medicinal products which satisfy all of the following conditions may be subject to authorisation by means of a special, simplified registration procedure:

(a) they are administered by a route described in the European Pharmacopoeia or, in absence thereof, by the pharmacopoeias currently used officially in the Republic of Croatia or in the Member States;

(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 may not contain more than one part per 10000 of the mother tincture.

2) If it appears justified in the light of new scientific evidence, provisions of paragraph 1, items (b) and (c) of this Article may be adapted. At the time of registration, the classification for the dispensing of the medicinal product shall be determined.

3) The criteria and rules of procedure provided for in Chapter 3 of this Title, with the exception of Article 29, shall apply by analogy to the special, simplified registration procedure for homeopathic veterinary medicinal products, with the exception of the proof of therapeutic effect.

Article 22

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

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

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

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

– manufacturing authorisation for the medicinal products concerned,

– copies of any authorisations obtained for the same medicinal products in the Republic of Croatia or in the Member States,

– one or more mock-ups of the outer packaging and immediate packaging of the medicinal product,

– data concerning the stability of the medicinal product,

– proposed withdrawal period together with all requisite justification.

Article 23

Homeopathic veterinary medicinal products other than those referred to in Article 21, paragraphs 1 and 2 of this Ordinance shall be authorised in accordance with Articles 12, 14, 15, 16, 17 and 18 of this Ordinance.

Article 24

1) The provisions of his Chapter shall not apply to immunological homeopathic veterinary medicinal products.

2) The provisions of Titles VI and VII of this Ordinance shall apply to homeopathic veterinary medicinal products.

Chapter 3
PROCEDURE FOR MARKETING AUTHORISATION

Article 25

1) The procedure for granting an authorisation to place a veterinary medicinal product on the market shall be completed within 210 days of the submission of a valid application.

2) Applications for marketing authorisations for the same veterinary medicinal product in two or more Member States, shall be submitted in accordance with Chapter 4 of this Title.

3) In the case referred to in paragraph 2 of this Article the competent authority shall decline to assess the application and shall advise the applicant thereof.

Article 26

Where the competent authority is informed that a Member State has authorised a veterinary medicinal product in accordance with Article 12, paragraph 4, item (n) of this Ordinance, shall reject the application unless it was submitted in compliance with Chapter 4 of this Title.

Article 27

In order to examine the application submitted pursuant to Articles 12 to 17 of this Ordinance, the competent authority:

1. shall check that the documentation submitted in support of the application complies with Articles 12. – 17 of this Ordinance 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 a laboratory designated for that purpose, in order to ensure that the testing methods employed by the manufacturer and described in the application documents, in accordance with Article 12, paragraph 4., item (i) of this Ordinance, are satisfactory;

3. may similarly check, in particular through consultation of a national or Community reference laboratory, that the analytical method used for detecting residues presented by the applicant for the purposes of Article 12, paragraph 4, item (j), the second indent of this Ordinance is satisfactory;

4. may, where appropriate, require the applicant to provide further information as regards the items listed in Articles 12 to 17 of this Ordinance. Where the competent authorities take this course of action, the time-limits specified in Article 25 of this Ordinance 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.

Article 28

The competent authority shall take all appropriate measures to ensure that:

(a) the manufacturers and importers of veterinary medicinal products from third countries are able to manufacture them in compliance with the details supplied pursuant to Article 12, paragraph 4, item (d) of this Ordinance and/or to carry out control tests in accordance with the methods described in the application documents under Article 12, paragraph 4, item (i) of this Ordinance.

(b) 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 item (a) of this Article; in such cases, checks by the competent authorities shall also be carried out in the establishments concerned.

Article 29

1) When granting a marketing authorisation, the competent authority shall inform the holder of the summary of product characteristics that it has approved.

2) Information concerning the veterinary medicinal product, and in particular the labelling and package leaflet shall be in conformity with the summary of product characteristics approved when the marketing authorisation was granted or subsequently.

3) The competent authority 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 competent authority 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.

5) The competent authority may authorise a legal person to perform the activities referred to in paragraph 4 of this Article.

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

Article 30

1) The marketing authorisation may require the holder to indicate on the container and/or the outer wrapping and the package insert, where the latter is required, other particulars essential for safety or health protection, including any special precautions relating to use and any other warnings resulting from the clinical and pharmacological trials prescribed in Articles 12, paragraph 4, items (j) and 13 to 17 of this Ordinance 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 authorisation 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 authorisation shall be linked to the annual reassessment of these conditions.

Article 31

1) After a marketing authorisation has been issued, the holder must, in respect of the manufacturing methods and control methods provided for in Article 12, paragraph 4, items (d) and (i) of this Ordinance take account of scientific and technical progress and introduce any changes that may be required to enable that veterinary medicinal product to be manufactured and checked by means of generally accepted scientific methods. These changes shall be subject to the approval of the competent authority.

2) The competent authority 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.

3) At the competent authority's 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 the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin (Official Gazette 79/08)2[26]6.

4) The authorisation holder shall immediately supply the competent authority with any new information that might entail the amendment of the particulars or documents referred to in Article 12, paragraph 4, Articles 13, 14, 15, and 18 and/or of Annex to this Ordinance.

In particular, he shall immediately inform the competent authority 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 competent authority may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable.

5) The marketing authorisation holder shall immediately inform the competent authorities, with a view to authorisation, of any alteration which he proposes to make to the particulars or documents referred to in Articles 12 to 17 of this Ordinance.

Article 32

1) After a marketing authorisation has been granted, the holder of the authorisation shall inform the competent authority of the date of the actual placing on the market of the veterinary medicinal product, taking into account the various presentations authorised.

2) The holder shall also notify the competent authority if the product ceases to be placed on the market, 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.

3) Upon request by the competent authority, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the competent authority 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.

Article 33

1) Without prejudice to paragraphs 4 and 5 of this Article, 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 authorisation was granted, at least six months before the marketing authorisation ceases to be valid in accordance with paragraph 1 of this Article. The competent authority 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 competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal in accordance with paragraph 2 of this Article.

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 shall cease to be valid.

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

6) The competent authority may, in exceptional circumstances, and on human or animal health grounds, grant exemptions from paragraphs 4 and 5 of this Article. Such exemptions shall be duly justified.

Article 34

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

Article 35

1) The marketing authorisation shall be refused if the file submitted to the competent authorities does not comply with Articles 12 to 17 and Article 19 of this Ordinance.

2) The authorisation shall also be refused if, after examination of the documents and particulars listed in Articles 12 and 13, paragraph 1 of this Ordinance 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 this Ordinance; or

(f) the veterinary medicinal product is offered for sale for a use prohibited under provisions of special regulations.

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

Chapter 4
MUTUAL RECOGNITION OF AUTHORISATION AND DECENTRALISED PROCEDURE

Article 36

1) With a view to the granting of a marketing authorisation 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 Articles 12 to 18 of this Ordinance. 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 paragraphs 2 or 3 of this Article.

Where appropriate, the assessment report shall contain an evaluation for the purposes of Article 13, paragraph 7 or Article 14, paragraph 3 of this Ordinance.

2) If the veterinary medicinal product has already received a marketing authorisation at the time of application, the concerned Member States shall recognise the marketing authorisation granted by the reference Member State. To this end, the marketing authorisation 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 90 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 120 days of the receipt of a valid application and shall send them to the concerned Member States and the applicant.

4) Within 90 days after receipt of the documents referred to in paragraphs 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 of this Article has been submitted shall adopt a decision in conformity with the approved assessment report, summary of product characteristics, labelling and package leaflet within 30 days after acknowledgement of the agreement.

Article 37

1) If a Member State cannot, within the period allowed in Article 36, paragraph 4 of this Ordinance 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 EMEA. If a Member State to which an application has been submitted invokes the reasons referred to in Article 71, paragraph 1 of

this Ordinance[27]* it shall no longer be regarded as a Member State concerned by this Chapter.

2) If, within 60 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. Article 36, paragraph 5 of this Ordinance shall apply.

3) If within the period of 60 days the Member States fail to reach an agreement referred to in paragraph 2 of this Article, EMEA shall be immediately informed with a view to application of the procedure.

4) In the case referred to in paragraph 3 of this Article, 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 carried out by EMEA. In that case, the authorisation granted shall be without prejudice to the outcome of that procedure.

Article 38

If two or more applications submitted in accordance with Articles 12 to 18 of this Ordinance 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 EMEA shall carry out a special procedure.

Article 39

1) The provisions of Article 37, paragraphs 3 and 4 and Article 38 of this Ordinance shall not apply to homeopathic veterinary medicinal products referred to in Article 21 of this Ordinance.

2) The provisions of Articles 36 to 38 of this Ordinance shall not apply to homeopathic veterinary medicinal products referred to in Article 23 of this Ordinance.

Title IV
MANUFACTURE AND IMPORTS

Article 40

1) The manufacture of veterinary medicinal products shall be subject to the holding of an authorisation issued by the competent authority. This manufacturing authorisation shall likewise be required for veterinary medicinal products intended for export.

2) The authorisation referred to in paragraph 1 of this Article 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 authorised persons in dispensing pharmacies.

3) The authorisation referred to in paragraph 1 of this Article shall also be required for imports from third countries; this Chapter and Article 78 of this Ordinance, shall apply to such imports in the same way as to manufacture.

4) Veterinary medicinal products brought into the territory of the Republic of Croatia from a third country and destined for Member States, shall be accompanied by a copy of the authorisation referred to in paragraph 1 of this Article.

5) The competent authority shall submit to EMEA the information on issued authorisations referred to in paragraph 1 of this Article.

Article 41

1) 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 laid down as regards both manufacture and control and the storage of products, in accordance with Article 24 of this Ordinance;

(c) he shall have at his disposal the services of at least one qualified person within the meaning of Article 48 of this Ordinance.

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

Article 42

1) The competent authority shall not issue manufacturing authorisation for a veterinary medicinal product after establishing requirements from Article 41 of this Ordinance.

2) Manufacturing authorisation for a veterinary medicinal product 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.

Article 43

The time taken for the procedure for granting the manufacturing authorisation shall not exceed 90 days from the day on which the competent authority receives the application.

Article 44

If the holder of the manufacturing authorisation requests a change in any of the particulars referred to in Article 41, paragraph 1, items (a) and (b) of this Ordinance, the time taken for the procedure relating to this request shall not exceed 30 days. In exceptional cases, this period of time may be extended to 90 days.

Article 45

The competent authority may require from the applicant further information concerning both the particulars supplied pursuant to Article 41 of this Ordinance and the qualified person referred to in Article 48 of this Ordinance. Where the competent authority concerned exercises this right, application of the time-limits referred to in Articles 43 and 44 of this Ordinance shall be suspended until the additional data required have been supplied.

Article 46

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 as regards both manufacture and controls;

(b) act in accordance with the legislation on disposal of medical waste;

(c) give prior notice to the competent authority of any changes which he may wish to make to any of the particulars supplied pursuant to Article 41 of this Ordinance, the competent authority shall, in any event, be immediately informed if the qualified person referred to in Article 48 of this Ordinance is replaced;

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

(e) enable the qualified person referred to in Article 48 of this Ordinance to carry out his duties, particularly by placing at his disposal all the necessary facilities;

(f) comply with the principles and the guidelines of good manufacturing practice for medicinal products 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:

– date

– name of the veterinary medicinal product

– quantity supplied

– name and address of the recipient

– batch number.

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

Article 47

For the purposes of this Ordinance, 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 Annex, Title I, Part 2, Section C of this Ordinance 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.

Article 48

1) The holder of the manufacturing authorisation shall have permanently and continuously at his disposal the services of at least one qualified person who fulfils the conditions laid down in Article 49 of this Ordinance, and is responsible, in particular, for carrying out the duties specified in Article 51 of this Ordinance.

2) If he personally fulfils the conditions laid down in Article 49 of this Ordinance, he shall be considered to be a qualified person referred to in paragraph 1 of this Article.

Article 49

1) The qualified person referred to in Article 48, paragraph 1 of this Ordinance shall fulfil the conditions of qualification set out in paragraphs 2 and 3 of this Article.

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, 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.

3) Where two university or recognised equivalent courses coexist and where one of these extends over four years and the other over three years, the diploma, certificate or other evidence of formal qualifications awarded on completion of the three-year university course or its recognised equivalent shall be considered to fulfil the condition of duration referred to in paragraph 1 of this Article, in so far as the diplomas, certificates or other evidence of formal qualifications awarded on completion of both courses are recognised as equivalent.

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

– experimental physics

– general and inorganic chemistry

– organic chemistry

– analytical chemistry

– pharmaceutical chemistry, including analysis of medicinal products

– general and applied biochemistry (medical)

– physiology

– microbiology

– pharmacology

– pharmaceutical technology

– toxicology

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

5) In so far evidence of formal qualifications do not fulfil the criteria from this paragraph evidence on having the knowledge required for the manufacture and control of veterinary medicinal products shall be submitted to the competent authority.

6) 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.

Article 50

A person engaging in the activities of the person referred to in Article 48, paragraph 1 of this Ordinance, at the date on which this Ordinance became applicable, without complying with the provisions of Article 49 of this Ordinance, shall be eligible to continue to engage in those activities.

Article 51

1) The qualified person referred to in Article 48 of this Ordinance, is, without prejudice to his relationship with the holder of the manufacturing authorisation, responsible, in the context of the procedures referred to in Article 48 of this Ordinance for ensuring that:

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

(b) in the case of veterinary medicinal products coming from third countries, each production batch imported, even if it was manufactured in the European Union, has undergone 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.

2) Batches of veterinary medicinal products which have undergone such controls in the Republic of Croatia shall be exempt from the above controls if they are placed on the market accompanied by the control reports signed by the qualified person.

3) In the case of veterinary medicinal products imported from a third country, where appropriate arrangements have been made by the Republic of Croatia with the exporting country to ensure that the manufacturer of the veterinary medicinal product applies standards of good manufacturing practice equivalent to those laid down by the European Union and to ensure that the controls referred to under paragraph 1, item (b) of this Article have been carried out in the exporting country, the qualified person may be relieved of responsibility for carrying out those controls.

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

Article 52

The competent authority shall ensure that actions are taken against the qualified person referred to in Article 48, in case of irregular proceeding, including substitution of such person with another person.

Article 53

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

Title V
LABELLING AND PACKAGE INSERT

Article 54

1) Except in the case of the medicinal products referred to in Article 21, paragraphs 1 and 2 of this Ordinance, the competent authority 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 Articles 12 and 13 of this Ordinance 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, if necessary, the representative of the marketing authorisation 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 Article 30, paragraph 1 of this Ordinance, if any;

(l) The words ‘For animal treatment only’ or, in the case of the medicinal products referred to in Article 67, 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 Annex, Title I, Part 1, Section A of this Ordinance, in so far as they concern the qualitative and quantitative composition of veterinary medicinal products in respect of active substances, shall apply to the particulars provided for in paragraph 1, item (b) of this Article.

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

5) In the case of medicinal products that have been granted a marketing authorisation under a special regulation[28]27, the outer packaging may bear additional information concerning distribution, possession, sale or any necessary precautions, provided that such information is not in infringement of regulations in force 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 paragraph 1 of this Article.

Article 55

1) As regards ampoules, the particulars listed in Article 54, paragraph 1 of this Ordinance shall be given on the outer package. On the immediate packaging, however, only the following particulars shall be necessary:

– name of veterinary medicinal product

– quantity of the active substances

– route of administration

– manufacturer's batch number

– date of expiry

– the words ‘For animal treatment only’.

2) As regards small immediate packaging containing a single dose, other than ampoules, on which it is impossible to give the particulars mentioned in paragraph 1 of this Article, the requirements of Article 54 of this Ordinance paragraphs 1 to 3 shall apply only to the outer package.

3) The particulars mentioned in paragraph 1, the third and the sixth indents of this Article, shall appear on the outer package and on the immediate packaging of the medicinal products in the Croatian language or languages of the country in which they are placed on the market.

Article 56

Where there is no outer package, all the particulars which should feature on such a package pursuant to the Articles 54 and 55 of this Ordinance shall be shown on the immediate packaging.

Article 57

1) The inclusion of a package leaflet in the packaging of veterinary medicinal products shall be obligatory unless all the information required by this Article can be conveyed on the immediate packaging and the outer packaging. The leaflet shall relate 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 Croatian language and in accordance with the summary of product characteristics, and it may be written also in other languages provided that the information given is identical to those in the Croatian language.

2) The competent authorities 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 Articles 12 to 17 of this Ordinance 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 authorisation 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.

(c) the therapeutic indications;

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

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

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

(g) special storage precautions, if any;

(h) particulars required to be indicated pursuant to Article 30, paragraph 1 of this Ordinance, if any;

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

Article 58

Where the provisions of this Title are not observed and, after the expiry of the deadline for removal of deficiencies, the competent authority shall withdraw marketing authorisation.

Article 59

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

Article 60

1) Without prejudice to provisions of paragraph 2 of this Article, 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 Article 21, paragraphs 1 and 2 of this Ordinance shall bear the following information and no other information:

– the scientific name of the stock or stocks followed by the degree of dilution, using the symbols of the pharmacopoeia. 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,

– name and address of the marketing authorisation holder and, where appropriate, of the manufacturer

– method of administration and, if necessary, route

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

– pharmaceutical form

– contents of the sales presentation

– special storage precautions, if any

– target species

– a special warning if necessary for the medicinal product,

– manufacturer's batch number

– registration number.

Title VI
POSSESSION, WHOLESALE DISTRIBUTION AND DISPENSING OF VETERINARY MEDICINAL PRODUCTS

Article 61

1) Wholesale distribution of veterinary medicinal products shall be carried out by wholesalers subject to the holding of an authorisation, issued by the competent authority within 90 days from the date on which the competent authority receives the application.

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 a special regulation as regards the storage and handling of veterinary medicinal products.

3) The holder of the authorisation for distribution shall be required to keep 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 an audit shall be carried out to compare incoming and outgoing medicinal supplies with supplies currently held in stock, any discrepancies being recorded.

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

4) 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;

5) Wholesalers shall supply veterinary medicinal products only to persons permitted to carry out retail activities in accordance with Article 62 of this Ordinance, or to other persons who are lawfully permitted to receive veterinary medicinal products from wholesalers.

6) Any distributor, not being the marketing authorisation holder, who imports a product from another Member State shall notify the marketing authorisation holder and the competent authority in the Member State 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 a special regulation[29]28, the notification to the competent authority shall be without prejudice to additional procedures.

7) The marketing authorisation holder referred to in paragraph 1 of this Article, at the request of the competent authority, shall submit all information relating to volume of sale of the veterinary medicinal product and all information at its disposal, relating to volume of prescriptions of the veterinary medicinal product.

Article 62

1) Retail supply of veterinary medicinal products shall be conducted pursuant to the licence referred to in Article 62, paragraph 2 of the Act on Veterinary Medicinal Products.

2) Any person permitted under paragraph 1 of this Article 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 an audit shall be carried out, and incoming and outgoing veterinary medicinal products shall be reconciled with products currently held in stock, any discrepancies being recorded.

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

3) The marketing authorisation holder referred to in paragraph 1 of this Article, at the request of the competent authority, shall submit all information relating to volume of sale of the veterinary medicinal product and all information at its disposal, relating to volume of prescriptions of the veterinary medicinal product.

Article 63

1) Without prejudice to stricter provisions of special regulations relating to dispensing veterinary medicinal products and to protect human and animal health, a veterinary prescription shall be required for dispensing to the public the following veterinary medicinal products:

1.1. those products subject to official restrictions on supply or use, such as:

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

– the restrictions on the use of veterinary medicinal products resulting from special regulations;

1.2. veterinary medicinal products for food-producing animals.

1.3. The competent authority may approve exceptions from the abovementioned requirements in a separate procedure.

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

– the target species,

– the person administering the products to the animal,

– the environment;

3. 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;

4. official formula, intended for food-producing animals.

2) 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.

3) The prescription shall be obligatory for all veterinary medicinal products containing active substances that have been approved for use in veterinary medicinal products for less than five years.

Article 64

1) Only persons empowered to 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 competent authority shall maintain a register of manufacturers and dealers permitted to be in possession of active substances which may be used in the manufacture of veterinary medicinal products having the properties referred to in paragraph 1 of this Article. Such persons must maintain records of all dealings in substances which may be used in the manufacture of veterinary medicinal products and keep these records available for inspection by the competent authorities for a period of at least three years.

Article 65

1) The owners or keepers of food-producing animals shall 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.

2) Persons referred to in paragraph 1 of this Article shall maintain a record giving at least the following information:

(a) date;

(b) name of the veterinary medicinal product;

(c) quantity;

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

(e) identification of the animals treated.

Article 66

Notwithstanding Article 9 and notwithstanding the provisions of Article 63 of this Ordinance, veterinarians providing services in the Republic of Croatia and, upon accession of the Republic of Croatia to the European Union, in a Member State, can take with them and administer to animals small quantities of ready-made veterinary medicinal products not exceeding daily requirements other than immunological veterinary medicinal products which are not authorised for use in the Republic of Croatia providing that the following conditions are satisfied:

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

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

(c) the veterinary medicinal products intended for administration to food-producing animals have the same qualitative and quantitative composition in terms of active substances as the medicinal products authorised in accordance with Articles 5, 7 and 8 of this Ordinance in the Republic of Croatia;

(d) the veterinarian providing services in the Republic of Croatia acquaints himself with the good veterinary practices applied in the Republic of Croatia 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 Republic of Croatia, unless this is permissible on the basis of a special regulation. 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 for a period of at least five years;

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

Article 67

1) In the absence of specific legislation concerning the use of immunological veterinary medicinal products for the eradication or control of animal disease, the competent authority may prohibit the manufacture, import, possession, sale, supply and/or use of immunological veterinary medicinal products on the whole or part of its territory if it is established that:

(a) the administration of the product to animals will interfere with the implementation of a national programme for the diagnosis, control or eradication of animal disease, or will cause

difficulties in certifying the absence of contamination in live animals or in foodstuffs or other products obtained from treated animals;

(b) the disease to which the product is intended to confer immunity is largely absent from the territory of the Republic of Croatia.

2) The competent authority, due to reasons stated in paragraph 1 of this Article, may refuse to issue the marketing authorisation by a decentralised procedure laid down in Title III, Chapter IV of this Ordinance;

3) The competent authorities shall inform the European Commission of all instances in which the provisions of paragraph 1 of this Article apply.

Title VII
PHARMACOVIGILANCE

Article 68

The competent authority shall encourage the reporting to the competent authorities of suspected adverse reactions to veterinary medicinal products.

Article 69

1) Having regard to information obtained about suspected adverse reactions to veterinary medicinal products under normal conditions of use, the competent authority shall establish a veterinary pharmacovigilance system in order to ensure the adoption of appropriate decisions concerning veterinary medicinal products. This system shall be used to collect information useful in the surveillance of veterinary medicinal products, with particular reference to adverse reactions in animals and in human beings related to the use of veterinary medicinal products, and to evaluate such information scientifically.

2) Suitable information collected within this system shall be communicated to other Member States and EMEA. This information shall be recorded in the database referred to in Article 57, paragraph 1, item (k) of a special regulation[30]29 and shall be permanently accessible to all Member States and without delay to the public.

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

4) The pharmacovigilance system also takes into account any available information related to the lack of expected efficacy, off-label use, investigations of the validity of the withdrawal period and on potential environmental problems, arising from the use of the product, interpreted in accordance with the European Commission guidelines (hereinafter: guidelines)[31]****, which may have an impact on the evaluation of their benefits and risks.

Article 70

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 competent authorities in order to guarantee their independence.

Article 71

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

2) That qualified person referred to in paragraph 1 of this Article shall reside in the Republic of Croatia and, upon accession of the Republic of Croatia to the European Union, shall reside in the European Union 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;

(b) the preparation for the competent authorities of the reports referred to in Article 72 of this Ordinance, in accordance with the guidance [32]****;

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

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

Article 72

1) The marketing authorisation holder shall maintain detailed records of all suspected adverse reactions occurring in the Republic of Croatia, in the European Union or in a third country.

2) Save in exceptional circumstances, these reactions shall be communicated electronically in the form of a report in accordance with the guidelines ****.

3) The marketing authorisation holder shall record all suspected serious adverse reactions and human adverse reactions related to the use of veterinary medicinal products:

(a) which are brought to his attention,

(b) of which he can reasonably be expected to have knowledge, and report them immediately to the competent authority, and in no case later than 15 calendar days following the receipt of the information.

4) The marketing authorisation holder shall ensure that the suspected serious and unexpected adverse reactions and human adverse reactions related to the use of veterinary medicinal products, as well as any suspicion of transmission through a veterinary medicinal product of any infectious agent, occurring in the territory of a third country, are reported immediately in accordance with the guidance ****, so that they are available to EMEA and to the competent authorities in the Member States where the veterinary medicinal product is authorised, and in no case later than 15 calendar days following the receipt of the information.

5) By way of derogation from provisions of paragraphs 3 and 4 of this Article, in the case of veterinary medicinal products which have been considered within the scope of a special regulation30[33] and which have benefited from the procedures of mutual recognition under Article 36 of this Ordinance[34]*, the marketing authorisation holder shall additionally ensure that all suspected serious adverse reactions and human adverse reactions, occurring in the European Union 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.

6) Unless other requirements have been laid down as condition of the granting of authorisation or as stated in the guideline[35]****, reports of all adverse reactions shall be submitted to the competent authorities 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 be submitted immediately upon request or at least every six months during the first two years during the first two years following the initial placing on the market and once a year for the following two years. Thereafter, the periodic safety update reports shall be submitted at three-yearly intervals, or immediately upon request. The periodic safety update report shall include a scientific evaluation of the benefits and risks afforded by the veterinary medicinal product.

7) Following the granting of a marketing authorisation, the marketing authorisation holder may request the amendment of the periods referred to in paragraph 5 of this Article in accordance with a special regulation[36]31.

8) The holder of a marketing authorisation may not communicate information relating to pharmacovigilance concerns to the general public in relation to its authorised veterinary medicinal product without giving prior or simultaneous notification to the competent authority. In any case, the marketing authorisation holder shall ensure that such information is presented objectively and is not misleading.

9) Penalties for acting contrary to the provisions relating to pharmacovigilance are laid down in the Act on Veterinary Medicinal Products.

Article 73

1) Setting up a data-processing network to facilitate the exchange of pharmacovigilance information regarding medicinal products marketed in the European Union is laid down in Article 65, paragraph 7 of the Act on Veterinary Medicinal Products.

2) Making use of the network foreseen in paragraph 1 of this Article the competent authority shall ensure that reports of suspected serious adverse reactions and human adverse reactions that have taken place on the territory, in accordance with guidelines****, are immediately made available to EMEA and Member States, and in any case within 15 calendar days of their notification at the latest.

3) Reports of suspected serious adverse reactions and human adverse reactions shall immediately be made available to the marketing authorisation holder, and in any case within 15 calendar days of their notification at the latest.

Article 74

Emergency measures are laid down in Article 66 of the Act on Veterinary Medicinal Products.

Title VIII
SUPERVISION AND SANCTIONS

Article 75

1) The competent authority 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.

2) The competent authority 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 this Ordinance.

3) The competent authority may carry out inspections of starting material manufacturers at the manufacturer's own request.

4) Inspections shall be carried out by authorised representative of the competent authority who shall be empowered to:

(a) inspect manufacturing or trading establishments and any laboratories entrusted by the holder of the manufacturing authorisation, with the task of carrying out control tests pursuant to Article 28 of this Ordinance;

(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 the competent authority;

(c) examine any documents relating to the object of the inspection;

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

5) The manufacturing processes used in the manufacture of immunological veterinary medicinal products shall be completely validated and batch-to-batch consistency shall be ensured.

6) The authorised representatives of the competent authority shall report after each of the inspections mentioned in paragraph 1 of this Article, on whether the manufacturer complies with the principles and guidelines of good manufacturing practice referred to in Title VII of this Ordinance. The inspected manufacturer or the marketing authorisation holder shall be informed of the content of such reports.

7) Within 90 days after an inspection as referred to in paragraph 1 of this Article, 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.

8) 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.

9) Data on issued certificates of good manufacturing practice shall be entered into European Union database governed by EMEA.

10) Data on detected non-compliances shall be entered in the database from paragraph 6 of thi Article, as well.

Article 76

1) 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 paragraph 1 of this Article the marketing authorisation holder for immunological veterinary medicinal products shall submit to the competent authority copies of all the control reports signed by the qualified person in accordance with Article 51 of this Ordinance.

3) 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 competent authorities on request.

Article 77

1) Where it considers it necessary for reasons of human or animal health, the marketing authorisation holder for an immunological veterinary medicinal product shall 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 competent authority, the marketing authorisation holder shall promptly supply the samples referred to in paragraph 1 of this Article, together with the reports of the control referred to in Article 76, paragraph 2 of this Ordinance.

3) The competent authority 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.

4) After studying the control reports referred to in Article 76, paragraph 2 of this Ordinance, 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 authorised under special regulation [37]32, the list of tests to be repeated by the control laboratory may be reduced only after agreement by the EMEA.

All Member States concerned shall recognise the results of the tests.

5) Unless the European Commission is informed that a longer period is necessary to conduct the tests, control shall be completed within 60 days of receipt of the samples.

6) The competent authority 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.

7) If a competent authority 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.

Article 78

The competent authorities shall withdraw marketing authorisation in the cases from Article 42, paragraph 1 of the Act on Veterinary Medicinal Products.

Article 79

1) Notwithstanding the provisions of Article 78 of this Ordinance, a veterinary medicinal product is withdrawn form the market in accordance with Article 59, paragraph 2 of the Act on Veterinary Medicinal Products and where:

– 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 people.

– the control tests referred to in Article 76, paragraph 1 of this Ordinance have not been carried out.

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

Article 80

1) The competent authority shall withdraw the marketing authorisation for a category of preparations or for all preparations if any of the requirements laid down in Article 41 of this Ordinance are no longer met.

2) The competent authority may, in addition to the measures provided for in Article 79 of this Ordinance 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) Advertising of veterinary medicinal products is permitted in accordance with the Act on Veterinary Medicinal Products.

Article 81

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

Article 82

Veterinarians and other professionals concerned shall report to the competent authorities any adverse reaction of veterinary medicinal products in accordance with provisions of the Act on Veterinary Medicinal Products.

Title X
GENERAL PROVISIONS

Article 83

The competent authority shall take all measures necessary to ensure that appropriate data are communicated, in particular regarding compliance with the requirements adopted for issuance of authorisations referred to in Article 40 of this Ordinance, issuance of certificates referred to in Article 80, paragraph 7 of this Ordinance, and for authorisation to place products on the market.

Upon reasoned request, the competent authority shall forthwith communicate the reports referred to in Article 75, paragraph 6 of this Ordinance, to the competent authorities of the Member State.

The conclusions reached following an inspection as referred to in Article 75, paragraph 1 of this Ordinance, carried out by the inspectors of the Member State concerned shall be valid for the entire European Union.

By way of exception, if the competent authority has not been able, for serious reasons of human or animal health, to accept the conclusions of an inspection as referred to in Article 80, paragraph 1 of this Ordinance it shall forthwith inform the European Commission and EMEA.

Article 84

1) The competent authority shall take all appropriate measures to ensure that EMEA 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 competent authority 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 competent authority shall ensure that this information is brought to the attention of the EMEA.

3) The competent authority shall ensure that appropriate information about actions taken pursuant to paragraphs 1 and 2 of this Article, 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 EMEA.

Article 85

The competent authority shall communicate to the Member States all the information necessary to guarantee the quality and safety of homeopathic veterinary medicinal products manufactured and marketed within the European Union and in particular the information referred to in Articles 83 and 84 of this Ordinance.

Article 86

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

(a) it 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 their territory, it shall supply the summary of the product characteristics as approved in accordance with Article 25 of this Ordinance or, in the absence thereof, an equivalent document.

2) Where the manufacturer is not in possession of an authorisation to place the veterinary medicinal product on the market, he shall provide the competent authority with a declaration explaining why such authorisation is not available.

Article 87

Any decision taken by the competent authority in the course of implementing this Ordinance shall be well-reasoned; in addition, it shall contain information on legal remedies and shall be made publicly available.

Article 88

Manufacture of foodstuffs for human consumption from test animals shall not be permitted, unless the competent authority has established an appropriate withdrawal period. The withdrawal period shall either:

(a) be at least as laid down in Article 11, paragraph 5 of this Ordinance, including, where appropriate, a safety factor reflecting the nature of the substance being tested; or

(b) if maximum residue limits have been established in accordance with the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin [38]33, ensure that practice shall be in accordance with the regulation.

Article 89

Collecting of veterinary medicinal products that are unused or expired shall be conducted in line with special regulation.

Title XI
TRANSITIONAL AND FINAL PROVISIONS

Article 90

The Annex is printed along with this Ordinance and forms an integral part thereof.

Article 91

The provisions of Article 8, paragraph 3, Article 40, paragraph 3, Article 51, paragraph 1, item (b) of this Ordinance shall be also applicable to the Member States as of the date of accession of the Republic of Croatia to the European Union.

Article 92

On the date of entry of this Ordinance, provisions of the Ordinance on the methods and procedure of granting the marketing authorisation for finished veterinary medical devices, medicated pre-mixes and veterinary medicinal products (OG 142/03) and the Ordinance on the manner of quality control of finished veterinary medical devices, medicated pre-mixes and veterinary medicinal products, the manner of keeping these products and keeping of registers on conducted quality controls (OG 148/99) shall cease to have effect .

Article 93

1) This Ordinance shall enter into force on 1 July 2009.

2) By way of derogation from paragraph 1 of this Article, the provisions of:

– Article 32, paragraph 3, Article 61, paragraph 7, Article 62, paragraph 3 shall enter into force on the eighth day following the day of publication in the Official Gazette,

– Article 8, paragraph 2, Article 13, paragraph 4, Article 20, paragraph 4, Article 25, paragraph 2 and 3, Article 26, Article 29, paragraphs 1, 3 and 6, Title III, Chapter IV, Article 40, paragraph 5, Article 51. paragraphs 2 and 3, Article 57, paragraph 2, item (j), Article 63, paragraph 1, item 1.3, Article 66, Article 67, paragraph 3, Article 69, paragraph 4, Article 71, paragraph 2, item (b), Article 72 , paragraphs 2, 4, 5 and 6, Article 73, paragraph 2, Article 75, paragraphs 8, 9 and 10, Article 77, Article 83, Article 84, paragraphs 1 and 3, Annex, items 1.1 and 2.1 and Annex, Title I, Part 2, Section D, second indent of this Ordinance shall enter into force on the date of accession of the Republic of Croatia to the European Union.

Class: 011-02/09-01/33

Reg. No.: 525-6-09-1

Zagreb, 25 February 2009

The Minister
Božidar Pankretić, m.p.

ANNEX

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

INTRODUCTION

1. The person submitting application for issuing marketing authorisations for veterinary medicinal products shall present particulars and documents in accordance with Article 12 and Article 13, paragraph 1 of this Ordinance in accordance with the requirements set out in this Annex.

1.1. When submitting application for issuing marketing authorisations for veterinary medicinal products, the applicant shall take account of the guidance contained in the "Notice to applicants for marketing authorisations for veterinary medicinal products in the Member States of the European Union" published by the European Commission in "The rules governing medicinal products in the European Union", volume V: Veterinary Medicinal Products.

2. In assembling the dossier for application for marketing authorisation, applicants shall take into account the guidelines relating to the quality, safety and efficacy of veterinary medicinal products.

2.1. Guidelines referred to in item 2 of this Ordinance published by the European Commission in "The rules governing medicinal products in the European Union".

Comment [s1]: Annex?

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

All experiments on animals are conducted in accordance with the Ordinance on conditions for keeping animals used for experimental purposes, standards for breeding and user establishments and types of experiments (Official Gazette 176/04)[39]33.

TITLE I
REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS OTHER THAN IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

PART 1
SUMMARY OF THE DOSSIER

A. ADMINISTRATIVE DATA

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

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

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

Annexed to the administrative data shall be a document showing that the manufacturer is authorised to produce the veterinary medicinal products concerned, as defined in Article 40 of this Ordinance, together with a list of countries in which authorisation has been granted, copies of all the summaries of product characteristics in accordance with Article 18 of this Ordinance, as approved by Member States and a list of countries in which an application has been submitted.

B. SUMMARY OF PRODUCT CHARACTERISTICS

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

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

C. Expert reports

In accordance with Article 19, paragraphs 2 and 3 of this Ordinance, expert reports must be provided on the analytical documentation, the pharmacotoxicological documentation, the residues documentation and the clinical documentation.

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

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

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

Part 2
ANALYTICAL (PHYSICO-CHEMICAL, BIOLOGICAL OR MICROBIOLOGICAL) TESTS OF VETERINARY MEDICINAL PRODUCTS

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

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

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

The particulars and documents which must accompany applications for marketing authorisation, pursuant to Article 12, paragraph 4, item (c), shall be submitted in accordance with the following requirements.

1. Qualitative particulars

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

– the active substance(s),

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

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

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

2. The "usual terminology", to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions of Article 12, paragraph 4,

item (c) of this Ordinance The "usual terminology", to be used in describing the constituents of veterinary medicinal products, shall mean, notwithstanding the application of the other provisions of Article:

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

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

– in respect of colouring matter, designation by the "E" code in accordance with a special regulation[40]34.

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.

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

This information shall be supplemented:

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

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

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

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

3.3. For veterinary medicinal products containing an active substance which is the subject of an application for marketing authorisation in the Republic of Croatia, 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 shall have their quantitative composition stated in the same way for the same active substance.

4. Development pharmaceutics

An explanation shall be provided with regard to the choice of composition, constituents and container and the intended function of the excipients in the finished product. This explanation shall be supported by scientific data on development pharmaceutics; shelf-life shall be determined and laid down, as well.

B. DESCRIPTION OF THE MANUFACTURING METHOD

The description of the manufacturing method accompanying the application for marketing authorisation pursuant to Article 12, paragraph 4, item (d) of this Ordinance, 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 veterinary medicinal product,

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

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

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

– for sterile products, details of the sterilisation processes and/or aseptic procedures used.

C. CONTROL OF STARTING MATERIALS

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

In the case of:

– an active substance not described in the European Pharmacopoeia or Croatian pharmacopoeia or in the pharmacopoeia of Member States,

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

– an active substance, which is manufactured by a person different from the applicant, the latter may arrange for the detailed description of the manufacturing method, quality control during manufacture and process validation to be supplied directly to the competent authorities by the manufacturer of the active substance. In this case, the manufacturer shall however provide the applicant with all the data which may be necessary for the latter to take responsibility for the 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.

The particulars and documents accompanying the application for marketing authorisation pursuant to Article 12, paragraph 4, items (i) and (j) and Article 13, paragraph 1 shall include the results of the tests, including batch analyses particularly for active substances, relating to quality control of all the constituents used. These shall be submitted in accordance with the following provisions.

1.1. Starting materials listed in pharmacopoeias

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

In addition to the European Pharmacopoeia for veterinary medicinal products manufactured on its territory, the Croatian pharmacopoeia shall be also applicable.

All substances meeting the requirements of the European Pharmacopoeia or requirements of the Croatian/national pharmacopoeia shall be deemed to comply sufficiently with Article 12, paragraph 4, item (i). In this case the description of the analytical methods may be replaced by a detailed reference to the pharmacopoeia in question.

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

Colouring matter shall, in all cases, satisfy the requirements of a special regulation [41]35.

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 contained in a monograph of the European Pharmacopoeia or in Croatian pharmacopoeia or in the pharmacopoeia of Member States might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorisation holder.

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

1.2. Starting materials not in a pharmacopoeia

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

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

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

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

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

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

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

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

1.3. Physico-chemical characteristics liable to affect bioavailability

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

- crystalline form and solubility coefficients,

- particle size, where appropriate after pulverisation,

- state of solvation,

- oil/water coefficient of partition [42]36.

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

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

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

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

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

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

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

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

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

The particulars and documents accompanying an application for marketing authorisation, pursuant to Article 12, paragraph 4, items (i) and (j) and Article 13, paragraph 1 of this Ordinance 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.

F. TESTS ON THE FINISHED PRODUCT

1. For the control of the finished product, a batch of a finished product comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or 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 particulars and documents accompanying the application for marketing authorisation pursuant to Article 12, paragraph 4, items (i) and (j) and Article 13, paragraph 1 of this Ordinance, shall include particulars relating to control tests on the finished product at release. They shall be submitted in accordance with the following requirements:

- the provisions of the general monographs of the European Pharmacopoeia, or failing that, of the national pharmacopoeia of the Republic of Croatia, shall be applicable to all products defined therein.

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

1.1. General characteristics of the finished product

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

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

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

1.2. Identification and assay of active substance(s)

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

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

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

In certain exceptional cases of particularly complex mixtures, where assay of active substances which are very numerous or present in very low amounts would necessitate an intricate investigation difficult to carry out in respect of each production batch, the assay of one or more active substances in the finished product may be omitted, on the express condition that such assays are made at intermediate stages in the production process. This relaxation may not be extended to the characterisation of the substances concerned. This simplified technique shall be supplemented by a method of quantitative evaluation, enabling the competent authority to have the conformity of the medicinal product with its specification verified after it has been placed on the market.

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

Where the particulars given in Section B of this Part show that a significant overage of an active substance is employed in the manufacture of the medicinal product, the description of the control tests on the finished product shall include, where appropriate, the chemical and, if

necessary, the toxico-pharmacological investigation of the changes that this substance has undergone, and possibly the characterisation and/or assay of the degradation products.

1.3. Identification and assay of excipient components

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

The test procedure proposed for identifying colouring matters must enable a verification to be made that such matters appear in the list annexed to a special regulation[43]37.

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

1.4. Safety tests

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

G. STABILITY TEST

The particulars and documents accompanying the application for marketing authorisation pursuant to Article 12, paragraph 4, items (f) and (i) of this Ordinance shall be submitted in accordance with the following requirements.

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

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

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

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

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

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

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

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

PART 3

SAFETY AND RESIDUES TESTING

The particulars and documents which shall accompany the application for marketing authorisation pursuant to Articles 12, paragraph 4, item (j) and Article 13, paragraph 1 of this Ordinance shall be submitted in accordance with the requirements below.

Test shall be carried out in accordance with the principles of good laboratory practice laid down by provisions of Ordinance on good laboratory practice (GLP) and verification of application of the principles of good laboratory practice for test on veterinary medicinal products (OG 69/07)[44]38 and a special regulation[45]39.

A. SAFETY TESTING

Chapter I

PERFORMANCE OF TESTS

1. Introduction

The safety documentation shall show:

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

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

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

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

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

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

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

2. Pharmacology

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

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

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

3. Toxicology

3.1. Single-dose toxicity

Single-dose toxicity studies can be used to predict:

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

- the possible effects of accidental administration to humans,

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

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

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

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

3.2. Repeated-dose toxicity

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

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

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

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

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

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

3.3. Tolerance in the target species

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

3.4. Reproductive toxicity including teratogenicity

3.4.1. Study of the effects on reproduction

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

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

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

3.4.2. Study of embryotoxic/fetotoxic effects including teratogenecity

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

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

3.5. Mutagenicity

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

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

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

3.6. Carcinogenicity

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

- which have a close chemical analogy with known carcinogens,

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

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

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

3.7. Exceptions

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

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

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

4. Other requirements

4.1. Immunotoxicity

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

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

4.2. Microbiological properties of residues

4.2.1. Potential effects on the human gut flora

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

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

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

4.3. Observations in humans

Information shall be provided showing whether the constituents of the veterinary medicinal product are used as medicinal products in human therapy; if this is so, a report should be

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

5. Ecotoxicity

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

5.2. An assessment of ecotoxicity shall be compulsory for any application for marketing authorisation for a veterinary medicinal product other than applications submitted in accordance with Articles 12, paragraph 4, item (j) and Article 13, paragraph 1 of this Ordinance.

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

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

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

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

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

- the disposal of unused or waste product.

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

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

- fate and behaviour in soil,

- fate and behaviour in water and air,

- effects on aquatic organisms,

- effects on other non-target organisms.

These further investigations shall be carried out in accordance with the test protocols laid down in Annex V of a special regulation on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances[46]40, or where an end point is not adequately covered by these protocols, in accordance with other internationally recognised protocols on the veterinary medicinal product and/or the active substance(s) and/or the excreted metabolites as appropriate. The number and types of tests and the criteria for their evaluation shall depend upon the state of scientific knowledge at the time the application is submitted.

Chapter II

PARTICULARS AND DOCUMENTS

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

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

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

- international non-proprietary name (INN),

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

- Chemical Abstract Service (CAS) number,

- therapeutical and pharmacological classification,

- synonyms and abbreviations,

- structural formula,

- molecular formula,

- molecular weight,

- degree of impurity,

- qualitative and quantitative composition of impurities,

- description of physical properties,

- melting point,

- boiling point,

- vapour pressure,

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

- density,

- spectra of refraction, rotation, etc;

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

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

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

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

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

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

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

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

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

B. RESIDUE TESTING

Chapter I

PERFORMANCE OF TESTS

1. Introduction

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

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

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

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

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

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

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

2. Metabolism and residue kinetics

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

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

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

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

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

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

2.2. Depletion of residues

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

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

3. Routine analytical method for the detection of residues

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

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

The following characteristics shall be described:

- specificity,

- accuracy, including sensitivity,

- precision,

- limit of detection,

- limit of quantitation,

- practicability and applicability under normal laboratory conditions,

- susceptibility to interference.

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

Chapter II

PRESENTATION OF PARTICULARS AND DOCUMENTS

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

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

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

- composition,

- purity,

- batch identification,

- relationship to the final product,

- specific activity and radio-purity of labelled substances,

- position of labelled atoms in the molecule;

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

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

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

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

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

PART 4

PRE-CLINICAL AND CLINICAL TESTING

The particulars and documents which shall accompany applications for marketing authorisations pursuant to Articles 12, paragraph 4, item (j) and Article 13, paragraph 1 of this Ordinance shall be submitted in accordance with the provisions of this Part.

Chapter I

PRE-CLINICAL REQUIREMENTS

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

A. PHARMACOLOGY

A.1. Pharmacodynamics

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

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

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

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

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

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

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

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

A.2. Pharmacokinetics

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

Pharmacokinetic objectives can be divided into two main areas:

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

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

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

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

A.2.1. Bioavailability/bioequivalence

Appropriate bioavailability studies shall be undertaken to establish bioequivalence:

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

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

- in all cases referred to in Article 13, paragraph 1 of this Ordinance.

B. TOLERANCE IN THE TARGET SPECIES OF ANIMAL

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

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

C. RESISTANCE

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

Chapter II

CLINICAL REQUIREMENTS

1. General principles

The purposes of clinical trials are to demonstrate or substantiate the effect of the veterinary medicinal product after administration of the recommended dosage, to specify its indications and contra-indications according to species, age, breed and sex, its directions for use, any

adverse reactions which it may have and its safety and tolerance under normal conditions of use.

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

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

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

- the yield of animal produce,

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

- nutritional efficiency and growth of animal,

- the general status of health of the animal.

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

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

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

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

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

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

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

2. Performance of trials

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

into consideration during the elaboration of any trial protocol and throughout the conduct of the trial.

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

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

Unless the trial is conducted with a blind design, the provisions of Articles 54, 55 and 56 of this Ordinance concerning the labelling of veterinary medicinal products shall apply by analogy to the labelling of formulations intended for use in veterinary clinical trials. In all cases, the words "for veterinary clinical trial use only" shall appear prominently and indelibly upon the labelling.

Chapter III

PARTICULARS AND DOCUMENTS

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

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

1. Records of pre-clinical observations

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

(a) tests demonstrating pharmacological actions;

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

(c) tests demonstrating the main pharmacokinetic processes.

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

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

(a) a summary;

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

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

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

Total or partial omission of these data must be explained.

2.1. Records of clinical observations

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

The particulars supplied shall take the following form:

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

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

(c) details of the trial protocol giving a description of the methods used, including methods of 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 rearing and feeding, stating the composition of the feed and the nature and quantity of any additives contained in the feed;

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

(f) diagnosis and means used to make it;

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

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

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

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

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

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

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

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

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

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

Comment [s2]: U hrvatskom tekstu nedostaje točka (p)

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.

2.2. Summary and conclusions of clinical observations

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

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

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

- received no treatment;

- received a placebo;

- received another authorised medicinal product of known effect;

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

(d) the frequency of observed adverse reactions;

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

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

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

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

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

3. Concluding expert report

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

TITLE II

REQUIREMENTS FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

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

PART 5

SUMMARY OF THE DOSSIER

A. ADMINISTRATIVE DATA

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

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

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

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

The applicant shall submit a list of countries in which authorisation has been granted, copies of all the summaries of approved product characteristics in accordance with Article 18 of this Ordinance and a list of countries in which an application has been submitted.

B. SUMMARY OF PRODUCT CHARACTERISTICS

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

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

C. EXPERT REPORTS

In accordance with Article 19, paragraphs 2 and 3 of this Ordinance, expert reports must be provided on all aspects of the documentation.

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

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

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

PART 6

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

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

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

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

The particulars and documents which must accompany applications for marketing authorisation, pursuant to Article 12, paragraph 4, item (c) of this Ordinance, shall be submitted in accordance with the following requirements.

1. Qualitative particulars

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

- the active substance(s),

- the constituents of the adjuvants,

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

- the constituents of the pharmaceutical form administered to animals.

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

2. The "usual terminology", to be used in describing the constituents of immunological veterinary medicinal products, shall mean, notwithstanding the application of the other provisions of Article 12, paragraph 4, item (c) of this Ordinance:

- in respect of substances which appear in the European Pharmacopoeia or, failing this, in Croatian pharmacopoeia or pharmacopoeia of a Member State, 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 by special regulation[47]41.

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 of this Part.

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

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

4. Development pharmaceutics

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

B. DESCRIPTION OF MANUFACTURING METHOD OF THE FINISHED PRODUCT

The description of the manufacturing method accompanying the application for marketing authorisation pursuant to Article 12, paragraph 4, item (d) of this Ordinance, shall be drafted in such a way as to give an adequate description of the nature of the operations employed.

For this purpose the description shall include at least:

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

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

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

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

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

C. PRODUCTION AND CONTROL OF STARTING MATERIALS

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

In the case of:

- an active substance not described in the European Pharmacopoeia or in the pharmacopoeia of the Republic of Croatia, or in the pharmacopoeia of a Member State,

or

- an active substance described in the European Pharmacopoeia or in the pharmacopoeia of the Republic of Croatia or in the pharmacopoeia of a Member State when prepared by a method liable to leave impurities not mentioned in the pharmacopoeial monograph and for which the monograph is inappropriate to adequately control its quality, which is manufactured by a person different from the applicant, the latter may arrange for the detailed description of the manufacturing method, quality control during manufacture and process validation to be supplied directly to the competent authorities by the manufacturer of the active substance. In this case, the manufacturer shall however provide the applicant with all the data which may be necessary for the latter to take responsibility for the medicinal product. The manufacturer shall confirm in writing to the applicant that he shall ensure batch-to-batch consistency and not modify the manufacturing process or specifications without informing the applicant. Documents and particulars supporting the application for such a change shall be supplied to the competent authority.

The particulars and documents accompanying the application for marketing authorisation pursuant to Article 12, paragraph 4, items (i) and (j) and Article 13, paragraph 1 of this Ordinance shall include the results of the tests relating to quality control of all the components used and shall be submitted in accordance with the following provisions.

1. Starting materials listed in pharmacopoeias

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

In respect of other substances, the competent authority may require observance of its own national pharmacopoeia with regard to products manufactured in its territory.

Components fulfilling the requirements of the European Pharmacopoeia or Croatian pharmacopoeia or pharmacopoeia of a Member State shall be deemed to comply sufficiently with Article 12, paragraph 4, item (i) of this Ordinance. In this case the description of the analytical methods may be replaced by a detailed reference to the pharmacopoeia in question.

Reference to pharmacopoeias of third countries may be permitted in cases where the substance is described neither in the European Pharmacopoeia nor in the pharmacopoeia of the Republic of Croatia or pharmacopoeia of a Member State; in that case the monograph shall be submitted, accompanied where necessary by a translation for which the applicant will be responsible.

Colouring matter shall, in all cases, satisfy the requirements of a special regulation[48]42.

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 Croatian pharmacopoeia or in pharmacopoeia of a Member State might

be insufficient to ensure the quality of the substance, the competent authority may request more appropriate specifications from the applicant for marketing authorisation.

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

In cases where a starting material is described neither in the European Pharmacopoeia nor in Croatian pharmacopoeia or in pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia can be accepted; in such cases, the applicant shall submit a copy of the monograph accompanied where necessary by the validation of the test procedures contained in the monograph and by a translation where appropriate. For active ingredients, demonstration of the ability of the monograph adequately to control their quality shall be presented.

2. Starting materials not listed in a pharmacopoeia

2.1. Starting materials of biological origin

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

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

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

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

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

- details of the source of the materials,

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

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

If the presence of adventitious agents is detected or suspected, the corresponding material shall be discarded or used in very exceptional circumstances only when further processing of

the product ensures their elimination and/or inactivation; elimination and/or inactivation of such adventitious agents shall be demonstrated.

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

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

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

2.2. Starting materials of non-biological origin

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

- the name of the starting material meeting the requirements of Section A, item 2 of this Part shall be supplemented by any trade or scientific synonyms,

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

- the function of the starting material,

- methods of identification,

- purity shall be described in relation to the sum total of predictable impurities, especially those which may have a harmful effect and, if necessary, those which, having regard to the combination of substances to which the application refers, may adversely effect the stability of the medicinal product or distort analytical results. A brief description shall be provided of the tests undertaken to establish the purity of each batch of the starting material,

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

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

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

E. CONTROL TESTS DURING PRODUCTION

1. The particulars and documents accompanying an application for marketing authorisation, pursuant to Article 12, paragraph 4, items (i) and (j) and Article 13, paragraph 1 of this Ordinance, shall include particulars relating to the control tests which are carried out on

intermediate products with a view to verifying the consistency of the production process and the final product.

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

F. CONTROL TESTS ON THE FINISHED PRODUCT

The particulars and documents accompanying the application for marketing authorisation pursuant to Article 12, paragraph 4, items (i) and (j) and Article 13, paragraph 1 of this Ordinance, 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 Croatian pharmacopoeia or pharmacopoeia of a Member State, are used, proof must be supplied that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned. The application for marketing 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.

1. General characteristics of the finished product

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

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

2. Identification and assay of active substance(s)

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

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

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

In certain exceptional cases where assay of active substances which are very numerous or present in very low amounts would necessitate an intricate investigation difficult to carry out in respect of each production batch, the assay of one or more active substances in the finished product may be omitted, on the express condition that such assays are made at intermediate stages as late as possible in the production process. This relaxation may not be extended to the characterisation of the substances concerned. This simplified technique shall be supplemented by a method of quantitative evaluation, enabling the competent authority to verify that the

immunological veterinary medicinal product is in accordance with its formula after it has been placed on the market.

3. Identification and assay of adjuvants

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

4. Identification and assay of excipient components

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

The test procedure proposed for identifying colouring matters must enable a verification to be made that such matters are permitted under special regulation[49]43.

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

5. Safety tests

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

6. Sterility and purity test

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

7. Inactivation

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

8. Residual humidity

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

9. Batch-to-batch consistency

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

G. STABILITY TESTS

The particulars and documents accompanying the application for marketing authorisation pursuant to Article 12, paragraph 4, items (f) and (i) of this Ordinance shall be submitted in accordance with the following requirements.

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

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

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

Where a finished product requires reconstitution prior to administration, details of the proposed shelf-life are required for the product reconstituted as recommended. Data in support of the proposed shelf-life for the reconstituted product shall be submitted.

Part 7

SAFETY TESTING

A. INTRODUCTION

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

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

2. The particulars and documents which shall accompany the application for marketing authorisation pursuant to Article 12, paragraph 4, item (j) and Article 13, paragraph 1 of this Ordinance shall be submitted in accordance with the requirements of Section B of this Part.

3. The competent authority shall ensure that the laboratory tests are carried out in conformity with the principles of good laboratory practice laid down in the Ordinance on good laboratory practice (GLP) and verification of application of the principles of good laboratory practice for test on veterinary medicinal products (OG 69/07)[50]44 and a special regulation [51]45.

B. GENERAL REQUIREMENTS

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

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

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

C. LABORATORY TESTS

1. Safety of the administration of one dose

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

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

2. Safety of one administration of an overdose

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

3. Safety of the repeated administration of one dose

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

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

4. Examination of reproductive performance

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

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

5. Examination of immunological functions

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

6. Special requirements for live vaccines

6.1. Spread of the vaccine strain

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

6.2. Dissemination in the vaccinated animal

Faeces, urine, milk, eggs, oral, nasal and other secretions shall be tested for the presence of the organism. Moreover, studies may be required of the dissemination of the vaccine strain in the body, with particular attention being paid to the predilection sites for replication of the organism. In the case of live vaccines for well established zoonotic diseases for food producing animals, these studies must be undertaken.

6.3. Reversion to virulence of attenuated vaccines

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

6.4. Biological properties of the vaccine strain

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

6.5. Recombination or genomic reassortment of strains

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

7. Study of residues

For immunological veterinary medicinal products, it will normally not be necessary to undertake a study of residues. However, where adjuvants and/or preservatives are used in the manufacture of immunological veterinary medicinal products, consideration shall be given to

the possibility of any residue remaining in the foodstuffs. If necessary, the effects of such residues shall be investigated. Moreover, in the case of live vaccines for zoonotic diseases, the determination of residues at the injection site may be required in addition to the studies described in paragraph 6.2.

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

8. Interactions

Any known interactions with other products shall be indicated.

D. FIELD STUDIES

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

E. ECOTOXICITY

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

An assessment of ecotoxicity shall be compulsory for any application for marketing authorisation for an immunological veterinary medicinal product other than applications submitted in accordance with Article 12, paragraph 4, item (j) and Article 13, paragraph 1 of this Ordinance.

This assessment shall normally be conducted in two phases.

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

- the target species and the proposed pattern of use (e.g. mass medication or individual animal medication),

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

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

- the disposal of unused or waste product.

Where the conclusions of the first phase indicate potential exposure of the environment to the product, the applicant shall proceed to the second phase and evaluate the potential ecotoxicity of the product. For this purpose, he shall consider the extent and duration of exposure of the environment to the product, and the information about the physical/chemical,

pharmacological and/or toxicological properties of the compound obtained during the conduct of the other tests and trials required by this Ordinance. Where necessary, further investigations on the impact of the product (soil, water, air, aquatic systems, non-target organisms) shall be carried out.

These further investigations shall be carried out in accordance with the test protocols laid down in Annex V to the special regulation[52]46 or where an end point is not adequately covered by these protocols, in accordance with other internationally recognised protocols on the immunological veterinary medicinal product and/or the active substances and/or the excreted metabolites as appropriate. The number and types of tests and the criteria for their evaluation shall depend upon the state of scientific knowledge at the time the application is submitted.

Part 8

EFFICACY TRIALS

A. INTRODUCTION

1. The purpose of the trials described in this Part is to demonstrate or to confirm the efficacy of the immunological veterinary medicinal product. All claims made by the applicant with regard 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. The particulars and documents which shall accompany applications for marketing authorisations pursuant to Article 12, paragraph 4, item (j) and Article 13, paragraph 1 of this Ordinance shall be submitted in accordance with the provisions below.

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

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

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

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

B. GENERAL REQUIREMENTS

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

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

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

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

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

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

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

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

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

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

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

C. LABORATORY TRIALS

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

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

D. FIELD TRIALS

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

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

Part 9

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

A. INTRODUCTION

As in any scientific work, the dossier of safety and efficacy studies shall include an introduction defining the subject and indicating the tests which have been carried out in compliance with Parts 7 and 8 of this Title, as well as a summary, with references to the published literature. Omission of any tests or trials listed in Parts 7 and 8 of this Title shall be indicated and discussed.

B. LABORATORY STUDIES

The following shall be provided for all studies:

1. a summary;

2. the name of the body having carried out the studies;

3. a detailed experimental protocol giving a description of the methods, apparatus and materials used, details such as species, breed or strain of animals, categories of animals, where they were obtained, their identification and number, the conditions under which they were housed and fed (stating inter alia whether they were free from any specified pathogens and/or specified antibodies, the nature and quantity of any additives contained in the feed), dose, route, schedule and dates of administration, a description of the statistical methods used;

4. in the case of control animals, whether they received a placebo or no treatment;

5. all general and individual observations and results obtained (with averages and standard deviations), whether favourable or unfavourable. The data shall be described in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author. The raw data shall be presented in tabular form. By way of explanation and illustration, the results may be accompanied by reproductions of recordings, photomicrographs, etc.;

6. the nature, frequency and duration of observed side-effects;

7. the number of animals withdrawn prematurely from the studies and reasons for such withdrawal;

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

9. occurrence and course of any intercurrent disease;

10. all details concerning medicinal products (other than the product under study), the administration of which was necessary during the course of the study;

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

C. FIELD STUDIES

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

1. a summary;

2. name, address, function and qualifications of the investigator in charge;

3. place and date of administration, name and address of the owner of the animal(s);

4. details of the trial protocol, giving a description of the methods, apparatus and materials used, details such as the route of administration, the schedule of administration, the dose, the categories of animals, the duration of observation, the serological response and other investigations carried out on the animals after administration;

5. in the case of control animals, whether they received a placebo or no treatment;

6. identification of the treated and control animals (collective or individual, as appropriate), such as species, breeds or strains, age, weight, sex, physiological status;

7. a brief description of the method of rearing and feeding, stating the nature and quantity of any additives contained in the feed;

8. all the particulars on observations, performances and results (with averages and standard deviation); individual data shall be indicated when tests and measurements on individuals have been carried out;

9. all observations and results of the studies, whether favourable or unfavourable, with a full statement of the observations and the results of the objective tests of activity required to evaluate the product; the techniques used must be specified and the significance of any variations in the results explained;

10. effect on the animals' performances (e.g. egg laying, milk production, reproductive performance);

11. the number of animals withdrawn prematurely from the studies and reasons for such withdrawal;

12. the nature, frequency and duration of observed adverse reactions;

13. occurrence and course of any intercurrent disease;

14. all details concerning medicinal products (other than the product under study) which have been administered either prior to or concurrently with the test product or during the observation period; details of any interactions observed;

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

D. GENERAL CONCLUSIONS

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

E. BIBLIOGRAPHICAL REFERENCES

The bibliographical references cited in the summary mentioned under Section A of this Part shall be listed in detail.

[1]1 Ordinance transposes provisions of Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.

[2]2 Ordinance on the conditions governing the preparation, placing on the market and use of medicated feedingstuffs (OG 101/05) transposes provisions of Council Directive 90/167/EEC of 26 March 1990 laying down the conditions governing the preparation, placing on the market and use of medicated feedingstuffs in the Community.

[3]3 Ordinance on additives for use in animal nutrition (OG 09/07) and the Ordinance on feedingstuffs and compound feedingstuffs (OG 112/08) transposes provisions of 70/524/EEC: Council Directive of 23 November 1970 concerning additives in feeding-stuffs.

[4]4-6 Annexes to the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin (OG 75/08) transpose provisions of Annexes to Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.

[5]7 Ordinance on identification and registration of equidae (OG 74/07) transposes provisions of 93/623/EEC: Commission Decision of 20 October 1993 establishing the identification document (passport) accompanying registered equidae.

[6]8 Special regulation will transpose provisions of Council Directive 2004/68/EC of 26 April 2004 laying down animal health rules for the importation into and transit through the Community of certain live ungulate animals, amending Directives 90/426/EEC and 92/65/EEC and repealing Directive 72/462/EEC.

[7]9 Annex IV to the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin (OG 75/08) transposes provisions of Annex IV to Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.

[8]10 Ordinance on the methods and procedure of granting the marketing authorisation for finished medicinal products (OG 113/08) transposes provisions of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

[9]11,14 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency will be directly applied as of the date of accession of the Republic of Croatia into the European Union.

[10]12 Ordinance on identification and registration of equidae (OG 74/07) transposes provisions of 93/623/EEC: Commission Decision of 20 October 1993 establishing the identification document (passport) accompanying registered equidae.

[11]13 Special regulation will transpose provisions of Council Directive 2004/68/EC of 26 April 2004 laying down animal health rules for the importation into and transit through the Community of certain live ungulate animals, amending Directives 90/426/EEC and 92/65/EEC and repealing Directive 72/462/EEC.

[12]15 Ordinance on the methods and procedure of granting the marketing authorisation for finished medicinal products (OG 113/08) transposes provisions of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

[13]16 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency will be directly applied as of the date of accession of the Republic of Croatia into the European Union.

[14]17 Annexes I to III to the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin (OG 75/08) transpose provisions of Annexes I to III to Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.

[15]18 Annex II to the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin (OG 75/08) transposes provisions of Annex II to

Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.

[16]19 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency will be directly applied as of the date of accession of the Republic of Croatia into the European Union.

[17]20 Annexes I to III to the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin (OG 75/08) transpose provisions of Annexes I to III to Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.

[18]21 Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin (OG 75/08) transposes provisions of Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.

[19]* Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.

[20]** Article 25 of Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.

[21]22 Annexes I to III to the Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin (OG 75/08) transpose provisions of Annexes I to III to Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.

[22]*** Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.

[23]23 Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin (OG 75/08) transposes provisions of Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.

[24]24, 25 Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin (OG 75/08) transposes provisions of Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.

[25]* Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.

[26]26 Ordinance on the monitoring of certain substances and residues thereof in live animals and animal products (OG 79/08) transposes provisions of Council Directive 96/23/EC of 29 April 1996 on measures to monitor certain substances and residues thereof in live animals and animal products and repealing Directives 85/358/EEC and 86/469/EEC and Decisions 89/187/EEC and 91/664/EEC.

[27]* Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.

[28]27 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency will be directly applied as of the date of accession of the Republic of Croatia into the European Union.

[29]28 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency will be directly applied as of the date of accession of the Republic of Croatia into the European Union.

[30]29 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency will be directly applied as of the date of accession of the Republic of Croatia into the European Union.

[31]**** The European Commission guidelines laid down in Article 77, paragraph 1 of Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.

[32]**** The European Commission guidelines laid down in Article 77, paragraph 1 of Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.

[33]30 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency will be directly applied as of the date of accession of the Republic of Croatia into the European Union.

[34]* Articles 31, 32, 36, 37 and 38 of Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.

[35]**** The European Commission guidelines laid down in Article 77, paragraph 1 of Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.

[36]31 Commission Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State.

[37]32 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency will be directly applied as of the date of accession of the Republic of Croatia into the European Union.

[38]33 Ordinance on maximum residue limits of veterinary medicinal products in foodstuffs of animal origin (OG 75/08) transposes provisions of Annexes to Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.

[39]33 Ordinance on conditions for keeping animals used for experimental purposes, standards for breeding and user establishments and types of experiments (OG 176/04) transposes provisions of Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes.

[40]34 Council Directive 78/25/EEC of 12 December 1977 on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products.

[41]35 Council Directive 78/25/EEC of 12 December 1977 on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products.

[42]36 The competent authorities may also request the pK/pH values if they think that this information is essential.

[43]37 Council Directive 78/25/EEC of 12 December 1977 on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products.

[44]38 Ordinance on good laboratory practice (GLP) and verification of application of the principles of good laboratory practice for test on veterinary medicinal products (OG 69/07) transposes provisions of Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances.

[45]39 Council Directive 88/320/EEC of 9 June 1988 on the inspection and verification of Good Laboratory Practice (GLP).

[46]40 Ordinance on classification, packaging and labelling of dangerous substances (OG 23/08) transposes provisions of Annex V to Council Directive 67/548/EEC of 27 June 1967

on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.

[47]41 Council Directive 78/25/EEC of 12 December 1977 on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products.

[48]42 Council Directive 78/25/EEC of 12 December 1977 on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products.

[49]43 Council Directive 78/25/EEC of 12 December 1977 on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products.

[50]44 Ordinance on good laboratory practice (GLP) and verification of application of the principles of good laboratory practice for test on veterinary medicinal products (OG 69/07) transposes provisions of Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances.

[51]45 Council Directive 88/320/EEC of 9 June 1988 on the inspection and verification of Good Laboratory Practice (GLP).

[52]46 Ordinance on classification, packaging and labelling of dangerous substances (OG 23/08) transposes provisions of Annex V to Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.