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If a whole or part of a paragraph has been amended, the date of the amending regulation appears in square brackets at the end of the paragraph. If a whole paragraph or sub-paragraph has been deleted, the date of the deletion appears in square brackets beside the deleted paragraph or sub-paragraph.

Republic of Latvia

Cabinet

Regulation No. 600

Adopted 18 July 2006

Procedures for the Authorisation of Veterinary Medicinal Products

*Issued pursuant to
Section 5, Paragraphs three and six of the
Pharmaceutical Law*

I. General Provisions

1. This Regulation prescribes the procedures by which the Food and Veterinary Service shall register veterinary medicinal products.

[28 December 2010]

2. The following terms are used in this Regulation:

2.1. reference medicinal products - veterinary medicinal products which have been registered in a European Economic Area State or by centralised registration procedure in compliance with 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;

2.2. generic medicinal products - medicinal products which have the same qualitative and quantitative composition of active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of active substances shall be considered to be the same active substance, unless they have significantly different properties with regard to safety and efficacy or safety or efficacy. Different immediate release oral pharmaceutical forms shall be regarded as one pharmaceutical form;

2.3. batch of ready-made veterinary medicinal products – units of a pharmaceutical form which have been prepared from the same initial quantity of material and have undergone the same manufacturing and sterilisation or manufacturing or sterilisation. If the manufacturing process is continuous, a batch of ready-made veterinary medicinal products is all the units which have been manufactured in a specific time period;

2.4. strength – the content of active substances, expressed quantitatively per dosage unit, per unit of volume or weight according to the dosage form;

2.5. immunological veterinary medicinal product – a veterinary medicinal product administered to animals in order to produce active or passive immunity or to diagnose the state of immunity;

2.6. veterinary medicinal product:

2.6.1. any substance or combination of substances for treating or preventing disease in animals;

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

2.7. homeopathic veterinary medicinal product – a veterinary medicinal product prepared from homeopathic stocks (products, substances or combinations) in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or by the pharmacopoeias used officially in European Union Member States (hereinafter – Member States). A homeopathic medicinal product may contain a number of substances;

2.8. withdrawal period – the period between the last administration of the veterinary medicinal product to animals under normal conditions of use, and the production of foodstuffs from such animals. This time period shall be observed in order to protect public health by ensuring that such foodstuffs do not contain residues in quantities in excess of the maximum residue limits laid down pursuant to Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council (hereinafter – Regulation No 470/2009);

2.9. the name of the medicinal product:

2.9.1. the name assigned by the manufacturer, which shall not be confused with the common name (the International Non-proprietary Name (INN) recommended by the World Health Organisation or, if such has not been recommended, the usual common name); and

2.9.2. the common or scientific name supplemented by the trademark or the name of the holder (owner) of the marketing authorisation.

[15 September 2009; 16 November 2010]

3. It is permitted to distribute veterinary medicinal products for which the Food and Veterinary Service has issued a veterinary medicinal product marketing authorisation (hereinafter – marketing authorisation) in compliance with Annex 1 to this Regulation or which have been registered with the European Medicines Agency, by centralised registration procedure in compliance with 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.

[28 December 2010]

4. The Food and Veterinary Service shall take a decision regarding the re-authorisation of medicinal products or regarding the inclusion of data in the initial marketing authorisation for veterinary medicinal products for which the Food and Veterinary Service has issued a marketing authorisation in compliance with the requirements of this Regulation, in relation to additional information on the strength of such medicinal products, the pharmaceutical form, the method of administration, the presentation and extension of the marketing authorisation (supplementary application of the marketing authorisation). This decision shall be included in the initial decision regarding the authorisation of a veterinary medicinal product (especially in relation to the veterinary medicinal products referred to in Paragraphs 22, 23 and 24 of this Regulation.

[28 December 2010]

5. This Regulation shall not apply to:

5.1. medicated feedingstuffs, which is defined in regulatory enactments regarding the procedures for the circulation of medicated and dietary feed. It shall be taken into account that when preparing medicated feedingstuffs, pre-mixes are used (medicinal products prepared in advance in order to manufacture medicated feedingstuffs), which are registered in compliance with the requirements of this Regulation;

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

5.3. veterinary medicinal products based on radio-active isotopes;

5.4. any additives which, in accordance with Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition are published on the home page of the European Commission in the Register of Authorised Feed Additives, if these additives are added to animal feed or supplementary animal feed;

5.5. veterinary medicinal products intended for research and trials during the development of veterinary medicinal products; or

5.6. medicinal products prepared in a pharmacy;

5.7. [15 September 2009].

6. The holder (owner) of the marketing authorisation shall be responsible for the promotion of veterinary medicinal products on the market. The appointing of a representative shall not exempt the holder (owner) of the marketing authorisation from liability.

7. Veterinary medicinal products intended for use in food-producing animals (animals from which foodstuffs of animal origin are obtained) shall be registered if the active substances contained in the composition thereof are indicated in Commission Regulation (EU) No 37/2010 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin (hereinafter – Regulation No 37/2010).

[16 November 2010]

8. The holder (owner) of the marketing authorisation or, if necessary, the Food and Veterinary Service, shall perform the necessary measures in order to make changes in the authorisation documents or to cancel the marketing authorisation if the maximum residue limits of active substances specified in compliance with Regulation No 470/2009 differ from the quantity indicated in the authorisation documents. Changes shall be made or the marketing authorisation shall be cancelled within 60 days from the day that the amendments to Regulation No 37/2010 are published in the Official Journal of the European Communities.

[16 November 2010; 28 December 2010]

8.¹ When registering veterinary medicinal products, the Food and Veterinary Service shall determine whether they belong to the group of non-prescription or prescription veterinary medicinal products.

[15 September 2009; 28 December 2010]

8.² Veterinary medicinal products intended for administering to food-producing animals shall be classified as non-prescription veterinary medicinal products, if:

8.²1. they are not injectable and when administered externally or orally (*per os*), special knowledge or skills are not necessary;

8.²2. even if used in non-conformity with the package leaflet of the respective veterinary medicinal product, they do not cause a direct or indirect risk to the animal

(animals) being treated, to the person administering the medicinal product to the animal, or to the environment;

8.²³. they do not contain anti-parasitic and anti-microbial substances and even if used in non-conformity with the package leaflet of the respective veterinary medicinal product, do not cause a risk to human or animal health;

8.²⁴. the following is not present in the description thereof:

8.^{24.1}. warnings regarding potential serious side-effects (adverse reactions), which depend on the correct administration thereof;

8.^{24.2}. contra-indications towards other veterinary medicinal products which are used without a prescription are mentioned;

8.^{24.3}. a restriction period for the use of animal products following the administering of medicinal products has been determined;

8.²⁵. special conditions for storage are not necessary; or

8.²⁶. there has been no prior notification regarding frequent and severe side-effects (adverse reactions) caused by an active substance which the veterinary medicinal product or other medicinal products contain.

[2 October 2007]

8.³ If veterinary medicinal products are intended for administering both to food-producing animals and to domestic (household) animals and they do not comply with the conditions referred to in Paragraph 8.² of this Regulation, they shall be registered as prescription veterinary medicinal products.

[2 October 2007]

8.⁴ Only practicing veterinarians are permitted to perform operations with the following groups of medicinal products:

8.^{4.1}. immunological medicinal products;

8.^{4.2}. anaesthetics, general;

8.^{4.3}. narcotic analgesics;

8.^{4.4}. psychotropic agents; and

8.^{4.5}. medicinal products of a specific pharmaco-therapeutic group, if special precautionary measures must be observed during the administering thereof or if they may be harmful to human or animal health.

[15 September 2009]

8.⁵ If the veterinary medicinal products are distributed in Latvia or the holder (owner) of the veterinary medicinal product marketing authorisation has submitted a notification to the Food and Veterinary Service regarding the commencement of actual distribution (trade) of the veterinary medicinal products in Latvia or a notification regarding medicinal products which are no longer being placed on the market in Latvia (temporarily or permanently), the Food and Veterinary Service shall determine tax reliefs to the post-authorisation annual fee for veterinary medicinal products in accordance with the regulatory enactments on the State monitoring and control activities performed by the Food and Veterinary Services and payment of the paid services provided, if the following conditions are in effect:

8.^{5.1}. the respective veterinary medicinal products were distributed in Latvia in the previous calendar year and the annual turnover thereof did not exceed LVL 1500; and

8.^{5.2}. the holder (owner) of the veterinary medicinal product marketing authorisation has submitted a notification to the Food and Veterinary Service regarding the commencement date of actual distribution (trade) in Latvia or regarding veterinary medicinal products which are no longer being put on the market in Latvia (temporarily or permanently).

[15 September 2009; 28 December 2010]

8.⁶ The Food and Veterinary Service:

8.⁶1. shall include veterinary medicinal products for which a marketing authorisation has been issued in Latvia, veterinary medicinal products which have been registered by centralised registration procedure and parallel imported veterinary medicinal products in the Register of Veterinary Medicinal Products of the Republic of Latvia (hereinafter – Register of Veterinary Medicinal Products). The following minimum information shall be shown regarding veterinary medicinal products in the Register of Veterinary Medicinal Products:

8.⁶1.1. the name, strength or concentration, the pharmaceutical form, the number in a unit of immediate packaging, the classification group (in accordance with Paragraph 8.¹ of this Regulation) and the target species;

8.⁶1.2. the name of the active substance contained in the composition (the international non-proprietary name or widely used name) and the veterinary anatomical therapeutic chemical classification system code (ATC code);

8.⁶1.3. the date of issue, the authorisation number and holder (owner) of the marketing authorisation or authorisation for the distribution of parallel imported veterinary medicinal products; and

8.⁶1.4. the name and country of the manufacturer;

8.⁶2. shall ensure public access to the information referred to in Sub-paragraph 8.⁶1 of this Regulation, as well as to the approved veterinary medicinal product description, package leaflet and draft labelling on the Internet homepage of the Food and Veterinary Service;

8.⁶3. shall update information in the Register of Veterinary Medicinal Products, if changes have been made to the authorisation documents of veterinary medicinal products; and

8.⁶4. shall exclude veterinary medicinal products from the Register of Veterinary Medicinal Products, if the marketing authorisation or authorisation for the distribution of parallel imported veterinary medicinal products has expired or has been cancelled.

[16 November 2010; 28 December 2010]

8.⁷ The Food and Veterinary Service is entitled to perform an assessment of a product (including feed additives, biocides and animal care products) and to provide an opinion regarding the compliance of the definition of the veterinary medicinal product specified in the Pharmaceutical Law, if a submission is received or if a competent authority has shown initiative. In assessing a product, the following shall be taken into account:

8.⁷1. the qualitative and quantitative composition of the product;

8.⁷2. the pharmacological and immunological properties of a product, performing the assessment in accordance with scientific and technical opinions available during the period of the product assessment;

8.⁷3. the form, method of use and purpose of use of the product;

8.⁷4. whether a product with the same or a similar composition and method of use has been registered as a veterinary medicinal product;

8.⁷5. the risk to human and animal health which may be caused by using the product; and

8.⁷6. the information indicated in the product labelling and package leaflet, information regarding the effect of the product as well as other information available regarding the product.

[16 November 2010; 28 December 2010]

8.⁸ In order to provide the opinion referred to in Paragraph 8.⁷ of this Regulation, the Food and Veterinary Service may request the following information from the manufacturer or distributor of the product being assessed:

8.⁸1. the name, address and registration number of the authorisation for manufacturing or distributing operations;

8.⁸2. the product name, components and quantity thereof in units of mass or volume in one packaging unit;

8.⁸3. a description on the product properties, composition and specific components, which determine the product properties and effects, and the quantity of these ingredients in the product;

8.⁸4. the recommended method of use of the product and the dosage unit or exposure (product quantity and duration of the effect during one period of processing an animal);

8.⁸5. the type and amount of the packaging; and

8.⁸6. the labelling wording and, if necessary, a sample of the package leaflet, as well as other information regarding the product being assessed.

[16 November 2010; 28 December 2010]

8.⁹ The person who has submitted a submission for the conformity assessment of a product shall cover the expenses of the assessment referred to in Paragraph 8.⁷ of this Regulation in accordance with regulatory enactments on the State monitoring and control activities performed by the Food and Veterinary Services and payment of the paid services provided.

[16 November 2010; 28 December 2010]

8.¹⁰ Within one working day following the preparation of the opinion referred to in Paragraph 8.⁷ of this Regulation, the Food and Veterinary Service shall send it to the person who has requested the provision of an opinion and in electronic document form – to the competent authority at whose initiative the product assessment was performed. If a product in accordance with the opinion of the Food and Veterinary Service conforms with the definition of a veterinary medicinal product, the requirements of the regulatory enactments regulating the circulation of veterinary medicinal products shall be applied to the product.

[16 November 2010; 28 December 2010]

II. Procedures by which an Application for the Receipt of a Veterinary Medicinal Product Marketing Authorisation Shall be Submitted

9. In order to receive a marketing authorisation, a person in whose name it is anticipated to register a veterinary medicinal product (hereinafter – applicant), shall submit an application to the Food and Veterinary Service regarding the authorisation of a veterinary medicinal product (hereinafter – authorisation application).

[28 December 2010]

10. A sample authorisation application is published on the homepage of the Food and Veterinary Service. A authorisation application is drawn up observing the recommendations of the European Commission referred to in Section 28.¹ of the Pharmaceutical Law, which the European Commission has published in The Rules Governing Medicinal Products in the European Union, Volume 6B “Notice to Applicants, Veterinary Medicinal Products, Presentation and Content of the Dossier”.

[15 September 2009; 28 December 2010]

11. A authorisation application for the receipt of a marketing authorisation for such veterinary medicinal products which are intended for one or several species of food-producing animals and contain active substances which are not yet listed in relation to these animal species in Regulation No 37/20101, shall be submitted no sooner than six months following the submission of an application drawn up in conformity with the requirements for the determination of the maximum residue limits in accordance with Regulation No 470/2009.

[16 November 2010]

12. The Food and Veterinary Service shall issue a marketing authorisation to the applicant whose legal address is in a European Economic Area State (registered firm, central administration or actual place of operation).

[28 December 2010]

13. An applicant shall append to the authorisation application referred to in Paragraph 10 of this Regulation documents containing administrative information and scientific documentation which is necessary in order to prove the safety, efficacy and quality of the veterinary medicinal product to be registered in compliance with the requirements referred to in Annex 2 (in relation to pneumonological veterinary medicinal products), Annex 3 (in relation to immunological veterinary medicinal products), Annex 3.¹ or Annex 3.² to this Regulation, indicating or appending the following information:

13.1. the given name and surname of the applicant or the name and actual or legal address of the firm of a merchant. If the addresses differ, the applicant shall indicate information regarding the manufacturer or manufacturers of the veterinary medicinal product which are involved in the manufacture of the veterinary medicinal product, as well as information regarding the location of the manufacturing premises and the actual address thereof;

13.2. the name of the veterinary medicinal product;

13.3. the qualitative and quantitative values of the active substances and components included in the composition of the veterinary medicinal product. The International Non-proprietary Name (INN) which the World Health Organisation has recommended, if any, or the chemical name of the active substances shall be used;

13.4. a description of the method of manufacturing the veterinary medicinal product;

13.5. the therapeutic indications, contra-indications and side-effects (adverse reactions) of the veterinary medicinal product;

13.6. the dosage unit for the animal species for which the medicinal product is intended, the pharmaceutical form, the method of use and the method of administration and the term of validity thereof;

13.7. the precautionary and safety measures to be performed, which shall be observed when storing the medicinal product, administering the medicinal product to animals or disposing of the medicinal product waste. The potential risks (risk factors which are related to undesirable effects), which the medicinal product may cause to the surrounding environment and to human, animal or plant health, shall be indicated;

13.8. the period in which the medicinal product withdraws from the organism of an animal, if the medicinal product is intended for administering to food-producing animals;

13.9. a description of control methods used by the manufacturer;

13.10. results which have been obtained in:

13.10.1. pharmaceutical (physico-chemical, biological or microbiological) tests;

13.10.2. safety tests and residue tests;

13.10.3. non-clinical and clinical studies;

13.10.4. assessing the potential risk of the veterinary medicinal product to the surrounding environment. Each case of potential risk shall be examined separately, providing recommendations for reducing such risk;

13.11. a detailed description of the system for monitoring the side-effects of use of the veterinary medicinal product and, if necessary, a detailed description of the risk control system, which the applicant has intended to introduce;

13.12. a description of the veterinary medicinal product in accordance with Paragraph 35 of this Regulation;

13.13. a sample of the veterinary medicinal product package leaflet (hereinafter – package leaflet), which has been prepared in compliance with the regulatory enactments on the conditions for the labelling, distribution and control of veterinary medicinal products;

13.14. samples of the immediate packaging (container or other packaging which is in direct contact with the respective medicinal product) and secondary packaging (packaging into which the immediate packaging is placed), which have been prepared in compliance with the regulatory enactments of the conditions for the labelling, distribution and control of veterinary medicinal products;

13.15. a document certifying that the veterinary medicinal product manufacturer is authorised in its own country to produce veterinary medicinal products;

13.16. copies of the marketing authorisations which certify the authorisation of this medicinal product in another European Economic Area State or in a country which is not a European Economic Area State (hereinafter – third country), as well as:

13.16.1. a list of the European Economic Area States in which an application for the receipt of a marketing authorisation in compliance with the requirements of this Regulation is in the process of being examined. Copies of the description of each veterinary medicinal product submitted in a country referred to in the list and copies of the package leaflets shall be appended to this list (which has been prepared in compliance with Paragraph 35 of this Regulation or which has been recognised by a competent authority in compliance with Paragraphs 51, 52, 53, 54 and 55 of this Regulation);

13.16.2. information regarding a decision on refusal in relation to the issuance of a veterinary medicinal product marketing authorisation in a European Economic Area State or in a third country and the grounds for such a decision;

13.16.3. the information referred to in Sub-paragraphs 13.16.1 and 13.16.2 of this Regulation which shall be supplemented by the applicant as soon as there is additional information regarding the relevant decisions;

13.17. certification that there is a qualified person at the disposal of the applicant, who is responsible for the system of monitoring the side-effects caused by the use of the medicinal product in compliance with the regulatory enactments on the procedures for the monitoring of the side-effects of veterinary medicinal products, and that there are means available in order to notify of side-effects, which may be observed in European Economic Area States or in third countries;

13.18. in relation to veterinary products which are intended for one or several species of food-producing animals and contain one or several pharmacological active substances which, in relation to these animal species, have not yet been included in Regulation No 37/2010, a document which certifies that an application for the determination of the maximum residue limits of the medicinal product has been submitted to the European Medicines Agency in accordance with the Regulation referred to; and

13.19. a document certifying payment for the relevant service in accordance with the regulatory enactments on the State monitoring and control activities performed by the Food and Veterinary Services and payment of the paid services provided.

[2 October 2007; 15 September 2009; 16 November 2010; 28 December 2010]

14. The colouring matter contained in the composition of the veterinary medicinal product indicated in the authorisation documents comply with the requirements specified in the regulatory enactments on the mandatory requirements for harmless of food additives and food products, in which food additives are used. Other colouring matter may be added to veterinary medicinal products which are intended for exporting to third countries, if the use of such colouring matter is permitted in the country to which it is intended to export the veterinary medicinal products.

[16 November 2010]

15. The applicant shall ensure that a detailed summary of the results of the tests and studies referred to in Sub-paragraph 13.10 of this Regulation is prepared. The summary shall be prepared and signed by a person (expert) whose corresponding technical or professional qualification is described in a *Curriculum vitae*. The applicant shall submit the summary approved by an expert and the *Curriculum vitae* of the expert to the Food and Veterinary Service.

[28 December 2010]

16. If an applicant, in compliance with Paragraph 28 of this Regulation is entitled to not submit the results of safety tests and non-clinical and clinical studies, the expert shall justify the use of scientific information in accordance with the conditions referred to in Annexes 2, 3, 3.¹ and 3.² to this Regulation.

[16 November 2010]

17. The summary is part of the documents which the applicant for the authorisation of a medicinal product shall submit together with the authorisation application to the Food and Veterinary Service.

[28 December 2010]

18. The applicant shall not submit the results of safety and residue tests or non-clinical and clinical tests if he or she proves that the veterinary medicinal product to be registered is a generic medicinal product to a reference medical product which has been registered for at least eight years in accordance with Paragraph 3 of this Regulation in Latvia or in other European Economic Area States.

19. The veterinary medicinal product referred to in Paragraph 18 of this Regulation shall not be put on the market until 10 years have passed following the issuance of the initial marketing authorisation for the reference medicinal product.

20. Paragraph 18 of this Regulation shall also be applicable if the applicant has submitted a authorisation application to the Food and Veterinary Service in relation to a generic medicinal product but a marketing authorisation has not been issued in Latvia for the reference medicinal product. In this case the applicant shall indicate the European Economic Area State in which the reference medicinal product is or has been registered. The Food and Veterinary Service:

20.1. shall request the competent authority of the European Economic Area State in which the reference medicinal product is or has been registered to provide evidence that the respective reference medicinal product is or has been registered in this country, as well as information about the full composition of the reference medicinal product and, if necessary, other appropriate documents, within one month; and

20.2. upon request of the competent authority of the European Economic Area State to which a authorisation application of a veterinary medicinal product has been submitted, shall send confirmation that the reference medicinal product is registered or has been registered in Latvia, and other documents requested, within one month.

[28 December 2010]

21. The 10 year time period specified in Paragraph 19 of this Regulation may be extended up to 13 years for veterinary medicinal products which are intended for fish, bees or other animal species determined by the relevant decision of the European Commission.

22. The applicant shall submit the results of safety and residue tests, non-clinical or clinical studies to the Food and Veterinary Service, in relation to generic medicinal products, if:

22.1. the definition of generic medicinal product referred to in Sub-paragraph 2.2 of this Regulation cannot be applied to these veterinary medicinal products;

22.2. when performing bioavailability studies, the bioequivalence for the reference medicinal product cannot be proved; or

22.3. there are variations in the therapeutic indications, strength, pharmaceutical form or method of administration in relation to the reference medicinal products.

[28 December 2010]

23. If a biological veterinary medicinal product which is similar to the reference biological medicinal product, does not conform to the conditions referred to in the definition of generic medicinal products (in particular – due to the differences in the starting materials or manufacturing process of the biological veterinary medicinal product and the reference biological medicinal product), the applicant shall submit the results of non-clinical or clinical studies which relate to the conditions referred to. The type and quantity of the additional data to be submitted shall comply with the conditions referred to in Annexes 2 and 3 to this Regulation and to the criteria specified in the guidelines of the European Commission referred to in Paragraph 37 of this Regulation. The applicant is entitled not to submit the remaining results of the studies and tests included in the reference medicinal product dossier.

24. The Food and Veterinary Service shall extend the 10 year time period referred to in Paragraph 23 of this Regulation for veterinary medicinal products which are intended for one or several species of food-producing animals and contain active substances which have not been registered in the Community until 30 April 2010 by one year for each extension of the marketing authorisation in relation to other food-producing animal species if such extension is approved within five years from the granting of the initial marketing authorisation.

[28 December 2010]

25. The time period referred to in Paragraph 24 of this Regulation shall not exceed 13 years in total for veterinary medicinal products which are intended for four or more food-producing animal species.

26. An extension of the 10 year time period up to 11, 12 or 13 years shall be granted for veterinary medicinal products which are intended for food-producing animals if the holder (owner) of the marketing authorisation has in accordance with Regulation No 470/2009 submitted an application to the European Medicines Agency for the determination of such maximum residue limits of a medicinal product which is intended for animal species which are referred to in the marketing authorisation.

[16 November 2010]

27. Studies and inspections, as well as practical requirements which shall be applied in compliance with Paragraphs 18, 19, 20, 21, 22, 23 and 24 of this Regulation shall not be considered as contrary to the patent rights or supplementary protection certificates of veterinary medicinal products.

28. The applicant shall not submit the results of safety and residue tests or non-clinical and clinical studies if he or she proves that the active substances incorporated in the composition of the veterinary medicinal product have been generally recognised in the veterinary practice of the European Community for at least 10 years, this medicinal product has a recognised efficacy and permissible degree of safety in compliance with the requirements referred to in Annex 2 (in relation to pneumonological veterinary medicinal products) or Annex 3 (in relation to immunological veterinary medicinal products) to this Regulation. The applicant shall indicate the scientific literature used.

[15 September 2009]

29. The applicant may use the assessment report published by the European Medicines Agency following the assessment of the application for the determination of the maximum residue limits of the medicinal product in accordance with Regulation No 470/2009 as the scientific literature referred to in Paragraph 28 of this Regulation (in particular - regarding the safety test of the veterinary medicinal product).

[16 November 2010]

30. If the applicant uses scientific literature in order to receive a marketing authorisation for a veterinary medicinal product which is intended for administering to food-producing animals, and in order to extend the marketing authorisation (in order that this medicinal product may be used for other food-producing animal species), the applicant shall submit new study results of veterinary medicinal product residue concurrently with the results of additional clinical studies, in compliance with Regulation No 470/2009. Third persons shall not use these studies and the results thereof for three years from the day when the marketing authorisation was granted, in connection with which the studies referred to were carried out.

[16 November 2010]

31. If veterinary medicinal products contain active substances which are used in the composition of the registered veterinary medicinal products (combined veterinary medicinal products), but which have not been used in the composition of one veterinary medicinal product for therapeutic reasons before, the results of non-clinical and clinical studies on the active substances of such veterinary medicinal product and, if necessary, the results of safety and residue tests, shall be submitted.

[15 September 2009]

32. In respect of the veterinary medicinal products referred to in Paragraph 31 of this Regulation, scientific references shall not be provided for each active substance separately (application for the informed consent of a person).

[15 September 2009]

33. Following the receipt of a marketing authorisation, the holder (owner) of a marketing authorisation is entitled to use pharmaceutical, safety and residue, non-clinical and clinical documentation, which is included in the dossier of a registered veterinary medicinal product, in order to examine a subsequent authorisation application of a veterinary medicinal product with the same qualitative and quantitative composition of active substances and pharmaceutical form.

34. In emergency situations the applicant for the authorisation of an immunological veterinary medicinal product is permitted not to submit the results of such field trials which have been performed on the target species (animal species for which the medicinal product is intended), if such investigations cannot be performed for explicitly expressed justified reasons and in compliance with other regulatory enactments of the European Union.

35. The following information shall be included in the summary of the veterinary medicinal product characteristics (in the order shown):

35.1. the name of the veterinary medicinal product, followed by the strength and pharmaceutical form;

35.2. qualitative and quantitative composition in terms of the active substances and excipient, the knowledge of which is essential for proper administration to animals (the usual common name or chemical name shall be used);

- 35.3. pharmaceutical form;
- 35.4. clinical data:
 - 35.4.1. target species;
 - 35.4.2. indications for use of the medicinal product, specifying the target species;
 - 35.4.3. contra-indications;
 - 35.4.4. side effects (frequency and degree of severity);
 - 35.4.5. special precautionary measures in respect of each target species;
 - 35.4.6. special precautions for use, including special precautions to be taken by the person administering the medicinal product to the animals;
 - 35.4.7. use of the medicinal product during pregnancy, lactation or lay;
 - 35.4.8. interaction with other medicinal products and other forms of interaction;
 - 35.4.9. amount of veterinary medicinal product to be administered (dosage unit) and the method of administration;
 - 35.4.10. symptoms and procedures in case of overdose (emergency procedures, antidotes);
 - 35.4.11. withdrawal periods for the various foodstuffs of animal origin, including those products for which the withdrawal period is zero;
- 35.5. pharmacological properties:
 - 35.5.1. pharmacodynamic properties;
 - 35.5.2. pharmacokinetic particulars;
- 35.6. pharmaceutical particulars:
 - 35.6.1. list of excipients;
 - 35.6.2. major incompatibilities of the medicinal product;
 - 35.6.3. term of validity of the medicinal product and indications regarding the term of validity of the medicinal product following the dilution of the medicinal product or the opening of the immediate packaging;
 - 35.6.4. special instructions for the storage of the medicinal product;
 - 35.6.5. type and content of the immediate packaging;
 - 35.6.6. special instructions for actions with unused medicinal products or the waste materials thereof, if any;
- 35.7. holder (owner) of the marketing authorisation (given name, surname or name and legal address or registered place of entrepreneurial activities);
- 35.8. marketing authorisation number or certificate numbers;
- 35.9. date when the marketing authorisation was initially issued or re-registered; and
- 35.10. date when the wording of the medicinal product description was clarified.

36. When submitting a veterinary medicinal product for authorisation in compliance with Paragraphs 18, 19, 20, 21, 22, 23, 24, 25, 26 and 27 of this Regulation, the parts of the summary of the medicinal product characteristics of the reference medicinal product, which relate to indications or dosages and to which patent rights are still applicable during the period of trade of the generic medicinal product, need not be indicated.

37. The applicant shall prepare the documentation to be appended to the authorisation application in conformity with the following requirements:

37.1. when drawing up the documentation to be appended to the authorisation application, the requirements specified in Chapter II and Annexes 2, 3, 3.¹ and 3.² to this Regulation and the recommendations of the European Commission referred to in Section 28.¹ of the Pharmaceutical Law (hereinafter – guidelines) published in The Rules Governing Medicinal Products in the European Union, Volume 6B “Notice to Applicants, Veterinary Medicinal Products, Presentation and Content of the Dossier” shall be observed;

37.2. newest scientific insights regarding veterinary medicinal products and the European Commission guidelines regarding the quality, safety and efficacy of veterinary medicinal products, which the European Commission has published in The Rules Governing Medicinal Products in the European Union, shall be taken into account;

37.3. in the documentation for veterinary medicinal products which are not immunological veterinary medicinal products in respect of the quality (physical, chemical, biological and microbiological tests) and immunological veterinary medicinal products in respect of the quality, safety and efficacy, the appropriate monographs shall be applied, as well as the general monographs of the European Pharmacopoeia and the general chapters thereof;

37.4. the process of manufacturing veterinary medicinal products described in the documentation shall conform to the principles of good manufacturing practice and the guidelines shown in Volume 5 of The Rules Governing Medicinal Products in the European Union, as well as the requirements specified in the regulatory enactments regulating the manufacturing of veterinary medicinal products;

37.5. information regarding the results of the assessment of the veterinary medicinal product shall be included in the documentation. The applicant shall submit to the Food and Veterinary Service information regarding the tests or studies performed on the veterinary medicinal products to be registered, which are incomplete or have not been finished;

37.6. the pharmacological, toxicological, residue determination and safety tests described in the documentation shall be performed in accordance with the requirements of the regulatory enactments regulating good laboratory practices;

37.7. experiments with animals shall be performed in compliance with regulatory enactments on the procedures by which activities shall be performed with experimental animals and the procedure by which the requirements of welfare shall be ensured for animals; and

37.8. an environmental risk assessment shall be indicated in the documentation for such veterinary medicinal products which contain or comprise of genetically modified organisms. Information shall be submitted in compliance with regulatory enactments regarding the procedures by which genetically modified organisms shall be distributed in the environment or put on the market, and 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.

[15 September 2009; 28 December 2010]

37.¹ The Food and Veterinary Service may determine exceptions to the authorisation of veterinary medicinal products, if the veterinary medicinal products are intended for specific animal species and small sectors of the market (for one animal species, rare diagnoses, for the performance of rare veterinary medicinal manipulation). When determining exceptions, the Food and Veterinary Service shall take into account the relevant scientific guidelines or perform scientific consultations.

[15 September 2009; 28 December 2010]

37.² The applicant shall submit all the information which has not initially been included in the documentation appended to the application, as well as the information on the monitoring of the safe use of medicinal products (pharmacovigilance) to the Food and Veterinary Service, in order to evaluate the risk/benefit balance.

[15 September 2009; 28 December 2010]

37.³ The holder (owner) of the veterinary medicinal product marketing authorisation shall submit information regarding changes to the content of the authorisation documents in

accordance with Commission Regulation (EC) No 1234/2008 of 28 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medical products (hereinafter - Regulation No 1234/2008), if the holder (owner) of the respective veterinary medicinal product marketing authorisation has received it in compliance with Article 1 of Regulation No 1234/2008.

[16 November 2010]

III. Procedures By Which Homeopathic Veterinary Medicinal Products Shall Be Registered

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

39. The Food and Veterinary Service:

39.1. shall register homeopathic veterinary medicinal products which are manufactured and distributed in Latvia, in accordance with the requirements of this Regulation;

39.2. for homeopathic veterinary medicinal products which comply with the requirements of Paragraph 40 of this Regulation:

39.2.1. shall establish a simplified registration procedure; and

39.2.2. shall apply Paragraphs 73, 74, 75, 76, 77, 78, 79, 80 and 81 of this Regulation.

[28 December 2010]

40. The Food and Veterinary Service shall apply the simplified registration procedure to homeopathic veterinary medicinal products, whose:

40.1. method of administration conforms to a monograph of the European Pharmacopoeia or, if there is none, to the monographs of the pharmacopoeia officially used by the European Economic Area States;

40.2. labelling and package leaflet or any of the documents submitted for authorisation do not indicate specific therapeutic indications; or

40.3. degree of dilution is sufficiently high to ensure the safety of the medicinal product. The medicinal products do not contain more than 10 000 parts of the mother tincture (basic tincture).

[28 December 2010]

41. When registering homeopathic veterinary medicinal products, the Food and Veterinary Service shall classify them as prescription or non-prescription (medicinal products which may be distributed without a prescription) medicinal products.

[28 December 2010]

42. The criteria and conditions in the simplified registration procedure for the homeopathic veterinary medicinal products referred to in Paragraph 40 of this Regulation shall be used in compliance with the requirements referred to in Chapter IV of this Regulation. The requirements referred to in Paragraphs 51, 52, 53, 54 and 55 of this Regulation and the requirements for the drawing up of documents certifying the therapeutic effects of medicinal products shall not be applicable.

43. The applicant who is registering a homeopathic veterinary medicinal product, applying the simplified registration procedure, shall submit the authorisation application to the Food and Veterinary Service. Homeopathic veterinary medicinal products which have been obtained

from the same homeopathic stock (stocks) may be included in the application for simplified authorisation. In order to prove the quality of the homeopathic veterinary medicinal product and the homogeneity of the batch produced (batch identity of the medicinal product), the applicant for the authorisation of a homeopathic veterinary medicinal product shall append the following to the authorisation application:

43.1. a document in which the scientific name of the homeopathic stock or stocks is described, or the name indicated in the pharmacopoeia, together with a description of the methods of administration of the medicinal product, the pharmaceutical forms and the degree of dilution;

43.2. a description regarding the acquisition, control and homeopathic effects of the homeopathic stock or stocks, using the relevant bibliography. If the homeopathic veterinary medicinal product contains biological substances, the measures performed for ensuring the medicinal product against pathogenic micro-organisms shall be described;

43.3. a document regarding the manufacture and control of each pharmaceutical form;

43.4. a description of the dilution and potentiation;

43.5. the special authorisation (licence) for manufacturing of the relevant homeopathic medicinal product;

43.6. copies of marketing authorisations issued in other European Economic Area states, which have been issued for the same homeopathic veterinary medicinal product;

43.7. samples of the primary and secondary packaging of one or several homeopathic medicinal products to be registered or sample advertisements thereof;

43.8. a document which certifies the stability of the homeopathic veterinary medicinal product; and

43.9. the recommended withdrawal period for the medicinal product and the grounds for the determination thereof.

[28 December 2010]

44. The simplified registration procedure shall not be applied to homeopathic veterinary medicinal products which are not referred to in Paragraph 40 of this Regulation (which are intended for the treatment of food-producing animals). The procedure for the issuance of a marketing authorisation for these homeopathic veterinary medicinal products shall comply with the requirements referred to in Paragraphs 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 37.¹ and 37.² of this Regulation.

[15 September 2009]

45. The Food and Veterinary Service is entitled to apply exemptions in respect of safety tests and clinical and non-clinical studies for homeopathic veterinary medicinal products which are intended for administering to pet species and non-food-producing exotic species in accordance with the principles and characteristics of homeopathy as practised in Latvia. In such case the Food and Veterinary Service shall notify the European Commission of the applicable exemptions.

[28 December 2010]

IV. Procedure by Which an Authorisation Application Shall Be Examined and a Veterinary Medicinal Product Marketing Authorisation Shall Be Issued

46. The Food and Veterinary Service shall issue a veterinary medicinal product marketing authorisation within 210 days from the day when the authorisation application drawn up in compliance with this Regulation is received. A authorisation application which has been submitted for one veterinary medicinal product in two or more European Economic Area States, shall be examined in accordance with the requirements specified in Chapter V of this Regulation.

[28 December 2010]

47. The Food and Veterinary Service is entitled to suspend the examination of a authorisation application if the authorisation application and the dossier is already being examined in another European Economic Area State. In such case the Food and Veterinary Service shall inform the applicant that it is applying the requirements referred to in Chapter V of this Regulation.

[28 December 2010]

48. If the Food and Veterinary Service receives information in accordance with Sub-paragraph 13.16 of this Regulation that veterinary medicinal products for which a authorisation application has been submitted to the Food and Veterinary Service have received a marketing authorisation in a European Economic Area State, the Food and Veterinary Service shall reject the authorisation application unless it has been submitted in compliance with the requirements referred to in Chapter V of this Regulation.

[16 November 2010; 28 December 2010]

49. The Food and Veterinary Service shall examine a authorisation application which has been submitted in accordance with the requirements referred to in Paragraphs 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33 and 34 of this Regulation, and:

49.1. shall check the information indicated in the documents appended to the authorisation application;

49.2. may send the main veterinary medicinal product, the starting materials thereof and, if necessary, the intermediate products or other constituent materials of the medicinal product for laboratory testing to a laboratory which is entitled to control medicinal products, in order to check whether the control methods of the medicinal product indicated by the medicinal product manufacturer in the registration dossier submitted are sufficient for the qualitative control of the veterinary medicinal product;

49.3. shall request that the applicant provides additional information, if the information submitted is not complete. The period of authorisation referred to in Paragraph 46 of this Regulation shall be extended up to the moment that the documents requested are submitted to the Food and Veterinary Service or, if necessary, the applicant has provided an oral or written explanation to questions arising when examining the registration dossier submitted; and

49.4. may request that the applicant submits to the Food and Veterinary Service the necessary substances in the quantities required in order to check the analytical methods for the determination of residue of such a veterinary medicinal product, which the applicant has indicated in the registration dossier.

[28 December 2010]

50. The Food and Veterinary Service:

50.1. shall inspect whether the manufacturer of the veterinary medicinal product is capable of producing the veterinary medicinal product in accordance with the information submitted in accordance with Sub-paragraph 13.4 of this Regulation and perform the quality control of the veterinary medicinal product with methods which are shown in the documents submitted for authorisation in accordance with Sub-paragraph 13.9 of this Regulation. If in separate justified cases a third person performs some phases of the manufacture of the veterinary medicinal product or the quality control of the veterinary medicinal product for the manufacturer of the veterinary medicinal product, the Food and Veterinary Service is entitled to perform an inspection of the respective undertaking;

50.2. shall inspect whether the importer of the veterinary medicinal product from a third country is capable of performing the quality control of the veterinary medicinal product with the methods which are shown in the documents submitted for authorisation in accordance with Sub-paragraph 13.9 of this Regulation. If in separate justified cases a third person performs the quality control of the veterinary medicinal product for the importer of the veterinary medicinal product from third countries, the Food and Veterinary Service is entitled to perform an inspection of the respective undertaking; and

50.3. when inspecting the conformity of a veterinary medicinal product with Sub-paragraph 50.1 of this Regulation, shall take into account the procedures specified in the European Commission's Compilation of Community Procedures on Inspections and Exchange of Information.

[28 December 2010]

51. The Food and Veterinary Service shall issue a marketing authorisation and approve the summary of the product characteristics. The Food and Veterinary Service shall inform the holder (owner) of the marketing authorisation of the approved summary of the product characteristics.

[28 December 2010]

52. The Food and Veterinary Service shall ensure that the information regarding a veterinary medicinal product (in particular, the labelling and package leaflet of the medicinal product) conforms with the summary of the product characteristics, which the Food and Veterinary Service has approved concurrently with the marketing authorisation or thereafter.

[28 December 2010]

53. The Food and Veterinary Service shall without delay ensure public access to the marketing authorisation of the registered veterinary medicinal product and the summary of the product characteristics on the Internet homepage of the Food and Veterinary Service.

[28 December 2010]

54. The Food and Veterinary Service shall prepare an assessment report of the veterinary medicinal product in which comments regarding the documents submitted for authorisation (including the results of pharmacological, safety and residue tests and non-clinical and clinical studies) are included. The assessment report of the veterinary medicinal product shall be supplemented with new information regarding the quality, safety and efficacy of the veterinary medicinal product as soon as such information becomes available.

[28 December 2010]

55. The Food and Veterinary Service shall remove commercially confidential information from the assessment report of the veterinary medicinal product referred to in Paragraph 54 of this Regulation and publish the remaining wording of the report on the Internet homepage of the Food and Veterinary Service.

[28 December 2010]

56. The Food and Veterinary Service is entitled to request that the holder (owner) of the marketing authorisation shows information on the primary or secondary packaging and the package leaflet information regarding precautionary measures to be observed when administering the medicinal product to an animal, or other information necessary for the protection or safety of human and animal health, which has become known following the results of pharmacological tests or clinical studies or use of the medicinal product in a veterinary medicinal practice.

[28 December 2010]

57. In exceptional cases due to objective and verifiable reasons the Food and Veterinary Service, following consultation with the applicant, is entitled to take a decision regarding the authorisation of a veterinary medicinal product, if the applicant fulfils specific requirements (in particular, in respect of the safety of the medicinal product), and may also notify of incidents in relation to the use of the veterinary medicinal product and measures performed. The marketing authorisation shall remain valid if the Food and Veterinary Service re-evaluates the fulfilment of requirements each year.
[28 December 2010]

58. Following the receipt of a marketing authorisation, the holder (owner) thereof, taking into account the progress of science and technology, shall improve the veterinary medicinal product control methods, in order for the veterinary medicinal product to be manufactured and tested in conformity with generally recognised scientific methods. The Food and Veterinary Service shall be informed of changes. The Food and Veterinary Service shall evaluate and approve the changes.
[28 December 2010]

59. Upon request of the Food and Veterinary service, the holder (owner) of the marketing authorisation shall:

59.1. ensure a sufficient quantity of substances in order to perform the determination of veterinary medicinal product residual substances in compliance with the regulations regarding the determination of medicinal product residue and the procedures for the financing thereof; and

59.2. based on his or her experience, provide technical consultations in order to ease the implementation of the analytical methods for the determination of veterinary medicinal product residue in the State scientific institute, “The Institute of Food Safety, Animal Health and Environment”.

[15 December 2009]

60. The holder (owner) of the marketing authorisation shall inform the Food and Veterinary Service without delay, if information is available:

60.1. due to which information or documents need supplementing, which have been drawn up in compliance with the requirements of Paragraphs 13, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 35, 36, 37, 37.² and 37.³ of this Regulation or Annexes 2, 3, 3.¹ and 3.² to this Regulation.

60.2. regarding the restrictions or prohibitions of the competent authorities in relation to the veterinary medicinal products in each country in which these veterinary medicinal products have been put on the market; and

60.3. which may affect the evaluation of the risk/benefit balance of these veterinary medicinal products. In order to continue the evaluation of the risk/benefit balance, the Food and Veterinary Service is entitled to request that the holder (owner) of the marketing authorisation provides information which certifies that the risk/benefit balance remains favourable.

[15 September 2009; 16 November 2010; 28 December 2010]

61. The holder (owner) of the marketing authorisation shall without delay inform the Food and Veterinary Service if amendments are necessary to the veterinary medicinal product registration dossier or the marketing authorisation referred to in Paragraphs 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33 and 34 of this Regulation.

[28 December 2010]

62. Following the receipt of a marketing authorisation the holder (owner) thereof shall inform the Food and Veterinary Service of:

62.1. the day that the registered veterinary medicinal product is put on the market, taking into account the registered pharmaceutical forms; and

62.2. the time period for which the putting of the veterinary medicinal product on the market or the withdrawal of the veterinary medicinal product from the market was suspended. The holder (owner) of the marketing authorisation shall notify the information referred to not later than two months before the day when the putting of the veterinary medicinal product on the market is suspended, except extraordinary circumstances.

[28 December 2010]

63. Upon request of the Food and Veterinary Service the holder (owner) of the marketing authorisation shall show all the data regarding the volume of the sale of the veterinary medicinal product and the data at the disposal thereof regarding the amount of prescriptions issued, in conformity with the system of monitoring the side-effects caused by the use of the veterinary medicinal product.

[28 December 2010]

64. A marketing authorisation shall be valid for five years.

65. After five years, the marketing authorisation shall be re-registered, based on the repeat assessment of the risk/benefit balance. The holder (owner) of the marketing authorisation shall submit an application to the Food and Veterinary Service and a consolidated list appended thereto, in which the documents which have been submitted regarding the quality, safety and efficacy of the veterinary medicinal product are indicated, and all the amendments which have been introduced since the initial issue of the marketing authorisation. The holder (owner) of the marketing authorisation shall submit the application and the consolidated list to the Food and Veterinary Service not later than six months before the expiry of the marketing authorisation. The Food and Veterinary Service is entitled to request at any time that the holder (owner) of the marketing authorisation submits the documents indicated in the list, in order to update the information submitted.

[28 December 2010]

66. Following re-authorisation the marketing authorisation in accordance with Paragraph 65 of this Regulation is valid for an indefinite period (except cases where the Food and Veterinary Service, based on the results of the system of monitoring the side-effects caused by the use of the veterinary medicinal product, determines one additional re-authorisation after five years in accordance with Paragraph 65 of this Regulation).

[28 December 2010]

67. A marketing authorisation shall be considered to be invalid if none of the pharmaceutical forms or the type of sales packaging:

67.1. are placed on the market within three years after the taking of the decision regarding the authorisation of the relevant veterinary medicinal product; or

67.2. are sold for three years in succession following the putting on the market thereof.

[15 September 2009]

68. The Food and Veterinary Service, taking into account extraordinary circumstances and considerations of the protection of human or animal health, is entitled to make exceptions in respect of the conditions referred to in Paragraph 67 of this Regulation, if a submission is received by the owner (holder) of the veterinary medicinal product marketing authorisation

regarding the retention of the operation of the relevant veterinary medicinal product marketing authorisation.
[28 December 2010]

69. The owner (holder) of the veterinary medicinal product certificate shall submit the submission referred to in Paragraph 68 of this Regulation to the Food and Veterinary Service not later than three months before the setting in of the conditions referred to in Sub-paragraphs 67.1 or 67.2 of this Regulation, indicating the grounds for the retention of the operation of the veterinary medicinal product marketing authorisation.
[15 September 2009; 28 December 2010]

69.¹ The Food and Veterinary Service:

69.¹1. following the receipt of the submission referred to in Paragraph 68 of this Regulation, in accordance with the procedures specified by the Administrative Procedure Law, shall evaluate:

69.¹1.1. the grounds referred to in the submission;

69.¹1.2. the significance of the relevant veterinary medicinal product to the protection of human and animal health (and whether the medicinal product is necessary for the treatment of rare diseases in animals, for the performance of rare medicinal manipulation, for the treatment or prevention of disease in rare, exotic or small-numbered animal species), by consulting with the Latvian Association of Veterinarians;

69.¹2. shall take a decision regarding the retention of the operation of the veterinary medicinal product marketing authorisation or the suspension of the operation of the marketing authorisation;

69.¹3. shall determine the extension of the period of operation of the veterinary medicinal product marketing authorisation referred to in the submission, for a period not exceeding three years. If, during the period of the extension of the period of operation, the veterinary medicinal product is put on the market and sold, the marketing authorisation shall be valid in accordance with the conditions referred to in Paragraphs 65 and 66 of this Regulation; and

69.¹4. shall inform the owner of the marketing authorisation of the decision taken.

[15 September 2009; 16 November 2010; 28 December 2010]

70. The issue of a marketing authorisation shall not affect the responsibility of the veterinary medicinal product manufacturer and the holder (owner) of the marketing authorisation.

71. The Food and Veterinary Service shall not issue a marketing authorisation, if:

71.1. when examining the documents submitted for the authorisation of a veterinary medicinal product, it is established that the documents submitted for authorisation do not comply with the requirements referred to in Paragraphs 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33 and 34 of this Regulation;

71.2. according to the documents submitted for authorisation and the inspection of the data, it is established that:

71.2.1. the risk/benefit balance when administering them in the method indicated in the registration dossier, are unfavourable (in particular, when evaluating the benefits in relation to the health and welfare of animals and consumer safety in respect of the veterinary medicinal product which is used for zootechnical purposes);

71.2.2. the veterinary medicinal product does not have the therapeutic effects indicated in the registration dossier or the applicant has not provided sufficient evidence of such effects in the target species of animals indicated in the registration dossier;

71.2.3. the qualitative and quantitative composition of the veterinary medicinal product does not comply with the data indicated in the registration dossier;

71.2.4. the withdrawal period of the veterinary medicinal product recommended by the applicant:

71.2.4.1. is not sufficiently long to ensure that the food products of animal origin acquired from treated animals do not contain residue of the veterinary medicinal product in quantities harmful to consumer health;

71.2.4.2. is not sufficiently justified;

71.2.5. the labelling or the package leaflet of the veterinary medicinal product offered by the applicant does not comply with the requirements specified in the regulations for the labelling, distribution and control of veterinary medicinal products; and

71.2.6. the method of administering the veterinary medicinal product is prohibited in the European Union.

[28 December 2010]

72. The applicant or the holder of the authorisation permit is responsible for the accuracy of the data submitted.

72.¹ The Food and Veterinary Service, observing the requirements specified in Section 31 of the Pharmaceutical Law and Paragraphs 47 or 71 of this Law or upon request of the applicant, shall suspend or cancel the authorisation, re-authorisation or examination of the changes to the registration dossier of the veterinary medicinal product. The Food and Veterinary Service shall cover the expenses of the operations performed from the payment which the applicant has paid in accordance with Paragraphs 13, 73, 94, 96 and 109 of this Regulation. When covering the expenses referred to, the Food and Veterinary Service shall observe the following conditions:

72.¹1. if the expert-examination referred to in Paragraphs 9, 43, 73, 94, 96 (in relation to the extension of the authorisation) and in Paragraph 109 of this Regulation has been performed, in which the compliance of the application with the requirements of this Regulation is determined (hereinafter – primary expert-examination), 10 percent shall be withheld from the payment for the relevant service specified in the regulatory enactments on the State monitoring and control activities performed by the Food and Veterinary Services and payment of the paid services provided;

72.¹2. if a primary expert-examination has been performed and the assessment of data and documentation has commenced, 50 percent of the payment for the relevant service specified in the regulatory enactments on the State monitoring and control activities performed by the Food and Veterinary Service and payment of the paid services provided shall be withheld; or

72.¹3. if the assessment of data and documentation has been performed, 90 percent of the payment for the relevant service specified in the regulatory enactments on the State monitoring and control activities performed by the Food and Veterinary Service and payment of the paid services provided shall be withheld.

[16 November 2010; 28 December 2010]

72.² The Food and Veterinary Service shall repay the remaining part of money from the amount which has been paid in by the applicant in accordance with Paragraphs 13, 73, 94, 96 and 109 of this Regulation to the applicant within 30 calendar days from the day when a submission is received from the applicant for the repayment of money, preparing an estimate and performing a transfer with the intermediation of a credit institution. In the submission for the repayment of money the applicant shall indicate the details of the credit institution and the account number to which the Food and Veterinary Service shall perform the transfer of money.

[16 November 2010; 28 December 2010]

V. Procedures by which Veterinary Medicinal Products are Registered Using the Mutual Recognition Procedure and the Decentralised Procedure

73. In order to register a medicinal product in more than one European Economic Area State (hereinafter - involved Member States), the applicant shall submit a authorisation application of a veterinary medicinal product to the competent authority of each involved Member State (in Latvia – the Food and Veterinary Service), fulfilling the following conditions:

73.1. the administrative information and scientific and technical information shall be included in the registration dossier of the veterinary medicinal product in compliance with the requirements referred to in Paragraphs 10, 11, 12, 13, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 35, 36, 37, 37.¹ and 37.² of this Regulation;

73.2. the same registration dossier shall be submitted to all involved Member States;

73.3. a list of the involved Member States to which the registration dossier has been submitted shall be appended to the registration dossier; and

73.4. a document certifying payment for the relevant service in accordance with the regulatory enactments on the State monitoring and control activities performed by the Food and Veterinary Services and payment of the paid services provided shall be appended to the registration dossier. The document regarding payment shall be drawn up in accordance with Sub-paragraph 13.19 of this Regulation.

[2 October 2007; 16 November 2010; 28 December 2010]

74. If during the period of submission of the authorisation application, the veterinary medicinal products in the involved Member States:

74.1. are registered, the veterinary medicinal products shall be registered in accordance with the mutual recognition procedure; or

74.2. are in the process of authorisation, the veterinary medicinal products shall be registered by the decentralised procedure.

75. Prior to the submission of a authorisation application of a veterinary medicinal product, using the mutual recognition procedure, the applicant shall request one of the involved Member States to be the reference Member State and prepare an assessment report for the veterinary medicinal product. If the reference Member State is Latvia, the Food and Veterinary Service shall prepare an assessment report for the relevant veterinary medicinal product or renew the assessment report in accordance with the procedures specified in the Administrative Procedure Law, but not later than within 90 days following the receipt of the authorisation application conforming to the requirements. If necessary, the Food and Veterinary Service shall incorporate the assessment in the assessment report in compliance with the requirements referred to in Paragraphs 26, 27 and 28 or the requirements referred to in Paragraph 32 of this Regulation. The Food and Veterinary Service shall send the assessment report with the approved summary of the veterinary medicinal product characteristics, the labelling and package leaflet to the applicant and involved Member States.
[28 December 2010]

76. If until the day of the submission of the authorisation application a marketing authorisation has not been issued in another involved Member State and Latvia is the reference Member State, the applicant shall request that the Food and Veterinary Service prepares a draft assessment report and draft summary of the product characteristics, labelling and package leaflet. The Food and Veterinary Service shall prepare the draft project in accordance with the procedures specified by the Administrative Procedure Law, but not later than within 120 days following the receipt of the valid authorisation application and send it to the involved Member States and to the applicant.
[28 December 2010]

77. Within 90 days following the receipt of the draft assessment report and the draft summary of the product characteristics, labelling and package leaflet referred to in Paragraphs 75 or 76 of this Regulation, the Food and Veterinary Service shall:

77.1. approve the documents referred to and inform the reference Member State thereof, if Latvia is an involved Member State; and

77.2. following the receipt of information from the involved Member States, register the agreement of the involved Member States, conclude the procedure and inform the applicant thereof without delay, if Latvia is the reference Member State.

[28 December 2010]

78. If a authorisation application of a veterinary medicinal product has been submitted to the Food and Veterinary Service in accordance with Paragraph 73 of this Regulation, the Food and Veterinary Service shall:

78.1. take a decision in conformity with the approved assessment report, summary of the product characteristics, labelling and package leaflet in accordance with the procedures specified by the Administrative Procedure Law, but not later than within 30 days following the approval of the agreement referred to in Sub-paragraph 77.2 of this Regulation; and

78.2. inform the reference Member State, the applicant for authorisation and other involved Member States of the decision taken.

[28 December 2010]

79. If the Food and Veterinary Service, on the grounds that the veterinary medicinal product to be registered may threaten human or animal health or the surrounding environment, does not approve the assessment report, summary of the product characteristics, labelling and package leaflet within 90 days, the Food and Veterinary Service shall:

79.1. submit a detailed statement of reasons to the applicant, reference Member State and involved Member States; and

79.2. regarding matters on which agreement has not been reached, without delay inform the Co-ordination Group, which has been established in the European Medicines Agency, in order to examine all matters related to the authorisation of medicinal products in two or more European Economic Area States (hereinafter – Co-ordination Group). The European Medicines Agency shall ensure the work of the Co-ordination Group secretariat.

[28 December 2010]

80. In order to justify the refusal to issue a marketing authorisation for an immunological veterinary medicinal product by the decentralised procedure, the Food and Veterinary Service is entitled to apply conditions on the prohibition to distribute the veterinary medicinal product, specified in the regulatory enactments on the regulations regarding the labelling, distribution and control of veterinary medicinal products.

[28 December 2010]

81. Within 60 days following the receipt of the information referred to in Sub-paragraph 79.2 of this Regulation, the Food and Veterinary Service shall ensure that the applicant has the opportunity of providing an oral or written explanation.

[28 December 2010]

82. If, on matters on which agreement has not been reached, the involved Member States, within 60 days following the notification to the Co-ordination Group:

82.1. agree:

82.1.1. and Latvia is the reference Member State, the Food and Veterinary Service shall register the agreement, conclude the procedure and inform the applicant thereof;

82.1.2. and Latvia is an involved Member State, the Food and Veterinary Service shall take a decision in compliance with the procedure referred to in Paragraph 78 of this Regulation;

82.2. do not agree and Latvia is the reference Member State, the Food and Veterinary Service shall without delay submit a detailed description of facts to the European Medicines Agency regarding the matter on which agreement was not reached, and the reasons for the difference of opinion. A copy of this document shall be sent to the applicant.

[28 December 2010]

83. As soon as the applicant has been informed of the non-agreement and received the copy of the document referred to in Sub-paragraph 82.2 of this Regulation, the applicant shall without delay send the information and document copies referred to in Paragraph 73 of this Regulation to the European Medicines Agency.

84. If the Food and Veterinary Service has received two or more applications for the authorisation of a specific veterinary medicinal product in accordance with the procedures specified in Paragraphs 10, 11, 12, 13, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 35, 36 and 37 of this Regulation and other European Economic Area States have accepted differing opinions in respect of the authorisation of this veterinary medicinal product, the suspension or cancellation of the marketing authorisation, the Food and Veterinary Service, the European Commission or holder (owner) of the marketing authorisation is entitled to turn to the Committee of Veterinary Medicinal Products (hereinafter – Committee) to identify the problem and submit all the information at its disposal.

[28 December 2010]

85. In conformity with the decision of the European Medicines Agency and the European Commission, within 22 days following the examination of the dispute the Food and Veterinary Service may send a written opinion regarding the draft decision of the European Commission. The Food and Veterinary Service is entitled to submit a written request for the draft decision to be considered by the Committee. If following the opinion of the European Commission the written opinion of the Food and Veterinary Service raises significant new scientific and technological matters of nature, to which attention has not been paid, the consideration and examination of documents shall be continued by the European Medicines Agency.

[28 December 2010]

86. The Food and Veterinary Service and the competent authority of the reference Member State shall take a decision regarding the authorisation of the veterinary medicinal product or the cancellation of the marketing authorisation, or the necessity to amend the registration dossier, in order to fulfil the decision of the European Commission within 30 days following the notification of the decision of the European Commission. The Food and Veterinary Service shall inform the European Commission and the European Medicines Agency of the decision taken.

[28 December 2010]

87. The holder (owner) of the marketing authorisation, who has registered the veterinary medicinal product by mutual recognition procedure or by decentralised procedure, shall submit any amendments (variations) to the veterinary medicinal product marketing authorisation, which has been granted in accordance with the requirements referred to in this Chapter, to all the European Economic Area States in which the respective veterinary medicinal product has been registered.

88. If, for reasons of human and animal health and environmental protection the Food and Veterinary Service considers that:

88.1. amendments are necessary to the marketing authorisation which has been issued in accordance with the requirements referred to in this Chapter, or that it is necessary to suspend or revoke the marketing authorisation, it shall turn to the European Medicines Agency without delay, identify the problem and submit all the relevant information at the disposal thereof; or

88.2. urgent action is required in order to protect human or animal health or the environment, the Food and Veterinary Service, in the territory of Latvia, is entitled to suspend the operation of the issued veterinary medicinal product marketing authorisation in accordance with the requirements referred to in this Chapter. Not later than the following working day the Food and Veterinary Service shall inform the European Commission and other European Economic Area States in which this veterinary medicinal product has been registered of the reasons for the action thereof.

[28 December 2010]

89. The requirements referred to in Paragraphs 81, 82, 83, 84, 85 and 86 of this Regulation shall not be applicable to the homeopathic veterinary medicinal products referred to in Paragraph 40 of this Regulation.

90. The requirements referred to in Paragraphs 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84 and 85 of this Regulation shall not be applicable to the homeopathic veterinary medicinal products referred to in Paragraph 45 of this Regulation.

VI. The Clinical Investigation and Observations of the Use of Veterinary Medicinal Products

91. If the applicant performs the clinical investigation and observations regarding the use of veterinary medicinal products in the Republic of Latvia, a permit for the performance thereof shall be received from the Food and Veterinary Service.

92. The applicant shall ensure the clinical investigation and observations of the use of the veterinary medicinal products in compliance with the requirements referred to in Paragraph 37, as well as in Annexes 2 and 3, of this Regulation.

93. The applicant shall send the data acquired from clinical investigation and observations of the use of the veterinary medicinal products to the Food and Veterinary Service. The data shall be sufficient in order to provide a scientifically justified opinion regarding the conformity of the veterinary medicinal product with the criteria for the authorisation of the veterinary medicinal product.

[28 December 2010]

VII. Variations to the Veterinary Medicinal Product Registration Dossier and Extension of Authorisation

94. In order to approve variations to the veterinary medicinal product registration dossier, the holder (owner) of the marketing authorisation shall submit a submission for the approval of the variations. Data and documents which have been prepared in accordance with the European Commission guidelines referred to in Paragraph 37 of this Regulation and the conditions of Regulation No 1234/2008, as well as a document certifying the payment for the relevant service in accordance with the regulatory enactments on the State monitoring and control activities performed by the Food and Veterinary Service and payment of the paid

services provided, shall be appended to the submission, if the documents are being submitted to the Food and Veterinary Service. The document regarding payment shall be drawn up in accordance with the requirements referred to in Sub-paragraph 13.19 of this Regulation. In accordance with the conditions of Regulation No 1234/2008, the submission and documents referred to shall be submitted:

94.1. to the Food and Veterinary Service and appropriate competent authority of the European Economic Area State, if the medicinal products have been registered by mutual recognition procedure or decentralised registration procedure; or

94.2. to the European Medicines Agency if the medicinal products have been registered by centralised registration procedure.

[16 November 2010; 28 December 2010]

95. According to its competence the Food and Veterinary Service shall fulfil the duties of the competent supervision authority specified in Regulation No 1234/2008.

[16 November 2010; 28 December 2010]

96. In order to receive a decision on the extension of the authorisation of a veterinary medicinal product or a decision on the approval of the variations to the registration dossier for medicinal products registered by national registration procedure (which have not been registered by mutual recognition procedure or decentralised registration procedure), the holder (owner) of the marketing authorisation shall submit the following to the Food and Veterinary Service:

96.1. an application for the extension of the authorisation of the veterinary medicinal product or variations to the registration dossier. The application shall be drawn up observing the European Commission guidelines referred to in Paragraph 37 of this Regulation. The description of variations included in the documentation appended to the application shall conform with the following requirements:

96.1.1. information regarding Type IA, IB and II variations shall be included in accordance with Annex 6 to this Regulation;

96.1.2. the date of the implementation of each variation described shall be shown additionally regarding minor variations of Type IA and a list of the minor variations of Type IA which have been made to the registration dossier within the last 12 months and have not yet been notified to the Food and Veterinary Service, if immediate notification is not determined for minor variations of Type IA; and

96.1.3. if the incorporation of variations causes other variations to the conditions of the same registration dossier or arise from other variations, the mutual connection of these variations shall be described;

96.2. a document certifying payment for the relevant service in accordance with the regulatory enactments on the State monitoring and control activities performed by the Food and Veterinary Service and payment of the paid services provided. The document regarding payment shall be drawn up in accordance with Sub-paragraph 13.19 of this Regulation.

[16 November 2010; 28 December 2010]

96.¹ If minor variations of Type IA have been made to the registration dossier, the holder (owner) of the marketing authorisation shall submit a submission for the approval of the variations to the Food and Veterinary Service within 12 months following the implementation of the variations. If immediate notification is required for Type IA variations, for the permanent supervision of the relevant medicinal product, the Food and Veterinary Service shall submit the submission without delay following the implementation of the variations.

[16 November 2010; 28 December 2010]

96.² If the Food and Veterinary Service does not approve any or one of the minor variations of Type IA referred to in Sub-paragraph 96.1.2 of this Regulation, the holder (owner) of the marketing authorisation shall suspend the application of the respective variations without delay following the receipt of the refusal.

[16 November 2010; 28 December 2010]

97. In respect of veterinary medicinal products registered by national registration procedure (which are not registered by mutual recognition procedure or by decentralised procedure) the Food and Veterinary Service:

97.1. shall take a decision regarding the extension of the authorisation of the veterinary medicinal product, if the submitted data and documents confirm the compliance with the criteria referred to in Annex 5 to this Regulation. In such case the name of the veterinary medicinal product shall comply with the name of the veterinary medicinal product indicated in the original decision regarding the authorisation of the medicinal product; and

97.2. in accordance with Chapter VIII or IX of this Regulation shall evaluate the submission submitted for the approval of variations and take a decision regarding the approval or non-approval of the variations.

[28 December 2010]

97.¹ If the holder (owner) of the marketing authorisation makes several variations to the registration dossier, a separate submission shall be submitted for each of the variations referred to, except for the following cases:

97.¹1. the same minor variations of Type IA are applied for concurrently to the dossier of one authorisation or dossier of several authorisations belonging to one holder (owner) of the marketing authorisation. One submission may be submitted for all variations;

97.¹2. several variations to the dossier of one authorisation are submitted concurrently (variation grouping), if these variations comply with one of the conditions referred to in Paragraph 97.² of this Regulation. If the variations do not comply with the conditions referred to in Paragraph 97.² of this Regulation, one submission may be submitted for all the variations, if the Food and Veterinary Service agrees to examine these variations in one procedure. The submission shall be submitted in accordance with the following conditions:

97.¹2.1. a submission for minor variations of Type IB shall not be submitted if at least one of the variations in the group belongs to Type IB and all the variations are minor variations;

97.¹2.2. a submission for major variations of Type II shall be submitted if at least one of the variations in the group belongs to the major variations of Type II and the variations are not the extension of the authorisation; and

97.¹2.3. a submission for the extension of authorisation shall be submitted if at least one of the variations in the group is the extension of the authorisation.

[16 November 2010; 28 December 2010]

97.² It is permitted to submit one submission for several variations to a registration dossier in accordance with Sub-paragraph 97.¹2 of this Regulation, if the variations to the registration dossier comply with one of the following conditions:

97.²1. one of the variations in the group is the extension of the authorisation;

97.²2. one of the variations in the group belongs to the major variations of Type II, and all the other variations in the group arise from these major variations of Type II;

97.²3. one of the variations in the group belongs to the minor variations of Type IB, and all the other variations in the group arise from these minor variations of Type IB;

97.²4. all the variations in the group (including the active substances of the holder (owner) of the marketing authorisation or the change of the name or address of the manufacturer of the finished product or supplier of the active substance, the name of the

medicinal product or variations to the ATC code) shall relate only to variations of an administrative nature in the summary of the product characteristics, labelling or package leaflet;

97.²⁵. all the variations in the group are variations to the master file (in the master dossier), the master file of the vaccine antigen (in the master dossier) or in the plasma master file (in the master dossier);

97.²⁶. all the variations in the group relate to the improvement of the quality and manufacturing process of the veterinary medicinal product or the active substances in accordance with Paragraph 58 of this Regulation;

97.²⁷. all the variations in the group relate to the system of monitoring the safety of the use of the veterinary medicinal product (pharmacovigilance system) referred to in Sub-paragraphs 13.11 and 13.17 of this Regulation;

97.²⁸. all the variations in the group arise from an urgent restriction related to the safety of the veterinary medicinal product (temporary variations to the information regarding the veterinary medicinal product if new information has become known regarding the safety of the use of the veterinary medicinal product). Restrictions shall in particular relate to the points of the summary of the veterinary medicinal product characteristics such as therapeutic indications, dosage units, contra-indications, warnings, the target species and the withdrawal period of the medicinal product;

97.²⁹. all the variations in the group are related to the implementation of the labelling of the respective group of medicinal products;

97.²¹⁰. all the variations arise from the assessment of the periodically updated safety report;

97.²¹¹. all the variations arise from post-authorisation investigations which have been performed under the supervision of the holder (owner) of the marketing authorisation; or

97.²¹². all the variations arise from the condition which is implemented in accordance with Paragraph 57 of this Regulation.

[16 November 2010]

97.³ In the case of the threat to human or animal health, the holder (owner) of the marketing authorisation, or the Food and Veterinary Service may determine urgent restrictions related to the safety of the veterinary medicinal product. The holder (owner) of the marketing authorisation shall inform the Food and Veterinary Service without delay regarding urgent restrictions related to the safety of the veterinary medicinal product, which have been determined at his or her own initiative. Within 15 days following the application of the urgent restrictions related to the safety of the veterinary medicinal product the holder (owner) of the marketing authorisation shall submit a submission to the Food and Veterinary Service for the examination of the variations.

[16 November 2010; 28 December 2010]

VIII. Minor Variations of Type IA and IB and Major Variations of Type II to the Registration Dossier of a Veterinary Medicinal Product

[16 November 2010]

98. Minor variations of Type IA are variations which have a minimal impact or no impact on the quality, safety or efficacy of the medicinal product concerned. The following minor variations of Type IA shall be classified for veterinary medicinal products which are registered by national registration procedure (which are not registered by mutual recognition procedure or by decentralised procedure):

98.1. variations of an administrative nature, which are related to:

98.1.1. the identity and contact information of the holder (owner) of the marketing authorisation;

98.1.2. the identity and contact information of the manufacturer or supplier of the starting material, reagent, intermediate product or active substance used in the finished product or in the process of manufacturing the veterinary medicinal product;

98.2. the replacement of any location of manufacture in the entire process of manufacturing (including the manufacturing units of the active substance, intermediate product or finished product, the packaging undertaking, the manufacturer responsible for the batch release, and places where batch control takes place;

98.3. variations related to minor changes to the approved physico-chemical test procedures, where the updated procedure is demonstrated to be at least equivalent to the former test procedure or of higher value and that appropriate validation studies have been performed;

98.4. variations to the specifications of the active substance or of an excipient, if the specific variations have been made exclusively to comply with the monograph updated in the European Pharmacopoeia, and the specifications for product specific properties are unchanged;

98.5. variations related to changes in the packaging material not in contact with the finished product, which do not affect the delivery, use, safety or stability of the medicinal product; or

98.6. the determination of tighter specification limits, where the change is not a consequence of any commitment from previous assessment to review specification limits and does not result from unexpected events arising during manufacture.

[16 November 2010]

98.¹ Major variations of Type II are variations which are not an extension to the authorisation and which may have a significant impact on the quality, safety or efficacy of the medicinal product concerned. The following major variations of Type II shall be classified for veterinary medicinal products which are registered by national registration procedure (which are not registered by mutual recognition procedure or by decentralised procedure) in the registration dossier:

98.¹1. the addition of a new therapeutic indication or the modification of an existing one;

98.¹2. significant modifications to the summary of veterinary medicinal product characteristics, in particular to new quality, non-clinical (pre-clinical), clinical or pharmacovigilance findings;

98.¹3. variations related to changes outside the range of approved specifications, limits or acceptance criteria;

98.¹4. variations to the manufacturing process, formulation, specifications or impurity profile of the manufacturing process, if these variations may have a significant impact on the quality, safety or efficacy of the veterinary medicinal product;

98.¹5. variations to the manufacturing process or site (production unit) of the active substance for a biological medicinal product;

98.¹6. the introduction of a new development design or the extension of an approved development design;

98.¹7. a change to or addition of a non-food producing target animal species (the species of animals from which food products of animal origin are not acquired);

98.¹8. a vaccine against avian influenza, foot-and-mouth disease or bluetongue disease (infectious catarrhal fever of sheep and goats), the replacement or addition of a serotype, vaccine strain, antigen or combination thereof;

98.¹9. the replacement of a strain for a vaccine against equine influenza; and

98.¹10. variations to the withdrawal period for a medicinal product.

[16 November 2010]

98.² Variations which are not the extension of authorisation and whose classification in accordance with Paragraphs 98 and 98.¹ of this Regulation are not clear shall be evaluated in compliance with Annex 6 to this Regulation and considered as minor variations of Type IB, if the variations do not comply with the conditions referred to in Paragraph 98.³ of this Regulation.

[16 November 2010]

98.³ Variations which are not the extension of authorisation and whose classification in accordance with Paragraphs 98 and 98.¹ of this Regulation are not clear shall be considered as major variations of Type II, if:

98.³1. the submission for the major variations of Type II has been submitted by the holder (owner) of the marketing authorisation; or

98.³2. if the Food and Veterinary Service, following the examination of the submission and the assessment of the compliance of the variations with the requirements referred to in Annex 6 to this Regulation recognises that the variations may have a significant impact on the quality, safety or efficacy of the medicinal product concerned.

[16 November 2010; 28 December 2010]

99. If due to variations amendments have to be made to the product description, labelling or package leaflet of the medicinal product concerned, these amendments shall be considered to be part of the variations.

[16 November 2010]

99.¹ [20 January 2011]

100. The Food and Veterinary Service shall examine the compliance of a submission for the approval of variations with the conditions referred to in Paragraphs 96, 96.¹, 97.¹, 97.², 97.³, 98, 98.¹, 98.², 98.³ and 99 of this Regulation, evaluate the data and documents submitted and take a decision in accordance with the procedures specified by the Administrative Procedure Law regarding the approval of the variations in the registration dossier or the non-approval of the variations, observing the following conditions:

100.1. if a submission is submitted only for minor variations of Type IA, the matter shall be examined within 14 days following the receipt of the submission;

100.2. if at least one of the variations incorporated in the submission belongs to the minor variations of type IB, the matter shall be examined within one month following the receipt of the submission;

100.3. a decision may be taken to extend the term for the examination of the matter, if the variations indicated in the submission comply with the following conditions:

100.3.1. at least one of the variations incorporated in the submission belongs to the major variations of Type II;

100.3.2. the non-food producing target animal species have been changed or added;

100.3.3. a vaccine against avian influenza, foot-and-mouth disease or bluetongue disease (infectious catarrhal fever of sheep and goats) has been replaced or the serotype, vaccine strain, antigen or combination thereof has been added to; or

100.3.4. the strain for a vaccine against equine influenza has been replaced.

[16 November 2010; 28 December 2010]

101. The Food and Veterinary Service is entitled to request that the holder (owner) of the marketing authorisation provides additional information. In such case the procedure referred to in Paragraph 100 of this Regulation shall be suspended until the day when the holder

(owner) of the marketing authorisation submits the requested additional information to the Food and Veterinary Service.
[28 December 2010]

102. If, following the evaluation of the submission for the approval of variations and the data, documents and other information appended thereto, the Food and Veterinary Service considers that the submission referred to is not acceptable, the Food and Veterinary Service shall provide a substantiated opinion to the holder (owner) of the marketing authorisation in accordance with the procedures specified by the Administrative Procedure Law but not exceeding 30 days following the receipt of the submission. The holder (owner) of the marketing authorisation is entitled to make amendments to the submission or to the data and documents appended thereto within 30 days following the receipt of the opinion of the Food and Veterinary Service, observing the justification referred to in the opinion of the Food and Veterinary Service. If the holder (owner) of the marketing authorisation makes the amendments referred to, he or she shall inform the Food and Veterinary Service in writing that amendments have been made within the referred to 30 days.
[16 November 2010; 28 December 2010]

103. If the holder (owner) of the marketing authorisation does not make amendments to the submission for the approval of variations in accordance with the conditions referred to in Paragraph 102 of this Regulation, the submission shall be considered to be rejected and the Food and Veterinary Service shall notify the holder (owner) of the marketing authorisation of the non-approval of the variations within 30 days in accordance with the procedures specified in the Administrative Procedure Law.
[16 November 2010; 28 December 2010]

104. If the Food and Veterinary Service has not notified the holder (owner) of the marketing authorisation of the non-approval of the variations in compliance with the procedures referred to in Paragraph 102 of this Regulation, it shall be considered that the Food and Veterinary Service has approved the variations and the holder (owner) of the marketing authorisation may implement the variations.
[28 December 2010]

104.¹ If the Food and Veterinary Service takes a decision regarding the approval of such variations with which the information indicated in the marketing authorisation needs to be changed, or a decision regarding the extension of authorisation, it shall issue a new marketing authorisation within three working days following the taking of the decision in compliance with Annex 1 to this Regulation.
[28 December 2010]

**IX. Change of a Firm or Address of the
Holder (Owner) of a Marketing Authorisation**
[16 November 2010]

105. [16 November 2010]

106. [16 November 2010]

107. [16 November 2010]

108. [16 November 2010]

109. In case of a change in the name or legal address of the holder (owner) of a marketing authorisation for a veterinary medicinal product registered by national registration procedure, the existing holder (owner) of the marketing authorisation shall submit a submission to the Food and Veterinary Service if the holder (owner) of the marketing authorisation is not the same person. The following documents shall be appended to the submission and the following information shall be indicated:

109.1. a document confirming the change of the holder (owner) of the marketing authorisation;

109.2. the name of the veterinary medicinal product, the number and date of registration of the marketing authorisation;

109.3. the existing firm name and address of the holder (owner) of the marketing authorisation, as well as the name and address of such a person to whom the transfer of the medicinal product marketing authorisation is intended;

109.4. a document certifying availability of complete and, at the moment of transfer, the renewed veterinary medicinal product registration dossier or a copy thereof, and handing over to the person to whom the medicinal product marketing authorisation is being transferred;

109.5. the date when the person to whom the medicinal product marketing authorisation is intended to be transferred will be able to take over the duties of the previous holder (owner) of the marketing authorisation;

109.6. a document confirming that the person to whom the marketing authorisation is being transferred is able to perform the duties of the holder (owner) of the marketing authorisation in compliance with the requirements specified in regulatory enactments regarding the manufacturing and control of veterinary medicinal products, the distribution, advertising, adverse effects and clinical studies of veterinary medicinal products. The following shall be indicated in the document referred to:

109.6.1. the person who is responsible for operations in relation to the system of monitoring the side-effects of veterinary medicinal products (the address, telephone and fax number of the person, a short description of work and experience);

109.6.2. the service responsible for advertising and distribution of the veterinary medicinal product (the address, telephone number and fax number of the service);

109.7. the draft of the summary of the product characteristics, the package leaflet and labelling of veterinary medicinal products; and

109.8. a document certifying payment for the assessment in accordance with the regulatory enactments on the State monitoring and control activities performed by the Food and Veterinary Service and payment of the paid services provided. The document regarding payment shall be drawn up in accordance with Sub-paragraph 13.19 of this Regulation.

[16 November 2010; 28 December 2010]

110. The date when the marketing authorisation shall be transferred to a new holder (owner) of the marketing authorisation, shall be determined by the Food and Veterinary Service and this date shall be written in the contract which shall be entered into by the existing and new holder (owner) of the marketing authorisation. The validity period of the marketing authorisation shall not change.

[28 December 2010]

X. Closing Provisions

111. Cabinet Regulation No. 409 of 22 April 2004, Procedures for the Registration of Veterinary Medicinal Products (*Latvijas Vēstnesis*, 2004, No. 69/201; 2006, No.68), is repealed.

112. Veterinary medicinal product marketing authorisations issued up to the date of the coming into force of this Regulation shall be valid until the expiry of the validity period indicated therein.

Informative Reference to European Union Directives
[2 October 2007; 15 September 2009; 16 November 2010]

This Regulation contains legal norms arising from:

- 1) 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) Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products;
- 3) Commission Directive 2006/130/EC of 11 December 2006 implementing Directive 2001/82/EC of the European Parliament and of the Council as regards the establishment of criteria for exempting certain veterinary medicinal products for food-producing animals from the requirements of a veterinary prescription;
- 4) Commission Directive 2009/9/EC of 10 February 2009 amending Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to medicinal products for veterinary use;
- 5) Directive 2009/35/EC of the European Parliament and of the Council of 5 April 2006 on the colouring matters which may be added to medicinal products; and
- 6) Directive 2009/53/EC of the European Parliament and Council of 18 June 2009 amending Directive 2001/82/EC and Directive 2001/83/EC, as regards variations to the terms of marketing authorisations for medicinal products.

Prime Minister

A. Kalvītis

Acting for the Minister for Agriculture –
the Minister for the Interior

Dz. Jaundžeikars

LATVIJAS REPUBLIKA
PĀRTIKAS UN VETERINĀRAIS
DIENESTS

REPUBLIC OF LATVIA
STATE AGENCY OF MEDICINES

(adrese, reģistrācijas numurs, tālruna, faksa
numurs)

(address, registration number, phone, fax
number)

VETERINĀRO ZĀĻU REĢISTRĀCIJAS APLIECĪBA
MARKETING AUTHORIZATION OF VETERINARY MEDICINAL PRODUCT

Rīga/Rīga

Reģistrācijas numurs/Authorisation number

1. Veterināro zāļu nosaukums, stiprums, zāļu
forma/*Name of the veterinary medicinal product,
strength, pharmaceutical form*

2. Aktīvās(-o) vielas(-u) nosaukums/*Name of
active substance*

3. Atļauts lietot šādām mērķa sugām/*Usage
allowed for such target species*

4. Informācija par iepakojumu/*Packaging
information*

5. Reģistrācijas apliecības īpašnieks/*Marketing
authorization holder*

6. Lēmums par veterināro zāļu reģistrāciju
(pārreģistrāciju)/*Decision on authorization of the
veterinary medicinal product/renewal*

(numurs, datums/*number, date*)

7. Lēmums spēkā līdz/*Decision valid until*

(diena, mēnesis, gads/*day, month, year*)

8. Lēmums par izmaiņu apstiprināšanu/
Decision on variation approval

(numurs, datums/*number, date*)

Pārtikas un veterinārā dienesta atbildīgā
amatpersona/
*Responsible person of the State Agency of
Medicines*

(amats, vārds, uzvārds, paraksts/*position,
name, surname, signature*)

Z.v./Seal

Datums/Date

Note. The “signature” and “place for seal” boxes shall not be completed if the electronic document has been drawn up in conformity with the regulatory enactments regarding the drawing up of electronic documents.

**Requirements for Veterinary Medicinal Products Which Are Not Immunological
Veterinary Medicinal Products**

[15 September 2009; 28 December 2010]

1. Summary of the Dossier

1. In the authorisation application of a veterinary medicinal product:

1.1. the veterinary medicinal product shall be identified according to the name and the name of the active substance together with the strength, pharmaceutical form, route and method of administration (in accordance with Sub-paragraph 13.6 of this Regulation) and a description of the finished product, including the packaging, labelling and package leaflet (in accordance with Sub-paragraphs 13.13, 13.14 and Paragraph 17 of this Regulation);

1.2. the name and address of the applicant, the name and address of the veterinary medicinal product manufacturer, the facilities involved in the different phases of manufacturing, testing and release, the name and address of the finished product manufacturer and the manufacturer and importer of the active substance (if applicable) shall be indicated;

1.3. the number and names of the documents which are submitted together with the application shall be clearly identified, as well as information regarding samples of the veterinary medicinal product submitted;

1.4. a document shall be appended which certifies that the manufacturer has received a special authorisation (licence) for the manufacture of the relevant veterinary medicinal product in accordance with the requirements of the regulatory enactments regulating the manufacture of veterinary medicinal products;

1.5. information shall be appended with a list of those states in which the special authorisation (licence) has been granted for the manufacture of the relevant veterinary medicinal product;

1.6. copies of the summary of the veterinary medicinal product characteristics shall be appended in accordance with the requirements referred to in Paragraph 35 of this Regulation. The copies of the summary of the characteristics shall be approved by the relevant competent authorities of the involved states; and

1.7. information shall be appended with a list of those states in which a authorisation application has been submitted or rejected.

2. The applicant shall submit the summary of the veterinary medicinal product characteristics which have been prepared in accordance with the requirements referred to in Paragraph 35 of this Regulation and a mock-up of the labelling of the immediate packaging and secondary packaging together with the package leaflet, if such is necessary, which have been prepared in accordance with the regulatory enactments regarding the procedures for the labelling, distribution and control of veterinary medicinal products. The applicant shall indicate one or more finished trade samples of veterinary medicinal products containing information in at least one official language of the European Union. The mock-ups may be submitted in printed form or electronically, if the Food and Veterinary Service has given prior consent.

3. The detailed summary (hereinafter – summary) shall be drawn up in compliance with the requirements referred to in Paragraphs 13, 15 and 17 of this Regulation. The following shall be indicated in the summary:

3.1. the results of the pharmaceutical (physico-chemical, biological or microbiological), safety and residue research and testing;

- 3.2. the pre-clinical and clinical investigation results; and
- 3.3. the results of the potential environmental risk assessment of the veterinary medicinal product.

4. The summary shall be prepared, observing the following requirements:

4.1. the scientific data available at the time of the submission of the application shall be taken into account;

4.2. the different assays, tests and studies which justify the documentation appended to the marketing authorisation shall be indicated and evaluated in the summary;

4.3. matters relating to the quality, safety and efficacy assessment of the veterinary medicinal product shall be included and described in the summary;

4.4. detailed results of the assays, tests and studies and accurate bibliographical references shall be provided;

4.5. the significant data of the summary shall be compiled in the Annex, if possible, in tabular or graphic form; and

4.6. accurate cross-references to the documentation appended to the authorisation application shall be included in the summary and the annexes thereto.

5. Information regarding the education, training and work experience of the expert shall be appended to the summary, and the professional relationship of the applicant and the expert shall also be reflected. The summary shall be dated and signed by the expert.

6. If the active substance included in the veterinary medicinal product to be registered is also included in a medicinal product intended for humans, which has been registered in accordance with Cabinet Regulation No. 376 of 9 May 2006 "Procedures for the Registration of Medicinal Products" (hereinafter - Regulation No. 376), the summary referred to in Paragraph 3 of this Annex may be replaced by a general quality summary of the active substance concerned, which is provided in accordance with Annex 3, Module 2, Paragraph 14 to Regulation No. 376.

7. If the Food and Veterinary Service has publicly notified that the chemical, pharmaceutical and biological or microbiological information of the finished product may only be included in the dossier in Common Technical Document (CDT) format, the summary of the pharmaceutical test results shall be submitted in the form of an overall quality summary.

8. Prior to the consent from the Food and Veterinary Service, the overall quality summary may be used for an application for a veterinary medicinal product for a specific animal species or for indications which affect a small part of the market (for one animal species, rare diagnoses, the performance of rare veterinary medicinal manipulations).

2. Pharmaceutical (Physico-chemical, Biological or Microbiological) Information

(Quality Section)

2.1. General Information

9. The information and documents which are appended to an application for the receipt of a veterinary medicinal product marketing authorisation, in compliance with Sub-paragraph 13.10 of this Regulation, shall be as follows:

9.1. information regarding the pharmaceutical (physico-chemical, biological or microbiological) data of the active substance, as well as information regarding the manufacturing process, description and properties of the finished veterinary medicinal

product, the quality control procedures and requirements, stability, and the description, development and appearance of the composition of the veterinary medicinal product;

9.2. the developed test procedures which conform with the requirements of the quality analysis of the starting materials and finished product, taking into account the guidelines and requirements specified for the respective processes. The results of the confirmatory (hereinafter – validation) studies shall be presented.

9.3. detailed and accurate descriptions of the testing procedures in order that they may be repeated in control tests, which are performed upon request of the Food and Veterinary Service. Detailed descriptions of the special apparatus and equipment which may be used in tests (if possible, appending diagrams);

9.4. information regarding the laboratory reagent formulae, which shall be supplemented with the preparation method (if necessary);

9.5. a description of the procedure shall be replaced with a detailed reference to the relevant pharmacopoeia, if the testing procedures are included in the European Pharmacopoeia or in the officially used pharmacopoeia of the Member States. Chemical and biological reference material of the European Pharmacopoeia shall mainly be used in the tests. If other reference preparations and standards are used, they shall be identified and described in detail;

9.6. the chemical, pharmaceutical, biological or microbiological information which is provided in accordance with the provision of Annex 3, Module 3 (Paragraphs 19, 20, 21, 22 and 23) to Regulation No. 376. This information may be replaced with the appropriate documents which are related to the veterinary medicinal product to be registered, if the active substance contained in the veterinary medicinal product to be registered is also used in a medicinal product intended for humans, which has been registered in accordance with the requirements referred to in Regulation No. 376; and

9.7. documentation regarding the chemical, pharmaceutical and biological or microbiological information of the active substance or finished veterinary medicinal product, which shall be included in the Common Technical Document, if the Food and Veterinary Service has publicly announced that this is permitted. Without the prior consent of the Food and Veterinary Service, the Common Technical Document may be used for an application for a veterinary medicinal product for a specific animal species or for indications which affect a small part of the market (for one animal species, rare diagnoses, the performance of rare veterinary medicinal manipulations).

10. In the development of the information and documents referred to in Paragraph 9 of this Annex the common monographs and general chapters of the European Pharmacopoeia shall be taken into account or, if this is not possible, the monographs of the official pharmacopoeia used in the Member States shall be applied.

2.2. Quality and Control of the Components

11. The concept of the qualitative information of the components (constituents) of veterinary medicinal products shall comprise the following information:

11.1. regarding the active substance;

11.2. regarding excipient components irrespective of the type and quantity used, including colouring matters, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances;

11.3. the components intended to be ingested or otherwise administered to animals, of the outer covering of the medicinal products (capsules, gelatine capsules); and

11.4. data regarding the immediate packaging and, if necessary, regarding the secondary packaging of the medicinal product. Data regarding the manner of closure, as well

as the devices for using and administering the medicinal product, which are supplied together with the medicinal product.

12. The usual terminology is the terminology used when describing components of a veterinary medicinal product notwithstanding the application of the provisions referred to in Sub-paragraph 13.3 of this Regulation:

12.1. for components which appear in the European Pharmacopoeia or, if none, in the official pharmacopoeia used in a Member State, the main title of the monograph shall be indicated, with reference to the pharmacopoeia concerned;

12.2. for components which do not appear in the European Pharmacopoeia or the official pharmacopoeia used in a Member State, the international non-proprietary name recommended by the World Health Organisation shall be used, which may be accompanied by another non-proprietary name or, if none, the exact scientific designation. Components to which an international non-proprietary name or scientific designation has not been allocated, shall be described by a statement of how and from what components they have been prepared, supplemented where appropriate by any other significant information; and

12.3. colouring matters shall be designated the "E" code assigned to them in accordance with the regulatory enactments regarding the mandatory requirements for the harmlessness of food additives and food products, in which food additives are used.

13. In order to provide information regarding the quantitative composition of the active substances contained in the composition of the veterinary medicinal product, the number of dosage-units of each mass of active substance or biological activity shall be determined for the pharmaceutical form.

14. Units of biological activity shall be used for substances which cannot be determined chemically. If an international unit of biological activity has been defined by the World Health Organisation, this shall be used.

15. If no international unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information regarding the activity of the substances by using where applicable the European Pharmacopoeia units.

16. If possible, the mass or volume unit of biological activity shall be indicated, as well as the following additional information:

16.1. for single dose veterinary medicinal products – mass or units of biological activity of the active substance in the packaging (container) of one dose, if necessary, taking into account the amount of veterinary medicinal product administered following the preparation for use;

16.2. for veterinary medicinal products to be administered by drops – the mass or units of biological activity of the active substance contained per drop or contained in the number of drops corresponding to 1 ml or 1 g of the preparation; or

16.3. for syrups, emulsions, granular preparations and other pharmaceutical forms to be administered in measured quantities - the mass or units of biological activity of the active substance per measured quantity.

17. Active substances 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.

18. If a veterinary medicinal product contains an active substance which is the subject of an application for a marketing authorisation in any Member State for the first time, the

quantitative statement of the active substance (salt or hydrate) shall be systematically expressed in terms of the mass of the active entity or entities in the molecule. All subsequently registered veterinary medicinal products in the Member States shall have their quantitative composition stated in the same way for the same active substance.

19. During the course of the pharmaceutical form development:

19.1. an explanation shall be provided with regard to the choice of composition, components, immediate packaging, possible further packaging, secondary packaging, if relevant, and the intended function of the excipients in the finished product and the method of manufacture of the finished product. The explanation shall be supported by scientific data regarding the development of the pharmaceutical form;

19.2. the overage, with justification thereof, shall be stated; and

19.3. the microbiological characteristics (microbiological purity and antimicrobial activity) and package leaflet shall be proven to be appropriate for the intended use of the veterinary medicinal product as specified in the dossier appended to the marketing authorisation.

2.3. Description of the Manufacturing Method

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

21. The description of the manufacturing method shall be appended to the application for the marketing authorisation which, in accordance with Sub-paragraph 13.4 of this Regulation shall be drafted in such a way as to give an adequate synopsis of the manufacturing process. The following shall be included in the description of the manufacturing method:

21.1. mention of the various stages of manufacture so that an assessment can be made of whether the operations employed in producing the pharmaceutical form might have produced an adverse change in the components of the medicinal product;

21.2. in the case of continuous manufacture, full details concerning safety precautions taken to ensure the homogeneity of the finished product;

21.3. the actual manufacturing formula in which the following shall be indicated:

21.3.1. the quantitative particulars of the substances used in manufacture. The quantities of excipients may be given in approximate terms insofar as the pharmaceutical form makes this necessary;

21.3.2. substances that may disappear in the course of manufacture;

21.3.3. justification for overage;

21.4. a statement of the stages of manufacture at which sampling is carried out for control tests during manufacture and the limits (amounts) applied, where other data in the documents supporting the application show such tests to be necessary for the quality control of the finished product;

21.5. a description of the experimental studies with which the manufacturing process is validated and, if necessary, a process validation scheme for production scale batches; and

21.6. for sterile products, where non-pharmacopoeial standard sterilisation conditions are used, details of the sterilisation process or aseptic procedures used.

2.4. Control of Starting Materials

22. Starting materials are the components of a veterinary medicinal product and, where appropriate, of the immediate packaging (container) of a veterinary medicinal product, including the manner of closure, as referred to in Paragraph 11 of this Annex.

23. Specifications and information regarding all the quality control tests performed on batches of starting material shall be included in the starting material control dossier.
24. The regular tests which are performed on each batch of starting materials shall be indicated in the application for a marketing authorisation. If tests are used on a batch of starting materials which are not referred to in the relevant pharmacopoeia, the use of the test shall be justified by providing evidence that the starting materials conform to the quality requirements of the pharmacopoeia concerned.
25. If the Quality Directorate of the European Medicines Agency has issued a Certificate of Suitability for starting materials, active substances or excipients, reference to the relevant monograph of the European Pharmacopoeia shall be shown in the certificate.
26. If reference is made to the Certificate of Suitability referred to in Paragraph 25 of this Annex, the manufacturer of the veterinary medicinal product shall provide the applicant with written assurance that the manufacturing process of the medicinal product concerned has not been changed since the issuance of the Certificate of Suitability by the Quality Directorate of the European Medicines Agency.
27. In order to confirm compliance with the specified specification, a certificate of analysis of the starting materials shall be submitted.
28. The name, address and responsibility of each manufacturer and each proposed production site or undertaking (facility) involved in manufacturing and testing shall be indicated.
29. The manufacturer of the active substance or the applicant may agree that the manufacturer of the active substance shall submit the widely described information on the active substance directly to the Food and Veterinary Service in the form of a separate document, as the Active Substance Master File, in which the following information shall be included:
- 29.1. a detailed description of the manufacturing process;
 - 29.2. a description of the quality control of the manufacturing process; and
 - 29.3. a description of the process validation.
30. If the Active Substance Master File is being developed, the manufacturer shall:
- 30.1. provide all the particulars which are necessary to the applicant, undertaking responsibility for the veterinary medicinal product;
 - 30.2. confirm to the applicant in writing that the manufacturer ensures the conformity of the entire batch with the sample and shall not modify the manufacturing process or specifications without informing the applicant; and
 - 30.3. submit documents and information which certifies the modifications referred to in Sub-paragraph 30.2 of this Annex to the Food and Veterinary Service, as well as to the applicant, insofar as it affects the applicant's part of the Active Substance Master File.
31. If the Certificate of Suitability for the active substance is not available, the applicant or the manufacturer shall provide information regarding the method of manufacture, on quality control and impurities, as well as evidence of the molecular structure, taking into account the following conditions:
- 31.1. information on the manufacturing process shall include a description of the active substance manufacturing process that represents the applicant's commitment for the manufacture of the active substance. All materials needed in order to manufacture the active substance shall be listed, identifying where each material is used in the process. Information on the quality and control of those materials shall be provided, as well as information

demonstrating that the materials meet the standards which are appropriate for their intended use;

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

31.3. information on impurities shall indicate predictable impurities together with the levels and nature of impurities, as well as information on the safety of these impurities, where relevant; and

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

32. The control of active substances listed in pharmacopoeias shall be performed and described in accordance with the following conditions:

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

32.2. components fulfilling the requirements of the European Pharmacopoeia or the requirements of the officially used pharmacopoeia of a Member State shall be deemed to comply sufficiently if they comply with the requirements referred to in Sub-paragraph 13.9 of this Regulation. In this case the description of the analytical methods and procedures shall be replaced in each relevant section by an appropriate reference to the pharmacopoeia in question;

32.3. if a specification contained in the European Pharmacopoeia or in the officially used pharmacopoeia of the Member States is insufficient to ensure the quality of the active substance, the Food and Veterinary Service may request more appropriate specifications from the applicant, including limits for specific impurities with validated test procedures. The Food and Veterinary Service shall inform the authorities responsible for the pharmacopoeia in question. The holder (owner) of the marketing authorisation shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied;

32.4. in the absence of a European Pharmacopoeia monograph for an active substance and where the active substance is described in the officially used pharmacopoeia of the Member States, that monograph may be applied; or

32.5. where an active substance is described neither in the European Pharmacopoeia nor in the pharmacopoeia officially used in the Member States, the pharmacopoeial monograph of a third country may be used if the suitability is demonstrated. The applicant shall submit a copy of the monograph and a translation, where appropriate, together with data confirming the compliance of the test procedures included in the monograph with the quality control of the active substance.

33. Active substances which are not shown in a pharmacopoeia shall be described indicating the following information (components which are not given in any pharmacopoeia shall be described in the form of a monograph);

33.1. the name of the component which complies with the requirements referred to in Paragraph 12 of this Annex and shall be supplemented by any trade or scientific synonyms;

33.2. the definition of the substance in compliance with the European Pharmacopoeia. Any necessary explanations shall be appended, especially concerning the molecular structure. Where substances can only be described by their manufacturing method, the description shall be sufficiently detailed to characterise a substance which is constant both in its composition and in its effects;

33.3. 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 carried out routinely;

33.4. purity tests shall be described in relation to the total amount of each individual predictable impurity. The total amount shall be formed by each predictable impurity, especially those which may have a harmful effect and, if necessary, those which, having regard to the combination of substances to which the application refers, might adversely affect the stability of the medicinal product or distort analytical results;

33.5. tests and limits shall be described. Tests shall be performed to control parameters of the finished product, such as particle size and sterility and methods shall be validated where relevant; and

33.6. for 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 substances having similar activity, in respect of which an overall method of assay may be accepted.

34. The set of test procedures referred to in Paragraph 33 of this Annex is sufficient to control the quality of the active substances obtained from the defined source.

35. If the active substances affect the bioavailability of the veterinary medicinal product, the following information shall be provided as part of the general description of the active substances whether or not listed in the pharmacopoeias (the physico-chemical characteristics of the active substances liable to affect bioavailability shall be indicated):

35.1. the crystalline form and solubility coefficients of the substance;

35.2. particle size (where appropriate, after pulverisation);

35.3. the state of hydration;

35.4. the oil/water coefficient of partition; and

35.5. the pK/pH values.

36. Sub-paragraphs 35.1, 35.2 and 35.3 of this Annex shall not be applicable to substances used solely in solutions.

37. The control of excipients shall be performed and described in accordance with the following conditions:

37.1. for all substances which are listed in the European Pharmacopoeia, the general and special monographs of the European Pharmacopoeia shall be applied;

37.2. the conformity of the excipient with the requirements specified in the relevant monograph of the European Pharmacopoeia shall be controlled. If there are no such monographs of the European Pharmacopoeia, the officially used pharmacopoeias of the Member States may be used. If there are no appropriate monographs in the officially used pharmacopoeia of the Member States, the pharmacopoeia of a third country may be used. If the monograph of a third country pharmacopoeia is used, the conformity of this monograph shall be certified. Additional tests to control parameters (such as particle size, sterility, residual solvents) shall supplement the requirements of the monograph. In the absence of a pharmacopoeial monograph a specification shall be proposed and justified. The requirements for specifications referred to in Paragraph 32 of this Annex shall be followed. The proposed methods and their validation data shall be presented;

37.3. the compliance of the colouring matters for inclusion in veterinary medicinal products specified in the regulatory enactments regarding the colouring matters to be added to medicinal products, shall be controlled, except for veterinary medicinal products intended for topical use (for example, insecticidal collars and ear tags, where the use of other colouring matters is justified);

37.4. the compliance of the purity criteria of colouring matters included in veterinary medicinal products specified in regulatory enactments regarding the requirements for the harmlessness of food additives and food, in which food additives are used, shall be controlled; and

37.5. new excipients (excipients used for the first time in a veterinary medicinal product, or by a new method of administration), detailed information of the manufacture, characterisation and controls, with cross-references to supporting safety data, both clinical and non-clinical, shall be provided.

38. The control of the container-closure system shall be performed and described in accordance with the following conditions:

38.1. information on the container-closure system for the active substance shall be given. The level of information required shall be determined by the physical state (for example, liquid, solid) of the active substance;

38.2. information on the container-closure system for the finished product shall be given. The level of information required shall be determined by the method of administration of the veterinary medicinal product and the physical state (for example, liquid, solid) of the dosage form;

38.3. the compliance of the packaging materials of the finished product with the requirements of the appropriate monograph of the European Pharmacopoeia shall be controlled. In the absence of such pharmacopoeial monograph, the officially used pharmacopoeia of the Member States may be used. If there are no appropriate monographs in the officially used pharmacopoeia of the Member States, the pharmacopoeia of a third country may be used, demonstrating the suitability thereof. In the absence of a pharmacopoeial monograph a specification shall be proposed and justified for the packaging material;

38.4. scientific data on the choice and suitability of the packaging material shall be presented;

38.5. information shall be presented for the composition, manufacture and safety of new packaging materials in contact with the finished product; and

38.6. specifications and performance data shall be presented for any dosing or administration device supplied with the veterinary medicinal product.

39. The control of substances of biological origin shall be performed and described in accordance with the following conditions:

39.1. where microorganisms, tissues of either plant or animal origin, cells or fluids (including blood) of human or animal origin or biotechnological cell constructs are used in the manufacture of veterinary medicinal products, the origin and history of the starting materials shall be described and documented;

39.2. the description of the starting material shall include the manufacturing strategy, purification or 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;

39.3. when cell banks are used, the cell characteristics shall be shown to have remained unchanged before and after the passage level used for manufacturing;

39.4. tests shall be performed to determine whether there are any extraneous agents in the culture materials, cell banks, pools of serum and, whenever possible, the source materials from which they are derived;

39.5. when starting materials of animal or human origin are used, the measures used to ensure freedom from potentially pathogenic agents in these starting materials shall be described. If the presence of potentially pathogenic extraneous agents is inevitable, the starting material shall be used only when further processing ensures their elimination or inactivation and this operation is validated; and

39.6. the applicant shall submit documentary evidence that the culture materials, cell seeds, batches of serum and other material originating from animals relevant for the transmission of transmissible spongiform encephalopathy (TSE) comply with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, as well as with the corresponding monograph of the European Pharmacopoeia. Certificates of Suitability issued by the European Directorate for the Quality of Medicines with reference to the relevant monograph of the European Pharmacopoeia, may be used to demonstrate compliance.

2.5. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

40. The control tests of the intermediate stages of the manufacturing process shall be documented. Particulars relating to the control tests that may be carried out at an intermediate stage of the manufacturing process shall be included in the dossier, with a view to ensuring the consistency of the technical characteristics and the production process.

41. The control tests are essential for checking the conformity of the veterinary medicinal product with the formula when:

41.1. exceptionally, an applicant proposes an analytical method for testing the finished product which does not include the assay of all the active substances or all the excipient components subject to the same requirements as the active substances; or

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

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

2.6. Tests on the Finished Product

43. 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.

44. Control of the finished product shall be carried out on a batch of the finished product.

45. The authorisation application shall list those tests which are carried out routinely on each batch of the finished product, as well as the frequency of the tests which are not carried out routinely. Release limits of the veterinary medicinal product shall be indicated.

46. The registration dossier shall include particulars relating to control tests on the finished product at release, which are performed when releasing the finished veterinary medicinal product. The dossier shall be submitted in accordance with the following conditions:

46.1. the provisions of the relevant monographs and general chapters of the European Pharmacopoeia, or failing that, of the Member States, which are applicable to all products defined therein, shall be used; and

46.2. if test procedures and limits other than those mentioned in the relevant monographs and general chapters of the European Pharmacopoeia or of the officially used pharmacopoeia of the Member States are used, it shall be proved that the finished product would, if tested in accordance with these monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned.

47. Certain tests of the general characteristics of a product shall be included in the general characteristics test of a finished product. These tests shall relate to the control of average masses and maximum deviations, to mechanical, physical or microbiological tests, organoleptic characteristics, physical characteristics (for example, density, pH, refractive index).

48. For the testing referred to in Paragraph 47 of this Annex, for each of the characteristics, the applicant shall specify the standards and tolerance limits in each particular case.

49. The applicant shall:

49.1. describe the conditions of the tests of the finished product in precise details, the equipment, apparatus and standards employed, whenever they are not given in the European Pharmacopoeia or in the officially used pharmacopoeia of the Member States or where the methods prescribed by the pharmacopoeias are not applicable; and

49.2. perform a test on solid pharmaceutical forms intended for oral (per os) administration, so that *in vitro* the liberation and dissolution rate of the active substance or substances may be determined, unless other action is justified. The Food and Veterinary Service may also request the performance of these tests where the method of administering the solid pharmaceutical form is different.

50. The identification and assay of the active substance shall be carried out either on a representative sample from the production batch or on a number of dosage units analysed individually.

51. Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished product may not exceed $\pm 5\%$ at the time of manufacture.

52. On the basis of the stability tests, the manufacturer shall propose and justify maximum acceptable deviation limits in the active substance content of the finished product up to the expiry of the proposed validity period.

53. Where active substances in mixtures are very numerous or present in such low amounts that an intricate investigation difficult to carry out would be required in respect of each batch of the veterinary medicinal product, the assay of one or more active substances may be omitted on condition that such assays are made at intermediate stages in the manufacturing process. Such deviation in the requirements shall not be applicable to the description of the substance concerned. The simplified method shall be supplemented by a method of quantitative evaluation enabling the Food and Veterinary Service to have the conformity of the veterinary medicinal product with its specification verified after it has been put on the market.

54. When physico-chemical methods cannot provide adequate information on the quality of a veterinary medicinal product, *in vivo* or *in vitro* biological assays shall be used. Such an assay, whenever possible, shall include reference materials and statistical analysis allowing calculation of confidence limits. Where testing of the finished veterinary medicinal product cannot be carried out, tests may be performed at an intermediate stage, as late as possible during manufacture.

55. Where degradation occurs during the process of manufacture of the product, the maximum acceptable levels of individual and total degradation products immediately following manufacture shall be indicated.

56. Where the particulars provided in accordance with Paragraphs 20 and 21 of this Annex show that a significant overage of an active substance is employed in the manufacture of the veterinary medicinal product or where the stability data show that the assay of the active substance declines on storage, the description of the control tests on the finished product shall include, where appropriate, the chemical and, if necessary, the toxico-pharmacological investigation and the characterisation or assay of the degradation products.

57. In the identification test of excipient components:

57.1. an identification test and upper and lower limit test shall be performed for each individual antimicrobial preservative and for any excipient that is liable to affect the bioavailability of the active substance, unless the bioavailability is guaranteed by other appropriate tests; and

57.2. an identification test and an upper limit test shall be performed for each antioxidant and for any excipient liable to adversely affect physiological functions, with a lower limit test also included for antioxidants at the time of release.

58. Apart from the toxico-pharmacological tests included in the dossier appended to the authorisation application, particulars of safety tests, such as sterility and bacterial endotoxins, shall be included in the analytical particulars wherever such tests must be undertaken regularly in order to verify the quality of the veterinary medicinal product.

59. A stability test of the active substance shall be performed and described in accordance with the following conditions:

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

59.2. stability data shall be presented in order to support the defined retest period and storage conditions. The stability test conducted, the test protocols used, the analytical procedures and their validation together with the detailed results shall be presented. The stability requirements (commitments) with a summary of the test protocol shall be provided; and

59.3. where a Certificate of Suitability for the active substance from the proposed source shown in the application dossier is available in which a retest period and storage conditions are specified, stability data for the active substance are not required.

60. A stability test of the finished product shall be performed and described in accordance with the following conditions:

60.1. a description shall be submitted of the investigations by which the validity period of the finished product, the recommended storage conditions and the specifications at the expiry of the validity period proposed by the applicant have been determined;

60.2. the stability tests conducted, the test protocols used, the analytical procedures and their validation together with the detailed results shall be presented;

60.3. where a finished veterinary medicinal product requires reconstitution or dilution prior to administration, detailed information in respect of the proposed validity period and specification of the reconstituted or diluted medicinal product shall be presented, to which the relevant stability data shall be appended;

60.4. in the case of multi-dose packaging, stability data shall be presented in order to justify the period of validity for the finished product after the packaging has been opened for the first time and the in-use specification shall be defined;

60.5. where a finished veterinary medicinal product may give rise to degradation products, the applicant shall indicate the identification methods and test procedures;

60.6. the report shall contain the results of analyses, justifying the proposed validity period and the in-use shelf life under the recommended storage conditions and the specifications of the finished veterinary medicinal product and the in-use shelf life under these recommended storage conditions;

60.7. the maximum acceptable level of individual and total degradation products at the expiry of the validity period of the veterinary medicinal product shall be indicated;

60.8. a study of the interaction between the veterinary medicinal product and the packaging shall be submitted, if this interaction is regarded as possible, especially for injectable preparations; and

60.9. the stability requirements (commitments) of the finished veterinary medicinal product with a summary of the test protocol shall be provided.

61. Other information relating to the quality of the veterinary medicinal product not covered in this Annex may be included in the dossier.

62. The following information shall be provided regarding medicated premixes:

62.1. the amount or dosage unit of premix to be added to feed;

62.2. instructions for the incorporation of premixes into feed;

62.3. the homogeneity of medicated feedingstuffs (feed to which medicated premix has been added);

62.4. the compatibility of the feed components with the premix;

62.5. stability of the premix in feed; and

62.6. the validity period of the medicated feedingstuffs.

63. A specification for the medicated feedingstuffs, manufactured using the relevant medicated premixes in accordance with the recommended instructions for use, shall also be provided.

3. Safety and Residue Tests

3.1. Performance of Safety Tests

64. The safety documentation shall show the following information:

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

64.2. the potential harmful effects to humans which may be caused by the residues of the veterinary medicinal product or substance in foodstuffs obtained from animals treated by the veterinary medicinal product. The difficulties these residues may create in the industrial processing of foodstuffs shall be indicated;

64.3. the potential risks to humans being exposed to the veterinary medicinal product, for example, during its administration to an animal; and

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

65. The information referred to in Paragraph 64 of this Annex shall be shown with credible and justified data. Mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results. Information shall be provided regarding

the latest therapeutic potential of the veterinary medicinal product and about the risk related to the use of this medicinal product.

66. It is permitted to test the metabolites of the parent compound where these represent the residues of concern.

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

68. The following information shall be shown for the precise identification of the product and of its active substance:

- 68.1. the international non-proprietary name (INN);
- 68.2. the International Union of Pure and Applied Chemistry Name (IUPAC);
- 68.3. the Chemical Abstract Service (CAS) number;
- 68.4. the therapeutic, pharmacological and chemical classification;
- 68.5. synonyms and abbreviations;
- 68.6. structural formula;
- 68.7. molecular formula;
- 68.8. molecular weight;
- 68.9. degree of impurity;
- 68.10. the qualitative and quantitative composition of the impurities;
- 68.11. description of physical properties;
- 68.12. melting point;
- 68.13. boiling point;
- 68.14. vapour pressure;
- 68.15. solubility in water and organic solvents expressed in g/l, with indication of temperature;
- 68.16. density;
- 68.17. spectra of refraction, rotation, etc; and
- 68.18. the pharmaceutical form.

69. Pharmacological studies shall be performed and described in accordance with the following conditions:

69.1. information regarding pharmacological studies conducted with experimental (laboratory) animals and target species shall be included in accordance with Part 4 of this Annex;

69.2. if the veterinary medicinal product produces pharmacological effects, in the absence of a toxic response at the same time, or at doses lower than those required to elicit toxicity, these pharmacological effects shall be taken into account during the evaluation of the safety of the veterinary medicinal product. The results of pharmacological studies may assist in the understanding of toxicological phenomena; and

69.3. detailed information of the pharmacological investigations undertaken in experimental (laboratory) animals and all relevant information regarding clinical studies with the target species shall be included in the veterinary medicinal product safety dossier.

70. The following shall be assessed in pharmacological investigations:

70.1. pharmacodynamics. Information on the mechanism of action of the active substance shall be provided together with information on primary and secondary pharmacodynamic effects in order to understand and describe the side-effects observed in the animal studies;

70.2. pharmacokinetics. Data on the active substance and its metabolites in the species used in the toxicological studies shall be provided, covering absorption, distribution,

metabolism and excretion (ADME). The data related to the dose or effect of the veterinary medicinal product in the pharmacological and toxicological studies, to determine the adequate effect and exposure of the veterinary medicinal product shall be evaluated. Comparison with the pharmacokinetic data obtained in the studies on the target species shall be included in the dossier prepared in accordance with Part 4 of this Annex, in order to determine the relevance of the results obtained in the toxicology studies for the toxicity to the target species;

70.3. toxicology. The documentation on toxicology shall be prepared in accordance with the guidance of the European Medicines Agency on the general approach to testing and guidance on particular studies. The documentation shall include information regarding:

70.3.1. basic tests performed on new veterinary medicinal products for use in food-producing animals in order to assess the degree of safety of any residues present in foodstuffs of animal origin;

70.3.2. additional tests that may be performed taking into account specific toxicological concerns, for example those associated with the structure, class and mode of action of the active substance; and

70.3.3. tests which might assist in the interpretation of data obtained in the basic or additional tests.

71. Single-dose toxicity tests shall be performed on the finished product. Single-dose toxicity studies reveal the acute toxic effects of the substance and the time course for their onset and remission. The studies to be carried out shall be selected with a view to providing information on the safety for the person administering the veterinary medicinal product to an animal, for example if substantial exposure by inhalation or dermal contact is anticipated, those methods of administration shall be studied. Single-dose toxicity tests shall be performed in order to determine:

71.1. the possible effects of acute overdosage in the target species;

71.2. the possible effects of accidental administration of the active substance to a human; and

71.3. the doses which may usefully be employed in the repeat dose toxicity tests.

72. Repeat dose toxicity tests shall be performed in accordance with the following conditions:

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

72.2. for pharmacologically active substances or veterinary medicinal products intended solely for use in non-food producing animals, a repeat-dose toxicity trial in one species of experimental animal for scientific purposes shall be permitted. This trial may be replaced by a trial on the target animal. The frequency and method of administration and the duration of the trial shall be chosen having regard to the proposed conditions of clinical use. The person responsible for performing the trial or test (hereinafter – investigator), shall give his or her reasons for the extent and duration of the trial and the dosages chosen;

72.3. if the pharmacologically active substances or veterinary medicinal products are intended for use in food-producing animals, repeat-dose toxicity testing shall be performed in a rodent and a non-rodent species in order to identify the target organs and toxicological endpoints and identify the appropriate species and the dose levels to be used in chronic toxicity testing if such are intended. The duration of the repeat-dose toxicity testing shall not be less than 90 days;

72.4. the investigator shall give his or her reasons for the choice of species, having regard to scientific discoveries of the metabolism of the product in animals and man. The test substance shall be administered orally (*per os*). The investigator shall clearly state and give his or her reasons for the method and frequency of the administration and the length of the trials;

72.5. the maximum dose shall be selected in order as to reveal harmful effects of the veterinary medicinal product. The lowest dose level should not produce any evidence of toxicity;

72.6. evaluation of the toxic effects shall be based upon observation of behaviour, growth, haematological 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 specific time;

72.7. if substances which have been investigated in accordance with the requirements of this Regulation are combined to make new combinations, the repeat-dose toxicity tests may be modified by the investigator, with reasons for such modifications, except where toxicity tests have demonstrated potentiation or new toxic effects.

73. Tolerance in the target species. A summary shall be provided of any signs of intolerance of the veterinary medicinal product, which have been observed during trials conducted with the target species in accordance with the requirements referred to in Paragraph 108 of this Annex (the finished product shall usually be investigated). The trials concerned, the dosages at which the intolerance occurred and the species and breeds concerned shall be identified. Details of any unexpected physiological changes shall be provided. The full reports of the relevant trial shall be included in the documentation in accordance with Part 4 of this Annex.

74. Reproductive toxicity tests, including developmental toxicity (the individual development of an organism) shall be performed and described in accordance with the following conditions:

74.1. studies of the effect on reproduction shall be performed in order to identify the possible impairment of male or female reproductive function or harmful effects on progeny resulting from the administration of the veterinary medicinal products or substance under investigation;

74.2. for pharmacologically active substances or veterinary medicinal products intended for use in food-producing animals, the study of the effects on reproduction shall be performed in the form of a multi-generation reproduction study, designed to detect any effect on mammalian reproduction. The effects on male and female fertility, mating, conception and implantation, ability to maintain pregnancy to term, parturition, lactation, survival, growth and development of the offspring from birth through to weaning, sexual maturity and the subsequent reproductive function of the offspring as adults, shall be described in the study. At least three different doses shall be used. The maximum dose shall be selected in order to reveal the harmful effects. The lowest dose level should not produce any evidence of toxicity.

75. A study of developmental toxicity shall be performed and described in accordance with the following conditions:

75.1. if pharmacologically active substances or veterinary medicinal products are intended for use in food-producing animals, tests on developmental toxicity shall be performed. This test shall be performed in order to detect any side-effects caused by the use of the medicinal product or substance on the pregnant female and development of the embryo and foetus consequent to exposure of the female from implantation through gestation to the day before predicted birth. The following side-effects may be possible: enhanced toxicity relative to that observed in non-pregnant females, embryo or foetal death, altered foetal growth and structural changes to the foetus;

75.2. a developmental toxicity test in a rat shall be performed. When assessing the results, tests may have to be performed in a second species in accordance with established guidelines; and

75.3. if pharmacologically active substances or veterinary medicinal products are intended for use in non-food producing animals, a developmental toxicity test shall be performed in at least one species, which may be the target species, if the medicinal product is intended for use in female animals which may be used for breeding. However, where the use of the veterinary medicinal product would result in significant exposure to the persons administering the medicinal product to animals, standard developmental toxicity tests shall be performed.

76. Genotoxicity tests shall be performed and described in accordance with the following conditions:

76.1. tests for genotoxic potential shall be performed in order to determine changes which a substance may cause in the genetic material of cells. Any substance intended to be included in a veterinary medicinal product for the first time must be assessed for genotoxic properties; and

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

77. Carcinogenicity tests shall be performed and described in accordance with the following conditions:

77.1. in order to take a decision on whether carcinogenicity testing is required on pharmacologically active substances or veterinary medicinal products, the results of genotoxicity tests shall be examined, the structure-activity relationships and the findings in systemic toxicity tests that may be relevant to neoplastic lesions in longer term studies;

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

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

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

78.1. under the intended conditions of use laid down, oral ingestion (*per os*) of the veterinary medicinal product by the animal is possible;

78.2. under the intended conditions of use laid down, exposure of the person applying the medicinal product to an animal by other routes than the dermal route (for example, inhalation, contact with the mucous membranes) is possible; or

78.3. the active substance or metabolites may enter foodstuffs of animal origin obtained from the animal treated by the relevant medicinal product (for example, preparations administered through the udder).

79. Special studies:

79.1. shall be performed for particular groups of substances or if the effects observed during repeated dose toxicity tests in animals include changes indicative of e.g. immunotoxicity, neurotoxicity or endocrine dysfunction. Further testing shall be performed, for example, sensitisation studies or delayed neurotoxicity tests;

79.2. may be performed, when assessing the principal qualities of the product, in order to assess the underlying mechanism of the toxic effect or the irritation potential. Such studies shall usually be conducted with the finished product; and

79.3. when designing such studies and evaluating their results, the state of scientific knowledge at the time the documentation appended to the application for submission was prepared, shall be taken into account.

80. Microbiological properties of residues:

80.1. the potential effects on the human gut flora shall be described. The potential microbiological risk presented by residues of antimicrobial compounds for the human intestinal flora shall be investigated in accordance with established guidelines; and

80.2. the potential effects on the microorganisms used for industrial food processing shall be described. In certain cases tests may be carried out to determine whether microbiologically active residues may interfere in technological processes in the industrial processing of foodstuffs.

81. Information shall be provided on observations in humans in relation to whether the pharmacologically active substances of the veterinary medicinal product are used as medicinal products in human therapy. If this is so, a compilation shall be made of the effects observed (including side-effects) in humans and of the cause of the effects observed and assessment of the safety of the veterinary medicinal product shall be performed, where appropriate including results from published studies (bibliography). If components of the veterinary medicinal product are not used or are no longer used as medicinal products in human therapy, the reasons shall be stated.

82. Development of resistance:

82.1. data on the potential emergence of resistant bacteria (related to human health) shall be submitted, which may be caused by administering veterinary medicinal products to animals. The mechanism of the development of such resistance shall be described. Where necessary, measures to limit resistance development from the intended use of the veterinary medicinal product shall be proposed; and

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

83. User safety. The effects found on humans administering or applying veterinary medicinal products to animals shall be described, indicating the effect, significance and duration of these medicinal products. Appropriate user warnings and other risk management measures shall be formulated.

84. An environmental risk assessment of veterinary medicinal products not containing or consisting of genetically modified organisms shall be performed to assess the potential harmful effects which the use of the veterinary medicinal product may cause to the environment and to identify the risk of such effects. The assessment shall also identify any precautionary measures which may be necessary to reduce the risks to the environment. The environmental risk assessment shall be performed in accordance with the following requirements:

84.1. the first phase of the environmental risk assessment shall always be performed. More detailed information regarding the assessment shall be provided in accordance with accepted guidelines. The potential exposure of the environment to the veterinary medicinal product and the level of risk associated with such exposure shall be described in the assessment, taking into account in particular the following items:

84.1.1. the target species and the proposed pattern of use;

84.1.2. the method of administration, in particular the likely extent to which the veterinary medicinal product will enter directly into environmental systems,

84.1.3. the possible excretion of the veterinary medicinal product, its active substances or relevant metabolites into the environment by treated animals and persistence in such excreta;

84.1.4. the disposal of unused veterinary medicinal product or other waste product;

84.2. in the second phase of the environmental risk assessment, further specific investigation of the fate and effects of the product on particular ecosystems shall be conducted, in accordance with established guidelines. The extent of exposure of the product to the environment and the available information about the physical/chemical, pharmacological and (or) toxicological properties of the substance concerned, including metabolites in case of an identified risk which has been obtained during the conduct of the other tests and trials required by this Regulation, shall be taken into consideration; and

84.3. if a veterinary medicinal product contains genetically modified organisms, an environmental risk assessment for veterinary medicinal products containing genetically modified organisms shall be performed and the documents required in accordance with the regulatory enactments regulating the circulation of genetically modified organisms shall be appended to the application.

3.2. Particulars and Documents Regarding Safety Tests

85. The dossier of safety tests shall include the following information:

85.1. an index of all studies included in the dossier;

85.2. a statement confirming that all data known by the applicant at the time of submission, whether favourable or unfavourable, are included;

85.3. a justification for the omission of any type of study;

85.4. an explanation of the inclusion of an alternative type of study; and

85.5. a discussion of the contribution that any study that pre-dates the coming into force of regulatory enactments regarding good laboratory practice can make to the overall risk assessment.

86. Each study report shall include:

86.1. a copy of the study plan (protocol);

86.2. a statement of compliance with good laboratory practice, where applicable;

86.3. a description of the methods, apparatus and materials used in the study;

86.4. a description and justification of the test system;

86.5. a description of the results obtained in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author;

86.6. a statistical analysis of the results where appropriate;

86.7. a discussion of the results, with comment on observed (non-observed) effect levels and unusual findings; and

86.8. a detailed description and a thorough discussion of the results of the study of the safety profile of the active substance and its relevance for the evaluation of potential risks presented by residues to humans.

3.3. Performance of Residue Tests

87. Residue tests shall be performed in order to establish:

87.1. the depletion of residues from the edible tissues or of eggs, milk and honey derived from animals treated by medicinal products;

87.2. under what conditions and to what extent residue may persist in foodstuffs of animal origin; and

87.3. the withdrawal period of the medicinal product.

88. If the medicinal product is intended for food-producing animals, the residue documentation shall show:

88.1. to what extent and how long the veterinary medicinal product or its metabolite residues persist in the tissues of the animal or in milk, eggs or honey obtained therefrom;

88.2. information that it is possible to establish realistic withdrawal periods of the veterinary medicinal product, which can be observed under practical farming condition, in order to prevent risks to consumer health or complications in the industrial processing of foodstuffs; and

88.3. information that the analytical methods used in the residue tests are sufficiently validated to provide the necessary reassurance that the residues data submitted are suitable as the basis for a withdrawal period of the veterinary medicinal product.

89. Pharmacokinetics (absorption, distribution into the organism, metabolism and excretion) shall be described in accordance with the following conditions:

89.1. a summary of the pharmacokinetic data shall be submitted with cross reference to the pharmacokinetic studies in target species submitted in accordance with Part 4 of this Annex (the full study report does not need to be submitted);

89.2. pharmacokinetic studies of residues of veterinary medicinal products are performed to evaluate the absorption, distribution into the organism, metabolism and excretion of the medicinal product concerned in the organism of the target species;

89.3. information shall be shown about how the finished veterinary medicinal product or formulation which has comparable characteristics in terms of bioavailability as the finished veterinary medicinal product concerned, is administered to the target animal species at the maximum recommended dose;

89.4. the extent of absorption of the veterinary medicinal product shall be fully described, having regard to the method of administration. If the systemic absorption of the veterinary medicinal product for topical application is negligible, further residue tests will not be required;

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

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

90. The depletion of residues shall be determined by establishing which residues subside and the rate at which the residues subside after the last administration of the veterinary medicinal product to the target animal.

91. In order to determine the withdrawal period of the veterinary medicinal product from the organism of an animal, the sufficient quantities of residues present in the test animal in a specific time period shall be determined, selecting the sufficient number of times the test is performed in different time periods after the test animal has received the final dose of the veterinary medicinal product. The appropriate validated analytical methods shall be used. The technical procedures and the reliability and sensitivity of the methods employed shall be specified.

92. The analytical method used in the residues depletion tests and its validation shall be described in detail.

93. The characteristics of the following analytical methods shall be described:

93.1. the specificity;

- 93.2. thoroughness;
- 93.3. accuracy;
- 93.4. limit of detection;
- 93.5. the quantitative limit;
- 93.6. practicability and applicability under normal laboratory conditions;
- 93.7. susceptibility to interference; and
- 93.8. stability of incurred residues.

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

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

3.4. Particulars and Documents Regarding Residue Tests

96. The veterinary medicinal products used in testing shall be identified and the following information shall be included in the dossier for the identification of the medicinal product concerned:

- 96.1. the composition of the veterinary medicinal product;
- 96.2. the physical and chemical (potency and purity) test results for the relevant batch;
- 96.3. batch identification;
- 96.4. relationship to the final product;
- 96.5. specific activity and radio-purity of labelled substances; and
- 96.6. position of labelled atoms in the molecule.

97. The dossier of residue tests shall include:

- 97.1. an index of all studies included in the dossier;
- 97.2. a statement by the applicant that all data known by the applicant at the time of submission, whether favourable or unfavourable, are included in the dossier;
- 97.3. a justification for the omission of a study or any type of study;
- 97.4. an explanation of the inclusion of an alternative type of study, if appropriate;
- 97.5. a discussion of the contribution that any study that pre-dates the coming into force of regulatory enactments regarding good laboratory practice can make to the overall risk assessment; and
- 97.6. a proposal for the withdrawal period of the veterinary medicinal product from the organism of the animal.

98. The following information shall be included in each study report (statement):

- 98.1. a copy of the study plan (protocol);
- 98.2. a statement of compliance of the study with good laboratory practice, where applicable;
- 98.3. a description of the methods, apparatus and materials used;
- 98.4. a description of the results obtained in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author;
- 98.5. a statistical analysis of the results where appropriate;
- 98.6. a discussion of the results; and
- 98.7. an objective discussion of the results obtained and proposals concerning the withdrawal periods of the veterinary medicinal product to ensure that no residues which might cause a hazard for consumer health and life are present in food products obtained from treated animals.

4. Pre-clinical (Non-clinical) and Clinical Trials

4.1. Pre-clinical Studies

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

100. The pharmacodynamic effects of the active substances included in the veterinary medicinal product shall be characterised in accordance with the following conditions:

100.1. 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. If the applicant wishes to determine the higher efficacy for an active substance than a substance whose efficacy is well known, the difference, and the statistical significance thereof shall be demonstrated;

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

100.3. the effect of other characteristics of the finished product on the pharmacological activity of the active substance shall be described (for example, the administration route, the pharmaceutical form);

100.4. detailed information shall be shown regarding the active substance, if the recommended dose is equal to or slightly smaller than the dose which may cause side-effects;

100.5. the methods used in the investigations which are not standard procedures, shall be described in such detail as to allow them to be reproduced. The investigator shall validate the methods concerned, set out the experimental results and for certain types of tests, their statistical significance shall be quoted;

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

100.7. information regarding substance combinations shall be shown, justifying these pharmacologically or with clinical indications. Pharmacodynamic or pharmacokinetic studies shall demonstrate the interactions which might make the combination of substances appropriate for clinical use. Where scientific justification for the combination is scientifically justified in clinical studies, it shall be indicated whether the effect caused by the combination can be demonstrated in animals and the importance of any side-effects shall be checked. If a combination includes a new active substance, it shall be studied in depth beforehand.

101. In the study report on the development of resistance:

101.1. data on the potential emergence of resistant organisms of clinical relevance which may be caused by administering veterinary medicinal products, shall be shown. The mechanism of the development of such resistance shall be described. Measures to limit resistance development which may be caused by the intended use of the veterinary medicinal product shall be proposed by the applicant; and

101.2. cross reference to the data described in Part 3 of this Annex shall be made, if necessary.

102. In pharmacokinetic studies:

102.1. basic pharmacokinetic data concerning a new active substance in the context of assessment of the clinical safety and efficacy of the veterinary medicinal product shall be described; and

102.2. the objectives of pharmacokinetic studies in the target animal species shall be indicated.

103. The pharmacokinetic studies in the target animals shall be divided into the following areas:

103.1. descriptive pharmacokinetics, in order to determine the basic parameters;

103.2. use of the basic parameters to investigate the relationship between dosage regimen, plasma and tissue concentration over time and pharmacological, therapeutic or toxic effects; and

103.3. comparable kinetics in order to explore possible species differences which may impact on target animal safety and efficacy of the veterinary medicinal product.

104. Pharmacokinetic studies in the target animal species are necessary as a complement to the pharmacodynamic studies to support the establishment of effective dosage regimens (route and site of administration, dose, dosing interval, number of administrations). Additional pharmacokinetic studies shall be performed to establish dosage regimens according to certain population variables (for example, age, illness).

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

106. Where new active substances are used in a new combination, which have been investigated in accordance with the provisions of this Regulation, and if it can be justified that the administration of these substances as a fixed combination does not change their pharmacokinetic properties, pharmacological studies of the fixed combination are not required.

107. Appropriate bioavailability studies shall be undertaken in pharmacological studies, in order to establish bioequivalence in the following cases:

107.1. when comparing a reformulated veterinary medicinal product with the existing one; and

107.2. for the comparison of a new route or method of administration with an established one.

108. The local and systemic tolerance of the veterinary medicinal product shall be investigated in the target animal species. The purpose of these studies is to characterise signs of intolerance and to establish an adequate margin of safety using the recommended methods of administration. The margin of safety may be determined by increasing the therapeutic dose or the duration of treatment. The report on the trials shall contain details of all possible pharmacological effects and side-effects.

4.2. Clinical Investigations

109. The purpose of clinical trials is to reveal or substantiate the effect of the veterinary medicinal product after administration at the proposed dosage regimen via the proposed method of administration and to specify its indications and contra-indications according to species, age, breed and sex of the animal, instructions for use and possible side-effects.

110. Experimental data shall be confirmed by data obtained under normal practical (field) conditions.

111. Unless justified, clinical trials shall be carried out with control animals (controlled clinical trials). The efficacy results obtained shall be compared with those from the target animal species that have received a veterinary medicinal product authorised in the European Union with the same indications for use in the same target species as the medicinal product to be investigated, or with a *placebo* (medicinal products without an active substance).

112. All the results of clinical trials obtained, whether positive or negative, shall be reported. Statistical principles shall be used in protocol design, analysis and evaluation of clinical trials.

113. If a veterinary medicinal product is intended for use as a performance enhancer of an animal, particular attention shall be given to:

- 113.1. animal productivity (yield);
- 113.2. the quality of animal produce (organoleptic, nutritional, hygienic and technological qualities);
- 113.3. nutritional efficiency and growth of the target animal species; and
- 113.4. general state of health of the target animal species.

114. Clinical trials of veterinary medicinal products shall be conducted in accordance with a detailed trial protocol.

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

116. Before the commencement of any field trial, the owner (keeper) of the animals to be used in the trials shall be consulted and his or her consent for the use of the animals in the field trials shall be documented. The animal owner shall be informed in writing of the terms for the disposal of the animals used in the trials and the restrictions for the acquisition of foodstuffs from an animal used in the trial. A copy of this notification, signed and dated by the animal owner shall be included in the trial documentation.

117. Unless the field trials are conducted with a blind design, the provisions specified in the regulatory enactments regulating the labelling of veterinary medicinal products shall apply to the labelling of formulations of the veterinary medicinal products intended for use in veterinary field trials. In any case, the words “for veterinary field trial use only” shall appear prominently and indelibly upon the labelling.

4.3. Particulars and Documents

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

119. Results of pre-clinical trials shall be described in detail, obtained from:

- 119.1. tests demonstrating pharmacological efficacy;
- 119.2. tests demonstrating the pharmacodynamic mechanisms underlying the therapeutic effect;
- 119.3. tests demonstrating the main pharmacokinetic profile;
- 119.4. tests demonstrating target animal safety; and
- 119.5. tests investigating resistance.

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

121. The following particulars shall also be provided in pre-clinical studies:

- 121.1. a summary of the study;
- 121.2. a detailed experimental protocol giving a description of the methods, apparatus and materials used, the species, age, weight, gender, number, breed or strain of animals, identification of animals, dose, method and schedule of administration of the medicinal product;
- 121.3. a statistical analysis of the results; and
- 121.4. an objective discussion of the results obtained, leading to conclusions on the safety and efficacy of the product.

122. If any data is not included fully or partly in the description of the pre-clinical trials, this shall be substantiated.

123. Each investigator shall submit particulars regarding the clinical trials on individual record sheets in the case of individual treatment of animals by the medicinal product being investigated, and on collective record sheets if the medicinal product being investigated is administered to animals in groups (collectively).

124. The particulars regarding the clinical trials shall indicate the following information:

- 124.1. the given name, surname, function and qualifications of the investigator in charge;
- 124.2. the place and date of treatment of animals with the medicinal product being investigated;
- 124.3. the surname and address of the owner of the animals;
- 124.4. the clinical trial protocol, giving a description of the methods, including methods of randomisation and blinding, details regarding the method of administration, the schedule of administration, the dose, identification of the trial animals, species, breeds or strains, age, weight, sex, number and physiological status;
- 124.5. the method of management and feeding of the animals used in the trials, stating the composition of the feed and the nature and quantity of any feed additives;
- 124.6. the case history of the animals involved in the trials (as full as possible), describing any occurrences and course of any intercurrent diseases;
- 124.7. diagnosis and the means used to make the diagnosis;
- 124.8. clinical signs of illness (described according to conventional criteria);
- 124.9. precise identification of the final formulation of the veterinary medicinal product used in the clinical trials and the chemical and physical test results of the relevant batches;
- 124.10. dosage of the veterinary medicinal product, route, method and frequency of administration and precautions, if any, taken during administration (for example, during injection);
- 124.11. duration of administration of the medicinal product and the period of subsequent observation;
- 124.12. details concerning other veterinary medicinal products which have been administered during the period of examination, either prior to or concurrently with the test product. Where the medicinal product is administered concurrently with the test product, details of any interactions observed shall be described;
- 124.13. results of the clinical trials obtained based on the efficacy criteria and end points (illness, symptoms or signs in clinical investigation, to be achieved, one of the target aims of the study), specified in the clinical trial protocol, including the results of the statistical analysis;
- 124.14. unforeseen effects whether harmful or not, and any measures taken in consequence. The cause-and-effect relationship shall be investigated if possible;

124.15. effect on the animal performance (for example, lay, milk, reproductive functions), if any;

124.16. effects of the veterinary medicinal product on the quality of foodstuffs obtained from treated animals, in particular in the case of veterinary medicinal products intended for use as performance enhancers of the animal;

124.17. conclusions on the safety and efficacy of the test product in each individual case or summarised information in terms of frequencies or other appropriate variables, insofar as this relates to the administration of the test product to animals in a group; and

124.18. justification, if any of the aforementioned conditions are not applied.

125. The marketing authorisation holder (owner) shall keep or ensure the keeping of the original documents which formed the basis of the data supplied for at least five years after the end of the authorisation of the veterinary medicinal product.

126. The clinical trial results shall summarise the trials and the results thereof in a summary (synopsis), indicating:

126.1. the number of control and test animals used in the trials, treated with the test product individually or collectively, preparing the documentation according to animal species, breeds or strains, age and sex;

126.2. the number of animals withdrawn prematurely from the trials and the reasons for such withdrawals;

126.3. control animals and details whether they have received no treatment, or received a placebo, other veterinary medicinal products authorised in the European Union for the same indication for use in the same target animal species, or received the same active substance under investigation in a different formulation or by a different method of administration;

126.4. the frequency of observed side effects;

126.5. observations as to the effect on animal performance;

126.6. 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 considerations; or

126.7. a statistical evaluation of the results.

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

128. In respect of combination veterinary medicinal products the investigator shall draw conclusions concerning the safety and efficacy thereof when compared with the separate administration of the active substances involved in each medicinal product.

Requirements for Immunological Veterinary Medicinal Products
[15 September 2009; 28 December 2010]

Summary of the Dossier

1. In the authorisation application of a veterinary medicinal product:

1.1. immunological veterinary medicinal products shall be identified by name and by name of the active substance, information regarding the biological activity, the potency or titre, the pharmaceutical form, the route and method of administration, and by the final presentation, including, packaging, labelling, package leaflet and summary of the veterinary medicinal product characteristics. Diluents may be packed together with the vaccine vials or separately. Information on diluents needed for making the final vaccine preparation shall be included in the dossier. An immunological veterinary medicinal product is regarded as one product, even when more than one diluent is required so that different preparations of the final product can be prepared, intended for administration to animals using different routes or methods of administration;

1.2. the name and address of the applicant shall be given, together with the name and address of the manufacturer and the sites involved in the different stages of manufacture and control, the manufacturer of the finished product and the manufacturer of the active substances and, where relevant, the name and address of the importer;

1.3. the documents (number and titles) submitted together with the application shall be identified;

1.4. information regarding samples submitted shall be provided;

1.5. copies of a document shall be appended, certifying that the manufacturer is authorised to produce immunological veterinary medicinal products in accordance with the regulatory enactments regulating the manufacture of veterinary medicinal products;

1.6. a list of organisms handled at the production site shall be appended;

1.7. a list of the countries in which the respective veterinary medicinal product marketing authorisation has been granted, and a list of the countries in which an application has been submitted or refused, shall be appended; and

1.8. bibliographical references shall be given and copies thereof shall be appended.

2. The applicant shall submit:

2.1. the summary of the veterinary medicinal product characteristics prepared in accordance with the requirements referred to in Paragraph 35 of this Regulation;

2.2. proposed labelling for the immediate packaging and secondary packaging together with the package leaflet, if required. The documents referred to shall be prepared in accordance with the regulatory enactments regarding the procedures for the labelling, distribution and control of veterinary medicinal products; and

2.3. one or more finished trade samples or drafts of veterinary medicinal products containing information in at least one official language of the Member States. The mock-ups may be submitted in printed form on paper or electronically, if the Food and Veterinary Service has given prior consent.

3. A detailed summary (hereinafter – summary) shall be prepared in accordance with Paragraph 15 of this Regulation, taking into account the following requirements:

3.1. the scientific data available at the time of the submission of the application shall be included in the summary;

3.2. an evaluation of the tests and trials which constitute the marketing registration dossier, and an assessment of the quality, safety and efficacy of the immunological veterinary medicinal product shall be included in the summary;

3.3. the results of the tests and trials and precise bibliographic references shall be given in the summary;

3.4. the significant data of the summary shall be compiled in the summary, if possible, in tabular or graphic form; and

3.5. precise cross-references to the documentation appended to the authorisation application shall be included in the summary and the annexes thereto.

4. Information regarding the education, training and work experience of the expert shall be appended to the summary, and the professional relationship of the applicant and the expert shall also be reflected. The summary shall be dated and signed by the expert.

2. Chemical, Pharmaceutical and Biological or Microbiological Information

2.1. General Information

5. The information and documents which are appended to an application for the receipt of a veterinary medicinal product marketing authorisation, in compliance with Sub-paragraph 13.10 of this Regulation, shall be as follows:

5.1. the test procedures formulated which conform with the requirements for analysis and control of the quality of the starting materials and the finished product, providing the results of the validation studies;

5.2. detailed descriptions of the special apparatus and equipment which may be used in tests (if possible, appending diagrams);

5.3. information on the formulae of the laboratory reagents (if necessary, the manufacturing method of the reagents shall be shown); and

5.4. if the test procedures are included in the European Pharmacopoeia or in the official pharmacopoeia used in the Member States, the description of the procedures may be replaced by a detailed reference to the pharmacopoeia in question. Chemical and biological reference material of the European Pharmacopoeia shall generally be used in tests. If other reference preparations and standards are used, they shall be identified and described in detail.

6. When developing the information and documents referred to in Paragraph 5 of this Annex, the common monographs and general chapters of the European Pharmacopoeia shall be taken into account or, if this is not possible, the monographs of the official pharmacopoeia used in the Member States shall be applied.

2.2. Qualitative and Quantitative Particulars of the Components

7. The following shall be included in the particulars of the quality of the components (constituents) of immunological veterinary medicinal products:

7.1. information regarding the active substance;

7.2. information regarding the excipient components irrespective of the type and quantity used, including colouring matters, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances;

7.3. information on the components of the pharmaceutical form administered to animals; and

7.4. particulars on the immediate packaging (container) and the manner of closure thereof, as well as particulars regarding the administration of immunological veterinary medicinal products and devices used for administration, supplied together with the veterinary

medicinal product concerned. If a device is not supplied together with immunological veterinary medicinal products, information regarding the device shall be provided, if necessary for the performance of the evaluation of the medicinal product.

8. The usual terminology is the terminology used when describing components of a veterinary medicinal product notwithstanding the application of the provisions referred to in Sub-paragraph 13.3 of this Regulation:

8.1. for substances which appear in the European Pharmacopoeia or in the official pharmacopoeia used in the Member States, the main title of the monograph shall be indicated, with reference to the pharmacopoeia concerned;

8.2. in respect of other substances the international non-proprietary name recommended by the World Health Organisation shall be indicated, which may be accompanied by a non-proprietary name or, if none exists, the exact scientific name. Substances which have not been allocated an international non-proprietary name or scientific designation shall be described by a statement of how and from what substances they have been prepared, supplemented where appropriate by any other significant information; and

8.3. colouring matters shall be designated the "E" code assigned to them in accordance with the regulatory enactments regarding the mandatory requirements for the harmlessness of food additives and food products, in which food additives are used.

9. In order to give the quantitative particulars of an immunological veterinary medicinal product, the number of organisms, the specific protein content, the mass, the International Units (IU) or units of biological activity per dosage-unit or volume shall be given. The mass and the volume of the components of the adjuvants and excipients shall be shown, with due consideration to Paragraph 13 of this Annex.

10. A unit of biological activity shall be used, if defined.

11. 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 components, for example, stating the immunological effect on which the method of determining the dose is based.

12. During the course of the development of the medicinal product:

12.1. an explanation shall be provided with regard to the composition, components and packaging of the immunological veterinary medicinal product. The explanation shall be supported by scientific data regarding the development of the medicinal product; and

12.2. the overage, with justification thereof, shall be stated;

2.3. Description of the Manufacturing Method

13. The description of the manufacturing method appended to the authorisation application in accordance with Sub-paragraph 13.4 of this Regulation shall be drafted in such a way as to give an adequate synopsis of the manufacturing process. The following shall be included in the description of the manufacturing method:

13.1. a list of the manufacturing stages (including production of the antigen and purification procedures), so that the reproducibility of the manufacturing procedure and the risks of side-effects may be assessed;

13.2. the validation of key stages in the production process and the production process as a whole, providing the results of three consecutive batches produced using the method described;

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

- 13.4. a list of all the substances at the appropriate manufacturing stages where they are used, including substances which cannot be recovered in the course of manufacturing;
- 13.5. detailed information of the blending, including the quantitative particulars of the substances used; and
- 13.6. stages of the manufacture at which sampling is carried out.

2.4. Production and Control of Starting Materials

14. Starting materials are all the components used in the production of the immunological veterinary medicinal product.

15. One starting material is the culture media consisting of several components used for production of the active substance. The qualitative and quantitative composition of the culture media shall be presented in accordance with the information specified by the Food and Veterinary Service regarding the quality of the finished product and any potential risk. If materials of animal origin are used for preparation of these culture media, information regarding the animal species and the tissue used shall be included.

16. The regular tests which are performed on each batch of starting materials shall be indicated in the application for a marketing authorisation.

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

18. In respect of other substances, the Food and Veterinary Service may require observance of the European Pharmacopoeia or the officially used pharmacopoeia of the Member States for medicinal products manufactured in the Republic of Latvia.

19. Where components fulfil the requirements of the European Pharmacopoeia or the requirements of the officially used pharmacopoeia of the Member States and the requirements referred to in Sub-paragraph 13.9 of this Regulation, the description of the analytical methods and procedures shall be replaced by a reference to the pharmacopoeia in question.

20. Colouring matters shall, in all cases, comply with the requirements specified in the regulatory enactments regulating the colouring matters to be added to medicinal products.

21. The routine tests carried out on each batch of starting materials shall be stated in the authorisation application, and in cases where 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.

22. The Food and Veterinary Service may request more appropriate specifications from the applicant for a marketing authorisation, if the specification or other provisions shown in the European Pharmacopoeia or the officially used pharmacopoeia of the Member States are not sufficient to ensure the quality of the substance. The alleged insufficiency shall be reported to the authority responsible for the pharmacopoeia in question.

23. The monograph of a third country pharmacopoeia may be used if the starting material is not described in the European Pharmacopoeia or the officially used pharmacopoeia of the Member States. In such cases a copy of the monograph used shall be submitted and, where necessary, the validation and translation of the test procedures contained in the monograph shall be appended.

24. Starting materials of animal origin shall comply with the requirements of the relevant monograph, including the general monographs and general chapters of the European Pharmacopoeia. The tests and controls conducted shall be appropriate to the starting material.

25. Documentation shall be appended to the application for a marketing authorisation which certifies that the starting materials and the manufacture of the veterinary medicinal product is in compliance with European Commission requirements specified in the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, as well as with the requirements of the corresponding monograph of the European Pharmacopoeia. Certificates of Suitability issued by the European Directorate for the Quality of Medicines and HealthCare, with reference to the relevant monograph of the European Pharmacopoeia, may be used to demonstrate the compliance referred.

26. Starting materials not listed in a pharmacopoeia shall be described in conformity with the following conditions:

26.1. starting materials of biological origin:

26.1.1. the description shall be given in the form of a monograph;

26.1.2. whenever possible, vaccine production shall be based on a seed lot system and on established cell banks. Where immunological veterinary medicinal products are produced consisting of serums, the general health and immunological status of the producing animals shall be indicated. Defined pools of starting materials shall be used in production;

26.1.3. the history and origin, including the geographical origin, of the starting materials shall be described and documented. The following details shall be included in the information regarding genetically engineered starting materials: a 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, oligonucleotide sequences of plasmid vector in cells, plasmid used for contransfection, added or deleted genes, biological properties of the final structure and the genes expressed, copy number and genetic stability;

26.1.4. seed materials, including cell banks and starting materials for anti-serum production, shall be tested for identity and extraneous agents;

26.1.5. information shall be provided on all substances of biological origin used at each stage in the manufacturing process. This information shall include detailed information of the source of the materials, of any processing, purification and inactivation applied, with data on the validation of these processes and controls during production, as well as details of any tests for contamination carried out on each batch of the substance;

26.1.6. if the presence of extraneous agents is detected or suspected, the corresponding material shall be discarded or used in very exceptional circumstances if further processing of the product ensures the elimination or inactivation of the extraneous agents. In such case proof of the elimination or inactivation of the extraneous agents shall be given;

26.1.7. 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;

26.1.8. for live attenuated vaccines, proof of the stability of the attenuation characteristics has to be given;

26.1.9. documentation shall be supplied to demonstrate that the seed materials, cell banks, batches of serum and other material originating from animals relevant for the transmission of transmissible spongiform encephalopathy (TSE) comply with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, as well as with the corresponding monograph

of the European Pharmacopoeia. Certificates of Suitability issued by the European Directorate for the Quality of Medicines with reference to the relevant monograph of the European Pharmacopoeia, may be used to demonstrate compliance; and

26.1.10. when required, samples of the biological starting material or reagents used in the testing procedures shall be provided to enable the Food and Veterinary Service to arrange for inspection tests to be carried out;

26.2. a description of starting materials of non-biological origin shall be provided in the form of a monograph, indicating the following information:

26.2.1. the name of the starting material meeting the requirements referred to in Paragraph 8 of this Annex shall be supplemented by any trade or scientific synonyms;

26.2.2. the starting material shall be described similarly to that used in the European Pharmacopoeia;

26.2.3. the function of the starting material;

26.2.4. methods of identification; and

26.2.5. any special precautions for the storage of the starting material and, if necessary, its maximum storage life.

2.5. Control During the Manufacturing Process

27. In order to ensure the homogeneity of the manufacturing process and the finished product, documentation on the production control tests which may be carried out in the intermediate phase of manufacturing shall be appended to the application for a marketing authorisation.

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

29. In order to perform quality assessments, the techniques for analysing the finished product shall be described in detail. The dossier shall include particulars relating to control tests on the finished product. Where appropriate monographs exist, but test procedures and limits other than those mentioned in the monograph of the European Pharmacopoeia or the officially used pharmacopoeia of the Member States, are used, the applicant shall provide proof that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned.

30. The application for the receipt of a marketing authorisation shall list those tests which are carried out on representative samples of each batch of finished product, and the frequency of the tests which are not carried out on each batch, and the batch release limits shall be stated.

31. Chemical and biological reference material of the European Pharmacopoeia shall generally be used in sampling tests of the finished product. If other reference preparations and standards are used, they shall be identified and described in detail.

32. Tests shall be carried out to determine the general characteristics of the product for the control of average masses and maximum deviations of the finished product, for mechanical, physical or chemical tests, physical characteristics (for example, pH, viscosity). For each of these characteristics, specifications, with appropriate confidence limits, shall be established by the applicant in each particular case.

33. Where necessary, a specific test for identification of the active substance shall be carried out.

34. A quantification of the active substance shall be defined to determine the batch titre or potency for each batch, certifying that each batch contains the appropriate titre or potency to ensure the safety and efficacy of the finished product.

35. Identification and assay of adjuvants shall be performed insofar as testing procedures are available, checking (verifying) the quantity and nature of the adjuvant and its components in the finished product.

36. Identification and assay of excipient components shall be performed in accordance with the following conditions:

36.1. insofar as is necessary, identification tests of the excipients shall be performed;

36.2. an obligatory upper and lower limit test of preserving agents shall be performed;

and

36.3. an upper limit test for any other excipient components liable to give rise to side-effects shall be obligatory.

37. Apart from the results of tests submitted in accordance with Part 3 of this Annex (Safety Tests), detailed information on the batch safety tests shall be submitted. These tests shall be studies on the overdosage of veterinary medicinal products in at least one of the most sensitive target species and by at least the route of administration posing the greatest risk. In the interests of animal welfare, routine batch safety tests may be waived when a sufficient number of consecutive production batches have been produced which comply with the testing conditions.

38. Sterility and purity tests shall be performed in order to determine the absence of contamination by extraneous agents or other substances. These shall be performed, taking into account the nature of the immunological veterinary medicinal product, the method and conditions of manufacture. If fewer tests than required by the relevant European Pharmacopoeia are routinely performed for each batch, the tests carried out shall be significant (critical) in order to ensure compliance with the monograph. Therefore, proof must be supplied that the immunological veterinary medicinal product would meet the specified requirements, if they are tested according to the monograph.

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

40. An inactivated vaccine test shall be performed on the finished product in the immediate packaging, thereby verifying inactivation, unless the test has been conducted at a late stage in-process.

41. In order to ensure the consistent quality of the product from batch to batch and to demonstrate conformity with specifications, a full protocol of three consecutive batches giving the results for all tests performed during production and the results on the finished product shall be provided.

2.6. Stability Tests

42. Information on stability tests and the documents appended to the application for a marketing authorisation in accordance with Sub-paragraphs 13.6 and 13.9 of this Regulation shall be submitted in accordance with the following requirements:

42.1. the tests undertaken to establish the period of validity proposed by the applicant shall be described. These tests shall be real-time studies which shall be carried out on a

sufficient number of product batches, produced in accordance with the described production process and on products which are stored in the final packaging. Biological and physico-chemical stability tests shall be performed;

42.2. the report shall contain the results of analyses, justifying the proposed period of validity under all proposed storage conditions;

42.3. for veterinary medicinal products administered in feed, information shall be provided on the period of validity of the veterinary medicinal product in different phases of mixing the feed and veterinary medicinal product, when mixed in accordance with the package leaflet;

42.4. where a finished product requires reconstitution prior to administration or the finished veterinary medicinal product is intended for administration (use) in drinking water, detailed information shall be provided on the period of validity for the reconstituted medicinal product in question, with justification;

42.5. stability data obtained from combined products may be used as preliminary data for derivative products containing one or more of the same components;

42.6. the period of validity of the product shall be justified; and

42.7. the efficacy of any preservative system shall be demonstrated. Information on the efficacy of preservatives in other similar immunological veterinary medicinal products from the same manufacturer may be used.

3. Safety Tests

3.1. General Requirements

43. The safety tests shall determine the potential risks which may be posed by administering the immunological veterinary medicinal product to animals under the proposed conditions of use.

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

45. The safety studies shall be carried out on the target animal species. The dose of the veterinary medicinal product to be used shall be the quantity to be recommended for use and the product to be used in testing shall be taken from a batch produced in accordance with the manufacturing process described in Part II of the application.

46. Where immunological veterinary medicinal products contain live organisms, the dose to be used in laboratory tests described in Paragraphs 48 and 49 of this Annex shall conform with the quantity of the product containing the maximum titre. The concentration of the antigen may be adjusted to achieve the required dose of the medicinal product. For inactivated vaccines the dose to be used shall be that quantity recommended for use containing the maximum antigen content without justification.

47. The safety test shall assess the potential risks which may result from the exposure of human beings to the veterinary medicinal product, for example during its administration to the animal.

3.2. Laboratory Tests

48. The safety of the administration of one dose shall be tested and described in accordance with the following requirements:

48.1. immunological veterinary medicinal products shall be administered at the recommended dose and by each recommended route of administration to animals of the target species and category, including animals of the minimum age of administration. The animals shall be observed and examined for any evidence of signs of systemic and local reactions. Where appropriate, detailed post-mortem macroscopic and microscopic examinations of the injection site shall be performed. Other objective criteria shall also be described, such as the rectal temperature and the performance measurements of the animals;

48.2. the animals shall be observed and examined until reactions are no longer expected, but at least for 14 days following the administration of the test product; and

48.3. the safety test of one dose of administration may be part of the repeated dose safety study in accordance with Paragraph 50 of this Annex. The study shall not be required if the results of the overdose study performed in accordance with Paragraph 49 of this Annex has revealed no signs of systemic or local reactions.

49. The safety of one overdose (an amount of veterinary medicinal product administered, which exceeds the recommended dose of the medicinal product) shall be tested and described in accordance with the following conditions:

49.1. the safety of an overdose of live immunological veterinary medicinal products shall be tested;

49.2. an overdose of the immunological veterinary medicinal products shall be performed by each recommended route of administration to the most sensitive animals of the target species, unless the selection of the most sensitive of several similar routes is justified. Where immunological veterinary medicinal products are administered by injection, the doses and routes of administration shall be chosen to take account of the maximum volume which can be administered at any one single injection site. The animals shall be observed and examined for at least 14 days after administration of the medicinal product for signs of systemic and local reactions. Other objective criteria shall also be described, such as the rectal temperature and the performance measurements; and

49.3. where appropriate, these studies shall include detailed post-mortem macroscopic and microscopic examinations of the injection site, if this has not been performed in accordance with Paragraph 47 of this Annex.

50. The safety of the repeated administration of one dose shall be tested and described in accordance with the following conditions:

50.1. if immunological veterinary medicinal products are administered more than once (as part of the basic vaccination scheme), a study of the repeated administration of one dose shall be performed in order to reveal any side-effects induced by repeat administration. These tests shall be carried out on the most sensitive categories of the target animal species (such as certain breeds, age groups), using each recommended route of administration; and

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

51. The effect on reproductive performance shall be examined if the starting material from which the veterinary medicinal product is derived may be a potential risk factor. The effect on reproductive performance shall be investigated by administering the recommended dose by the most sensitive route of administration to male animals and non-pregnant female animals. The harmful effects on the progeny, as well as teratogenic and abortifacient effects shall be

investigated. These studies may be performed concurrently with the safety tests referred to in Paragraphs 48, 49 and 50 of this Annex or the field studies referred to in Paragraph 58.

52. The effect on immunological functions shall be investigated where the immunological veterinary medicinal product might adversely affect the immune response of the vaccinated animal or of its progeny. Suitable tests investigating the immunological functions shall be carried out.

53. Special requirements in respect of live vaccines:

53.1. the spread of the vaccine strain from vaccinated to unvaccinated target animal species shall be investigated, administering the medicinal product by the intended route of administration most likely to result in the spread of the vaccine strain. Where necessary, the spread to non-target animal species and which could be more susceptible to a live vaccine strain, shall be investigated;

53.2. in order to determine the spread of a vaccine strain in a vaccinated animal, its milk, eggs, faeces, urine and other bodily secretions shall be examined. Where necessary, the dissemination of the vaccine strain in the body of the animal shall be investigated, with particular attention being paid to the predilection sites for replication of the organism. In respect of zoonoses, in compliance with the regulatory enactments regulating the dissemination of zoonoses and zoonose agents, live vaccines are administered to food producing animals, these studies shall particularly take into account the persistence of the organism at the injection site;

53.3. reversion to virulence of attenuated vaccines shall be investigated with the master seed. If the master seed is not available in sufficient quantity, the lowest passage seed used for production shall be examined. Use of another passage option shall be justified. The initial vaccination shall be carried out using the route of administration most likely to lead to reversion to virulence. Serial passages shall be performed in target animal species consequently through five groups of animals, unless there is justification to make more passages or the organism disappears from the test animals sooner. Where the organism fails to replicate adequately, as many passages as possible shall be carried out in the target species;

53.4. biological properties of the vaccine strain. Other tests may be used in order to determine as precisely as possible the intrinsic biological properties of the vaccine strain (for example, neurotropism); and

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

54. The description of user safety shall include a discussion of the type of effects found in this Annex, of immunological veterinary medicinal products on humans and to what extent this occurs, in order to formulate appropriate user warnings and other risk management measures.

55. For immunological veterinary medicinal products, a study of residues shall not be performed, except in the case referred to in Paragraph 56 of this Annex.

56. Where adjuvants or preservatives are used in the manufacture of immunological veterinary medicinal products, there is a possibility that residue may remain in foodstuffs originating from treated animals. If necessary, the effects of such residues shall be investigated, proposals for the withdrawal period shall be made and the adequacy of the period concerned shall be evaluated in relation to any residue studies which have been undertaken prior to the study.

57. When investigating the safety of association, the interaction with other known veterinary medicinal products shall be described, if there is a compatibility statement in the summary of product characteristics.

3.3. Field Studies

58. Data from field studies using batches of the product in accordance with the manufacturing process described in the authorisation application dossier shall be appended to the results from laboratory studies, unless justified elsewhere. The following may be investigated for immunological veterinary medicinal products in field studies:

- 58.1. safety; and
- 58.2. efficacy.

3.4. Environmental Risk Assessment

59. An environmental risk assessment shall be performed in order to assess the potential harmful effects of immunological veterinary medicinal products on the environment and to identify any precautionary measures for reducing such risks.

60. The first phase of the assessment shall be performed in accordance with established guidance. The potential exposure of the environment to the product and the level of risk associated with any such exposure shall be established, in particular describing the following items:

- 60.1. the target species and the proposed pattern of use;
- 60.2. the method of administration, in particular the extent to which the veterinary medicinal product will enter directly into the environmental system;
- 60.3. the possible excretion of the veterinary medicinal product and its active substances into the environment by treated animals and the persistence of such excreta in the surrounding environment; and
- 60.4. the disposal of unused veterinary medicinal product or other waste product caused thereby.

61. The potential risk to humans shall be assessed if the live vaccine strain may be zoonotic.

62. The second phase of the environmental risk assessment shall be performed if the conclusions made following the first phase of the assessment indicate potential exposure of the environmental to the veterinary medicinal product. The potential risks that the veterinary medicinal product might pose to the environment shall be assessed. Where necessary, further investigations on the impact of the veterinary medicinal product (such as, the effect on soil, water, air, aquatic systems, non-target species) shall be carried out.

63. Where immunological veterinary medicinal products contain genetically modified organisms the application shall also be accompanied by the documents required in accordance with the requirements of the regulatory enactments regulating the circulation of genetically modified organisms.

4. Efficacy Tests

4.1. General Provisions

64. In order to confirm the efficacy of the immunological veterinary medicinal products, efficacy tests shall be performed. The applicant shall approve all information regarding the

properties, effects and use of the medicinal product with the results of tests which are described in the documentation appended to the application for a marketing authorisation.

65. Efficacy tests shall be conducted in accordance with a fully considered detailed protocol which shall be recorded in writing prior to commencement of the test. Animals used in trials and tests shall be subject to veterinary supervision and the welfare of the animals shall be observed;

65.1. pre-established, systematic, written procedures in respect of the organisation, conduct, data collection, documentation and verification of data shall be used; and

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

66. Before the commencement of any field trial, the owner (keeper) of the animals to be used in trials shall be consulted and his or her consent for the use of the animals in the field trials shall be documented. The animal owner shall be informed in writing of the terms for the disposal of the animals used in the trials and the restrictions for the acquisition of foodstuffs from an animal used in the trial. A copy of this notification, signed and dated by the animal owner shall be included in the trial documentation.

67. The medicinal products for use in trials shall be labelled in compliance with the requirements specified by the regulatory enactments on the labelling of veterinary medicinal products, unless the field trial is conducted with a blind design. In any case, the words “for veterinary field trial use only” shall appear prominently and indelibly upon the labelling.

4.2. Basic Requirements for Trials and Tests

68. Antigens or vaccine strains shall be chosen on the basis of epizootological data.

69. Efficacy trials carried out in the laboratory shall be controlled trials, including untreated control animals, unless this is not justified for the observance of the requirements of animal welfare and efficacy can be otherwise demonstrated. The trials shall be described in accordance with the following conditions:

69.1. laboratory trials shall be supported by trials carried out in field conditions, including untreated control animals;

69.2. the trials shall be described in sufficient detail so as to be reproducible in controlled trials carried out at the request of the Food and Veterinary Service. The investigator shall confirm the validation of all the techniques involved in the trial; and

69.3. all results obtained, whether favourable or unfavourable, shall be reported.

70. The efficacy of an immunological veterinary medicinal product shall be demonstrated for each category of target animal species recommended for vaccination, taking into account each recommended route of administration and schedule of administration. If the influence of the vaccine, immunity, is acquired passively or antibodies derived maternally, such option shall be adequately evaluated and described. The onset and duration of immunity shall be established and supported by data from trials, if the facts referred to have not been justified previously.

71. The efficacy of each of the components of multivalent and combined immunological veterinary medicinal products shall be demonstrated. If the medicinal 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.

72. If an immunological veterinary medicinal product forms part of a vaccination scheme recommended by the applicant, the primary or booster effect or the contribution of the veterinary medicinal product to the efficacy of the scheme as a whole shall be demonstrated.

73. The dose of the medicinal product to be used shall be administered in the recommended quantity and the batch to be used for testing shall be taken from the batch produced according to the manufacturing process described in Part II of the application.

74. If there is a compatibility statement with other immunological products in the summary of product characteristics, the efficacy of the association shall be investigated. Any other known interaction with other veterinary medicinal products shall be described. Concurrent or simultaneous use with other veterinary medicinal products is permissible if this is supported by appropriate studies.

75. For diagnostic immunological veterinary medicinal products administered to animals, the applicant shall show how reactions of the animal to the product are to be interpreted.

76. For vaccines intended for the distinction of vaccinated and infected animals (marker vaccines) and whose efficacy claim is justified by *in vitro* diagnostic tests, the applicant shall submit data on the diagnostic tests to allow adequate assessment of the claims related to the marker properties.

4.3. Laboratory Tests

77. Efficacy shall be demonstrated in controlled laboratory conditions by demonstrating the reaction invoked in the animal after administration of the immunological veterinary medicinal product under the recommended schedule of use of the medicinal product. Insofar as possible the conditions under which the challenge is carried out shall mimic the natural conditions for infection. Details of the challenge strain and its relevance shall be provided. For live vaccines batches containing the minimum titre or potency shall be used unless otherwise justified. For other immunological veterinary medicinal products, batches containing the minimum active content shall be used unless otherwise justified. The immune mechanism (cell-mediated, local classes of immunoglobulin) which is initiated after the administration of the immunological veterinary medicinal product to target animals by the recommended use of administration, shall be specified and documented.

4.4. Field Trials

78. Data from field trials shall be appended to results from laboratory tests, using batches manufactured in accordance with the manufacturing process described in the application. The safety and efficacy of the medicinal product may be investigated in the same field trial.

79. Where laboratory trials cannot be supportive of medicinal product efficacy, field trials may be used.

5. Information and Documents

5.1. General Requirements

80. The dossier of the safety and efficacy studies shall include an introduction defining the subject being investigated and the tests and investigations which have been carried out in compliance with Parts 3 and 4 of this Annex, as well as a summary with detailed references to

the published literature. The summary shall contain an objective discussion of the results obtained and lead to a conclusion on the safety and efficacy of the immunological veterinary medicinal product. If any of the tests or investigations listed are not carried out, this shall be indicated and discussed.

5.2. Information Regarding Laboratory Tests

81. The following information regarding laboratory tests shall be provided:

81.1. a summary;

81.2. the name of the body having carried out the tests;

81.3. a detailed experimental protocol describing the methods, apparatus and materials used, providing detailed information on the species or breed of animals, categories of animals, where they were obtained, their identification and number, the conditions under which they were housed and feeding conditions (stating whether they were free from any specified pathogens or specified antibodies, indicating the nature and quantity of any additives contained in the feed), the dose, route, schedule and dates of medicinal product administration, a description and a justification of the statistical methods used;

81.4. for control animals it shall be indicated whether they received a placebo or no treatment;

81.5. information shall be provided regarding animals which have been treated with the test product and, where appropriate whether they received the product used in tests or another medicinal product authorised in the Member States;

81.6. the general and individual observations and results obtained (with averages and standard deviations), whether favourable or unfavourable, shall be described. The data shall be provided 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, for example, by reproduction of recordings, photomicrographs;

81.7. the nature, frequency and duration of observed side-effects shall be described;

81.8. the number of animals withdrawn prematurely from the studies and reasons for such withdrawal shall be indicated;

81.9. a statistical analysis of the results, where such is called for by the test programme, and variance within the data shall be reflected:

81.10. the occurrence and course of any intercurrent disease, if any, shall be described;

81.11. details concerning veterinary medicinal products, other than the product under study, shall be provided, if the administration thereof was necessary during the course of the study; and

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

5.3. Details Regarding Field Trials

82. The particulars regarding field trials shall include the following information:

82.1. a summary;

82.2. the surname, address, function and qualifications of the investigator in charge;

82.3. place and time of the studies, the identity code that can be linked to the surname and address of the owner of the animal;

82.4. detailed information regarding the study protocol, in which the methods, apparatus and materials used are described, details regarding the route and schedule of administration shall be provided, the dose, the categories of animals, the duration of observation, the serological response and other investigations carried out on the animals after administration of the product under study;

82.5. for control animals it shall be indicated whether they received a placebo or no treatment;

82.6. identification of the treated and control animals (collective or individual), such as species, breed or strain, age, weight, sex, physiological status;

82.7. a brief description of the method of animal rearing and feeding and the nature and quantity of additives contained in the feed;

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

82.9. the results of clinical trials shall be described, whether favourable or unfavourable, indicating the observations and results of the objective tests of activity required to evaluate the product. The techniques used shall be specified and the significance of any variations (deviations) in the results shall be explained;

82.10. the effect on the animal performance shall be described;

82.11. the number of animals withdrawn prematurely from the studies and reasons for such withdrawal shall be indicated;

82.12. the nature, frequency and duration of observed side-effects shall be described;

82.13. the occurrence and course of any intercurrent disease shall be described;

82.14. information regarding the veterinary medicinal products (other than the test product), which have been administered either prior to or concurrently with the test product or during the observation period of the test animal shall be provided. Information regarding interactions observed shall be provided; and

82.15. an objective discussion of the results obtained, indicating the conclusions on the safety and efficacy of the test product, shall be provided.

6. Bibliographical References

83. The bibliographical references cited in the summary referred to in Part 1 of this Annex shall be listed in detail and copies shall be provided.

Requirements for Specific Marketing Authorisation Applications
[15 September 2009; 28 December 2010]

1. Generic Veterinary Medicinal Products

1. The data referred to in Parts 1 and 2 of Annex 2 to this Regulation, the environmental risk assessment and data demonstrating that the veterinary medicinal product has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, as well as data showing bio-equivalence with the reference medicinal product, shall be appended to an application submitted in accordance with Paragraphs 22 and 23 of this Regulation. If the reference medicinal product is a biological veterinary medicinal product, the documentation requirements indicated in Annex 3 to this Regulation in respect of similar biological veterinary medicinal products shall be taken into account.

2. In the summaries of generic veterinary medicinal products on safety and efficacy, the main focus shall be on the following elements:

2.1. an explanation and justification if the generic veterinary medicinal product concerned is essentially similar to the reference medicinal product;

2.2. a report on impurities and, where relevant, on the decomposition products arising during storage, the active substances thereof and the batches of the finished veterinary medicinal products which are intended for use in the product to be marketed, together with an evaluation of these impurities;

2.3. an evaluation of the bio-equivalence studies or a justification as to why these studies were not performed with reference to established guidance; and

2.4. if necessary, additional data which demonstrates the equivalence of the safety and efficacy of different salts, esters or derivatives of an authorised active substance. Those data shall include evidence that there is no change in the pharmacokinetic or pharmacodynamic properties of the therapeutic part of the veterinary medicinal product or in toxicity which could influence the safety or efficacy of the product.

3. If an unknown claim is included in the summary of the veterinary medicinal product characteristics and it is not possible to verify the accuracy of this claim in the pre-clinical or clinical reports or summaries it shall be substantiated by published literature and (or) additional studies.

4. For generic veterinary medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes, the following additional data shall be provided:

4.1. evidence of the equivalent or differing depletion of residues from the administration site, which may be substantiated by appropriate residue depletion studies; and

4.2. evidence of the target animal tolerance at the administration site, which may be substantiated by appropriate target animal tolerance studies.

2. Similar Biological Veterinary Medicinal Products

5. In accordance with Paragraph 23 of this Regulation where a biological veterinary medicinal product which is similar to a reference biological veterinary medicinal product does not meet the conditions referred to in the definition of the generic medicinal product, the applicant shall

submit information in accordance with Parts 1 and 2 of Annexes 2 or 3 to this Regulation (pharmaceutical, chemical and biological data). The information to be submitted shall be supplemented with data on the bioequivalence and bioavailability of the veterinary medicinal product, and additional data shall be provided in particular on the safety and efficacy of the veterinary medicinal product.

6. The type and amount of additional data (for example, toxicological and other safety studies and appropriate clinical studies) shall be determined on a case-by-case basis in accordance with relevant scientific guidelines.

7. Due to the diversity of biological veterinary medicinal products, the Food and Veterinary Service shall determine the necessary studies in accordance with Parts 3 and 4 of Annexes 2 and 3 to this Regulation, taking into account the specific characteristics of each biological veterinary medicinal product.

8. The general principles to be applied shall be used as shown in the European Medicines Agency guidelines, taking into account the specific characteristics of the concerned veterinary medicinal product.

9. If the reference biological veterinary medicinal product has more than one indication, the efficacy and safety of the biological veterinary medicinal product claimed to be similar shall be justified or, if necessary, demonstrated separately for each of the claimed indications.

3. Generally Recognised Use in Veterinary Medicinal Practice

10. For veterinary medicinal products the active substances of which are generally recognised in veterinary medicinal practice, in accordance with Paragraph 28 of this Regulation, the following conditions shall apply:

10.1. the applicant shall submit documentation in accordance with Parts 1 and 2 of Annex 2 to this Regulation; and

10.2. the safety and efficacy aspects of Parts 3 and 4 of the documentation shall be justified by indicating references to the relevant sources of information (a detailed scientific bibliography).

11. In order to demonstrate that the active substance of a veterinary medicinal product is generally recognised in veterinary medicinal practice, the following factors shall be described:

11.1. the time over which a substance has been used;

11.2. the quantitative aspects of the use of the active substance;

11.3. the degree of scientific interest in the use of the active substance (reflected in the published scientific literature);

11.4. the coherence of scientific assessments;

11.5. an evaluation of the period of time since the active substance concerned has been used in the composition of the veterinary medicinal product. Different periods of time may be necessary for different substances in order to determine that they are generally recognised in veterinary medicinal practice. The period of time required for establishing that an active substance is generally recognised in veterinary medicinal practice shall not be less than 10 years from the first systematic and documented use of that substance as a veterinary medicinal product in the territory of the European Community;

11.6. the documentation submitted covers the aspects of the safety and efficacy of the veterinary medicinal product for the proposed indication in the target species using the proposed route of administration and dosage regimen. The documentation shall include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies

and published scientific literature concerning experience in epizootological studies and in particular of comparative epizootological studies. Information shall be submitted whether favourable or unfavourable to the medicinal product. With respect to the provisions on “well-established veterinary use”, the bibliographical references to other sources of evidence (such as, post-marketing studies, epidemiological, epizootological studies) and not just data related to tests and trials may be used as proof of the safety and efficacy of a product, if the documentation appended to the application explains and justifies the use of these sources of information satisfactorily;

11.7. if necessary, any missing information shall be shown and justification given as to why the degree of safety or efficacy may be considered as acceptable notwithstanding the fact that some studies are lacking;

11.8. the summaries on safety and efficacy shall provide explanations on the relevance of the data submitted which concern a veterinary medicinal product different from the veterinary medicinal product intended for marketing. It shall be judged whether the product studied can be considered as similar to the veterinary medicinal product for which application for a marketing authorisation has been made, in spite of the existing differences between them; and

11.9. the applicant shall in particular examine experience acquired following the putting of other veterinary medicinal products on the market, containing the same components as the medicinal product under study.

4. Combination Veterinary Medicinal Products

12. The documentation referred to in Parts 1, 2, 3 and 4 of Annexes 2 or 3 to this Regulation shall be provided for the combination veterinary medicinal product referred to in Paragraph 31 of this Regulation.

13. It shall not be necessary to perform studies on the safety and efficacy of each active substance. Information on the individual substances may be included in the application for a fixed combination.

14. The applicant, upon submission of data on each individual active substance with the user safety studies, residues depletion studies and clinical studies on the fixed combination veterinary medicinal product, with suitable justification, may omit the study data on the combination veterinary medicinal product based on animal welfare and unnecessary testing on animals unless there is potential interaction which may lead to added toxicity. Where appropriate, information regarding the production sites and the safety evaluation of adventitious agents shall be provided.

5. Application for the Informed Consent of a Person

15. An application submitted in accordance with Paragraph 33 of this Regulation shall contain the data described in Part 1 of Annex 2 to this Regulation (Summary of the Dossier), taking into account that the holder (owner) of the original veterinary medicinal product has given the applicant his consent to refer to the content of Parts 2, 3 and 4 of the original veterinary medicinal product dossier. In this case the applicant need not submit summaries on quality, safety and efficacy.

6. Documentation for Applications in Exceptional Circumstances

16. A marketing authorisation may be granted subject to certain specific obligations requiring the applicant to introduce specific procedures in particular concerning the safety and efficacy

of the veterinary medicinal product, if the applicant can prove, in accordance with Paragraph 57 of this Regulation, that he or she is unable to provide comprehensive data on the efficacy and safety of the medicinal product concerned under the intended conditions of use.

7. Mixed Marketing authorisation Applications

17. Mixed marketing authorisation applications are applications where Part 3 or 4 of the dossier appended consists of the safety and efficacy studies carried out by the applicant, as well as bibliographical references.

18. All other parts of the dossier shall be developed in accordance with the structure described in Part 1 of Annex 2 to this Regulation.

**Requirements for Applications for the Receipt of Marketing Authorisations for
Particular Veterinary Medicinal Products**
[15 September 2009; 16 November 2010]

The Annex lays down specific requirements for particular types of veterinary medicinal products related to the nature of the active substances contained in the respective medicinal products.

1. Immunological Veterinary Medicinal Products

1.1. Vaccine Antigen Master File (VAMF)

1. For particular immunological veterinary medicinal products the concept of a Vaccine Antigen Master File is introduced which determines exceptions to the requirements specified in Part 2 of Annex 3 to this Regulation (Chemical, Pharmaceutical and Biological or Microbiological Information) in respect of active substances.

2. Within the meaning of this Annex the Vaccine Antigen Master File of an immunological veterinary medicinal product is the separate part of the dossier appended to the application for an immunological veterinary medicinal product certificate, containing information on the quality of the active substance which is a component of this veterinary medicinal product. The stand-alone part may apply to one or more monovalent or combined vaccines presented by the same applicant or the holder (owner) of the marketing authorisation.

3. The applicant shall use the European Medicines Agency scientific guidelines in respect of the submission and evaluation of a Vaccine Antigen Master File. The antigen master file for an immunological veterinary medicinal product shall be submitted and evaluated in accordance with the procedures specified in the guidance published by the European Commission in The Rules Governing Medicinal Products in the European Union, Volume 6B, "Notice to Applicants".

1.2. Multi-Strain Vaccine Dossier

4. For certain immunological veterinary medicinal products containing several antigens (foot and mouth disease, avian influenza and bluetongue), the concept of the use of a multi-strain dossier is introduced (separate documentation containing single and enhanced scientific assessments on different strains and the possible combinations of strains), determining the exceptions to the requirements referred to in Part 2 of Annex 3 to this Regulation, in respect of active substances.

5. Multi-strain vaccine dossiers shall be submitted in order to receive an authorisation to use a vaccine against antigenically variable viruses.

6. When preparing a multi-strain vaccine dossier, the applicant shall use the European Medicines Agency scientific guidelines in respect of the submission and evaluation of multi-strain dossiers. A multi-strain dossier shall be submitted and evaluated in accordance with the guidance of the European Commission published by the Commission in The Rules Governing Medicinal Products in the European Union, Volume 6B, "Notice to Applicants".

2. Homeopathic Veterinary Medicinal Products

7. For the simplified authorisation of homeopathic veterinary medicinal products referred to in Paragraph 40 of this Regulation, in accordance with the requirements specified in Paragraphs 43 and 44 of this Regulation, in the documentation submitted:

7.1. the Latin name of the homeopathic stock described shall be in accordance with the Latin title of the European Pharmacopoeia or, in the absence thereof, of an official pharmacopoeia of the Member States. Where relevant the traditional name used in each Member State shall be provided;

7.2. the particulars and documents on the starting materials (all of the materials, including raw materials and intermediates up to the final dilution to be incorporated into the finished homeopathic veterinary medicinal product) shall be supplemented by data on the homeopathic stock; and

7.3. without prejudice to the provisions of Regulation No 470/2009 on substances contained in homeopathic stock intended for administration to food-producing animals, the requirements of Part 3, Annex 2 to this Regulation (Safety and Residue Tests) shall be observed. If the information provided is incomplete, it shall be demonstrated why the proof of the degree of safety is acceptable notwithstanding the absence of some studies.

8. The general quality requirements shall apply to all starting materials, as well as intermediate steps of the manufacturing process up to the final dilution to be incorporated into the finished medicinal product. Where a toxic component is present in the composition of a homeopathic veterinary medicinal product, the control of this component shall be performed in the final dilution (if possible). If the control of the component is not possible due to the high level of dilution, the toxic component shall be controlled at an earlier stage of manufacture. Every step of the manufacturing process from the starting materials up to the final dilution to be incorporated into the finished product shall be described in detail.

9. If dilutions are involved, the dilution shall be performed in accordance with the homeopathic manufacturing methods laid down in the relevant monograph of the European Pharmacopoeia, or in the absence thereof, in an officially used pharmacopoeia of the Member States.

10. General quality requirements shall apply to the homeopathic finished veterinary medicinal products. Any exception shall be duly justified by the applicant.

11. The toxicologically relevant components shall be identified and determined. If it can be justified that the identification or an assay on all the toxicologically relevant components is not possible, for example, due to the dilution degree, the quality shall be demonstrated by complete validation of the manufacturing and dilution process.

12. The applicant shall demonstrate the stability of the finished homeopathic veterinary medicinal product. If no identification or quantitative assay of the active substance is possible due to the degree of dilution, stability data of the pharmaceutical form may be considered.

Revised by the Ministry of Agriculture
Annex 4
Cabinet Regulation No.600
18 July 2006

Colouring Matters Permitted to be Added to Veterinary Medicinal Products

[16 November 2010]

Extension of the Authorisation of a Veterinary Medicinal Product

[16 November 2010]

Variations to a registration dossier, regarding which the owner of the authorisation of medicinal products shall submit an application for the extension of authorisation shall be as follows:

1. Variations related to active substance(s):

1.1. replacement of the active substance(s) by a different salt or ester complex or derivative thereof (with the same therapeutic component), where the efficacy and safety characteristics are not significantly different;

1.2. replacement of the active substance(s) with a different isomer or a different mixture of isomers, replacement of a mixture by an isolated isomer (for example, racemate is replaced by a single enantiomer), if the efficacy and safety characteristics are not significantly different;

1.3. the replacement of the biological substance or biotechnological product with a substance which differs slightly in molecular structure, if the efficacy and safety characteristics are not significantly different. The conditions shall not be applicable in the following cases:

1.3.1. a vaccine against avian influenza, foot-and-mouth disease or bluetongue disease (infectious catarrhal fever of sheep and goats), the replacement or addition of a serotype, vaccine strain, antigen or combination thereof;

1.3.2. the replacement of a strain for a vaccine against equine influenza;

1.3.¹ the antigen or starting material used in the modification of a vector (also a new master (main) cell bank from a different source), where the efficacy and safety characteristics are not substantially different;

1.4. a new ligand or coupling mechanism for a radiopharmaceutical preparation, if the efficacy and safety characteristics are not substantially different; and

1.5. variations to the extraction solvent or the ration of herbal drug to herbal drug preparation, where the efficacy and safety characteristics are not substantially different.

2. Variations to strength, pharmaceutical form or route of administration of the veterinary medicinal product:

2.1. variations to bioavailability;

2.2. variations to pharmacokinetics (for example, in the rate of release);

2.3. variations or addition of new strength, as well as efficacy;

2.4. variations or addition of a new pharmaceutical form; and

2.5. variations or addition of a new route of administration. If the medicinal products are administered parenterally, the route of administration (for example, intra-arterial, intravenous, intramuscular, subcutaneous) shall be indicated. The suitable route of administration for poultry is the respiratory, oral and ocular administration used for vaccination.

3. Other typical variations for veterinary medicinal products intended for food-producing animals: variation of the target species or the addition of a target species.

Acting for the Ministry of Agriculture –

the Minister for the Interior

Dz.Jaundžeikars

Classification of Minor Variations of Type IA, Minor Variations of Type IB and Major Variations of Type II

[16 November 2010; 28 December 2010]

1. Administrative Variations (A)

No.	Type and nature of variation	Conditions (numbers)	Documentation (numbers)	Type of procedure (number)
1.	Change in the name and (or) address of the marketing authorisation holder (A.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
		1	1, 2	IA
1.1.	Conditions:			
	1. The holder (owner) of the marketing authorisation is the same legal person.			
1.2.	Documentation:			
	1. The merchant marketing authorisation in which the new address or new name is shown, has been presented			
	2. Information reviewed regarding the veterinary medicinal product.			
2.	Variations to the name of the veterinary medicinal product (granted) (A.2.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
		1	1	IB
2.1.	Conditions:			
	1. The Food and Veterinary Service opinion on the variation in the name is favourable.			
2.2.	Documentation:			
	1. Information reviewed regarding the veterinary medicinal product.			
3.	Variation in the name of the active substance (A.3.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
		1, 2	1, 2	1A
3.1.	Conditions:			
3.1.1.	1. Active substance remains the same.			
3.1.2.	2. The name of the active substance intended for administration to food-producing animals prior to the introduction of the variation, published in Regulation No 37/2010 in accordance with Regulation 470/2009.			
3.2.	Documentation:			
3.2.1.	1. Evidence of the approval of the name by the World Health Organisation or a copy of the list of international non-proprietary names.			
3.2.2.	2. Information reviewed regarding the veterinary medicinal product.			

4.	A change in the name and (or) address of the manufacturer or supplier of active substances (if shown in the registration dossier), starting materials, reagent or intermediate (including the relevant quality control site) if a Certificate of Suitability of the European Pharmacopoeia is not included in the approved dossier (A.4.)	Conditions to be fulfilled	Documents to be appended	Type of procedure	
		1	1, 2, 3	IA	
4.1.	Conditions:				
	1. The production site and the manufacturing procedure remains the same				
4.2.	Documentation:				
4.2.1.	1. A copy of the Commercial Register marketing authorisation in which the new address or new name is shown				
4.2.2.	2. The relevant additions or variations to the summary of the product characteristics, submitted in the format contained in the European Commission Guidelines „EU Common Technical Dossier Format” or Volume 6, Part B “Notice to Applicants, Veterinary Medicinal Products, Presentation and Content of the Dossier” (hereinafter – CTD or Notice to Applicants Volume 6B).				
4.2.3.	3. If the variations are related to a change in the given name or name of the keeper of the active substance master file, the letter of access shall be updated.				
5.	A change in the name and (or) address of the finished product manufacturer (including the quality control authority) (A.5.).	Conditions to be fulfilled	Documents to be appended	Type of procedure	
		a) production unit responsible for batch release	1	1, 2	IA
		b) other manufacturers	1	1, 2	IA
5.1.	Conditions:				
	1. The production unit and manufacturing process remains the same.				
5.2.	Documentation:				
5.2.1.	1. Special authorisation (licence) for the manufacture of veterinary medicinal products (copy) with variations, if any, or the merchant marketing authorisation (copy) if the new address or new name is shown in this certificate.				
5.2.2.	2. If necessary, the relevant additions to the summary of the product characteristics, including the reviewed information on the product (submitted in CTD format or in “Notice to Applicants” Volume 6B format).				
6.	Variations to the Anatomic Therapeutic Chemical Code (ATC vet code) (A.6.)	Conditions to be fulfilled	Documents to be appended	Type of procedure	
		1	1, 2	IA	
6.1.	Conditions:				
	1. Variations after the granting of an ATC vet code or the performance of amendments.				
6.2.	Documentation				
6.2.1.	1. Copy of the ATC vet code list.				
6.2.2.	2. Information reviewed regarding the veterinary medicinal product.				

7.	Deletion of the production site (production unit) (including the production unit of active substances, intermediate products or finished products, the manufacturer responsible for batch release and the undertaking responsible for batch control or the supplier of starting materials, reagents or excipients) (if referred to in the registration dossier)	Conditions to be fulfilled	Documents to be appended	Type of procedure
		1, 2	1, 2	IA
7.1.	Conditions:			
7.1.1.	1. At least one previously approved production unit or manufacturer is retained, which performs the same functions as in the production site and (or) unit to be replaced.			
7.1.2.	2. The reason for deletion is not significantly connected to shortcomings in the manufacture.			
7.2.	Documentation:			
7.2.1.	1. The variations shall be indicated in the application (“current” and “proposed”).			
7.2.2.	2. The relevant additions to the summary of the veterinary medicinal product characteristics, including the reviewed information on the product (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			

2. Variations to Pharmaceutical Particulars (Quality Section) (B)

2.1. Active Substance (B.I)

2.1.1. Variations to the Manufacturing Process

8.	Variations related to the manufacturer of starting materials, intermediate products and reagents used in the manufacturing process of the active substance or the manufacturer of the active substance (including quality control bodies), if the Certificate of Suitability of the European Pharmacopoeia is not included in the registration dossier (B.1.a.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) the proposed manufacturer shall represent the same pharmacy group as the approved manufacturer	1, 2 ,3	1, 2, 3, 4, 5, 6, 7	IA
	b) application of the new manufacturer of the active substance, based on the active substance master file (ASMF)			II
	c) the proposed manufacturer uses a significantly different method of synthesis or manufacturing conditions which may change important quality indicators of the active substance, for example, the qualitative and (or) quantitative composition of the impurities, which requires qualification, or the physico-chemical properties which may affect bioavailability			II
	d) a new manufacturer of such material requiring a virus safety assessment and (or) assessment of conformity with the European Commission guidelines “Note for Guidance on minimising the risk of			II

	transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products” (hereinafter – TSE risk assessment)			
	e) the variations relate to a biologically active substance or starting material, reagent or intermediate product used in the manufacture of products of biological and immunological origin			II
	f) variations to the procedure for the quality control of active substances – sites where batch control takes place and (or) testing, replacement or addition	2, 4	1, 5	IA
8.1.	Conditions			
8.1.1.	1. The specifications of the starting materials and reagents (including in the process of manufacturing control, analytical methods of all materials) are identical to those currently approved. The specifications of intermediates and active substances (including in the process of manufacturing control, analytical methods of all materials), processing methods (including, batch volume) and a detailed method of synthesis are identical to those currently approved.			
8.1.2.	2. The active substance is not a substance of biological or immunological origin or a sterile substance.			
8.1.3.	3. If materials of animal origin are used in the manufacturing process, the manufacturer shall not use a new supplier for which a virus safety assessment or TSE risk assessment is required.			
8.1.4.	4. The handover of a technique from the previous to the new site is performed successfully.			
8.2.	Documentation:			
8.2.1.	1. The relevant additions to the summary of the medicinal product characteristics, if necessary (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			
8.2.2.	2. If necessary, the declaration of the manufacturing certificate holder (owner) or ASMF holder, that the method of synthesis of the active substance (or in the case of a medicinal product of plant origin, the processing method, the geographical source of origin, the manufacturing method), quality control procedures and specifications in the process of manufacturing the active substance, and the specifications of the starting materials, intermediate products and (or) reagents in the process of manufacturing the active substance are the same as the approved ones.			
8.2.3.	3. Either a Certificate of Suitability of the European Pharmacopoeia for animal spongiform encephalopathy (hereinafter – TSE) for each source of TSE risk material or, where appropriate, documentary evidence that the source of TSE risk material has previously been assessed and conforms to the European Commission guidelines “Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products”. The following information shall be included in the documentation: the name of the manufacturer, species and tissues from which the material has derived, the country of origin of the donor animal, the use of the material and previous approval.			
8.2.4.	4. The analytical data (in comparable table form) of at least two batches of active substance (the minimum number of experimental batches) from the approved and proposed production unit or manufacturer.			
8.2.5.	5. The application form for variations shall clearly indicate the “current” and “proposed” manufacturer.			
8.2.6.	6. The confirmation of the qualified person of the manufacturer indicated in the registration dossier, if the manufacturer uses the active substance as starting material and the confirmation of the qualified person of the manufacturer responsible for batch release. In the confirmation, the qualified person shall certify that the manufacturer of the active substance operates in accordance with the guidelines for the good manufacturing practice of active substances One confirmation may be submitted in the case referred to in Sub-paragraph 27.3 of this Annex.			
8.2.7.	7. If necessary, the undertaking of the manufacturer of the active substance to notify the marketing authorisation holder (owner) of all variations in the manufacturing process of the active substance, the specifications and the test procedures.			

9.	Variations in the manufacturing process of the active substance (B.1.a.2.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) minor variations in the manufacturing process of the active substance	1, 2, 3, 4, 5, 6, 7	1, 2, 3	IA
	b) major variations in the manufacturing process of the active substance which may significantly affect the quality, safety or efficacy of the medicinal product;			II
	c) variations relating to a biological or immunological substance or other chemically processed substance for use in the manufacture of biological or immunological veterinary medicinal products and do not apply to the protocol;			II
	d) variations relating to veterinary medicinal products of plant origin (the geographical place of origin, method of manufacture or manufacturing);			II
	e) minor variations to the restricted access section of the Active substance master file (ASMF)		1, 2, 3, 4	IB
9.1.	Conditions:			
9.1.1.	1. No unfavourable variations in the qualitative and quantitative impurity profile or in physico-chemical properties.			
9.1.2.	2. Method of synthesis remains unchanged (intermediate products remain unchanged and no new reagents, catalysers or solvents are used in the process). In the case of products of plant origin, the geographical place of origin, the substance manufacture and the veterinary medicinal product manufacture remains unchanged.			
9.1.3.	3. The specifications of the active substance or intermediate product remain unchanged.			
9.1.4.	4. The variations shall be fully described in the “open” section of the ASMF (of the applicant), if necessary			
9.1.5.	5. The active substance is not a biological or immunological substance.			
9.1.6.	6. The variations shall not apply to the geographical place of origin, the manufacturing method or development of the plant origin			
9.1.7.	7. The variations shall not apply to the restricted access section of the ASMF.			
9.2.	Documentation:			
9.2.1.	1. The relevant additions to the registration dossier or the approved ASMF, if necessary (submitted in CTD format or in “Notice to Applicants” Volume 6B format), including a direct comparison of the approved process and the proposed process.			
9.2.2.	2. The analytical data (in comparable table form) of at least two batches of the active substance (the minimum number of experimental batches) from the approved and proposed manufacturing process.			
9.2.3.	3. A copy of the approved specification of the active substance.			
9.2.4.	4. A declaration from the marketing authorisation holder or ASMF holder, that there are no variations in the qualitative or quantitative composition of the impurity or in the physico-chemical properties, that the method of synthesis remains unchanged and the specification of the active substance or intermediate product remains unchanged.			
9.3	Note: In relation to variations in the chemically active substance referred to in Sub-paragraph b) of this Paragraph, the requirements shall apply to major variations in the method of synthesis or manufacturing conditions, which may change the important quality indicators of the active substance, including the qualitative and (or) quantitative composition of the impurity requiring qualification, or in the physico-chemical properties affecting bioavailability.			

10.	Variations in the batch size of the active substance or intermediate product (including the range of the batch size) (B.1.a.3.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) increase in size up to tenfold, compared with the batch size approved in the registration dossier;	1, 2, 3, 4, 6, 7,8	1, 2, 5	IA
	b) reduction in size;	1, 2, 3, 4, 5	1, 2, 5	IA
	c) in order to make variations, a comparability assessment of immunological or biological active substances shall be performed;			II
	b) increase in size more than tenfold, compared with the batch size approved in the registration dossier;		1, 2, 3, 4	IB
	e) increase or reduction of the batch of biological or immunological active substance without variations to the manufacturing process (for example, duplication of the production line).		1, 2, 3, 4	IB
10.1.	Conditions:			
10.1.1.	1. Variations to the manufacturing methods shall only be those necessary for increasing or reducing the batch size, for example, the use of different sized equipment.			
10.1.2.	2. The results of tests of at least two batches shall be available in conformity with the specifications of the desired batch size.			
10.1.3.	3. The medicinal products concerned are not biological or immunological veterinary medicinal products.			
10.1.4.	4. The variations do not unfavourably affect the replicability (reproducibility) of the process.			
10.1.5.	5. The variations are not the result of unexpected events during manufacture or stability concerns are not the reason thereof.			
10.1.6.	6. The specifications of the active substance or intermediate product remain unchanged.			
10.1.7.	7. The active substance is not sterile.			
10.1.8.	8. The batch size approved in the valid marketing authorisation has not previously been approved in the variations of type IA procedure.			
10.2.	Documentation:			
10.2.1.	1. Additions to the relevant part of the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			
10.2.2.	2. The relevant tested batch numbers for the proposed batch size.			
10.2.3.	3. Batch analytical data (in comparable table form) for at least one batch of manufactured active substance or intermediate, manufactured both in the sizes approved in the marketing authorisation and in the proposed sizes (indicated in the application). Upon request by the Food and Veterinary Service, the holder (owner) of the marketing authorisation shall prepare and submit batch data for the subsequent two complete batches manufactured, if they do not conform to the specifications.			
10.2.4.	4. Copies of the approved specification of the active substance and, if necessary, the intermediate.			
10.2.5.	5. The confirmation of the marketing authorisation holder (owner) or the ASMF holder that the variations in manufacturing processes are only those necessary for increasing or reducing the size, for example, the use of different sized equipment, that the variations do not affect the reproducibility of the process unfavourably, the variations are not the result of unexpected events during manufacture, that stability concerns are not the reason thereof and that the specifications of the active substance and (or) intermediate remain unchanged.			

11.	Variations to tests performed in the manufacturing process of the active substance, or limits which are applied in the manufacturing process of the active substance (B.1.a.4.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) determination of stricter limits of the manufacturing process	1, 2, 3, 4	1, 2	IA
	b) inclusion of new tests or limits;	1, 2, 5, 6	1, 2, 3, 4, 6	IA
	c) deletion of insignificant tests;	1, 2	1, 2, 5	IA
	d) extension of test limits which may significantly affect the quality of the active substance;			II
	e) deletion of tests which may significantly affect the quality of the active substance;			II
	f) replacement or addition of test for safety or quality reasons.		1, 2, 3, 4, 6	IB
11.1.	Conditions:			
11.1.1.	1. The variations are not the result of fulfilling the previous commitments of the evaluation to review the specification limits (for example, performed in the registration procedure or in the approval procedure of major variations of type II).			
11.1.2.	2. The variations are not the result of unexpected events during the manufacture (for example, new, unqualified impurities, the limits of the total impurities changes).			
11.1.3.	3. Any variations which do not conform with the limits in effect.			
11.1.4.	4. The test procedures remain unchanged or insignificant variations are made thereto.			
11.1.5.	5. New test methods do not apply to new non-standard techniques or a standard technique is not used in a new way.			
11.1.6.	6. The new test method is not a biological, immunological or immunochemical method or a method in which a biologically active substance is proposed to be used as a biological reagent (not including the pharmacopoeia standard microbiological methods).			
11.2.	Documentation:			
11.2.1.	1. Additions to the relevant part of the registration dossier (submitted in CTD format or in "Notice to Applicants" Volume 6B format).			
11.2.2.	2. A comparable table on the approved and proposed test methods.			
11.2.3.	3. If necessary, detailed information on each proposed analytical method and approval (validation) data, not listed in a pharmacopoeia.			
11.2.4.	4. Analytical data on two production batches of the active substance (on three batches for biological veterinary medicinal product, unless otherwise specified) on all the indicators of the specifications.			
11.2.5.	5. The justification of the marketing authorisation owner (holder) or the ASMF holder or a risk assessment, certifying the insignificance of the parameters.			
11.2.6.	6. The grounds for the suitability of the proposed tests or limits prepared by the marketing authorisation holder (owner) or the ASMF holder.			

2.1.2. Control of Active Substance

12.	Variations to the parameters of specifications or limits which apply to the active substance and starting materials, intermediates or reagents used in the manufacturing process of the active substance (B.1.b.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure

	a) determination of stricter specification limits for veterinary medicinal products for which official batch release is performed;	1, 2, 3, 4	1, 2	IA
	b) determination of stricter specification limits	1, 2, 3, 4	1, 2	IA
	c) addition of new specification parameters to specifications, together with the appropriate test method;	1, 2, 5, 6, 7	1, 2, 3, 4, 7	IA
	d) deletion of insignificant specification parameters (for example, outdated parameters);	1, 2	1, 2, 6	IA
	e) deletion of specification parameters which may significantly affect the quality of the active substance or the quality of the finished product;			II
	f) variations which do not conform to the approved specification limits of the active substance;			II
	g) extension of the approved specification limits of starting materials or intermediates, which may significantly affect the overall quality of the active substance or finished product;			II
	h) addition or replacement of specification parameters (except biological or immunological substances) for safety or quality reasons.		1, 2, 3, 4, 5, 7	IB
12.1.	Conditions:			
12.1.1.	1. The variations are not the result of fulfilling one of the commitments arising from the previous evaluation to review the specification limits (for example, performed in the registration procedure or in the approval procedure of major variations of type II).			
12.1.2.	2. The variations are not the result of unexpected events during manufacture (for example, new, unqualified impurities, the total limits of the impurities change).			
12.1.3.	3. The variations conform to the currently approved limits.			
12.1.4.	4. The test procedures remain unchanged or insignificant variations are made thereto.			
12.1.5.	5. The test methods do not apply to new non-standard techniques or standard techniques are not used in a new way.			
12.1.6.	6. The test method is not a biological, immunological or immunochemical method or a method in which a biologically active substance is proposed to be used as a biological reagent (not including the pharmacopoeia standard microbiological methods).			
12.1.7.	7. The variations are not related to genotoxic impurities.			
12.2.1.	Documentation:			
12.2.2.	1. Additions to the relevant part of the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			
12.2.3.	2. A comparable table on approved and proposed specifications.			
12.2.4.	3. Information regarding new analytical methods and approval (validation) data, if necessary.			
12.2.5.	4. Batch analysis data of the relevant substance for two batches of the product (for three batches of a biological product, unless otherwise specified) on all the specification parameters.			
12.2.6.	5. If necessary, the dissolution profile shall be compared, which shall be determined for at least one experimental batch of the finished product containing the active substance, in conformity with the			

	approved specification and the proposed specification. Comparable degradation data may be submitted for veterinary medicinal products of plant origin.			
12.2.7.	6. The justification of the marketing authorisation owner (holder) or the ASMF holder or a risk assessment, certifying the insignificance of the parameters.			
12.2.8.	7. The grounds for the suitability of the proposed specification parameter and limits prepared by the marketing authorisation holder (owner) or the ASMF holder.			
13.	Variations to the active substance or starting materials used in the manufacturing procedures of the active substance, or in the test procedures of the starting material, reagent or intermediate (B.I.b.2.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) minor variations in the approved test procedure;	1, 2, 3, 4	1, 2	IA
	b) deletion of the test procedure if an alternative test procedure is approved;	7	1	IA
	c) other variations to reagent test procedures (including the replacement or addition), which do not significantly affect the quality of the active substance;	1, 2, 3, 5, 6	1, 2	IA
	d) variations (replacement) in the biological, immunological or immunochemical test method or in the method in which the use of a biological reagent as a biologically active substance is intended (for example, peptide mapping, glycomapping);			II
	e) other variations to the active substance, starting material or intermediate product test procedure (including replacement or addition).		1, 2	IB
13.1.	Conditions:			
13.1.1.	1. The relevant approval (validation) studies performed in accordance with the appropriate guidelines, and the results thereof prove that the updated test procedures are equivalent to or better than the approved test procedures.			
13.1.2.	2. The total impurity limits remain unchanged and no new unqualified impurities have been established			
13.1.3.	3. The analytical methods remain unchanged (for example, variations to the permissible temperature or column length, but there is no different column or method).			
13.1.4.	4. The test method is not a biological, immunological or immunochemical method or a method in which a biological reagent is proposed to be used as a biologically active substance (not including the pharmacopoeia standard microbiological methods).			
13.1.5.	5. Any new test method shall not apply to new non-standard techniques or standard techniques are not used in a new way.			
13.1.6.	6. The active substance is not a biological or immunological substance.			
13.1.7.	7. The test procedure of alternative specification parameters is approved and this procedure is not appended to the marketing authorisation for the approval procedure for variations of type IA.			
13.2.	Documentation:			
13.2.1.	1. Additions to the relevant part of the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format), including a description of the analytical method, a summary of the approval (validation) data, reviewed impurity specifications, if necessary.			
13.2.2.	2. Comparable validation results or comparable analysis results which prove that the approved tests in			

the marketing authorisation and the proposed tests are equivalent. This requirement shall not be applied if a new test procedure is added.

2.1.3. Container Closure (Sealing) System

14.	Variations to the immediate packaging of the active substance (B.I.c.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) qualitative or quantitative composition;	1, 2, 3	1, 2, 3, 4, 6	IA
	b) the qualitative or quantitative composition of the packaging of the sterile and unfrozen biological or immunological active substance;			II
	c) liquid active substances (non-sterile).		1, 2, 3, 5, 6	IB
14.1.	Conditions:			
14.1.1.	1. The proposed packaging material is at least equivalent to the approved packaging material in relation to the relevant properties.			
14.1.2.	2. The appropriate stability trials shall be commenced in accordance with the conditions referred to in the European Commission guidelines of the International Veterinary Conference on Harmonisation (hereinafter – VetICH) and the relevant stability parameters shall be evaluated for at least two experimental or industrial batches and sufficient (satisfactory) stability data of at least three months shall be available to the applicant during the introduction. If the proposed packaging is more resilient than the approved packaging, three months data of stability studies shall not be required. These studies shall be completed and the data (together with the proposed action) submitted without delay to the Food and Veterinary Service, if the studies at the end of the storage period or period of repeat testing do not conform with or may not conform with the specifications.			
14.1.3.	3. The relevant substance shall not be a sterile, liquid and biological or immunological active substance.			
14.2.	Documentation			
14.2.1.	1. Additions to the relevant part of the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			
14.2.2.	2. The relevant data regarding the new packaging (for example, comparable data on the permeability, including the permeability of O ₂ , CO ₂), including approval that the material complies with the relevant conditions of a pharmacopoeia or regulatory enactments regarding materials and objects in contact with food.			
14.2.3.	3. If necessary, evidence that there is no interaction between the packaging and the content of the packaging (for example, the entry or diffusion of medicinal product components into the packaging, the loss of product components in closed packaging), including confirmation that the material complies with the relevant conditions of a pharmacopoeia or regulatory enactments regarding materials and objects in contact with food.			
14.2.4.	4. A declaration of the marketing authorisation holder (owner) or ASMF holder that the appropriate stability studies have been commenced in accordance with the conditions of the VetICH (indicating the relevant batch numbers) and, if necessary, that at the time of the implementation of the relevant procedure, the applicant had at the disposal thereof the minimum satisfactory data on stability, and the data available do not indicate problems. Confirmation shall be submitted that these studies shall be completed and the data (together with the proposed action) submitted without delay to the Food and Veterinary Service, if the studies at the end of the storage period or period of repeat testing do not conform with or may not conform with the specifications.			
14.2.5.	5. The results of at least two stability studies on experimental or industrial batches regarding the relevant stability values incorporating a period of at least three months and confirmation that these studies shall be completed and the data (together with the proposed action) submitted without delay to the Food and Veterinary Service, if the data, at the end of the approved repeat testing period do not conform with or may not conform with the specifications.			
14.2.6.	6. A comparison of the approved and proposed packaging specification, if necessary.			

15.	Variations to the specification parameters or limits of the immediate packaging of the active substance (B.I.c.2.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) determination of stricter specification limits;	1, 2, 3, 4	1, 2	IA
	b) addition of new specification parameters, together with the appropriate test methods;	1, 2, 5	1, 2, 3, 4, 6	IA
	c) deletion of insignificant parameters (for example, outdated parameters);	1, 2	1, 2, 5	IA
	d) addition or replacement of specification parameters for safety or quality reasons.		1, 2, 3, 4, 6	IB
15.1.	Conditions:			
15.1.1.	1. The variations are not the result of the fulfilment of any commitments arising from the previous evaluations to review the specification limits (for example, performed in the registration procedure or in the approval procedure of major variations of type II), except cases where the variations are previously evaluated and approved as part of the supervision measures.			
15.1.2.	2. The variations are not the result of unexpected events during the period of manufacturing the packaging material or during the storage of the active substance.			
15.1.3.	3. All changes shall conform to the approved limits.			
15.1.4.	4. The test procedure remains unchanged or the variations to the test procedure are insignificant.			
15.1.5.	5. Any proposed test method does not apply to new non-standard techniques or standard techniques are not used in a new way.			
15.2.	Documentation:			
15.2.1.	1. Additions to the relevant part of the registration dossier (submitted in CTD format or in "Notice to Applicants" Volume 6B format).			
15.2.2.	2. A comparable table of the approved and proposed specifications.			
15.2.3.	3. Information regarding each new analytical method and approval (validation) data, if necessary.			
15.2.4.	4. Batch analysis data for two batches of immediate packaging for all specification parameters.			
15.2.5.	5. An explanation or risk assessment with which the marketing authorisation holder (owner) or ASMF holder certifies that the parameters are insignificant.			
15.2.6.	6. The grounds for the proposed specification parameters and limits prepared by the marketing authorisation holder (owner) or the ASMF holder.			
16.	Variations to the test procedures of the immediate packaging of the active substance (B.I.c.3.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) minor variations in the approved test procedure;	1, 2, 3	1, 2	IA
	b) other variations in the test procedure (inc. replacement or addition);	1, 3, 4	1, 2	IA
	c) deletion of the test procedure if an alternative test procedure is already approved.	5	1	IA
16.1.	Conditions:			
16.1.1.	1. The relevant approval (validation) studies are performed in accordance with the relevant guidelines and demonstrate that the updated test procedure is at least equivalent to the approved test procedure.			
16.1.2.	2. The analytical methods remain unchanged (for example, variations to the permissible temperature or column length, but there is no different column or method).			

16.1.3.	3. Each new test method shall not apply to new non-standard techniques or standard techniques are not used in a new way.
16.1.4.	4. The active substance or finished product is not a biological or immunological substance or finished product.
16.1.5.	5. The specification parameter test procedure is still registered and this procedure is not appended to the notification procedure of IA.
16.2.	Documentation:
16.2.1.	1. Additions to the relevant part of the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format), including a description of the analytical method, a summary of the approval (validation) data.
16.2.2.	2. Comparable approval (validation) results or comparable analytical results, with which it shall be proved that the approved test and proposed test procedures are equivalent. This condition shall not be applicable if a new test procedure is added.

2.1.4. Stability of the Active Substance

17.	Variations during the period of repeat testing or storage of the active substance or in the storage conditions, if the European Pharmacopoeia Certificate of Suitability for the repeat testing period is not appended to the approved documentation (B.I.d.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) repeat test or storage period:			
	1. reduction;	1	1, 2, 3	IA
	2. extension of the repeat test period, justified by the extrapolation of the stability data which does not conform to the guidelines of the ICH (shall not be applied to biological or immunological active substances);			II
	3. extension of the storage period for biological and immunological active substances which do not conform to the approved stability protocol;			II
	4. extension or introduction of a repeat test or storage period (justified with real time data);		1, 2, 3	IB
	b) storage conditions;			
	1. stricter (more limiting) storage conditions of the active substance;	1	1, 2, 3	IA
	2. variations to the conditions of storage for a biological or immunological active substance, if stability studies have not been performed in accordance with approved stability protocols;			II
	3. variations to the storage conditions of the active substances.		1, 2, 3	IB
17.1.	Conditions:			
17.1.1.	1. The variations are not the result of unexpected events during the manufacturing process or for reasons of stability.			

17.2.	Documentation:
17.2.1.	1. Additions to the relevant part of the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format). Contain the results of real time stability studies in accordance with the relevant stability guidelines for the active substances of at least two (or three, for biological veterinary medicinal products) experimental or manufacturing batches in the approved packaging material. Studies shall be performed in a specified repeat test period or in specific storage conditions.
17.2.2.	2. Confirmation that the stability studies are performed in accordance with approved protocols. The studies shall prove that conformity continues to be ensured with the relevant approved specifications.
17.2.3.	3. Copies of the approved specification of the active substance.

2.1.5. Design Space

18.	Determination of a new design space of an active substance or the extension of an approved design space (B.I.e.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) for the manufacture of one unit in the manufacturing process of the active substance, including for related investigations during manufacture or test procedures;		1, 2,3	II
	b) for test procedures of the starting materials, reagents, intermediates or active substance.		1, 2, 3	II
18.1.	Documentation:			
18.1.1.	1. The design space shall be determined in accordance with the relevant scientific guidelines. Results of product, process and analytical development studies (for example, the interaction of different parameters forming the design space shall be investigated, including the performance of the risk assessment in appropriate cases and studies of several parameters), which prove when necessary that a systematic and mechanical understanding of the material values and process parameters has been acquired, as well as the critical quality values of the active substance.			
18.1.2.	2. A description of the design space including the variable (in relevant cases the parameters of the material indices and the process) and the suggested range thereof, a description in tabular form.			
18.1.3.	3. Amendments to the relevant part of the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			
19.	Implementation of the management protocol for the variations performed after authorisation related to the active substance (B.I.e.2.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
			1, 2	II
	Documentation:			
	1. A detailed description of the proposed variations.			
	2. The management protocol of the variations related to the active substance.			
20.	Deletion of the management protocol for the approved variations related to the active substance (B.I.e.3.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
		1	1	IA
20.1.	Conditions:			
	1. The deletion of the protocol for the approved variations related to the active substance has not been caused by unexpected events or considerations of specification during the period of making the variations described in the protocol.			
20.2.	Documentation:			
	1. Grounds for the proposed deletion.			

2.2. Finished Product (Veterinary Medicinal Product) (B.II)

2.2.1. Qualitative Variations to the Summary of the Veterinary Medicinal Product Characteristics and Components

21.	Variations related to imprints, embossing or other marks, inc. the addition or replacement of colouring matters used in labelling (B.II.a.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) variations to imprints, embossing or other marks	1, 2, 3	1, 2	IA
	b) variations to scoring or dividing lines intended for distributing the medicinal product in equal doses		1, 2, 3	IB
21.1.	Conditions:			
21.1.1.	1. The specifications of the release and storage period of the finished product remains unchanged (except the appearance).			
21.1.2.	2. Each colouring matter complies with the relevant regulatory enactment in the field of veterinary medicinal products.			
21.1.3.	3. Scoring lines or dividing lines are not intended for dividing into equal doses.			
21.2.	Documentation:			
21.2.1.	1. Additions to the relevant part of the registration dossier (submitted in CTD format or in "Notice to Applicants" Volume 6B format), including the detailed image or description of the existing and proposed design or a description and the changed information about the product appended, if necessary.			
21.2.2.	2. Samples of the finished product, if necessary.			
21.2.3.	3. The relevant European Pharmacopoeia test results with which the equal worth of the characteristics and (or) precise dosage is demonstrated.			
22.	Variations to the pharmaceutical form or size (B.II.a.2.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) tablets, capsules, suppositories (suppositories) and pessaries with immediate release of the active substance	1, 2, 3, 4.	1,4	IA
	b) gastro-resistant, modified (transformed) or prolonged release pharmaceutical forms and scored tablets intended for dividing into equal doses.		1, 2, 3, 4, 5	IB
22.1.	Conditions			
22.1.1.	1. The dissolution profile of the reformulated product is comparable to the previous one. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.			
22.1.2.	2. The specifications of product release and storage time remain unchanged (except the size)			
22.1.3.	3. The qualitative or quantitative composition and average mass remain unchanged.			
22.1.4.	4. The variations shall not apply to scored tablets, intended to be divided into equal doses.			
22.2.	Documentation			
22.2.1.	1. Additions to the relevant part of the registration dossier (submitted in CTD format or in "Notice to Applicants" Volume 6B format), including the detailed description of the existing and proposed situation, appending the changed information about the product, if necessary.			

22.2.2.	2. Comparable dissolution data regarding the existing and proposed sizes of at least one experimental batch (there shall be no significant differences in the comparability, see the veterinary guidelines on bioavailability). Comparable disintegration data shall be permitted for herbal medicinal products.			
22.2.3.	3. An explanation as to why new bioavailability studies are not submitted in accordance with the veterinary guidelines on bioavailability.			
22.2.4.	4. Samples of the finished product, if necessary.			
22.2.5.	5. The relevant European Pharmacopoeia test results with which the equal worth of the characteristics and (or) precise dosage is demonstrated.			
23.	Variations to the components (excipients) of the finished product (B.II.a.3.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) variations to the components of the flavouring or colouring matter system:			
	1. addition, deletion or replacement;	1, 2, 3, 4, 5, 6, 7, 8	1, 2, 4, 5, 6	IA_I
	2. increase or reduction;	1, 2, 3, 4	1, 2, 4	IA
	3. biological veterinary medicinal product for oral administration, in which the colouring matters or flavourings are important. For the target species to absorb the medicinal product.			II
	b) other excipients:			
	1. adjustment to the quantitative composition of minor excipients in the finished product;	1, 2, 4, 7, 8,9	1, 2	IA
	2. qualitative or quantitative variations to one or several excipients which may significantly affect the safety, quality or efficacy of the medicinal product;			II
	3. variations applicable to biological or immunological medicinal products;			II
	4. a new excipient connected to human or animal material, whose data shall be evaluated for virus safety or TSE risk;			II
5. variations justified by bioavailability studies;			II	
6. replacement of one excipient with a comparable excipient with the same functional properties and with a similar level.		1, 3, 4, 5, 6, 7, 8, 9	IB	
23.1.	Conditions			
23.1.1.	1. No variations to the functional characteristics of the pharmaceutical form, for example, the division (deterioration), dissolution profile.			
23.1.2.	2. Any minor adjustment made to the formulation to maintain the total weight shall be made by an excipient, which currently makes up a major part of the finished product formulation.			

23.1.3.	3. The finished product specification shall only be updated in respect of the appearance, smell, taste and, where appropriate, the deletion of the identification test.
23.1.4.	4. Stability studies have been commenced in accordance with the conditions of VetICH (identifying the batch numbers) and the relevant stability parameters have been evaluated in at least two experimental batches or industrial batches and the applicant has access to the relevant stability data acquired within no less than three months (at the time of implementation of variations of Type IA and notification of variations of Type IB) and the stability profile is the same as in the current situation. Confirmation has been submitted that the studies shall be completed and the data submitted to the Food and Veterinary Service without delay, if they do not conform with, or may not conform with the specification at the end of the approved storage period. In addition, where relevant, photostability testing shall be performed.
23.1.5.	5. The proposed excipients comply with the requirements specified in regulatory enactments regarding the quality requirements for colouring matters or flavourings.
23.1.6.	6. The proposed excipients do not contain human or animal material requiring a viral safety assessment or conformity with the European Commission guidelines "Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products".
23.1.7.	7. The dissolution profile of the proposed product shall be determined for at least two experimental batches, is comparable to the current one and there are no significant differences when comparing, see the bioavailability guidelines.
23.1.8.	8. The variations are not the result of stability studies and (or) are not justified by safety considerations, for example, differences in strength.
23.1.9.	9. The finished product is not an immunological or biological medicinal product.
23.2.	Documentation:
23.2.1.	1. Additions to the relevant part of the registration dossier (submitted in CTD format or in "Notice to Applicants" Volume 6B format), including the identification methods of new colouring matters and including updated product information, if necessary.
23.2.2.	2. A declaration that the requested stability studies have been commenced in accordance with the conditions of the VetICH (indicating the batch numbers) and that the required minimum stability data are available to the applicant during the implementation of the procedure and the data available do not indicate any problems. Confirmation shall be provided that these studies shall be completed and that the data (together with the proposed action) shall be submitted to the Food and Veterinary Service without delay if the data do not conform with, or may not conform with the specifications at the end of the approved storage period.
23.2.3.	3. The results of at least two stability studies on experimental or industrial batches in accordance with the conditions of the VetICH regarding the relevant stability indices incorporating a period of at least three months and confirmation that these studies shall be completed and the data (together with the proposed action) submitted without delay to the Food and Veterinary Service, if the data, at the end of the approved storage period do not conform with or may not conform with the specifications.
23.2.4.	4. A sample of the new product, where appropriate.
23.2.5.	5. A European Pharmacopoeia Certificate of Suitability for all the TSE susceptible materials of animal origin or, where appropriate, documentary evidence that the specific TSE risk material has previously been assessed by the competent authority and is proved to conform to the European Commission guidelines "Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products". The following information shall be indicated regarding the materials: name of the manufacturer, animal species and tissues from which material is obtained (derived), the country of origin of the donor animal and the method of use.
23.2.6.	6. Data which demonstrates that the new excipient does not affect the finished product specification test methods, if such are used.
23.2.7.	7. Justification from the developer of the relevant medicinal product for the variation or selection of the excipients (including stability considerations and antimicrobial protection, if necessary).

23.2.8.	8. A comparable dissolution profile for solid pharmaceutical forms for at least two experimental batches of the finished product, both with the proposed and existing composition. Comparable degradation data may be submitted for herbal medicinal products.			
23.2.9.	9. Justification for the failure to submit the results of new bioavailability studies in accordance with existing guidelines on bioavailability and bioequivalence studies.			
23.2.10.	10. For veterinary medicinal products intended for food-producing animals, evidence that the excipient is classified in accordance with Article 14 (2)(c) of Regulation No 470/2009, or if not, evidence that the excipient has no pharmacological effect in a dose intended for the target animals.			
24.	Variations to the coating weight of the pharmaceutical form for internal (oral) administration or the coating weight of the capsule (B.II.a.4.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) other forms for oral administration;	1, 2, 3, 4	1,2	IA
	b) gastro-resistant, modified or prolonged release pharmaceutical forms, whose coating is a significant factor for the release mechanism.			II
24.1.	Conditions			
24.1.1.	1. The dissolution profile of the new product determined on a minimum of two experimental batches is comparable to the previous one. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the previous one.			
24.1.2.	2. The coating is not a critical factor for the release mechanism.			
24.1.3.	3. Where necessary the finished product specification is only updated in respect of the weight and measurements.			
24.1.4.	4. Stability studies in accordance with the relevant guidelines have been commenced with at least two experimental or industrial batches and at least three months satisfactory stability data are at the disposal of the applicant, as well as confirmation that these studies will be completed. Data (together with the proposed action) shall be provided to the Food and Veterinary Service without delay if they do not conform with or may not conform with the specifications at the end of the approved period of validity.			
24.2..	Documentation			
24.2.1.	1. Amendments to the relevant part of the registration dossier (submitted in CTD format or in "Notice to Applicants" Volume 6B format).			
24.2.2.	2. A declaration that the necessary stability studies have been commenced in accordance with the conditions of the VetICH (indicating the relevant batch numbers) and, that where appropriate, at the time of the implementation of the relevant procedure, the applicant had at the disposal thereof the minimum satisfactory data on stability, and the data available did not indicate problems. Confirmation has been submitted that these studies shall be completed and that the data (together with the proposed action) shall be submitted to the Food and Veterinary Service without delay if the data do not conform with, or may not conform with the specifications at the end of the approved period of validity. In addition, where relevant, photostability testing shall be performed.			
25.	Variations to the concentration of single-dose parenteral medicinal product where the quantity of the active substance in a dose (strength) is unchanged (B.II.a.5.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
				II
26.	Removal (deletion) of the solvent and (or) dilution container from the packaging (B.II.a.6.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
			1, 2	IB

26.1.	Documentation:
26.1.1.	1. Justification for the removal (deletion), including a notification on alternative options for acquiring solvent or diluent for the safe and effective use of the medicinal product.
26.1.2.	2. Information reviewed regarding the veterinary medicinal product.

2.2.2. Variations to the Manufacturing Process of the Finished Product

27.	Replacement or addition of the production unit of the finished product in respect of the whole manufacturing process or a stage thereof (B.II.b.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) secondary packaging site;	1, 2	1, 3, 8	IA
	b) immediate packaging site;	1, 2, 3, 4, 5	1, 2, 3, 4, 8, 9	IA
	c) site where any manufacturing operations of biological or immunological medicinal products takes place, except batch release, batch control and secondary packaging;			II
	d) site where initial or product-specific inspection is performed;			II
	e) site where manufacturing operations of non-sterile medicinal products takes place, except batch release, batch control and secondary packaging;		1, 2, 3, 4, 5, 6, 7, 8, 9	IB
	f) site where manufacturing operations of sterile medicinal products (except biological or immunological medicinal products) takes place, which are being manufactured using the aseptic method, except batch control and secondary packaging of the batch release.		1, 2, 3, 4, 5, 7, 8	IB
27.1	Conditions:			
27.1.1.	1. An inspectorate of an EEC Member State or a country which has a mutual recognition agreement with the EU on good manufacturing practice has performed an inspection within the last three years, and the inspection results are satisfactory.			
27.1.2.	2. A special authorisation (licence) for the manufacture of the relevant medicinal product or pharmaceutical form has been issued to the production unit.			
27.1.3.	3. Not a sterile product.			
27.1.4.	4. Where appropriate, for example, when manufacturing suspensions or emulsions, a validation scheme exists in the new production site or validation of the manufacturing has been successful in accordance with the existing protocol for at least three batches manufactured.			
27.1.5.	5. The product is not a biological or immunological medicinal product.			
27.2.	Documentation:			
27.2.1.	1. Evidence that a special authorisation (licence) for the manufacture of the relevant medicinal product or pharmaceutical form has been issued to the production unit.			
27.2.2.	2. Where appropriate, the batch numbers used in the validation studies shall be indicated (not less than 33), the size of the relevant batch and the date of batch preparation and validation data or a protocol (scheme) shall be submitted.			
27.2.3.	3. The existing and proposed manufacturers of the finished product shall be clearly indicated in the application form for variations.			
27.2.4.	4. Where appropriate, copies of the approved release specification and storage period.			

27.2.5.	5. The analytical data of one manufacturing batch and the analytical data of two experimental batches, acquired by stimulating the manufacturing process (or two manufacturing batches), and comparable data from the last three batches from the previous production unit; batch data for the next two manufacturing batches shall be submitted upon request or submitted (together with the proposed action), if they do not conform with the specifications.			
27.2.6.	6. For semi-solid and liquid pharmaceutical forms whose active substance is in non-soluble form, the appropriate validation data, including the microscopic image and morphology of the particle sizes.			
27.2.7.	7. i) if the proposed production unit uses the active substance as the starting material, the confirmation of the qualified person from the production unit responsible for the batch release, that the active substance is being manufactured in accordance with European Commission (EC) guidelines on the good manufacturing practice for starting materials; ii) In addition, if the proposed production unit is in the EEC and uses the active substance as the starting material, the confirmation of the qualified person from the proposed production unit that the active substance is being manufactured in accordance with EU guidance on the good manufacturing practice for starting materials.			
27.2.8.	8. Amendments to the relevant parts of the dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			
27.2.9.	9. If the manufacture and immediate packaging does not take place in one place, conditions for the transportation and storage of large scale production shall be developed and approved.			
27.3.	<p>Notes: The marketing authorisation holder (owner) may only use active substances which have been manufactured in accordance with the requirements of good manufacturing practice as starting material, therefore all marketing authorisation holders (owners) using the active substance as the starting material shall submit a confirmation. In addition, the qualified person responsible for batch release shall undertake responsibility for each batch, the qualified person shall submit another confirmation if the site of batch release is not the aforementioned site.</p> <p>If more than one marketing authorisation holder (owner) is involved, one confirmation may be submitted, signed by one qualified person. In such case:</p> <p>a) the confirmation shall clearly specify that it has been signed on behalf of all the qualified persons involved;</p> <p>b) at the basis of the measures is an agreement in accordance with the guidelines for good manufacturing practice and the qualified person in the agreement is the person undertaking particular responsibility.</p> <p>The qualified person shall comply with the requirements specified in Cabinet Regulation No. 319 of 15 May 2006, Regulations on the Manufacture and Control of Veterinary Medicinal Products, Procedures by which a Good Manufacturing Practice Certificate shall be Issued to a Veterinary Medicinal Product Manufacturer, and the Requirements for the Qualification and Professional Experience of Officials Responsible for the Manufacture of Veterinary Medicinal Products, and shall be located in the EEC, therefore the confirmations of qualified persons located in third countries shall not be acceptable.</p>			
28.	Variations in the procedures for batch release and the quality control testing of the finished product (B.II.b.2.):	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) replacement or addition of a batch control or testing site;	2, 3	1, 2, 4	IA
	b) replacement or addition of a manufacturer responsible for batch release;			
	1. without batch control and (or) testing;	1, 2	1, 2, 3, 4	IA
	2. with batch control and (or) testing;	1, 2, 3,	1, 2, 3, 4	IA
3. with the batch control and (or) testing of the biological or immunological product, as one of the control or testing methods using a biological, immunological or immunochemical method.			II	

28.1.	Conditions			
28.1.1.	1. The manufacturer responsible for batch release is located in the EEC			
28.1.2.	2. The relevant special authorisation (licence) has been granted to the production unit.			
28.1.3.	3. The product is not a biological or immunological medicinal product.			
28.1.4.	4. The handover of the method from the previous to the proposed production unit or testing laboratory has been completed successfully.			
28.2.	Documentation			
28.2.1.	1. A production unit, which: 1.1. is located in an EEC country, a copy of the special authorisation (licence) for the manufacture of veterinary medicinal products or, if none, the good manufacturing practice certificate issued by the relevant competent authority within the last three years; 1.2. is not located in a EEC country, if between the relevant country which has a mutual recognition agreement with the EU on good manufacturing practice, which is in force, a good manufacturing practice certificate issued by the relevant competent authority within the last three years. If there is no such agreement, a good manufacturing practice certificate issued by a competent authority of the EEC within the last three years.			
28.2.2.	2. The “existing” and “proposed” manufacturers of the finished product shall be clearly indicated in the application form for variations.			
28.2.3.	3. Confirmation from the qualified person responsible for batch approval, in which it is indicated that the manufacturer of the active substance referred to in the registration dossier is operating in accordance with EC guidelines on the good manufacturing practice for starting materials. In the case referred to in Sub-paragraph 27.3 of this Annex, one assurance may be submitted.			
28.2.4.	4. The relevant amendments to the registration dossier, including the reviewed information on the product (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			
29.	Variations to the Manufacturing Process of the Finished Product (B.II.b.3.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) minor variations to the manufacturing process of solid pharmaceutical forms for oral administration with immediate release of the active substance or for liquids for oral administration;	1, 2, 3, 4, 5, 6, 7	1, 3, 4, 6, 7, 8	IA
	b) major variations in the manufacturing process which may significantly affect the quality, safety or efficacy of the medicinal product;			II
	c) the product is a biological, including immunological, medicinal product and in order to make variations, a comparability assessment shall be performed;			II
	d) introduction of non-standard final (terminal) sterilisation methods;			II
	e) determination of the permissible excess or increase of the active substance;			II
	f) minor variations for the manufacturing process of water-based liquid (suspension) for oral administration;		1, 2, 4, 6, 7, 8	IB
29.1.	Conditions:			
29.1.1.	1. No change in qualitative and quantitative impurity profile or in physico-chemical properties.			
29.1.2.	2. The product is not a biological or immunological, or a herbal medicinal product.			
29.1.3.	3. The manufacturing principle, including separate manufacturing phases, for example, intermediate product processing, remains unchanged and the variations shall not apply to the solvent used in the manufacturing process.			

29.1.4.	4. The registered process shall be controlled performing the appropriate controls during the course of manufacturing, and these controls shall not be changed (extension or revocation of limits).			
29.1.5.	5. The specifications of the finished product or intermediate product remain unchanged.			
29.1.6.	6. As a result of the proposed process, an identical product is obtained in respect of all quality, safety and efficacy aspects.			
29.1.7.	7. Relevant stability studies in accordance with the relevant guidelines have been commenced with at least one experimental or industrial batch and at least three months stability data are at the disposal of the applicant. Confirmation is given that these studies will be completed and that the data (together with proposed action) will be provided to the Food and Veterinary Service without delay if the data at the end of the approved storage period do not conform or may not conform to the specifications.			
29.2.	Documentation:			
29.2.1.	1. The relevant amendments to the registration dossier, including a direct comparison of the current procedure and the proposed procedure (submitted in CTD format or in "Notice to Applicants" Volume 6B format).			
29.2.2.	2. For semi-solid and liquid products whose active substance is in non-soluble form, in conformity with the validation data of variations, including a microscopic image of the particle sizes, in order to check the visible morphological changes and comparable data of particle sizes acquired by using the appropriate method.			
29.2.3.	3. The dissolution profile of a representative manufacturing batch of solid pharmaceutical forms and comparable data on the previous manufacturing process for the last three batches. Data on the next two complete manufacturing batches are available upon request or they shall be submitted (together with the proposed action) , if there is no conformity with the specification. Comparable degradation data may be submitted for herbal medicinal products.			
29.2.4.	4. Justification for the failure to submit the results of new bioequivalence data in accordance with the relevant instructions in the instructions included in the guidelines on bioavailability and bioequivalence.			
29.2.5.	5. Validation data in the case of variations to the sterilisation process.			
29.2.6.	6. A copy of the approved specifications for release and storage periods.			
29.2.7.	7. The analytical data of at least one batch, prepared in accordance with the approved and proposed process (in comparable table form). The data of the next two complete manufacturing batches shall be prepared and submitted by the medicinal product authorisation holder (owner) upon request, if they are outside the determined specification and which are submitted together with the proposed action.			
29.2.8.	8. Confirmation that stability studies have commenced on at least one experimental or industrial batch in accordance with the VetICH conditions (indicating the relevant batch number) and the relevant stability parameters have been evaluated and that, on submission of the notification, the applicant for the variations has at least three months satisfactory data on stability at his or her disposal and that the stability profile is similar to the situation indicated in the currently registered documentation. A note shall be included in the confirmation that these studies will be completed and that the data (together with the proposed action) shall be provided without delay to the competent authority if they do not conform with or may not conform with the specifications at the end of the approved storage period.			
30.	Variations to the size of the finished product batch (including the range of the batch size) B.II.b.4.	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) scale-up up to 10-fold compared to the approved batch size;	1, 2, 3, 4, 5, 7.	1, 4	IA
	b) downscaling down to 10-fold;	1, 2, 3, 4, 5, 6	1., 4.	IA
	c) in order to make variations, a comparability assessment of biological or immunological medicinal products shall be performed;			II

	d) variations apply to other pharmaceutical forms manufactured in a complex manufacturing process;			II
	e) a scale-up more than 10-fold compared with the approved batch size of medicinal products with immediate release of the active substance;		1, 2, 3, 4, 5, 6	IB
	e) a scale-up or downscale of the batch of biological or immunological medicinal products without variations to the manufacturing process (for example, duplication of the production line);		1, 2, 3, 4, 5, 6	IB
30.1.	Conditions			
30.1.1.	1. The variations do not affect the reproducibility and/or conformity of the product.			
30.1.2.	2. The variations relate only to standard immediate release oral pharmaceutical forms and to non-sterile liquid forms.			
30.1.3.	3. Variations to manufacturing methods and (or) inspections during the course of manufacture shall only be those necessary in order to perform variations to the batch size, for example, the use of different sized equipment.			
30.1.4.	4. The existing validation scheme or validation of the manufacture has been successfully carried out in accordance with the current protocol with at least three manufactured product batches at the proposed new batch size, in accordance with the relevant guidelines.			
30.1.5.	5. The relevant product is not a biological or immunological medicinal product.			
30.1.6.	6. The variations are not be the result of unexpected events during the manufacture or because of stability concerns;			
30.1.7.	7. The current batch size was not approved as a variation of Type IA.			
30.2.	Documentation			
30.2.1.	Amendments to the relevant part of the registration dossier (submitted in CTD format or in "Notice to Applicants" Volume 6B format).			
30.2.2.	2. Analytical data of at least one production batch manufactured in accordance with the currently approved and proposed batch size (in comparable table form). Batch data for the next two complete production batches are available and the marketing authorisation holder (owner) shall notify of these upon request (together with the proposed action), if the data do not comply with the specifications.			
30.2.3.	3. Copies of the approved specifications for release and storage periods.			
30.2.4.	4. Where appropriate, the batch numbers used in the validation studies shall be indicated (not less than 3), the size of the relevant batch and the date of batch preparation or a validation protocol (scheme) shall be submitted.			
30.2.5.	5. Validation results are submitted.			
30.2.6.	6. The results of at least one stability study on experimental or industrial batches regarding the relevant stability indices incorporating a period of at least three months and confirmation that these studies shall be completed and the data (together with the proposed action) submitted without delay to the Food and Veterinary Service, if the data, at the end of the approved repeat testing period do not conform with or may not conform with the specifications. Confirmation that a comparability assessment of biological, including immunological, medicinal products is not necessary.			
31	Variations to tests performed during the course of manufacture or limits applied during the manufacture of the finished product (B.II.b.5.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) determination of stricter manufacturing process limits;	1, 2, 3, 4	1, 2	IA
	b) addition of new tests or limits;	1, 2, 5, 6	1, 2, 3, 4, 5, 7	IA

	c) deletion of a minor test during the course of manufacture to be performed;	1, 2	1, 2, 6	IA
	d) deletion of tests performed during the course of manufacture which may significantly affect the general quality of the finished product;			II
	e) extension of the approved test limits to be performed during the course of manufacture which may significantly affect the general quality of the finished product;			II
	f) addition or replacement of tests to be performed during the course of manufacture for safety or quality reasons.		1, 2, 3, 4, 5, 7	IB
31.1.	Conditions:			
31.1.1.	1. The variations are not a consequence of the fulfilment of any commitment from previous assessments to review specification limits (for example, they were not made during the procedure for authorisation application or a Type II variation procedure).			
31.1.2.	2. The variations are not the result of unexpected events during manufacture (for example, new, unqualified impurities or variations to the total limits of the impurity).			
31.1.3.	3. Any variation shall conform with the currently approved limits.			
31.1.4.	The test procedure remains unchanged or variations to the test procedure are minor.			
31.1.5.	5. The new test methods do not apply to new non-standard techniques or standard techniques used in a new way.			
31.1.6.	6. The new test method is not a biological, immunological or immunochemical method or a method which anticipates the use of a biological reagent as a biologically active substance (not including the pharmacopoeia standard microbiological methods).			
31.2.	Documentation:			
31.2.1.	1. Amendments to the relevant part of the registration dossier (submitted in CTD format or in 'Notice to Applicants' Volume 6B format).			
31.2.2.	2. A comparable table of the current and proposed limits and tests performed during the course of manufacture.			
31.2.3.	3. Where appropriate, information regarding the proposed analytical methods and validation data.			
31.2.4.	4. Data of two finished product production batches (analytical data for three production batches for finished biological products, unless otherwise specified) for all the specification parameters.			
31.2.5.	5. Comparable data of the dissolution profile of a finished product, determined for at least one experimental batch manufactured by performing current and new tests during manufacture. Comparable degradation data may be submitted for herbal medicinal products.			
31.2.6.	6. Justification and (or) a risk assessment which proves that the parameter is not significant.			
31.2.7.	7. Justification for the proposed test and limits.			

2.2.3. Control of Excipients

32	Variations to the excipient specifications and (or) limits (B.II.c.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) tightening of specification limits	1, 2, 3, 4	1, 2	IA
	b) addition of a new specification parameter to the specification, together with the appropriate test method	1, 2, 5, 6, 7	1, 2, 3, 4, 6, 8	IA

	c) deletion of an insignificant specification parameter (for example, deletion of an outdated parameter)	1, 2	1, 2, 7	IA
	d) variations exceeding the approved specification limit range			II
	e) deletion of a specification parameter which may significantly affect the general quality of the finished product			II
	f) the addition or replacement of a specification parameter (except biological or immunological medicinal products) for safety or quality reasons		1, 2, 3, 4, 5, 6, 8	IB
32.1.	Conditions:			
32.1.1.	1. The variations are not the result of the fulfilment of any commitment from previous assessments to review specification limits (for example, they were not made during the procedure for authorisation application or a Type II variation procedure).			
32.1.2.	2. The variations have not been caused by unexpected events during manufacture, for example, a new, unqualified impurity or variations to the total limits of the impurities).			
32.1.3.	3. Any variations shall conform with the currently approved limits.			
32.1.4.	The test procedure remains unchanged or the variations are minor.			
32.1.5.	5. The proposed test methods shall not apply to new non-standard techniques or standard techniques used in a new way.			
32.1.6.	6. The proposed test method is not a biological, immunological or immunochemical method or a method where the biological reagent is intended to be used as a biologically active substance (not including the pharmacopoeia standard microbiological methods).			
32.1.7.	7. The variations shall not apply to genotoxic impurities.			
32.2.	Documentation			
32.2.1.	1. Amendments to the relevant part of the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			
32.2.2.	2. A comparable table of the approved and proposed specifications.			
32.2.3.	3. Information regarding all proposed analytical methods and validation data.			
32.2.4.	4. Analytical data for all specification parameters for two excipient manufacturing batches (analytical data for three manufacturing batches of biological excipients).			
32.2.5.	5. Where necessary, comparable dissolution profile data of the finished product, determined for at least one experimental batch incorporating the excipient in accordance with the approved and proposed specification. Comparable degradation data may be submitted for herbal medicinal products.			
32.2.6.	6. Justification for the failure to submit the results of new bioequivalence data in accordance with bioavailability guidelines, if necessary.			
32.2.7.	7. Justification and (or) a risk assessment which proves that the parameter is not significant.			
32.2.8.	8. Justification for the proposed specification parameter and limits.			
33.	Variations to the excipient test procedures (B.II.c.2.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) minor variations in the approved test procedure;	1, 2, 3, 4	1, 2	IA
	b) deletion of the test procedure if an alternative test procedure is already approved;	5	1	IA

	c) replacement of the biological, immunological, immunochemical test method or method anticipating the use of a biological reagent			II
	d) other variations in the test procedure (inc. replacement or addition)		1, 2	IB
33.1.	Conditions			
33.1.1.	1. The appropriate validation studies have been performed (in accordance with the relevant guidelines) and the results thereof prove that the updated test procedure is at least equivalent to the previous test procedure.			
33.1.2.	2. The total impurity limits remain unchanged and new unqualified impurities have not been established.			
33.1.3.	3. The method of analysis shall remain the same (for example, change in column length or temperature variations are permitted, but not a different type of column or method).			
33.1.4.	4. The test method is not a biological, immunological or immunochemical method or a method anticipating the use of a biological reagent (not including the pharmacopoeia standard microbiological methods).			
33.1.5.	5. An alternative specification parameter test procedure is approved, and this procedure is not added when notifying of variations of Type IA.			
33.2.	Documentation			
33.2.1.	1. Amendments to the relevant part of the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format), including a description of the analytical method, a summary of the validation data and the reviewed impurity specification (if any).			
33.2.2.	2. Comparable validation results or, where appropriate, comparable analytical results which prove that the current test procedure is equivalent to the proposed one. This requirement shall not be applied if a new test procedure is being added.			
34	Variations to the excipients or reagent which may cause a risk of transmissible spongiform encephalopathy (TSE) risk (B.II.c.3.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) replacement of material which may cause a TSE risk, by a plant or synthetic material			
	1. excipients or reagents which are not used when manufacturing a biological or immunological active substance or a biological or immunological medicinal product	1	1	IA
	2. excipients or reagents which are used when manufacturing a biological or immunological active substance or a biological or immunological medicinal product		1, 2	IB
	b) variation or introduction of a material which may cause a TSE-risk, or replacement with another material which may cause a TSE-risk, to which a TSE conformity certificate does not apply			II
34.1.	Conditions			
34.1.1.	1. The release and storage period specifications for the excipient and finished product remain unchanged.			

34.2..	Documentation			
34.2.1.	1. Confirmation of the material manufacturer or the marketing authorisation holder (owner) that the material is plant or synthetic material.			
34.2.2.	2. A study on the equal worth of the material and the effect of the finished material on production and the efficacy on the finished product (for example, dissolution indicators).			
35.	Variations to synthesis or in extraction of excipients not listed in the pharmacopoeia (if described in the summary of the medicinal product characteristics (dossier)) (B.II.c.4.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) minor variations	1, 2	1, 2, 3, 4	IA
	b) changed specifications or variations to the physico-chemical properties of the excipient, which may affect the quality of the finished product			II
	c) the excipient is a biological or immunological substance			II
35.1.	Conditions			
35.1.1.	1. The synthesis route and specifications are identical, and there are no variations in the qualitative or quantitative composition of the impurities (except the composition of the remaining solvent, assuming that they are controlled in accordance with the conditions of VetICH) or in the physico-chemical properties.			
35.1.2.	2. Excipients are not included here.			
35.2.	Documentation			
35.2.1.	Amendments to the relevant part of the registration dossier (submitted in CTD format or in "Notice to Applicants" Volume 6B format).			
35.2.2.	2. Analytical data (in comparable table form) for at least two excipient batches (the minimum number of experimental batches), manufactured in accordance with the previous and proposed process.			
35.2.3.	3. Where necessary, comparable dissolution profile data for at least two batches of the finished product (the minimum number of experimental batches). Comparable degradation data may be submitted for herbal medicinal products.			
35.2.4.	4. Copies of the approved and proposed (if any) specifications of the excipient.			

2.2.4. Control on the Finished Product

36	Variations to the specification parameters and (or) limits of the finished product (B.II.c.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) determination of stricter specification limits	1, 2, 3, 4	1, 2	IA
	b) determination of stricter specification limits for medicinal products subject to official batch release	1, 2, 3, 4	1, 2	IA
	c) addition of a new specification parameter to the specification, together with the appropriate test method	1, 2, 5, 6, 7	1, 2, 3, 4, 5, 7	IA
	d) deletion of an insignificant specification parameter (for example, deletion of an outdated parameter)	1, 2	1, 2, 6	IA
	e) variations exceeding the approved specification limits			II

	f) deletion of a specification parameter which may significantly affect the general quality of the finished product			II
	g) the addition or replacement of the specification parameter (except biological or immunological medicinal products) for safety or quality reasons		1, 2, 3, 4, 5, 7	IB
36.1.	Conditions:			
36.1.1.	1. The variations are not the result of fulfilling any of the commitments from previous assessments to review specification limits (for example, they were not made during the procedure for authorisation application or a Type II variation procedure).			
36.1.2.	2. The variations have not been caused by unexpected events during manufacture, for example, a new, unqualified impurity or variations to the total limits of the impurities.			
36.1.3.	3. All the changes shall conform with the currently approved limits.			
36.1.4.	4. The test procedure remains unchanged or variations to the test procedure are minor.			
36.1.5.	5. The proposed test methods shall not apply to new non-standard techniques or to standard techniques used in a new way.			
36.1.6.	6. The proposed test method is not a biological, immunological or immunochemical method or a method where a biological reagent is intended to be used as a biologically active substance.			
36.1.7.	7. The variations shall not apply to genotoxic impurities.			
36.2.	Documentation:			
36.2.1.	1. Amendments to the relevant part of the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			
36.2.2.	2. A comparable table of the approved and proposed specifications.			
36.2.3.	3. Where appropriate, information regarding the proposed analytical methods and validation data.			
36.2.4.	4. Analytical data of all specification parameters for two finished product manufacturing batches (analytical data for three manufacturing batches of biological medicinal products, unless otherwise specified).			
36.2.5.	5. Where appropriate, comparable dissolution profile data of the finished product, which shall be determined for at least one experimental batch in accordance with the approved and proposed specification. Comparable degradation data may be submitted for herbal medicinal products.			
36.2.6.	6. Justification or a risk assessment which proves that the parameter is not significant.			
36.2.7.	7. Justification for the new specification parameter and limits.			
37	Variations to the finished product procedure (B.II.d.2.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) minor variations in the approved test procedure	1, 2, 3, 4	1,2	IA
	b) deletion of the test procedure if an alternative test procedure is already approved	4	1	IA
	c) replacement of a biological, immunological, immunochemical test method or method anticipating the use of a biological reagent			II
	d) other variations in the test procedure (inc. replacement or addition)		1, 2	IB
37.1.	Conditions:			
37.1.1.	1. The appropriate validation studies have been performed (in accordance with the relevant guidelines) and the results thereof prove that the updated test procedure is at least equivalent to the previous test procedure.			

39.1.3.	The appropriate stability studies in accordance with the VetICH regulations have been commenced with at least two experimental or industrial batches and the relevant stability indicators have been evaluated, and at least three months satisfactory stability data are at the disposal of the applicant during the implementation of the procedure. However, if the proposed packaging is more resistant than the current packaging, for example, thicker contour packaging, data acquired within three months regarding the stability shall not be required. These studies shall be completed and data (together with the proposed action) shall be provided without delay to the competent authorities if they do not conform with or may not conform with the specifications at the end of the approved storage period.			
39.2.	Documentation:			
39.2.1.	Amendments to the relevant part of the registration dossier, including the reviewed information on the product (submitted in CTD format or in "Notice to Applicants" Volume 6B format).			
39.2.2.	2. Data regarding the proposed packaging (comparable data about permeability, for example, the permeability of O ² , CO ₂).			
39.2.3.	3. Where necessary, it shall be proved that there is no cross-contamination of the content and the packaging material (for example, the diffusion of material components into the contents and the loss of product components in closed packaging), and a confirmation shall be submitted that the material complies with the relevant requirements of a pharmacopoeia or regulatory enactments regarding plastic materials and objects coming into contact with food.			
39.2.4.	4. The confirmation that the necessary stability studies have been commenced in accordance with the conditions of the VetICH (indicating the relevant batch numbers) and that at the time of the implementation of the procedure the applicant had at the disposal thereof the minimum satisfactory data on stability, and the data available did not indicate any problem. The confirmation shall also be given that these studies will be completed and that the data (together with the proposed action) will be provided without delay to the Food and Veterinary Service if the data do not conform with or may not conform with the specifications at the end of the approved storage period.			
39.2.5.	5. The results of stability studies performed on at least two experimental or industrial batches in accordance with the conditions of the VetICH regarding the relevant stability indices incorporating a period of at least three months and the confirmation that these studies shall be completed and the data (together with the proposed action) submitted without delay to the competent authorities, if the data, at the end of the approved storage period do not conform with or may not conform with the specifications.			
39.2.6.	6. A comparable table of the approved and proposed specifications of the immediate packaging.			
39.2.7.	7. Samples of the proposed packaging or seal.			
40.	Variations to the specification parameters of the immediate packaging of the finished product and (or) limits (B.II.e.2.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) determination of stricter specification limits	1, 2, 3, 4	1, 2	IA
	b) addition of a new specification parameter to the specification, together with the appropriate test method	1, 2, 5	1, 2, 3, 4, 6	IA
	c) deletion of insignificant specification parameters (for example, deletion of an outdated parameter)	1, 2	1, 2, 5	IA
	d) addition or replacement of the specification parameter for safety or quality reasons.		1, 2, 3, 4, 6	IB
40.1.	Conditions:			
40.1.1.	The variations have not arisen while fulfilling any of the commitments from previous assessments to review specification limits (for example, they were not made during the procedure for authorisation application or a Type II variation procedure).			
40.1.2.	2. The variations are not the result of unexpected events during the manufacture.			
40.1.3.	All the variations shall conform with the currently approved limits.			

40.1.4.	4. The test procedure remains unchanged or variations to the test procedure are minor.			
40.1.5.	5. The proposed test methods shall not apply to new non-standard techniques or standard techniques used in a new way.			
40.2.	Documentation:			
40.2.1.	1. The relevant amendments to the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			
40.2.2.	2. A comparable table of the approved and proposed specifications.			
40.2.3.	3. Information regarding all proposed analytical methods and validation data, if necessary.			
40.2.4.	4. Analysis data for two batches of immediate packaging for all the specification parameters.			
40.2.5.	5. Justification and (or) a risk assessment which proves that the parameter is not significant.			
40.2.6.	6. Justification for the new specification parameter and limits.			
41.	Variations to the immediate packaging test procedure of the finished product (B.II.e.3.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) minor variations in the approved test procedure	1, 2, 3	1, 2	IA
	b) other variations in the test procedure (inc. replacement or addition)	1, 3, 4	1, 2	IA
	c) deletion of the test procedure if an alternative test procedure is already approved	5	1	IA
41.1.	Conditions:			
41.1.1.	1. The appropriate validation studies have been performed (in accordance with the relevant guidelines) and the results thereof prove that the updated test procedure is at least equivalent to the previous test procedure.			
41.1.2.	2. The method of analysis shall remain the same (for example, variations in column length or temperature are permitted, but not a different type of column or method).			
41.1.3.	New test methods shall not apply to new non-standard techniques or to standard techniques used in a new way.			
41.1.4.	4. The active substance or finished product is not of biological or immunological origin.			
41.1.5.	5. An alternative specification parameter test procedure is approved, and this procedure is not added when notifying of variations of Type IA.			
41.2.	Documentation			
41.2.1.	1. The relevant amendments to the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format), including a description of the analytical methods and a summary of the validation data.			
41.2.2.	2. Comparable validation results or comparable analytical results which prove that the current test procedure is equivalent to the proposed one. This requirement shall not be applied if a new test procedure is being added.			
42.	Variations to the shape or size of the container or seal (immediate packaging) (B.II.e.4.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) non-sterile pharmaceutical forms	1, 2, 3	1, 2, 4	IA
	b) the variations in shape or size affect the fundamental parts of the packaging material, which may significantly affect the delivery, use, safety or stability of the finished product			II
	c) sterile pharmaceutical forms	5	1	IA

42.1.	Conditions			
42.1.1.	1. No change in qualitative or quantitative composition of the container.			
42.1.2.	2. The variations do not affect the fundamental parts of the packaging material, which affects the delivery, use, safety or stability of the finished product.			
42.1.3.	3. If the variations are related to the head space or a change in the surface/volume ratio, stability studies in accordance with the relevant guidelines have been commenced with at least two experimental (in respect of biological medicinal products – three) or industrial batches and at least three months (in respect of biological or immunological medicinal products – six months) stability data are at the disposal of the applicant. A confirmation is given that these studies shall be completed and that the data (together with the proposed action) shall be provided without delay to the Food and Veterinary Service, if the data do not conform or may not conform with the specifications at the end of the approved storage period.			
42.2.	Documentation			
42.2.1.	The relevant amendments to the registration dossier, including the reviewed information on the product (submitted in CTD format or in Notice to Applicants Volume 6B format), including a description of the container or seal material, a detailed drawing and composition and the reviewed information regarding the medicinal product, if necessary.			
42.2.2.	2. Where appropriate, samples of the new container and (or) seal.			
42.2.3.	3. Repeat validation studies are performed on completely sterile products. Where appropriate, the batch numbers used in the repeat validation studies shall be indicated.			
42.2.4.	4. If the variations are related to the head space or a change in the surface/volume ratio, a confirmation that the necessary stability studies in accordance with the VetICH provisions have been commenced (indicating the relevant batch numbers) and that where appropriate during the period of the implementation of the notification of variations of Type IA and the submission of the notification of variations of Type IB at least three months minimum stability data were at the disposal of the applicant, and the available data did not indicate any problem. Assurance shall be provided that these studies shall be completed and that the data (together with the proposed action) shall be provided without delay to the Food and Veterinary Service if they do not conform with or may not conform with the specifications at the end of the approved storage period.			
43.	Variations to the packaging size of the finished product (B.II.e.5.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) variations in the number of units (for example, tablets, ampoules etc) in one packaging			
	1. variations related to the currently approved packaging size	1, 2	1, 3	IA
	2. variations related to the currently non-approved packaging size		1, 2, 3	IB
	b) deletion of packaging size or sizes	3	1, 2	IA
	c) variations to the fill-weight and (or) fill volume of sterile, multi-dose (or single dose, partial administration) parenteral medicinal products and biological or immunological multi-dose parenteral medicinal products			II
	d) variations to the fill-weight and (or) fill volume of non-parenteral multi-dose (or single dose, partial administration) products		1, 2, 3	IB
43.1.	Conditions:			
43.1.	1. The proposed packaging size shall be consistent with the dosage and treatment duration of the medicinal product as approved in the summary of the medicinal product characteristics.			
43.1.	2. The immediate packaging material remains unchanged.			

43.1.	3. The remaining design of the product shall conform with the instructions referred to in the summary of the medicinal product characteristics regarding the dosage of the medicinal product and the duration of treatment.			
43.2.	Documentation			
43.2.	The relevant amendments to the registration dossier, including the reviewed information on the medicinal product, where appropriate (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			
43.2.	2. The justification for the use of the proposed and approved packaging size, which proves that the proposed and approved packaging size conforms with the dosage and duration of treatment indicated in the summary of the medicinal product characteristics.			
43.2.	3. The confirmation that stability studies shall be performed for products whose stability parameters may be affected. Data (together with the proposed action) shall be submitted, if they do not conform with the specifications.			
43.3.	Note. Where an application for variations is submitted in relation to Sub-paragraphs 43 c) and d) of this Annex, if the variations affect the strength of the medicinal product, an additional application for ascription shall be submitted.			
44.	Variations related to part of the (primary) packaging material not in contact with the finished product (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)) (B.II.e.6.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) variations affecting information about the product	1	1	IA
	b) variations not affecting information about the product	1	1	IA
44.1.	Conditions			
44.1.1.	1. Variations do not affect components of the packaging material, which affects the delivery, use, safety or stability of the finished product.			
44.2.	Documentation			
44.2.1.	The relevant amendments to the registration dossier, including the reviewed information on the medicinal product, where appropriate (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			
45.	Variations relating to the supplier of components or devices of the packaging (if referred to in the registration dossier) (B.II.e.7.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) deletion of the supplier	1	1	IA
	b) replacement or addition of the supplier	1, 2, 3, 4	1, 2	IA
	c) variations relating to the suppliers of spacer devices for metered dose inhalers			II
45.1.	Conditions:			
45.1.1.	1. No deletion of packaging component or device.			
45.1.2.	2. The qualitative and quantitative composition of the packaging components or device remains unchanged.			
45.1.3.	3. The specification and quality control method is at least equivalent.			
45.1.4.	4. The sterilisation method and conditions remain unchanged.			
45.2.	Documentation:			
45.2.1.	1. The relevant amendments to the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			

45.2.2.	2. A comparable table of the approved and proposed specifications, if necessary.
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2.2.6. Stability

46.	Variations to the storage period or storage conditions of the finished product (B.II.f.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) reduction of the storage period of the finished product			
	1. packaged for sale	1	1, 2, 3	IA
	2. after opening	1	1, 2, 3	IA
	3. after dilution or reconstitution	1	1, 2, 3	IA
	b) extension of the storage period of the finished product			
	1. packaged for sale (based on real time data)		1, 2, 3	IB
	2. after opening (based on real time data)		1, 2, 3	IB
	3. after dilution or reconstitution (based on real time data)		1, 2, 3	IB
	4. extension of the storage period based on the extrapolation of the stability data non-compliant with the ICH guidelines (shall not apply to biological or immunological medicinal products)			II
	5. extension of the storage period of biological or immunological medicinal products in accordance with the approved stability protocol		1, 2, 3	IB
	c) variations to the storage conditions of biological medicinal products, if stability studies are not performed in accordance with the approved stability protocol			II
	d) storage conditions of the finished product or diluted or reconstituted product		1, 2, 3	IB
46.1.	Conditions:			
46.1.1.	1. The variations are not the result of unexpected events during manufacture or because of stability concerns.			
46.2.	Documentation:			
46.2.1.	1. The relevant amendments to the registration dossier (submitted in CTD format or in "Notice to Applicants" Volume 6B format). They shall incorporate the results obtained in the appropriate real-time stability studies (which include the full storage period). Studies are performed on at least two experimental batches ⁽¹⁾ of the finished product (in accordance with the relevant guidelines on stability), in which the product is appropriately packed in the approved packaging material and (or) after the initial opening or reconstitution. The appropriate results of microbiological tests shall be incorporated, if necessary. ⁽¹⁾ Experimental batches may be used when undertaking to inspect the storage period of the manufactured batch.			
46.2.	2. Information reviewed regarding the medicinal product.			
46.2.	3. Copy of the approved specification for the storage period of the finished product and, where appropriate, a copy of the specification after dilution or reconstitution or initial opening.			

2.2.7. Design Space

47.	Specification of a new design space or the extension of the approved design space for the finished product, except biological medicinal products (B.II.g.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) for the preparation of one or several units in the manufacturing process of the finished product including related investigations during manufacture and (or) test procedures		1, 2, 3	II
	b) for the test procedures of the excipient or intermediate product and (or) the finished product		1, 2, 3	II
47.1.	Documentation:			
47.1.1.	1. Results of the design studies of the products and processes (including, where appropriate, the risk assessment and the studies of several parameters), which prove that a systematic mechanical understanding of the material values and process parameters in the critical quality indicators of the finished product has been acquired.			
47.1.2.	2. A description of the design space in tabular form including the variable (in relevant cases the parameters of the material values and the process) and the suggested range thereof.			
47.1.3.	3. The relevant amendments to the registration dossier (submitted in CTD format or in "Notice to Applicants" Volume 6B format).			
48.	Implementation of a management protocol of the variations performed after approval, related to the finished product (B.II.g.2.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
			1, 2	II
48.1.	Documentation:			
48.1.1.	1.. A detailed description of the proposed variations.			
48.1.2.	2. A management protocol of the variations, related to the finished product.			
49.	B.II.g.3. Deletion of the management protocol of the approved variations related to the finished product	Conditions to be fulfilled	Documents to be appended	Type of procedure
		1	1	IA
49.1.	Conditions:			
49.1.1.	1. The deletion of the management protocol for the approved variations related to the finished product is not the result of unexpected events or specification concerns during the period of making the variations described in the protocol.			
49.2.	Documentation:			
49.2.2.	1. Grounds for the proposed deletion.			

2.3. CEP, TSE, Monographs (B.III)

50.	Submission of a new or updated European Pharmacopoeia Certificate of Suitability (B.III.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	1. for the active substance; 2. for the starting material, reagent, intermediate product used in the manufacturing process of the active substance; 3. for the excipient			
	a) Submission of a European Pharmacopoeia Certificate of Suitability for the relevant monograph of the European Pharmacopoeia			
	1. the new certificate shall be submitted by the previously approved manufacturer	1, 2, 3, 4, 5, 8	1, 2, 3, 4, 5	IA
	2. the updated certificate shall be submitted by the previously approved manufacturer	1, 2, 3, 4, 8	1, 2, 3, 4, 5	II
	3. the new certificate shall be submitted by the new manufacturer (replacement or addition)	1, 2, 3, 4, 5, 8	1, 2, 3, 4, 5	IA
	b) a European Pharmacopoeia TSE Suitability Certificate for the active substance, starting material, reagent, intermediate product or excipient			
	1. the new or previously approved manufacturer shall submit a new certificate for the active substance	3, 6	1, 2, 3, 4, 5	IA
	2. the new or previously approved manufacturer shall submit a new certificate for the starting material, reagent, intermediate product or excipient	3, 6	1, 2, 3, 4, 5	IA
	3. the previously approved manufacturer shall submit the updated certificate	7	1, 2, 3, 4, 5	IA
50.1.	Conditions:			
50.1.1.	1. The period of validity and release specifications of the finished product remain unchanged.			
50.1.2.	2. Additional specifications (in addition to the European Pharmacopoeia) for impurities (except in relation to remaining solvents, on condition that they conform with the VetICH) and the specific requirements of the product (for example, particle size, polymorph form) remain unchanged (except stricter limits).			
50.1.3.	3. In the manufacturing process of the active substance, starting material, intermediate product and reagent the materials of human or animal origin, for which an assessment of viral safety data is required, are not used.			
50.1.4.	4. If a deadline for the repeat test is not included in the European Pharmacopoeia Certificate of Suitability for the active substance, or if data are not provided which certify the repeat test deadline, the active substance shall be tested directly before use.			
50.1.5.	5. The active substance, starting material, reagent, intermediate product or excipient is not sterile.			
50.1.6.	6. The substance is not included in a veterinary medicinal product intended for administration to animal species susceptible to TSE.			
50.1.7.	7. The material origin remains unchanged.			

50.1.8.	8. If the active substance is of plant origin, the manufacturing process, physical form, extraction solvent and the drugs and extract ratio remain unchanged.			
50.2.	Documentation:			
50.2.1.	1. A copy of the current (updated) European Pharmacopoeia certificate.			
50.2.2.	2. When adding a production unit, the “existing” and “proposed” manufacturers shall be clearly indicated in the application form for variations.			
50.2.3.	3. Amendments to the relevant part of the dossier (submitted in CTD format).			
50.2.4.	4. Where appropriate, the document in which information is provided regarding all the materials subject to the “Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products”, including the materials used in the manufacture of the active substance or excipient. The following information shall be indicated regarding all the materials: name of the manufacturer, animal species and tissues from which material is derived, the country of origin of the donor animal and the use thereof.			
50.2.5.	5. For the active substance: the confirmations of all the qualified persons (QP) specified by the marketing authorisation holder (owner) referred to in the application, if the active substance is used as a starting material and the confirmations of all the QP of the marketing authorisation holder referred to in the application which are responsible for batch release. It shall be indicated in the confirmations that the manufacturer of the active substance referred to in the application operates in accordance with the guidelines for good manufacturing practice of starting materials. One confirmation may be submitted in accordance with Sub-paragraph 27.3 of this Annex. The confirmation of QP shall also be necessary if intermediate products are manufactured, while for the updates to active substances and certificates, the assurance of QP shall only be necessary where, in comparison with the previous version of the registered certificate, such variations have taken place which affect the production units referred to.			
51.	Variations which shall be made in order to comply with the European Pharmacopoeia or with the national pharmacopoeia of a Member State (B.III.2.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) variations to a specification(s) of a substance which was not included in the pharmacopoeia previously that shall be made in order to comply with the European Pharmacopoeia or with the national pharmacopoeia of a Member State			
	1. active substance	1, 2, 3, 4, 5	1, 2, 3, 4, 5	IA
	2. excipient or starting material of the active substance	1, 2, 4	1, 2, 3, 4, 5	IA
	b) variations to be made in order to comply with an update of the relevant monograph of the European Pharmacopoeia or national pharmacopoeia of a Member State	1, 2, 4, 5	1, 2, 3, 4	IA
	c) variations to the specifications contained in the pharmacopoeia of a Member State in order to comply with the European Pharmacopoeia	1, 4, 5	1, 2, 3, 4	IA
51.1.	Conditions:			
51.1.	1. The variations shall be made exclusively to comply with the pharmacopoeia.			
51.1.	2. Unchanged specifications (additional to the pharmacopoeia) for product specific properties (for example, particle size, polymorphic form or biotests, summary readings).			
51.1.	3. No significant impurities in the qualitative and quantitative profile, unless stricter specification limits are determined.			
51.1.	4. Additional validation of the proposed or varied pharmacopoeial method shall not be necessary.			
51.1.	5. If the active substance is of plant origin, the manufacturing process, physical form, extraction			

	solvent and the drugs and extract ratio remain unchanged.
51.2.	Documentation:
51.2.1.	1. Amendments to the relevant part of the registration dossier (submitted in CTD format or in Notice to Applicants Volume 6B format).
51.2.2.	2. A comparable table of the approved and proposed specifications.
51.2.3.	3. Analytical data for two manufacturing batches of the relevant substance on all the tests intended for the proposed specification.
51.2.4.	4. Data with which the suitability of the monograph is proved for ensuring control of the substance, including a comparison of the potential impurity and monographical notes on translucency.
51.2.5.	5. Analytical data (in comparable table form) of two manufacturing batches of the finished product containing a substance corresponding to the current and proposed specification, as well as the comparable dissolution profile data where appropriate, for at least one experimental batch of the finished product. Comparable degradation data may be submitted for herbal medicinal products.
51.3.	Note: An updated monograph of the European Pharmacopoeia need not be notified if the conformity of the updated monograph is achieved within six months following the publication thereof and a reference to "Current wording" is in the dossier of the registered medicinal product.

2.4. Medical Devices (B.IV)

52.	Variations to the measuring device or administration devices (B.IV.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) addition or replacement of a device which is not an integral part of the immediate packaging			
	1. with CE marking,	1, 2, 3	1, 2, 4	IA
	2. without CE marking		1, 3, 4	IB
	3. spacer devices for metered dose inhalers			II
	b) deletion of a device	4, 5	1, 5	IA
	c) addition or replacement of a device which is an integral part of the immediate packaging (if a new pharmaceutical form is the result of variations, an additional application for ascription shall be submitted).			II
52.1.	Conditions:			
52.1.1.	1. The proposed measuring device measures the dose of the medicinal product precisely in conformity with the approved posology (approved doses of the medicinal product) and the results of the relevant studies are available.			
52.1.2.	2. The proposed device is compatible with the medicinal product.			
52.1.3.	3. Significant amendments need not be made to the information on the medicinal product as a result of the variations.			
52.1.4.	4. The medicinal product may be administered accurately.			
52.1.5.	5. The device is not essential for the safety of the person administering the medicinal product to an animal.			
52.2.	Documentation			
52.2.1.	1. Amendments to the relevant part of the registration dossier (submitted in CTD format or in "Notice to Applicants" Volume 6B format), including a material description of the device, a detailed drawing, the composition and, where necessary, information on the supplier and reviewed information on the medicinal product.			

52.2.2.	2. Assurance of the CE marking.			
52.2.3.	3. Data with which the correctness, accuracy and compatability of the device is demonstrated.			
52.2.4.	4. If necessary, a sample of the new device.			
52.2.5.	5. Grounds for the deletion of the device.			
53.	Variations to the specification parameters of the measuring device or administration device and (or) limits (B.IV.2.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) determination of stricter specification limits	1, 2, 3, 4	1, 2	IA
	b) addition of a new specification parameter to a specification, together with the appropriate test method	1, 2, 5	1, 2, 3, 4, 6	IA
	c) extension of the approved specification limits, which may significantly affect the overall quality of the device			II
	d) deletion of a specification parameter which may significantly affect the overall quality of the device			II
	e) addition of a specification parameter for safety or quality reasons		1, 2, 3, 4, 6	IB
	f) deletion of an insignificant specification parameter (for example, deletion of an outdated parameter)		1, 2, 5	IA
53.1.	Conditions:			
53.1.	1. The variations are not the result of fulfilling any commitment from previous assessments to review specification limits (for example, they were not made during the procedure for authorisation application or a Type II variation procedure).			
53.1.	2. The variations are not the result of unexpected events during manufacture.			
53.1.	3. The variations conform to the approved limits.			
53.1.	4. The test procededure remains unchanged.			
53.1.	5. The proposed test methods do not apply to new non-standard techniques or standard techniques used in a new way.			
53.2.	Documentation:			
53.2.	1. Amendments to the relevant part of the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			
53.2.	2. A comparable table of the approved and proposed specifications.			
53.2.	3. Information regarding the proposed analytical methods and a summary of validation data.			
53.2.	4. Analytical data for two manufacturing batches of all the tests intended in the proposed specification.			
53.2.	5. Justification and (or) a risk assessment which proves that the parameter is not significant.			
53.2.	6. Justification for the proposed specification parameter and limits.			

54.	Variations to the measuring device or administration device (B.IV.3.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) minor variations in the approved test procedure	1, 2	1, 2	IA
	b) other variations in the test procedure (including replacement or addition)	1, 3	1, 2	IA
	c) deletion of a test procedure if an alternative test procedure is already approved	4	1	IA
54.1.	Conditions:			
54.1.	1. The approving validation studies have been performed (in accordance with the relevant guidelines) and the results thereof prove that the updated test procedure is at least equivalent to the previous test procedure.			
54.1.	2. The analytical method remains unchanged.			
54.1.	3. The proposed test method shall not apply to new non-standard techniques or standard techniques used in a new way.			
54.1.	4. An alternative specification parameter test procedure is approved, and this procedure is not added to the variations of Type IA procedure.			
54.2.	Documentation:			
54.2.1.	1. The relevant amendments to the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format), including the analytical methodology and a summary of the validation data.			
54.2.2.	2. Comparable validation results or, where appropriate, comparable analytical results which prove that the current test procedure is equivalent to the proposed one.			

2.5. Variations to the Registration Dossier as a Result of Other Regulatory Procedures (B.V)

2.5.1. Vaccine Antigen Master File (VAMF)

55.	Inclusion of a new, updated or amended Vaccine Antigen Master File (VAMF) into the registration dossier (VAMF 2.step procedure) (B.V.a.2.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) first inclusion of a new VAMF, which affects the finished product properties			II
	b) inclusion of an updated or amended VAMF, if the variations affect the finished product properties		1, 2, 3, 4	IB
	c) inclusion of an updated or amended VAMF, if the variations do not affect the finished product properties	1	1, 2, 3, 4	IA
55.1.	Conditions:			
55.1.	1. A certificate has been issued for the updated or amended VAMF for the compliance with regulatory enactments on the procedures for the authorisation of medicinal products.			
55.2.	Documentation			
55.2.	1. A confirmation that the VAMF certificate and assessment report apply completely to the registered medicinal products. The VAMF holder has submitted a VAMF certificate, assessment report and VAMF dossier (if the marketing authorisation holder (owner) is not the VAMF holder). The VAMF certificate and assessment report replace the previous VAMF documents for this marketing authorisation.			

55.2.	2. VAMF certificate and assessment report.
55.2.	3. The expert opinion in which all the certified VAMF variations implemented are emphasised and the potential effect thereof on the finished product is evaluated, including a specific risk assessment performed on the product.
55.2.	4. The “current” and “proposed” VAMF European Medicines Agency certificate (code number) included in the registration dossier shall be clearly indicated in the application for variations. Where appropriate, all the other VAMF related to the medicinal product shall be clearly indicated in the application form for variations, even if the application does not apply thereto.

2.5.2. Management Protocol for Variations

56.	Updating of the quality dossier, in order to perform variations requested by the Food and Veterinary Service following the evaluation of the management protocol for variations (B.V.c.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) in order to perform variations, additional justification data need not be submitted	1	1, 2, 4	IA
	b) in order to perform variations, additional justification data shall be submitted		1, 2, 3, 4	IB
	c) variations apply to biological or immunological medicinal products		1, 2, 3, 4, 5	IB
56.1.	Conditions:			
56.1.1.	1. Variations are performed in accordance with the approved management protocol for variations in which it is specified that following the performance of variations, they shall be notified without delay.			
56.2.	Documentation:			
56.2.1.	1. Reference to the approved management protocol for variations.			
56.2.2.	2. A confirmation that the variations are performed in accordance with the approved management procedures and the study results conform with the acceptance criteria specified in the protocol. Where appropriate, a confirmation shall be submitted that the biological or immunological medicinal products do not require a comparable assessment.			
56.2.3.	3. Results for studies performed in accordance with the approved management protocol for variations.			
56.2.4.	4. Amendments to the relevant part of the registration dossier (submitted in CTD format or in “Notice to Applicants” Volume 6B format).			
56.2.5.	5. Copies of the approved specifications of the active substance or finished product.			

3. Safety, Efficacy and Pharmacovigilance Variations (C)

3.1. Veterinary Medicinal Products (C 1)

57.	Variations to the summary of the product characteristics, labelling and package leaflet of generic medicinal products, hybrid medicinal products, and medicinal products equivalent to biological medicinal products, based on the same variation assessment performed on the reference medicinal products (C.I.2.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) performance of such variations in relation to which the marketing authorisation holder (owner) shall not submit new additional data		1, 2	IB
	b) performance of such variations which shall be justified with new data submitted by the marketing authorisation holder (owner) (for example, comparability)			II
57.1.	Documentation			
57.1.1.	1. The request of the competent authority of a Member State shall be appended to the letter accompanying the application for variations.			
57.1.2.	2. Information reviewed regarding the medicinal product.			
58.	Performance of variations requested by the Food and Veterinary Service, based on an urgent limit related to safety, the periodically updated safety report of the relevant class labelling, risk management plan (C.I.3.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) performance of accepted formulation variations in relation to which the marketing authorisation holder (owner) shall not submit new additional data		1, 2	IB
	b) performance of such variations which shall be justified with new data submitted by the marketing authorisation holder (owner)			II
	Documentation:			
	1. The request of the competent authority of a Member State shall be appended to the letter accompanying the application for variations.			
	2. Information reviewed regarding the medicinal product.			
59.	Variations related to significant amendments to the summary of the medicinal product characteristics, in particular, in order to take into account new qualitative, pre-clinical, clinical or pharmacovigilance data (C.I.4.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
				II

60	C.I.6. Variations to therapeutic indications	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) addition of a new therapeutic indication or amendments to the approved indication			II
	b) deletion of a therapeutic indication			IB
61.	C.I.7. Deletion	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) Pharmaceutical forms		1, 2	IB
	b) Strength of the medicinal product		1, 2	IB
61.1.	Documentation			
61.1.1.	1. A confirmation that the remaining design of the medicinal product shall conform with the instructions referred to in the summary of the medicinal product characteristics, regarding the dosage of the medicinal product and the duration of treatment.			
61.1.	2. Information reviewed regarding the medicinal product.			
61.2.	Note: If a marketing authorisation is issued for the relevant pharmaceutical form or strength, which does not apply to the marketing authorisations for other pharmaceutical forms or strengths, the deletion of the previous pharmaceutical form or strength shall not be regarded as variations but as the revocation of the marketing authorisation.			
62.	C.I.8. Introduction of a new pharmacovigilance system	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) system which the Food and Veterinary Service has not evaluated in respect of the product of another marketing authorisation holder (owner)			II
	b) system which the Food and Veterinary Service has evaluated in respect of the product(*) of another marketing authorisation holder (owner)		1	B
62.1.	Documentation			
62.1.1.	1. Detailed description of the new pharmacovigilance system (DDPS)			
62.2.	(*) (Note: The variations apply to the situation when the conformity of the previously evaluated pharmacovigilance system with the relevant new marketing authorisation shall be evaluated (for example, the handover period for the marketing authorisation).			
63.	Variations to the approved pharmacovigilance system described in the detailed description of the pharmacovigilance system (DDPS) (C.I.9.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) variations relating to the qualified person responsible for pharmacovigilance	1	1	IA
	b) variations to the contact information of the qualified person responsible for pharmacovigilance	1	2	IA
	c) variations to the safety procedures to be performed by the qualified person responsible for pharmacovigilance	1	2	IA

	d) variations to the safety database (for example, development of a new safety database, including the handover of the safety database and (or) analysis and provision of information in the new system)	1, 2, 3	2	IA
	e) variations to the basic provisions of contracts with other persons or organisations involved in the fulfilment of pharmacovigilance commitments and referred to in the approved DDPS, in particular, if sub-contracts are entered into in connection with the electronic notification of side-effects caused by the use of a specific medicinal product, the main databases, signal definition or periodically updated safety reports	1	2	IA
	f) deletion of the topics to which written procedures apply, which describe the safety of the pharmacovigilance system	1	2	IA
	g) variations related to the place where pharmacovigilance operations are performed	1	2	IA
	h) other variations not affecting the operation of DDPS (for example, variations relating to the main storage and archival locations, administrative variations, the updating of acronyms, variations to the names allocated to functions or procedures)	1	2	IA
	i) DDPS variations to take into account the same DDPS variations in respect of other medicinal products of the same marketing authorisation holder (owner).	4	2, 3	IA
63.1.	Conditions:			
63.1.1.	1. The pharmacovigilance system remains unchanged.			
63.1.2.	2. The database system is approved (validated).			
63.1.3.	3. The handover of data from another database system is approved (validated).			
63.1.4.	4. Equivalent variations shall be made to the DDPS for all the medicinal products of one marketing authorisation holder (owner) (the final DDPS version shall not be different).			
63.2.	Documentation:			
63.2.1.	1. DDPS new version, which includes: a) the new curriculum vitae of the qualified persons responsible for pharmacovigilance, b) confirmation that the qualified person responsible for pharmacovigilance is registered in the <i>EudraVigilance</i> database. c) a new notification signed by the marketing authorisation holder and person responsible for pharmacovigilance, regarding the availability of these persons and the methods for the notification of side-effects, and other variations arising shall be reflected, such as, for example, the structural layout.			
63.2.2.	2. The DDPS new version and (or) the new version of the product-specific addition. In respect of Sub-paragraph 63, if the contact information of the qualified person was not shown originally in the DDPS, a reviewed version of the DDPS need not be submitted, and an application form or notification will be sufficient.			
63.2.3.	3. Reference to the application or procedure and medicinal products, in respect of which the variations have been approved.			

3.2. Veterinary Medicinal Products – Special Variations (C II)

64.	Addition of the target species from which food products of animal origin are not acquired (C.II.1.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
				II
65.	Deletion of the target species of food-producing animals or the target species from which food products of animal origin are not acquired (C.II.2.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
	a) deletion for safety reasons			II
	b) deletion not related to safety reasons		1, 2	IB
65.1.	Documentation			
65.1.1.	1. Justification for the deletion of the target species.			
65.1.2.	2. Information reviewed regarding the medicinal product.			
66.	Variations to the withdrawal period of the veterinary medicinal product (C.II.3.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
				II
67.	Variations related to replacement or addition of a vaccine against avian influenza, foot-and-mouth disease or infectious catarrhal fever, serotype, strain, antigen or serotype combinations, strains or antigens (C.II.4.)	Conditions to be fulfilled	Documents to be appended	Type of procedure
				II
68.	C.II.5. The replacement of a strain for a vaccine against equine influenza	Conditions to be fulfilled	Documents to be appended	Type of procedure
				II
69.	C.II.6. Variations to the labelling or package leaflet, not connected to the summary of the veterinary medicinal product characteristics	Conditions to be fulfilled	Documents to be appended	Type of procedure
				IB

4. Vaccine Antigen Master File (D)

70.	Variations to the name and (or) address of the VAMF certificate holder	Conditions to be fulfilled	Documents to be appended	Type of procedure
		1	1	IA
70.1.	Conditions:			
70.1.1.	1. The VAMF holder (owner) remains the same person.			
70.2.	Documentation:			
70.2.1.	A copy of the merchant's marketing authorisation in which the new name or new address is shown.			

Notes: if one or more of the conditions referred to in this Annex have not been fulfilled in respect of minor variations of Type IA, the relevant variations may be submitted as variations of Type IB, if the variations are not classified as variations of Type II.