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ANNEX

ANNEX

to the

COMMISSION DELEGATED REGULATION (EU) .../...

amending Annex II to Regulation (EC) No 2019/6 of the European Parliament and of the Council

‘ANNEX II
REQUIREMENTS REFERRED TO IN ARTICLE 8(1), POINT (B)

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SECTION I
GENERAL PRINCIPLES AND REQUIREMENTS

I.1. General principles

I.1.1. The documentation accompanying an application for a marketing authorisation pursuant to Articles 8, and 18 to 25 shall be presented in accordance with the requirements set out in this Annex and shall take into account the guidance documents published by the Commission and the requirements for electronic format published by the Agency.

I.1.2. In assembling the dossier for application for a marketing authorisation, applicants shall also take into account the most up-to-date veterinary medicinal knowledge and the scientific guidelines relating to the quality, safety and efficacy of veterinary medicinal products published by the Agency.

I.1.3. For veterinary medicinal products, all relevant monographs of the European Pharmacopoeia, including general monographs and the general chapters, are applicable for the appropriate parts of the dossier.

I.1.4. The manufacturing processes for the active substance(s) and finished product shall comply with Good Manufacturing Practice (GMP).

I.1.5. All information which is relevant to the evaluation of the veterinary medicinal product concerned shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details related to any incomplete or abandoned study or trial relating to the veterinary medicinal product shall be given.

I.1.6. Pharmacological, toxicological, residue and pre-clinical studies shall be carried out in conformity with the provisions related to Good Laboratory Practice (GLP) laid down in Directives 2004/10/EC[1] and 2004/9/EC of the European Parliament and of the Council[2].

I.1.7. All experiments on animals shall be conducted taking into account the principles laid down in Directive 2010/63/EU, notwithstanding the place of conduct of the experiments.

I.1.8. The environmental risk assessment connected with the release of veterinary medicinal products containing or consisting of Genetically Modified Organisms (GMOs) within the meaning of Article 2 of Directive 2001/18/EC shall be provided in the dossier as a separate document. The information shall be presented in accordance with the provisions of Directive 2001/18/EC, taking into account guidance published by the Commission.

I.1.9. The applicant shall confirm in Part 1 of the dossier for an application for marketing authorisation that all submitted data relevant to the quality, safety and efficacy of the veterinary medicinal product, including data publicly available, are not subject to protection of technical documentation.

I.2. Dossier composition requirements

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1 Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (OJ L 50, 20.2.2004, p. 44).

2 Directive 2004/9/EC of the European Parliament and of the Council of 11 February 2004 on the inspection and verification of good laboratory practice (GLP)(OJ L 50, 20.2.2004, p. 28).

Any dossier for an application for marketing authorisation for a veterinary medicinal product shall consist of the following parts:

I.2.1. Part 1: Summary of the dossier

Part 1 shall include administrative information as outlined in Annex I, as follows:

(a) Part 1A: points 1 to 4 and 6.1 to 6.4;

(b) Part 1B: point 5;

(c) Part 1C: point 6.5.

With regard to Part 1B, point 5.1, in connection to Article 35(1), point (l), an application proposing classification of a veterinary medicinal product as "not subject to veterinary prescription" shall include a critical review of the product characteristics in order to justify the suitability of such classification taking into consideration target and non-target animal safety, public health as well as environmental safety, as outlined in the criteria given in Article 34 (3), points (a) to (g).

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Each critical expert report shall be prepared with regard to the state of scientific knowledge at the time of submission of the application. It shall contain an evaluation of the various tests and trials which constitute the marketing authorisation dossier, and shall address all aspects relevant to the assessment of the quality, safety and efficacy of the veterinary medicinal product. It shall give detailed results of the tests and trials submitted and precise bibliographic references. Copies of the bibliographic references cited shall be provided.

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

The critical expert reports and the appendices shall contain precise and clear cross-references to the information contained in the technical documentation.

Where Part 2 is presented using the format of the Common Technical Document (CTD), the quality overall summary (QOS) shall be used for the critical expert report on quality.

For Parts 3 and 4 the critical expert report shall also include a tabulated summary of all technical documentation and relevant data submitted.

I.2.2. Part 2: Quality documentation (physicochemical, biological or microbiological information)

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

(2) All monographs, including specific monographs, general monographs and general chapters of the European Pharmacopoeia are applicable. For immunological veterinary medicinal products, all monographs, including specific monographs, general monographs and general chapters of the European Pharmacopoeia are applicable, unless otherwise justified. In the absence of a European Pharmacopoeia monograph, the monograph of a Member State pharmacopoeia may be applied. In

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

(3) If tests other than those mentioned in the pharmacopoeia are used, the use of such tests shall be justified by providing proof that the materials, if tested in accordance with the pharmacopoeia, would meet the quality requirements of the relevant pharmacopoeial monograph.

(4) All test procedures for analysis and quality control shall take account of established guidance and requirements. The results of the validation studies shall be provided. All the test procedure(s) shall be described in sufficient detail so as to be reproducible in control tests, carried out at the request of the competent authority and in order to be properly assessed by the competent authority. Any special apparatus and equipment, which may be used shall be described in adequate manner, accompanied by a diagram, if relevant. The formulae of the laboratory reagents shall be supplemented, if necessary, by the method of preparation. In the case of test procedures included in the European Pharmacopoeia or the pharmacopoeia of a Member State, this description may be replaced by a detailed reference to the pharmacopoeia in question.

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

(6) The pharmaceutical quality (physicochemical, biological or microbiological) data for the active substance and/or the finished product may be included in the dossier in Common Technical Document (CTD) format.

(7) For biological veterinary medicinal products, including immunologicals, information on solvents needed for making the final product preparation shall be included in the dossier. A biological veterinary medicinal product is regarded as one product even when more than one solvent is required so that different preparations of the final product can be prepared, which may be for administration by different routes or methods of administration. Solvents supplied with biological veterinary medicinal products may be packed together with the active substance vials or separately.

(8) In accordance with Directive 2010/63/EU and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, tests shall be carried out in such a way as to use the minimum number of animals and to cause the least pain, suffering, distress or lasting harm. If available, an alternative *in vitro* test shall be used when this leads to replacement or reduction of animal use or reduction of suffering.

I.2.3. Part 3: Safety documentation (safety and residues tests)

(1) The dossier on the safety studies shall include the following:

(a) synthesis of the tests which have been carried out in compliance with this Part, with detailed references to the published literature containing an objective discussion of all the results obtained. Omission of any tests or trials listed and inclusion of an alternative type of study shall be indicated and discussed;

(b) a statement of compliance with good laboratory practice for pre-clinical studies, where applicable, together with a discussion of the contribution that any non-GLP study may make to the overall risk assessment, and justification of non-GLP status.

(2) The dossier shall include the following:

(a) an index of all studies and trials included in the dossier;

(b) a justification for the omission of any type of study and trial;

(c) an explanation of the inclusion of an alternative type of study or trial;

(d) a discussion of the contribution that any non-GLP study or trial may make to the overall risk assessment and justification of non-GLP status.

I.2.4. Part 4: Efficacy documentation (pre-clinical studies and clinical trial(s))

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

(2) The dossier on the efficacy studies shall include the following:

(a) synthesis of the tests which have been carried out in compliance with this Part, with detailed references to the published literature containing an objective discussion of all the results obtained. Omission of any tests or trials listed and inclusion of an alternative type of study shall be indicated and discussed;

(b) a statement of compliance with good laboratory practice for pre-clinical studies, where applicable, together with a discussion of the contribution that any non-GLP study may make to the overall risk assessment, and justification of non-GLP status.

(3) The dossier shall include the following:

(a) an index of all studies included in the dossier;

(b) a justification for the omission of any type of study;

(c) an explanation of the inclusion of an alternative type of study.

(4) The purpose of the trials described in this Part is to demonstrate the efficacy of the veterinary medicinal product. All claims made by the applicant with regard to the properties, effects and use of the product shall be fully supported by results of specific trials contained in the application for marketing authorisation.

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

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

(7) Before the commencement of any field trial, the informed consent of the owner of the animals to be used in the trial shall be obtained and documented. In particular, the animal owner shall be informed in writing of the consequences of participation in the trial for the subsequent disposal of treated animals or for the taking of foodstuffs from treated animals.

I.2.5. Detailed requirements for different types of veterinary medicinal products or marketing authorisation dossiers

(1) Detailed requirements for different types of veterinary medicinal products or specific types of marketing authorisation dossiers are outlined in the following Sections of this Annex:

(a) Section II describes the standardised requirements for applications for veterinary medicinal products other than biological veterinary medicinal products;

(b) Section III describes the standardised requirements for applications for biological veterinary medicinal products:

(i) Section IIIa describes the standardised requirements for applications for biological veterinary medicinal products other than immunological veterinary medicinal products;

(ii) Section IIIb describes the standardised requirements for applications for immunological veterinary medicinal products;

(c) Section IV describes the dossier requirements for specific types of marketing authorisation dossiers;

(d) Section V describes the dossier requirements for particular types of veterinary medicinal products.

SECTION II
REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS OTHER THAN BIOLOGICAL VETERINARY MEDICINAL PRODUCTS

The following detailed requirements shall apply to veterinary medicinal products other than biological veterinary medicinal products, except where otherwise set out in Section IV.

II.1. PART 1: Summary of the dossier

Please refer to Section I.

II.2. PART 2: Quality documentation (physicochemical, biological or microbiological information)

II.2A. Product description

II.2A1. Qualitative and quantitative composition

(1) Qualitative composition of all the constituents of the medicinal product shall mean the designation or description of:

(a) active substance(s);

(b) excipients, the constituents of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances;

(c) other constituents, intended to be ingested or otherwise administered to animals, of the outer covering of the veterinary medicinal products, such as capsules, gelatine capsules, intraruminal devices;

(d) any relevant data concerning the immediate packaging and if relevant the outer packaging and, where appropriate, its manner of closure, together with details of devices with which the veterinary medicinal product will be used or administered and which will be supplied with the medicinal product.

(2) The usual terminology to be used in describing the constituents of veterinary medicinal products means, notwithstanding the application of the other provisions of Article 8:

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

(b) in respect of other substances, the international non-proprietary name (INN) recommended by the World Health Organisation (WHO), which may be accompanied by another non-proprietary name, or, failing these, the exact scientific designation;

(c) constituents not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details;

(d) in respect of colouring matter, designation by the 'E' code assigned to them by Directive 2009/35/EC of the European Parliament and Council.

(3) In order to give the quantitative composition of all the active substances and excipients of the veterinary medicinal products, it is necessary, depending on the pharmaceutical form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active substance and excipient.

(4) Units of biological activity shall be used for substances which cannot be defined chemically. Where an international unit of biological activity has been defined, this shall be used. Where no international unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances by using where applicable the European Pharmacopoeia Units.

(5) Quantitative composition shall be supplemented:

(a) in respect of single-dose preparations: by the mass or units of biological activity of each active substance in the unit container, taking into account the usable volume of the product, after reconstitution, where appropriate;

(b) in respect of veterinary medicinal products to be administered by drops: by the mass or units of biological activity of each active substance contained per drop or contained in the number of drops corresponding to 1 ml or 1 g of the preparation;

(c) in respect of pharmaceutical forms to be administered in measured quantities: by the mass or units of biological activity of each active substance per measured quantity.

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

(7) For veterinary medicinal products containing an active substance which is the subject of an application for marketing authorisation in the Union for the first time, the quantitative statement of an active substance which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity or entities in the molecule. All subsequently authorised veterinary medicinal products in the Member States shall have their quantitative composition stated in the same way for the same active substance.

II.2A2. Product development

(1) An explanation shall be provided with regard to the choice of composition, constituents, packaging, the intended function of the excipients in the finished product and the method of manufacture including justification of the selection of the method and details of the sterilisation processes and/or aseptic procedures used of the finished product. This explanation shall be supported by scientific data on development pharmaceutics. Any overage, with justification thereof, shall be stated. The microbiological characteristics (microbiological purity and antimicrobial activity) and usage instructions shall be proven to be appropriate for the intended use of the veterinary medicinal product as specified in the marketing authorisation application dossier.

(2) A study of the interaction between finished product and the primary packaging shall be submitted wherever the risk of such interaction is regarded as possible, especially where injectable preparations are concerned.

(3) The proposed pack sizes shall be justified in relation to the proposed route of administration, the posology and the target species in particular for antimicrobial (active) substances.

(4) When a dosing device is provided with the finished product, the accuracy of the doses(s) shall be demonstrated.

(5) When an accompanying test is recommended to be used with the finished product (e.g. a diagnostic test), relevant information about the test shall be provided.

(6) For veterinary medicinal products intended for incorporation into feed, information shall be provided on inclusion rates, instructions for incorporation, homogeneity in-feed and compatibility/suitable feed.

II.2B. Description of the manufacturing method

(1) The description of the manufacturing method accompanying the application for marketing authorisation pursuant to Article 8 shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.

(2) For that purpose, it shall include at least:

(a) the actual manufacturing formula for the proposed commercial batch size(s), with the quantitative particulars of all the substances used. Any substances that may disappear in the course of manufacture shall be stated; any overage shall be indicated;

(b) description of the various stages of manufacture with information on process operating conditions, in a narrative way accompanied by a process flow chart;

(c) in the case of continuous manufacture, full details of precautions taken to ensure the homogeneity of the finished product. Information as to how a batch is defined shall be provided (for example, expressed in terms of a period of time or a quantity of product, and may be expressed as ranges);

(d) a list of in-process controls including the stage of manufacture at which they are conducted and the acceptance criteria;

(e) experimental studies validating the manufacturing process and, where appropriate, a process validation scheme for production scale batches;

(f) for sterile products, where non-pharmacopoeial sterilisation conditions are used, details of the sterilisation processes and/or aseptic procedures used.

II.2C. Production and control of starting material

(1) For the purposes of this point, 'starting materials' shall mean active substances, excipients and packaging (immediate packaging with its closure system and, if applicable, outer packaging and any dosing device supplied with the veterinary medicinal product).

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

(3) The routine tests carried out on starting materials shall be carried out in the same manner as stated in the dossier.

(4) Where a certificate of suitability has been issued by the European Directorate for the Quality of Medicines and HealthCare for a starting material, active substance or excipient, that certificate constitutes the reference to the relevant monograph of the European Pharmacopoeia.

(5) Where a certificate of suitability is referred to, the manufacturer shall give an assurance in writing to the applicant that the manufacturing process has not been modified since the granting of the certificate of suitability by the European Directorate for the Quality of Medicines and HealthCare. In case the field '*box of access*' in the certificate is completed and signed, that requirement shall be deemed to be fulfilled without the need for additional assurance.

(6) Certificates of analysis shall be presented for the starting materials in order to demonstrate compliance with the defined specification.

II.2C1. Active substance(s)

(1) The required data shall be submitted in one of the three ways as detailed in points (2) to (4).

(2) The following details shall be submitted:

(a) information on the identity, structure and a list of physicochemical and other relevant properties of the active substance shall be provided, in particular physicochemical properties that potentially affect the safety and efficacy of the active substance. Where relevant, evidence of molecular structure shall include the schematic amino acid sequence and relative molecular mass;

(b) information on the manufacturing process shall include a description of the active substance manufacturing process that represents the applicant's commitment for the manufacture of the active substance. All materials needed in order to manufacture the active substance(s) shall be listed, identifying where each material is used in the process. Information on the quality and control of those materials shall be provided. Information demonstrating that materials meet standards which are appropriate for their intended use shall be provided;

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

(d) information on impurities shall indicate predictable impurities together with the levels and nature of observed impurities. It shall also contain information on the safety of those impurities where relevant.

(3) Active Substance Master File

For a non-biological active substance, the applicant may arrange for the information on active substance in point (2) to be supplied directly to the competent authorities by the manufacturer of the active substance as an Active Substance Master File. In this case, the manufacturer of the active substance shall provide the applicant with all the data (applicant's part of the Active Substance Master File) which may be necessary for the latter to take responsibility for the veterinary medicinal product. A copy of the data provided by the active substance manufacturer to the applicant shall be included in the medicinal product dossier. The manufacturer of the active substance shall confirm in writing to the applicant that he shall ensure batch-to-batch consistency and not modify the manufacturing process or specifications without informing the applicant.

(4) Certificate of suitability issued by the European Directorate for the Quality of Medicines and HealthCare

The certificate of suitability and any additional data relevant to the dosage form not covered by the certificate of suitability shall be provided.

II.2C1.1. Active substances listed in pharmacopoeias

(1) Active substances fulfilling the requirements of the European Pharmacopoeia or, in the absence of a European Pharmacopoeia monograph, the pharmacopoeia of one of the Member States shall be deemed to comply sufficiently with Article 8. 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.

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

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

II.2C1.2. Active substances not listed in a pharmacopoeia

(1) Active substances which are not listed in any pharmacopoeia shall be described in the form of a monograph under the following headings:

(a) the name of the constituent, meeting the requirements of Part II.2A1, point (2) shall be supplemented by any trade or scientific synonyms;

(b) the definition of the substance, set down in a form similar to that used in the European Pharmacopoeia, shall be accompanied by any necessary explanatory

evidence, in particular concerning the molecular structure. Where substances may only be described by their manufacturing method, the description shall be sufficiently detailed to characterise a substance which is constant both on its composition and in its effects;

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

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

(e) tests and acceptance criteria to control parameters relevant to the finished product, such as sterility shall be described and methods shall be validated where relevant;

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

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

II. 2C1.3. Physicochemical characteristics liable to affect bioavailability

The following data concerning active substances shall be provided as part of the general description of the active substances if the bioavailability of the veterinary medicinal product depends on them:

(a) crystalline form and solubility;

(b) particle size;

(c) state of hydration;

(d) oil/water coefficient of partition;

(e) pK/pH values.

Points (a) to (c) are not applicable to substances used solely in solution.

II.2C2. Excipients

(1) Excipients fulfilling the requirements of the European Pharmacopoeia or, in the absence of a European Pharmacopoeia monograph, the pharmacopoeia of one of the Member States shall be deemed to comply sufficiently with Article 8. In that 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. Where appropriate, additional tests to control parameters such as particle size, sterility, and/or residual solvents, shall supplement the requirements of the monograph.

(2) In the absence of a pharmacopoeial monograph a specification shall be proposed and justified. The requirements for specifications as set out in Part II.2C1.2(1) points (a) to (e) for the active substance shall be followed. The proposed methods and their supporting validation data shall be presented.

(3) A declaration shall be submitted to confirm that colouring matters for inclusion in veterinary medicinal products satisfy the requirements of Directive 2009/35/EC of the European Parliament and of the Council[3] except where the application for a marketing authorisation concerns certain veterinary medicinal products for topical use, such as medicated collars and ear tags.

(4) A declaration shall be submitted to confirm that colouring matters used meet the purity criteria laid down in Commission Regulation (EU) No 231/2012[4].

(5) For novel excipients, that is to say excipient(s) used for the first time in the Union in a veterinary medicinal product or by a new route of administration, details of manufacture, characterisation, and controls, with cross references to support both clinical and non-clinical safety data shall be provided. For colouring matters, the declarations of compliance in points (3) and (4) shall be considered sufficient.

II.2C3. Packaging (containers and closure systems)

II. 2C3.1. Active substance

(1) Information on the container and itsclosure system for the active substance including the identity of each immediate packaging material and their specifications shall be given. The level of information required shall be determined by the physical state (liquid, solid) of the active substance.

(2) Where a certificate of suitability for the active substance from the proposed source is submitted and specifies a container and its closure system, the detailed information on these for the active substance from that source may be replaced by a reference to the valid certificate of suitability.

(3) Where an Active Substance Master File from the proposed source is submitted and specifies a container and its closure system, the detailed information on these for the active substance from that source may be replaced by a reference to the Active Substance Master File.

II. 2C3.2. Finished product

(1) Information on the container and its closure system and any device for the finished product including the identity of each immediate packaging material and their specifications shall be given. The level of information required shall be determined by the route of administration of the veterinary medicinal product and the physical state (liquid, solid) of the dosage form.

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

(3) For packaging materials that are used for the first time in the Union and that are in contact with the product, information on their composition, manufacture and safety shall be presented.

II.2C4. Substances of biological origin

(1) Information on the source, processing, characterisation and control of all materials of biological origin (human, animal, herbal or from microorganisms) used in the

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[3] Directive 2009/35/EC of the European Parliament and of the Council of 23 April 2009 on the colouring matters which may be added to medicinal products (OJ L 109, 30.4.2009, p. 10).

[4] Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council (OJ L 83, 22.3.2012, p. 1).

manufacture of the veterinary medicinal products shall be provided, including viral safety data, in accordance with relevant guidelines.

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

II.2D. Control tests carried out on isolated intermediates during the manufacturing process

(1) For the purposes of this section, 'isolated intermediate' shall mean partly processed material that may be stored for a defined amount of time and that shall undergo further processing step(s) before it becomes finished product.

(2) A specification shall be set for each intermediate and the analytical methods shall be described and validated, if applicable.

(3) Information on the primary packaging of the intermediate product shall be provided if different from that for the finished product.

(4) A shelf life and storage conditions for the intermediate product shall be defined on the basis of the data resulting from stability studies.

II.2E. Control tests on the finished product

(1) For the control of the finished product, a batch of a finished product comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations. In case of continuous manufacture, the batch size may be expressed in terms of a period of time or a quantity of product, and may be expressed as ranges.

(2) The tests, which are carried out on the finished product shall be listed. A justification for the proposed specification shall be provided. The frequency of the tests which are not carried out routinely shall be stated and justified. Acceptance criteria for release shall be indicated.

(3) The dossier shall include particulars relating to control tests on the finished product at release and their validation. They shall be submitted in accordance with the following requirements.

(4) If test procedures and acceptance criteria other than those mentioned in the relevant monographs and general chapters of the European Pharmacopoeia, or failing this, in the pharmacopoeia of a Member State are used, those procedures and criteria shall be justified by providing proof that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned.

II.2E1. General characteristics of the finished product

(1) Certain tests of the general characteristics of a product shall always be included among the tests on the finished product. Those tests shall, wherever applicable, relate to the control of average masses/volumes and maximum deviations, to mechanical, physical tests, visual appearance, physical characteristics such as, pH or particle size.

For each of those characteristics, standards and acceptance criteria shall be specified by the applicant.

(2) The conditions of the tests, where appropriate, the equipment/apparatus employed and the standards shall be described in sufficient detail whenever they are not given in the European Pharmacopoeia or the pharmacopoeia of a Member State; the same shall apply in cases where the methods prescribed by such pharmacopoeias are not applicable.

II. 2E2. Identification and assay of active substance(s)

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

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

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

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

(5) The maximum acceptable levels of individual and total degradation products immediately following manufacture shall be indicated. The rationale for the inclusion or exclusion of degradation products in the specification shall be presented.

II. 2E3. Identification and assay of excipient components

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

II. 2E4. Microbiological controls

Particulars of microbiological tests, such as sterility and bacterial endotoxins, shall be included in the analytical particulars wherever such tests shall be undertaken as a matter of routine in order to verify the quality of the product.

II. 2E5. Batch-to-batch consistency

In order to ensure the quality of the product is consistent from batch to batch and to demonstrate conformity with the specification, batch data shall be provided giving the results for all tests performed in general on [3] batches manufactured at the proposed manufacturing site(s) according to the described production process.

II. 2E6. Other controls

Any other test considered necessary to confirm the quality of the medicinal product shall be controlled.

II.2F. Stability test

II.2F1. Active substance(s)

(1) A retest period and storage conditions for the active substance shall be specified except when the manufacturer of the finished product fully retests the active substance immediately before its use in the manufacture of the finished product.

(2) Stability data shall be presented to provide evidence on how the quality of an active substance varies with time under the influence of a variety of environmental factors and to support the defined retest period and storage conditions, if applicable. The type of stability studies conducted, protocols used, the analytical procedures used and their validation together with the detailed results shall be presented.

(3) Where a certificate of suitability for the active substance from the proposed source is available and specifies a retest period and storage conditions, stability data for the active substance from that source may be replaced by a reference to the valid certificate of suitability.

(4) Where an Active Substance Master File from the proposed source is submitted and specifies stability data, the detailed information on the stability for the active substance from that source may be replaced by a reference to the Active Substance Master File.

II.2F2. Finished product

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

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

(3) Where a finished product requires reconstitution or dilution prior to administration, details of the proposed shelf life and specification for the reconstituted/diluted product are required, supported by relevant stability data.

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

(5) Where a finished product is liable to give rise to degradation products, the applicant shall declare those products and indicate the identification methods and test procedures used.

(6) Where the stability data show that the assay of the active substance declines on storage, the description of the control tests on the finished product shall include, where appropriate, the chemical and, if necessary, the toxico-pharmacological

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

(7) The maximum acceptable level of individual and total degradation products at the end of shelf life shall be indicated and justified.

(8) On the basis of the stability test results, the tests and their acceptance criteria, that are carried out on the finished product over the course of the shelf life shall be listed and justified.

(9) The conclusions shall contain the results of analyses, justifying the proposed shelf life and if appropriate, the in-use shelf life, under the recommended storage conditions.

(10) Additionally, for veterinary medicinal products intended for incorporation into feed, information shall be provided on the stability and the proposed shelf life after incorporation into feed. A specification for the medicated feed manufactured using those veterinary medicinal products in accordance with the recommended instructions for use shall also be provided.

II.2G. Other information

Information relating to the quality of the veterinary medicinal product not covered elsewhere in this Part may be included in the dossier under this point.

II.3 PART 3: Safety documentation (safety and residues tests)

(1) Each study report shall include:

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

(b) a statement of compliance with good laboratory practice, where applicable;

(c) a description of the methods, apparatus and materials used;

(d) a description and justification of the test system;

(e) a description of the results obtained, in sufficient detail, to allow the results to be critically evaluated independently of their interpretation by the author;

(f) a statistical analysis of the results where appropriate;

(g) a discussion of the results, with comment on observed and no-observed-effect levels, and on any unusual findings;

(h) the name of the laboratory;

(i) the name of the study director;

(j) signature and date;

(k) place and period of time during which the study was undertaken;

(l) key for abbreviations and codes, irrespective of whether they are internationally accepted or not;

(m) description of mathematical and statistical procedures.

(2) Published studies may be accepted if they contain a sufficient amount of data and sufficient details to allow an independent assessment. The experimental techniques shall be described in such detail as to allow them to be reproduced, and the investigator shall establish their validity. Summaries of studies for which detailed reports are not available shall not be accepted as valid documentation. When the

substance has been previously evaluated for the establishment of maximum residues limit ('MRL') to address certain safety requirements reference may be made to the European public MRL assessment reports ('EPMARs'). Where reference to EPMAR is made there is no need to submit studies already evaluated as part of the MRL evaluation; only new studies not available for the MRL assessment shall be provided. If the route of exposure (for example, for the user) is not identical to the route used in accordance with Commission Regulation (EU) 2018/782[5], new studies might be necessary.

II.3A. Safety tests

(1) The safety documentation shall be adequate for assessment of:

(a) the potential toxicity of the veterinary medicinal product and any dangerous or undesirable effects in target species which may occur under the proposed conditions of use;

(b) 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;

(c) the potential risks to the environment resulting from the use of the veterinary medicinal product.

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

(3) An excipient used for the first time in a veterinary medicinal product or by a new route of administration shall be treated in the same way as an active substance.

II.3A1. Precise identification of the product and of its active substance(s)

(a) International Non-proprietary Name (INN);

(b) International Union of Pure and Applied Chemistry Name (IUPAC);

(c) Chemical Abstract Service (CAS) number;

(d) therapeutic, pharmacological and chemical classification;

(e) synonyms and abbreviations;

(f) structural formula;

(g) molecular formula,

(h) molecular weight;

(i) degree of purity;

(j) qualitative and quantitative composition of impurities;

(k) description of physical properties:

(i) melting point,

(ii) boiling point,

(iii) vapour pressure,

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[5] Commission Regulation (EU) 2018/782 of 29 May 2018 establishing the methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) No 470/2009 (OJ L 132, 30.5.2018, p. 5).

(iv) solubility in water and organic solvents expressed in g/l, with indication of temperature,

(v) density,

(vi) refraction of light, optical rotation, etc.;

(l) formulation of the product.

II.3A2. Pharmacology

(1) Pharmacological studies are of fundamental importance in clarifying the mechanisms by which the veterinary medicinal product produces its therapeutic effects, and therefore pharmacological studies conducted in experimental and target species of animal shall be included. Cross reference may be made, if applicable, to studies submitted in Part 4 of the dossier.

(2) Where a veterinary medicinal product produces pharmacological effects in the absence of a toxic response, or at doses lower than those required to elicit toxicity, those pharmacological effects shall be taken into account during the evaluation of the safety for the user of the veterinary medicinal product.

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

II.3A2.1 Pharmacodynamics

Information on the mechanism of action of the active substance(s) shall be provided, together with information on primary and secondary pharmacodynamic effects in order to assist in the understanding of any adverse effects in the animal studies. Detailed reporting of pharmacodynamic properties relating to the therapeutic effect shall be reported in Part 4A of the dossier.

II.3A2.2 Pharmacokinetics

Data on the fate of the active substance and its metabolites in laboratory animals shall be provided, covering absorption, distribution, metabolism and excretion (ADME). The data shall be related to the dose/effect findings in the pharmacological and toxicological studies, to determine adequate exposure.

II.3A3. Toxicology

(1) The documentation on toxicology shall follow the guidance published by the Agency on the general approach to testing and guidance on particular studies. Generally, toxicity studies shall be conducted with the active substance(s), not with the formulated product, unless specifically required otherwise.

(2) Animal studies shall be conducted in established strains of laboratory animals for which (preferably) historical data are available.

(3) Single-dose toxicity

Single-dose toxicity studies may be used to predict:

(a) the possible effects of acute overdose in the target species;

(b) the possible effects of accidental administration to humans;

(c) the doses which may usefully be employed in the repeat dose studies.

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

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

(4) Repeat-dose toxicity

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

A repeat-dose toxicity study in one species of experimental animal shall normally be sufficient. This study may be replaced by a study conducted in the target animal. The frequency and route of administration, and the duration of the study shall be chosen having regard to the proposed conditions of clinical use and/or user exposure. The applicant shall give his reasons for the extent and duration of the studies and the dosages chosen.

(5) Tolerance in the target species

A summary shall be provided of any signs of intolerance which have been observed during studies conducted, usually with the final formulation, in the target species in accordance with the requirements of Part II.4A4 (Tolerance in the target animal species). The studies concerned, the dosages at which the intolerance occurred, and the species and breeds concerned shall be identified. Details of any unexpected physiological changes shall also be provided. The full reports of those studies shall be included in Part 4 of the dossier.

(6) Reproductive toxicity including developmental toxicity

Study of the effects on reproduction

For products intended for use in breeding animals, reproductive safety studies in line with VICH GL43 shall be provided. Reproduction toxicity studies in laboratory animals are not expected for the evaluation of effects on the user.

(7) Study of developmental toxicity

For the evaluation of effects in the target animal species, developmental toxicity studies are not required for products intended only for use in non-breeding animals. For other products a study of developmental toxicity shall be performed in at least one species, which may be the target species. If the study is conducted in the target species, a summary shall be provided here, and the full report of the study shall be included in Part 4 of the dossier.

For the evaluation of user safety, standard developmental toxicity testing in accordance with standard tests based on established guidance (including VICH GL32 and OECD tests) shall be performed in all cases where significant user exposure may be expected.

(8) Genotoxicity

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

A standard battery of genotoxicity tests in accordance with standard tests based on established guidance (including VICH GL23 and OECD tests) shall be carried out on the active substance(s).

(9) Carcinogenicity

The decision on whether carcinogenicity testing is required shall take into account the results of genotoxicity tests, structure-activity relationships and the findings in repeat dose toxicity tests that may demonstrate the potential for hyper-/neo-plastic changes.

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.

Carcinogenicity testing shall be conducted according to standard tests based on established guidance (including VICH GL28 and OECD tests).

(10) Exceptions

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

(a) under the intended conditions of use, oral ingestion of the veterinary medicinal product by the animal is to be expected, or

(b) under the intended conditions of use, oral exposure of the user of the veterinary medicinal product is to be expected.

II.3A4. Other requirements

II.3A.4.1 Special studies

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

For products for which there may be exposure to skin and eyes, irritation and sensitisation studies shall be provided. Those studies shall be conducted with the final formulation.

The state of latest scientific knowledge and established guidance shall be taken into account when designing such studies and evaluating their results.

II.3A.4.2. Observations in humans

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

II.3A.4.3. Development of resistance and related risk in humans

The data requirements described in this point are related to antibacterial substances and may not be fully applicable to other types of antimicrobial (namely antivirals, antifungals and antiprotozoals) although, in principle, the requirements may be followed, where applicable.

Data on the potential emergence of resistant bacteria or resistance determinants of relevance for human health and which are associated with the use of veterinary medicinal products are necessary for those products. The mechanism of the development and selection of such resistance is particularly important in this regard. Where necessary, measures to limit

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

Resistance data relevant for clinical use of the product in target animals shall be addressed in accordance with Part II.4A2. Where relevant, cross reference shall be made to the data set out in Part II.4A2.

(1) For food-producing animals the risk assessment shall address:

(a) the identification of resistant bacteria or resistance determinants that could be associated with human illness (zoonotic and/or commensal bacteria) and are selected by the use of the antimicrobial veterinary medicinal product in target animals (hazard identification);

(b) the probability of release of the identified hazard(s) from the target animal species as a result of the use of the veterinary medicinal product under consideration;

(c) the probability of subsequent human exposure to the identified hazard(s) via the foodborne route or through direct contact, and the resulting consequences (adverse health effects) to human health. Guidance is available in VICH GL27 and EU GLs.

(2) For companion animals consideration of risk to human or public health shall address:

(a) the identification of resistant bacteria or resistance determinants that could be associated with human illness and are selected by the use of the antimicrobial veterinary medicinal product in target animals;

(b) an estimate of exposure of zoonotic and commensal bacteria in the target animal species based on the conditions of use of the veterinary medicinal product under consideration;

(c) consideration of subsequent human exposure to antimicrobial resistance (AMR), and the resulting consequences to human health.

(3) Resistance in the environment shall be addressed.

II.3A5. User safety

This section shall include an assessment of the effects found in Part II.3A to II.3A4 and relate this to the type and extent of human exposure to the product with a view to formulating appropriate user warnings and other risk management measures.

User safety shall be addressed in accordance with Committee for Medicinal Products for Veterinary Use (CVMP) guidelines.

II.3A6. Environmental risk assessment

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

(2) This assessment consists of two phases. The first phase of the assessment shall always be performed. The details of the assessment shall be provided in accordance with guidance published by the Agency. It shall indicate the potential exposure of the environment to the product and the level of risk associated with any such exposure, in particular taking into account the following items:

(a) the target animal species, and the proposed pattern of use;

(b) the method of administration, in particular the likely extent to which the product will enter directly into environmental systems;

(c) the possible excretion of the product, its active substances or relevant metabolites into the environment by treated animals; persistence in such excreta;

(d) the disposal of unused veterinary medicinal product or other waste product.

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

(4) For products intended for food producing species, persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances shall be classified according to the criteria in Annex XIII to Regulation (EC) No 1907/2006 of the European Parliament and of the Council[6] (REACH Regulation) and assessed according to the guidance for PBT and vPvB assessment of substances in veterinary medicines published by the Agency.

II.3B. Residue tests

(1) For the purposes of this point, the definitions of Regulation (EC) No 470/2009 shall apply.

(2) The purpose of studying the depletion of residues from the edible tissues or from eggs, milk and honey (wax, if appropriate) derived from treated animals is to determine under what conditions and to what extent residues may persist in foodstuffs produced from those animals. In addition, the studies shall enable the determination of a withdrawal period.

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

(a) to what extent, and for how long residues of the veterinary medicinal product or its metabolites persist in the edible tissues of the treated animal or in milk, eggs and/or honey (wax, if appropriate) obtained therefrom;

(b) that in order to prevent any risk to the health of the consumer of foodstuffs from treated animals, it is possible to establish realistic withdrawal periods which may be observed under practical farming conditions;

(c) that the analytical method(s) used in the residues depletion study are sufficiently validated to provide the necessary reassurance that the residues data submitted are suitable as the basis for a withdrawal period.

II.3B1. Identification of the product

[6] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396, 30.12.2006, p. 1).

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

(a) composition;

(b) the physical and chemical (potency and purity) test results for the relevant batch(es);

(c) batch identification.

II.3B2. Depletion of residues (metabolism and residue kinetics)

(1) The purpose of these studies, which measure the rate at which residues deplete in the target animal after the last administration of the veterinary medicinal product, is to permit the determination of withdrawal periods necessary to ensure that no residues which may constitute a hazard for consumers are present in foodstuffs obtained from treated animals.

(2) The current status of the MRL for the components of the veterinary medicinal product in the relevant target species shall be reported.

(3) The levels of residues present shall be determined at a sufficient number of time points after the test animals have received the final dose of the veterinary medicinal product. The studies in mammals and birds shall be performed according to VICH GL48 and other relevant guidelines. Residue studies in honey shall be performed according to VICH GL56 and depletion studies in aquatic species according to VICH GL57.

(4) Based on the evaluation, the rationale for the proposed withdrawal period shall be addressed.

II.3B3. Residue analytical method

The residue depletion study (studies), the analytical method(s) and its (their) validation shall be performed in accordance with VICH GL49.

The analytical method shall have regard to the state of scientific and technical knowledge at the time the application is submitted.

II.4. PART 4: Efficacy documentation (pre-clinical studies and clinical trial(s))

II.4A. Pre-clinical studies

Pre-clinical studies aim to investigate the target animal safety and efficacy of the product and are required to establish the pharmacological activity, pharmacokinetic properties, dose and dosing interval, resistance (if applicable) and the target animal tolerance of the product.

II.4A1. Pharmacology

II.4A.1.1.Pharmacodynamics

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

(2) The mode of action and the pharmacological effects on which the recommended application is based in practice shall be adequately described, including secondary effects (if any). In general, the effects on the main body functions shall be investigated. The results shall be expressed in quantitative terms (for example, using dose-effect curves and/or time-effect curves) and, wherever possible, in comparison with a substance the activity of which is well known (where the activity is claimed to

be higher in comparison to the substance the activity of which is well known, the difference shall be demonstrated and shown to be statistically significant).

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

(4) The experimental techniques, unless they are standard procedures, shall be described in such detail as to allow them to be reproduced, and their validity to be established. The experimental results shall be set out clearly and the outcome of any statistical comparisons presented.

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

II.4A.1.2. Pharmacokinetics

(1) Basic pharmacokinetic data on the active substance are required in the context of assessment of the target animal safety and efficacy of the veterinary medicinal product in the target species, in particular if this concerns a new substance or formulation.

(2) The objectives of pharmacokinetic studies in the target animal species may be divided into four main areas:

(a) to describe the basic pharmacokinetic characteristics (namely absorption, distribution, metabolism and excretion) of the active substance in the formulation;

(b) use of this basic pharmacokinetic characteristics to investigate the relationships between dosage regimen, plasma and tissue concentration over time and pharmacological, therapeutic or toxic effects;

(c) where appropriate, to compare pharmacokinetic parameters between different target species and to explore possible species differences having an impact on target animal safety and efficacy of the veterinary medicinal product;

(d) where appropriate, to compare bioavailability to support bridging of safety and efficacy information between different products, pharmaceutical forms, strengths or routes of administration, or to compare the impact of changes in manufacturing or composition.

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

(4) Where pharmacokinetic studies have been submitted under Part 3 of the dossier, cross reference to such studies may be made. For fixed combinations, please refer to Section IV.

II.4A2. Development of resistance and related risk in animals

(1) For relevant veterinary medicinal products (for example, antimicrobials, antiparasitics), information on current resistance (if applicable) and on the potential emergence of resistance of clinical relevance for the claimed indication in the target animal species shall be provided. Where possible, information on the resistance

mechanism(s), the molecular genetic basis of resistance, and the rate of transfer of resistance determinants shall be presented. Whenever relevant, information on co-resistance and cross-resistance shall be presented. Measures to limit resistance development in organisms of clinical relevance for the intended use of the veterinary medicinal product shall be proposed by the applicant.

(2) Resistance relevant for risks to humans shall be addressed in accordance with Part II.3A4, point (3). Where relevant, cross-reference shall be made to data set out in Part II.3A4, point (3).

II.4A3. Dose determination and confirmation

Appropriate data shall be provided to justify the proposed dose, dosing interval, duration of treatment and any re-treatment interval.

For studies conducted under field conditions, relevant information shall be provided as outlined in Part II.4B, unless duly justified.

II.4A4. Tolerance in the target animal species

The local and systemic tolerance of the veterinary medicinal product shall be investigated in the target animal species. The purpose of target animal safety studies is to characterise signs of intolerance and to establish an adequate margin of safety using the recommended route(s) of administration. This may be achieved by increasing the dose and/or the duration of treatment. The study report(s) shall contain details of all expected pharmacological effects and all adverse reactions. The conduct of target animal safety studies shall be in accordance with the international guidelines of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products ('VICH') and relevant guideline(s) published by the Agency. . Other pre-clinical studies, including studies provided in part 3, and clinical trials, along with relevant information from the published literature, may also provide information on safety in the target species. Studies on developmental toxicity performed in the target animal species shall be included here, and a summary shall be provided in Part 3 of the dossier.

II.4B. Clinical trial(s)

II.4B1. General principles

(1) Clinical trials shall be designed, carried out and reported taking due account of the international guidelines on good clinical practice of the VICH and relevant guidance published by the Agency. Data stemming from clinical trials conducted outside the Union may be taken into consideration for the assessment of an application for a marketing authorisation only if the data are sufficiently representative for the Union situation.

(2) Experimental data such as exploratory/pilot trials, or results from non-experimental approaches shall be confirmed by clinical trials, unless otherwise justified.

(3) The purpose of clinical trials is to examine under field conditions the target animal safety and efficacy of a veterinary medicinal product under normal conditions of animal husbandry and/or as part of good veterinary practice. They shall demonstrate the effect of the veterinary medicinal product after administration to the intended target species using the proposed dosage regimen and the proposed route(s) of administration. The trial design shall aim to support the indications and to take into account any contra-indications according to species, age, breed and sex, directions for use of the veterinary medicinal product as well as any adverse reactions which it may have.

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

(5) For formulations intended for use in veterinary clinical trials in the Union, the words 'for veterinary clinical trial use only' shall appear prominently and indelibly on the labelling.

(6) Unless otherwise justified, clinical trials shall be carried out with control animals (controlled clinical trials). The efficacy results obtained with the new product shall be compared with those from the target animal species that have received a veterinary medicinal product authorised in the Union that has demonstrated an acceptable level of efficacy and been approved for the proposed indication(s) for use in the same target animal species, or a placebo or no treatment. All the results obtained, whether positive or negative, shall be reported.

(7) Established statistical principles in accordance with the relevant guidance published by the Agency shall be used in protocol design, analysis and evaluation of clinical trials, unless otherwise justified.

II.4B2. Documentation

II.4AB2.1. Results of pre-clinical studies

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

(a) tests demonstrating pharmacological activity, including tests demonstrating the pharmacodynamic mechanisms underlying the therapeutic effect and tests demonstrating the main pharmacokinetic profile;

(b) tests and investigations on resistance, if applicable;

(c) tests demonstrating target animal safety;

(d) tests to determine and confirm the dose (including dose interval, duration of treatment and any re-treatment interval).

Where unexpected results occur during the course of the tests, those results shall be described in detail. Omission of any of those data shall be justified. The following particulars shall be provided in all pre-clinical study reports:

(a) a summary;

(a) a study protocol;

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

(c) a statistical analysis of the results, if applicable;

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

II.4AB2.2. Results of clinical trials

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

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

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

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

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

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

(i) received no treatment,

(ii) received a placebo, or

(iii) received another veterinary medicinal product authorised in the Union that has demonstrated an acceptable level of efficacy and been approved for the proposed indication(s) for use in the same target animal species, or

(iv) received the same active substance under investigation in a different formulation or by a different route;

(d) the frequency of observed adverse reactions;

(e) observations as to the effect on animal performance, if appropriate;

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

(g) a statistical evaluation of the results.

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

SECTION III
REQUIREMENTS FOR BIOLOGICAL VETERINARY MEDICINAL PRODUCTS

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

SECTION IIIa
REQUIREMENTS FOR BIOLOGICAL VETERINARY MEDICINAL PRODUCTS OTHER THAN IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

The following requirements shall apply to biological veterinary medicinal products as defined in Article 4(6), except products defined in Article 4(5) or where otherwise set out in Section IV.

Flexibility is allowed regarding compliance to the requirements specified in this Section, but any deviations from the requirements in this Annex shall be scientifically justified and based on specific properties of the biological product. For particular substances, safety data in addition to the requirements listed in this Section may be required depending on the nature of the product.

IIIa.1. PART 1: Summary of the dossier

Please refer to Section I.

IIIa.2. PART 2: Quality documentation (physicochemical, biological or microbiological information)

IIIa.2A. Product description

IIIa.2A1. Qualitative and quantitative composition

(1) The qualitative and quantitative composition of the biological veterinary medicinal product shall be stated. This section shall include information regarding:

(a) the active substance(s);

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

(c) the composition, that is to say, list of all components of the dosage form and their amount on a per-unit basis (including overages, if any), the function of the components, and a reference to their quality standards (for example, compendial monographs or manufacturer´s specifications);

(d) accompanying reconstitution solvent(s);

(e) the type of container and its closure used for the dosage form and for any accompanying reconstitution solvents and devices, if applicable. If the device is not delivered together with the biological veterinary medicinal product, relevant information about the device shall be provided.

(2) In order to give the quantitative composition of all the active substances and excipients of the veterinary medicinal products, it is necessary, depending on the pharmaceutical form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active substance and excipient.

(3) Where possible, biological activity per units of mass or volume shall be indicated. Where an international unit of biological activity has been defined, this shall be used, unless otherwise justified. Where no international unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances by using, where applicable, the European Pharmacopoeia Units.

(4) The ‘usual terminology’ to be used in describing the constituents of biological veterinary medicinal products notwithstanding the application of the other provisions of Article 8, shall mean:

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

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

(c) in respect of colouring matter, designation by the ‘E’ code assigned to them in Directive 2009/35/EC.

IIIa.2A2. Product development

An explanation shall be provided including but not limited to:

(a) the choice of composition and the choice of the constituents, in particular relative to their intended functions and their respective concentrations;

(b) the inclusion of a preservative in the composition shall be justified;

(c) the immediate packaging and the suitability of the container and its closure system used for the storage and use of the finished product. A study of the interaction between the finished product and the primary packaging shall be submitted wherever the risk of such interaction is regarded as possible, especially where injectable preparations are concerned;

(d) the microbiological characteristics (microbiological purity and antimicrobial activity) and usage instructions;

(e) the possible further packaging, outer packaging, if relevant;

(f) the proposed pack sizes related to the proposed route of administration, the posology and the target species;

(g) any overage(s) in the formulation to guarantee minimum potency at end of shelf life with justification;

(h) the selection of the manufacturing process of the active substance and the finished product;

(i) differences between the manufacturing process(es) used to produce batches used in clinical trials and the process described in the application for marketing authorisation shall be discussed;

(j) when a dosing device is provided with the finished product, the accuracy of the doses(s) shall be demonstrated;

(k) when an accompanying test is recommended to be used with the finished product (e.g. a diagnostic test), relevant information about the test shall be provided.

(l) This explanation shall be supported by scientific data on product development.

IIIa.2A3. Characterisation

IIIa.2A3.1. Elucidation of structure and other characteristics

(1) Characterisation of a biotechnological or biological substance (which includes the determination of physicochemical properties, biological activity, immuno-chemical properties, purity and impurities) by appropriate techniques is necessary to allow a suitable specification to be established. Reference to literature data only is not acceptable, unless otherwise justified by prior knowledge from similar molecules for modifications where there is no safety concern. Adequate characterisation shall be performed in the development phase and, where necessary, following significant process changes.

(2) All relevant information available on the primary, secondary and higher-order structure including post- translational (for example, glycoforms) and other modifications of the active substance shall be provided.

(3) Details shall be provided on the biological activity (namely the specific ability or capacity of a product to achieve a defined biological effect). Usually, the biological activity shall be determined or evaluated using an appropriate, reliable and qualified method. Lack of such an assay shall be justified. It is recognised that the extent of characterisation data will increase during development.

(4) The rationale for selection of the methods used for characterisation shall be provided and their suitability shall be justified.

IIIa.2A3.2. Impurities

(1) Process-related impurities (for example, host cell proteins, host cell DNA, media residues, column leachables) and product-related impurities (for example, precursors, cleaved forms, degradation products, aggregates) shall be addressed. Quantitative information on impurities shall be provided including maximum amount for the highest dose. For certain process-related impurities (for example, antifoam agents), an estimation of clearance may be justified.

(2) In the case that only qualitative data are provided for certain impurities, this shall be justified.

IIIa.2B. Description of the manufacturing method

(1) The description of the manufacturing method accompanying the application for marketing authorisation pursuant to Article 8 shall be drafted in such a way as to give an adequate description of the nature of the operations employed.

(2) The name(s) and address(es) and responsibilities of each manufacturer, including contractors, and each proposed production site or facility involved in manufacture, testing and batch release shall be provided.

(3) The description of the manufacturing process shall include at least:

(a) the various stages of manufacture, including production of the active substance and description of the purification steps;

(b) a process flow chart of all successive steps shall be given so that an assessment can be made of the reproducibility of the manufacturing procedure and of the risks of adverse effects on the finished products, such as microbiological contamination;

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

Information on how a batch is defined and on the proposed commercial batch size(s) shall be provided;

(d) listing of all the substances at the appropriate steps where they are used, including those which cannot be recovered in the course of manufacturing;

(e) the details of the blending, with the quantitative particulars of all the substances used, including an example for a representative production batch;

(f) list of in-process controls including the stage of manufacture at which they are conducted and acceptance criteria;

(g) for sterile products, where non-pharmacopoeial sterilisation conditions are used, details of the sterilisation processes and/or aseptic procedures used.

(4) Description, documentation, and results of the validation and/or evaluation studies shall be provided for critical steps or critical assays used in the manufacturing process (for example, validation of the sterilisation process or aseptic processing or filling) and the validation of the production process as a whole shall be demonstrated with provision of results of three consecutive batches produced using the method described.

IIIa.2C. Production and control of starting materials

(1) For the purposes of this point 'starting materials' means all components, including the active substances used in the production of the biological veterinary medicinal product. Culture media used for production of the active substances shall be regarded as one starting material.

(2) The qualitative and quantitative composition shall be presented insofar as the authorities consider that this information is relevant to the quality of the finished product and any risks that might be posed.

(3) If materials of animal origin are used for preparation of those culture media, the animal species and the tissue used have to be included and compliance with the relevant monographs including general monographs and general chapters of the European Pharmacopoeia shall be demonstrated.

(4) The applicant shall supply documentation to demonstrate that the starting materials, including seed materials, cell seeds, batches of serum and other material originating from animal species relevant for the transmission of TSE and the manufacturing of the veterinary medicinal product is in compliance with the requirements of the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, as well as with the requirements of the corresponding monograph of the European Pharmacopoeia.

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

(6) The dossier shall include the specifications, information on the tests to be conducted for the quality control of all batches of starting materials and results from a batch of all components used and shall be submitted in accordance with the following provisions.

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

(8) Colouring matter shall in all cases satisfy the requirements of Directive 2009/35/EC.

(9) The use of antibiotics during production and preservatives shall be in compliance with the European Pharmacopoeia.

(10) For novel excipients - excipient(s) used for the first time in the Union in a veterinary medicinal product or by a new route of administration - details of manufacture, characterisation, and controls, with cross references to supporting safety data, both clinical and non-clinical, shall be provided. For colouring matters the declarations of compliance as mentioned under Part II.2C2, points (3) and (4) shall be considered sufficient.

IIIa.2C1. Starting materials listed in pharmacopoeias

(1) The monographs of the European Pharmacopoeia shall be applicable to all starting materials appearing in it, unless adequate justification is provided.

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

(3) The description of the analytical methods may be replaced by a detailed reference to the pharmacopoeia in question.

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

(5) Where a specification or other provisions contained in a monograph of the European Pharmacopoeia or in the pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the applicant for marketing authorisation. The alleged insufficiency shall be reported to the authorities responsible for the pharmacopoeia in question.

IIIa.2C2. Starting materials not listed in a pharmacopoeia

IIIa.2C2.1. Starting materials of biological origin

(1) Where source materials such as microorganisms, tissues of either plant or animal origin, cells or fluids (including blood) of human or animal origin or biotechnological cell constructs are used in the manufacture of veterinary medicinal products, the origin, including geographical region, and history of starting materials shall be described and documented. The origin, general health and immunological status of animals used for production shall be indicated and defined pools of source materials shall be used.

(2) Freedom from extraneous agents (bacteria, mycoplasma, fungi and viruses) shall be demonstrated in compliance with the European Pharmacopoeia for seed materials, including cell seeds and pools of serum and, whenever possible, the source materials from which they are derived.

(3) Information shall be provided on all substances of biological origin used at any stage in the manufacturing procedure. The information shall include the manufacturing strategy, purification and 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 as well as details of any tests for contamination carried out on each batch of the substance. Any special precautions which may be necessary during storage of the starting material and, if necessary, its storage life shall be given.

(4) When starting materials of animal or human origin are used, the measures used to ensure freedom from extraneous agents shall be described. If the presence of extraneous agents is detected or suspected, the corresponding material shall be discarded or processed to reduce the risk of presence with a validated treatment. If after treatment presence is detected or suspected, the corresponding material shall be used only when further processing of the product ensures their elimination and/or inactivation; elimination and/or inactivation of such extraneous agents shall be demonstrated.

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

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

(7) In the case of veterinary medicinal products containing or consisting of genetically modified organisms (GMO), the quality part of the application shall also be accompanied by the documents required in accordance with Directive 2001/18/EC.

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

IIIa.2C2.2. Starting materials of non-biological origin

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

(a) the name of the starting material meeting the requirements of point IIIa.2A1(4) shall be supplemented by any trade or scientific synonyms;

(b) the description of the starting material, set down in a form similar to that used in a descriptive item in the European Pharmacopoeia;

(c) the function of the starting material;

(d) methods of identification;

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

IIIa.2D. Control tests during the manufacturing process

(1) The dossier shall include particulars relating to the in-process control tests, which are carried out on intermediate stages of manufacture with a view to verify the consistency of the manufacturing process and the final product. Specifications shall be set for each control test and the analytical methods shall be described. Validation of the control tests shall be provided, unless otherwise justified.

(2) The specification for the batch(es) of active substance shall define acceptance criteria together with the tests used to exert sufficient control of the quality of the active substance. A test for biological activity shall be included unless otherwise justified. Upper limits, taking into account safety considerations, shall be set for the impurities. Microbiological quality for the active substance shall be specified. Freedom from extraneous agents (bacteria, mycoplasma, fungi and viruses) shall be demonstrated according to the European Pharmacopoeia.

(3) In accordance with Directive 2010/63/EU and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, tests shall be carried out in such a way as to use the minimum number of animals and to cause the least pain, suffering, distress or lasting harm. If available, an alternative in vitro test shall be used when this leads to replacement or reduction of animal use or reduction of suffering.

IIIa.2E. Control tests on the finished product

IIIa.2E1 Finish product specification

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

Where appropriate monographs exist, if test procedures and limits other than those mentioned in the monographs of the European Pharmacopoeia, or failing this, in the pharmacopoeia of a Member State, are used, proof must be supplied that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned. The application for marketing authorisation shall list those tests, which are carried out on representative samples of each batch of finished product. The frequency of the tests carried out on the final bulk instead of on the batch or batches prepared from it, shall be stated, if applicable. The frequency of the tests which are not carried out routinely shall be justified. Acceptance criteria for release shall be indicated and justified. Validation of the control tests carried out on the finished product shall be provided.

Upper limits, taking into account safety considerations, shall be set for the impurities.

IIIa.2E2 Method descriptions and validation of release tests

(1) General characteristics

The tests of general characteristics shall, wherever applicable, relate to the appearance of the finished product and to physical or chemical tests, such as, pH, osmolality, etc. For each of those characteristics, specifications, with appropriate confidence limits, shall be established by the applicant in each particular case.

(2) Identification and potency test

Where necessary, a specific test for identification of the active substance shall be carried out. When appropriate, the identification test may be combined with the potency test.

An activity test or test for quantification of the active substance or test to quantitatively measure the functionality (biological activity/ functional effect) which is linked to relevant biological properties shall be implemented to show that each batch will contain the appropriate potency to ensure its safety and efficacy.

A biological assay shall be obligatory when physicochemical methods does not provide adequate information on the quality of the product. Such an assay shall, whenever possible, include reference materials and statistical analysis allowing calculation of confidence limits.

Where those tests may not be carried out on the finished product, they may be performed at an intermediate stage, as late as possible in the manufacturing process.

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

(3) Identification and assay of excipient components

Insofar as is necessary, the excipient(s) shall be subject at least to identification tests. An upper and lower limit test shall be obligatory in respect of preserving agents. An upper limit test for any other excipient components liable to give rise to an adverse reaction shall be obligatory. If applicable, the quantity and nature of the adjuvant and its components shall be verified on the finished product, unless otherwise justified.

(4) Sterility and purity tests

Freedom from extraneous agents (bacteria, mycoplasma, fungi and bacterial endotoxin when relevant) shall be demonstrated in compliance with the European Pharmacopoeia. Appropriate tests to demonstrate the absence of contamination by other substances, shall be carried out according to the nature of the biological veterinary medicinal product, the method and the conditions of manufacture. If fewer tests than required by the relevant European Pharmacopoeia are routinely employed for each batch, the tests carried out shall be critical to the compliance with the monograph. Proof shall be supplied that the biological veterinary medicinal product would meet the requirements, if fully tested according to the monograph.

(5) Residual humidity

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

(6) Filling volume

Appropriate tests to demonstrate the correct filling volume shall be carried out.

IIIa.2E3. Reference standards or materials

Information regarding the manufacturing process used to establish the reference material shall be provided. If more than one reference standard has been used for a particular test during product development, a qualification history shall be provided describing how the relationship between the different standards was maintained.

If other reference preparations and standards than those of the European Pharmacopoeia are used, they shall be identified and described in detail.

IIIa.2F. Batch-to-batch consistency

IIIa.2F1. Active substance

In order to ensure that quality of the active substance is consistent from batch to batch and to demonstrate conformity with specifications data from representative batches shall be provided.

IIIa.2F2. Finished product

In order to ensure that quality of the product is consistent from batch to batch and to demonstrate conformity with specifications a full protocol of three consecutive batches representative of the routine production shall be provided.

IIIa.2G. Stability tests

(1) Stability tests cover stability of the active substance and the finished product, including solvent(s), if relevant. If active substance(s) are stored, the intended conditions and duration of storage shall be defined on the basis of stability data; they may be obtained either through testing of the active substances themselves or through appropriate testing of the finished product.

(2) A description shall be given of the tests undertaken to support the shelf life, the recommended storage conditions and the specifications at the end of the shelf life proposed by the applicant. Those tests shall always be real-time studies; they shall be carried out on not fewer than three representative batches produced according to the described production process and on products stored in the final container(s); those tests include biological and physicochemical stability tests carried out at regular intervals, for the finished product until the claimed end of the shelf life.

(3) The conclusions shall contain the results of analyses, justifying the proposed shelf life under all proposed storage conditions. The results obtained during the stability study shall be taken into account when defining appropriate formulation and release specifications to ensure the conformity of the product with the claimed shelf life.

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

(5) Where a finished product requires reconstitution prior to administration or is administered in drinking water, details of the proposed shelf life are required for the product reconstituted as recommended. Data in support of the proposed shelf life for the reconstituted product shall be submitted.

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

(7) Where a finished product is liable to give rise to degradation products, the applicant shall declare those products and indicate the identification methods and test procedures used.

(8) Stability data obtained from combined products may be used where adequately justified for derivative products containing one or more of the same components.

(9) The efficacy of any preservative system shall be demonstrated. Information on the efficacy of preservatives in other similar biological veterinary medicinal products from the same manufacturer may be sufficient.

IIIa.2H. Other information

Information relating to the quality of the biological veterinary medicinal product not covered by Part IIIa.2 to IIIa2G may be included in the dossier.

IIIa.3. PART 3: Safety documentation (safety and residues tests)

(1) Each study report shall include:

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

(b) a statement of compliance with good laboratory practice, where applicable;

(c) a description of the methods, apparatus and materials used;

(d) a description and justification of the test system;

(e) a description of the results obtained, in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author;

(f) a statistical analysis of the results where appropriate;

(g) a discussion of the results, with comment on observed and no-observed-effect levels, and on any unusual findings;

(h) the name of the laboratory;

(i) the name of the study director;

(j) signature and date;

(k) place and period of time during which the study was undertaken;

(l) key for abbreviations and codes, irrespective of whether they are internationally accepted or not;

(m) description of mathematical and statistical procedures.

(2) Published studies may be accepted if they contain a sufficient amount of data and sufficient details to allow an independent assessment. The experimental techniques shall be described in such detail as to allow them to be reproduced, and the investigator shall establish their validity. Summaries of studies for which detailed reports are not available shall not be accepted as valid documentation. To address certain safety requirements reference may be made to EPMAR when the substance has been previously evaluated for the establishment of MRLs. Where reference to EPMARs is made there is no need to submit studies already evaluated as part of the MRL evaluation; only new studies not available for the MRL assessment shall be provided. If the route of exposure (for example, for the user) is not identical to the route used in accordance with Regulation (EU) 2018/78, new studies may be necessary.

IIIa.3A. Safety tests

(1) The safety documentation shall be adequate for assessment of:

(a) the potential toxicity of the veterinary medicinal product and any dangerous or undesirable effects in target species which may occur under the proposed conditions of use;

(b) 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;

(c) the potential risks to the environment resulting from the use of the veterinary medicinal product.

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

(3) An excipient used for the first time in a veterinary medicinal product or by a new means of administration shall be treated like an active substance.

(4) All sections listed in Part IIIa.3A shall be addressed. Depending on the nature of the product, certain sections may not be relevant and studies may be omitted, where justified.

IIIa.3A1. Precise identification of the product and of its active substance(s):

(a) international non-proprietary name (INN);

(b) International Union of Pure and Applied Chemistry Name (IUPAC);

(c) Chemical Abstract Service (CAS) number;

(d) therapeutic, pharmacological and chemical classification;

(e) synonyms and abbreviations;

(f) structural formula;

(g) molecular formula;

(h) molecular weight;

(i) degree of impurity;

(j) qualitative and quantitative composition of impurities;

(k) description of physical properties;

(l) solubility in water and organic solvents expressed in g/l, with indication of temperature;

(m) refraction of light, optical rotation, etc.;

(n) formulation of the product.

IIIa.3A2. Pharmacology

(1) Pharmacological studies are of fundamental importance in clarifying the mechanisms by which the veterinary medicinal product produces its therapeutic effects, and therefore pharmacological studies conducted in the target species of animal and where applicable in non-target species, shall be included. Cross-reference may be made, if applicable, to studies submitted in Part 4 of the dossier.

(2) Pharmacological studies may also assist in the understanding of toxicological phenomena. Where a veterinary medicinal product produces pharmacological effects in the absence of a toxic response, or at doses lower than those required to elicit toxicity, those pharmacological effects shall be taken into account during the evaluation of the safety of the veterinary medicinal product.

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

IIIa.3A2.1. Pharmacodynamics

Information on the mechanism of action of the active substance(s) shall be provided, together with information on primary and secondary pharmacodynamic effects in order to assist in the understanding of any adverse effects in the animal studies. Detailed reporting of pharmacodynamic properties relating to the therapeutic effect shall be reported in Part 4A of the dossier.

IIIa.3A2.2. Pharmacokinetics

Data on the fate of the active substance and its metabolites in laboratory animals shall be provided, covering absorption, distribution, metabolism and excretion (ADME). The data shall be related to the dose/effect findings in the pharmacological and toxicological studies, to determine adequate exposure.

IIIa.3A3. Toxicology

(1) The documentation on toxicology shall follow the guidance published by the Agency on the general approach to testing and guidance on particular studies. This guidance includes toxicological data required for the establishment of user safety, and the assessment of adverse effects in target animals and the environment.

(2) Toxicity studies shall be conducted with the active substance(s), not with the formulated product, unless specifically required otherwise.

(3) Animal studies shall be conducted in established strains of laboratory animals for which (preferably) historical data are available.

IIIa.3A3.1. Single-dose toxicity

Single-dose toxicity studies may be used to predict:

(a) the possible effects of acute overdose in the target species;

(b) the possible effects of accidental administration to humans;

(c) the doses which may usefully be employed in the repeat dose studies.

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

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

IIIa.3A3.2. Repeat-dose toxicity

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

A repeat-dose toxicity study in one species of experimental animal shall normally be sufficient. This study may be replaced by a study conducted in the target animal. The frequency and route of administration, and the duration of the study shall be chosen having regard to the proposed conditions of clinical use and/or user exposure. The applicant shall give his reasons for the extent and duration of the studies and the dosages chosen.

IIIa.3A3.3. Tolerance in the target species

A summary shall be provided of any signs of intolerance which have been observed during studies conducted, usually with the final formulation, in the target species in accordance with the requirements of Part IIIa.4A4 (target animal safety). The studies concerned, the dosages at which the intolerance occurred, and the species and breeds concerned shall be identified. Details of any unexpected physiological changes shall also be provided. The full reports of those studies shall be included in Part 4 of the dossier.

IIIa.3A3.4. Reproductive toxicity including developmental toxicity

(1) Study of the effects on reproduction

For products intended for use in breeding animals, reproductive safety studies in line with VICH GL43 shall be provided. Reproduction toxicity studies in laboratory animals are not expected for the evaluation of effects on the user.

(2) Study of developmental toxicity

For the evaluation of effects in the target animal species, developmental toxicity studies are not required for products intended only for use in non-breeding animals. For other products a

study of developmental toxicity shall be performed in at least one species, which may be the target species.

For the evaluation of user safety, standard developmental toxicity testing in accordance with standard tests based on established guidance (including VICH GL32 and OECD tests) shall be performed in all cases where significant user exposure may be expected.

IIIa.3A3.5. Genotoxicity

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

A standard battery of genotoxicity tests in accordance with standard tests based on established guidance (including VICH GL23 and OECD tests) shall usually be carried out on the active substance(s).

IIIa.3A3.6. Carcinogenicity

The decision on whether carcinogenicity testing is required shall take into account the results of genotoxicity tests, structure-activity relationships and the findings in repeat dose toxicity tests that may demonstrate the potential for hyper-/neo-plastic changes.

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.

Carcinogenicity testing shall be conducted in accordance with standard tests based on established guidance (including VICH GL28 and OECD tests).

IIIa.3A3.7. Exceptions

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

(a) under the intended conditions of use, oral ingestion of the veterinary medicinal product by the animal is to be expected, or

(b) under the intended conditions of use, oral exposure of the user of the veterinary medicinal product is to be expected.

IIIa.3A4. Other requirements

IIIa.3A4.1. Special studies

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

For products for which there may be exposure to skin and eyes, irritation and sensitisation studies shall be provided. Those studies shall usually be conducted with the final formulation.

The state of scientific knowledge and established guidance shall be taken into account when designing such studies and evaluating their results.

IIIa.3A4.2. Observations in humans

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

IIIa.3A4.3. Development of resistance and related risk in humans

The data requirements mentioned in this point are related to antibacterial substances and may not be applicable to other types of antimicrobial (namely antivirals, antifungals and antiprotozoals); for substances other than antibacterial for which the existence of antimicrobial resistance is well established, the same requirements may be followed, where applicable.

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

Resistance data relevant for clinical use of the product in target animals shall be addressed in accordance with Part IIIa.4A2. Where relevant, cross reference shall be made to the data set out in Part IIIa.4A2.

(1) For food-producing animals the risk assessment shall address:

(a) the identification of resistant bacteria or resistance determinants that could be associated with human illness (zoonotic and/or commensal bacteria) and are selected by the use of the antimicrobial veterinary medicinal product in target animals (hazard identification);

(b) the probability of release of the identified hazard(s) from the target animal species as a result of the use of the veterinary medicinal product under consideration;

(c) the probability of subsequent human exposure to the identified hazard(s) via the foodborne route or through direct contact, and the resulting consequences (adverse health effects) to human health. Guidance is available in VICH GL27 and EU GLs.

(2) For companion animals, consideration of risk to human or public health shall address:

(a) the identification of resistant bacteria or resistance determinants that could be associated with human illness and are selected by the use of the antimicrobial veterinary medicinal product in target animals;

(b) an estimate of exposure of zoonotic and commensal bacteria in the target animal species based on the conditions of use of the veterinary medicinal product under consideration;

(c) consideration of subsequent human exposure to AMR, and the resulting consequences to human health.

(3) Resistance in the environment shall be addressed.

IIIa.3A5. User safety

The user safety section shall include an assessment of the effects found in Part IIIa.3A to IIIa.3A4 and relate this to the type and extent of human exposure to the product with a view to formulating appropriate user warnings and other risk management measures.

User safety shall be addressed in accordance with CVMP guidelines.

IIIa.3A6. Environmental risk assessment

IIIa.3A6.1. Environmental risk assessment of veterinary medicinal products not containing or consisting of genetically modified organisms

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

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

(a) the target animal species, and the proposed pattern of use;

(b) the method of administration, in particular the likely extent to which the product will enter directly into environmental systems;

(c) the possible excretion of the product, its active substances or relevant metabolites into the environment by treated animals; persistence in such excreta;

(d) the disposal of unused veterinary medicinal product or other waste product.

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

For products intended for food producing species persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances shall be classified according to the criteria in Annex XIII to the REACH Regulation and assessed in accordance with the guidance for PBT and vPvB assessment of substances in veterinary medicines published by the Agency

IIIa.3A6.2. Environmental risk assessment for veterinary medicinal products containing or consisting of genetically modified organisms

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

(2) Potential adverse effects on human health and the environment, which may occur through gene transfer from GMOs to other organisms or arise from genetic modifications, shall be accurately assessed on a case-by-case basis. The objective of such an environmental risk assessment is to identify and evaluate potential direct and indirect, immediate or delayed adverse effects of the GMO on human health and the

environment (including plants and animals) and shall be carried out in accordance with the principles of Annex II to Directive 2001/18/EC.

IIIa.3B. Residue tests

(1) For the purposes of this point, the definitions of Regulation (EC) No 470/2009 shall apply.

(2) The purpose of studying the depletion of residues from the edible tissues or from eggs, milk and honey (wax if appropriate) derived from treated animals is to determine under what conditions and to what extent residues may persist in foodstuffs produced from those animals. In addition, the studies shall enable the determination of a withdrawal period.

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

(a) to what extent, and for how long, residues of the veterinary medicinal product or its metabolites persist in the edible tissues of the treated animal or in milk, eggs and/or honey (wax if appropriate) obtained therefrom;

(b) that in order to prevent any risk to the health of the consumer of foodstuffs from treated animals, it is possible to establish realistic withdrawal periods which may be observed under practical farming conditions;

(c) that the analytical method(s) used in the residue depletion study are sufficiently validated to provide the necessary reassurance that the residues data submitted are suitable as the basis for a withdrawal period.

IIIa.3B1. Identification of the product

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

(a) composition;

(b) the physical and chemical (potency and purity) test results for the relevant batch(es);

(c) batch identification.

IIIa.3B2. Depletion of residues

(1) The purpose of these studies, which measure the rate at which residues deplete in the target animal after the last administration of the veterinary medicinal product, is to permit the determination of withdrawal periods necessary to ensure that no residues which might constitute a hazard for consumers are present in foodstuffs obtained from treated animals.

(2) The current status of the maximum residue limits for the components of the veterinary medicinal product in the relevant target species shall be reported.

(3) The levels of residues present shall be determined at a sufficient number of time points after the test animals have received the final dose of the veterinary medicinal product. The studies in mammals and birds shall be performed according to VICH GL48 and other relevant guidelines. Residue studies in honey shall be performed according to VICH GL56 and depletion studies in aquatic species according to VICH GL57.

(4) Based on the evaluation, the rationale for the proposed withdrawal period shall be addressed.

IIIa.3B3. Residue analytical method

(1) The residue depletion study (studies), the analytical method(s) and its (their) validation shall be performed in accordance with VICH GL49.

(2) The suitability of the analytical method proposed shall be evaluated with regard to the state of scientific and technical knowledge at the time the application is submitted.

IIIa.4. PART 4: Efficacy documentation (pre-clinical studies and clinical trial(s))

IIIa.4A. Pre-clinical studies

Pre-clinical studies aim to investigate the target animal safety and efficacy of the product and are required to establish the pharmacological activity, pharmacokinetic properties, dose and dosing interval, resistance (if applicable) and the target animal tolerance of the product.

IIIa.4A1. Pharmacology

IIIa.4A1.1. Pharmacodynamics

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

(1)(2) The mode of action and the pharmacological effects on which the recommended application in practice is based shall be adequately described, including secondary effects (if any). In general, the effects on the main body functions shall be investigated. The results shall be expressed in quantitative terms (using, for example, dose-effect curves, time-effect curves, etc.) and, wherever possible, in comparison with a substance the activity of which is well known. Where a higher activity is being claimed for an active substance, the difference shall be demonstrated and shown to be statistically significant.

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

(1)(4) The experimental techniques, unless they are standard procedures, shall be described in such detail as to allow them to be reproduced, and their validity to be established. The experimental results shall be set out clearly and the outcome of any statistical comparisons presented.

(1)(5) Unless adequate reasons are given to the contrary, any quantitative modification of responses resulting from repeated administration of the substance shall also be investigated.

IIIa.4A1.2. Pharmacokinetics

(2)(1) Basic pharmacokinetic data on the active substance are required in the context of assessment of the target animal safety and efficacy of the veterinary medicinal product in the target species, particularly if this concerns a new substance or formulation.

(2)(2) The objectives of pharmacokinetic studies in the target animal species may be divided into four main areas:

(a) to describe the basic pharmacokinetic characteristics (namely absorption, distribution, metabolism and excretion) of the active substance in the formulation;

(b) to investigate the relationships between dosage regimen, plasma and tissue concentration over time and pharmacological, therapeutic or toxic effects;

(c) where appropriate, to compare pharmacokinetic parameters between different target species and to explore possible species differences having an impact on target animal safety and efficacy of the veterinary medicinal product;

(d) where appropriate, to compare bioavailability to support bridging of safety and efficacy information between different products, pharmaceutical forms, strengths or routes of administration, or to compare the impact of changes in manufacturing or composition, including pilot and final formulations.

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

(2)(4) Where pharmacokinetic studies have been submitted under Part 3 of the dossier, cross-reference to such studies may be made.

(2)(5) For fixed combinations, please refer to Section IV.

IIIa.4A2. Development of resistance and related risk in animals

(1) For relevant biological veterinary medicinal products (for example, substances with antimicrobial and antiparasitic activity), information on current resistance (if applicable) and on the potential emergence of resistance of clinical relevance for the claimed indication in the target animal species shall be provided. Where possible, information on the resistance mechanism(s), the molecular genetic basis of resistance, and the rate of transfer of resistance determinants shall be presented. Whenever relevant, information on co-resistance and cross-resistance shall be presented. Measures to limit resistance development in organisms of clinical relevance for the intended use of the veterinary medicinal product shall be proposed by the applicant.

(2) Resistance relevant for risks to humans shall be addressed in Part 3 of the dossier. Where relevant, cross-reference shall be made to data set out in Part 3 of the dossier.

IIIa.4A3. Dose determination and confirmation

(1) Appropriate data shall be provided to justify the proposed dose, dosing interval, duration of treatment and any re-treatment interval.

(2) For studies conducted under field conditions, relevant information shall be provided as outlined under clinical studies.

IIIa.4A4. Tolerance in the target animal species

(1) The local and systemic tolerance of the veterinary medicinal product shall be investigated in the target animal species. The purpose of target animal safety studies is to characterise signs of intolerance and to establish an adequate margin of safety using the recommended route(s) of administration. This may be achieved by increasing the dose and/or the duration of treatment.

(2) The study report(s) shall contain details of all expected pharmacological effects and all adverse reactions. The conduct of target animal safety studies shall be in accordance with VICH and relevant guidance published by the Agency. Other pre-clinical studies and clinical studies, along with relevant information from the published literature may also provide information on safety in the target species.

IIIa.4B. Clinical trials

IIIa.4B1. General principles

(1) Clinical trials shall be designed, carried out and reported taking into account VICH and relevant guidance published by the Agency. Data stemming from clinical trials conducted outside the Union may be taken into consideration for the assessment of an application for a marketing authorisation only, if the data are sufficiently representative of the Union situation.

(2) Experimental data such as exploratory/pilot trials, or results from non-experimental approaches shall be confirmed by data obtained under normal field conditions, unless otherwise justified.

(3) The purpose of clinical trials is to examine under field conditions the target animal safety and efficacy of a veterinary medicinal product under normal conditions of animal husbandry and/or as part of good veterinary practice. They shall demonstrate the effect of the veterinary medicinal product after administration to the intended target species using the proposed dosage regimen and the proposed route(s) of administration. The trial design shall aim to support the indications and take into account any contra-indications according to species, age, breed and sex, directions for use of the veterinary medicinal product as well as any adverse reactions which it may have.

(4) All veterinary clinical trials shall be conducted in accordance with a detailed trial protocol. For formulations intended for use in veterinary clinical trials in the Union, the words 'for veterinary clinical trial use only' shall appear prominently and indelibly on the labelling.

(5) Unless otherwise justified, clinical trials shall be carried out with control animals (controlled clinical trials). The efficacy results obtained with the new product shall be compared with those from the target animal species that have received a veterinary medicinal product authorised in the Union that has demonstrated an acceptable level of efficacy and been approved for the proposed indication(s) for use in the same target animal species, or a placebo or no treatment. All the results obtained, whether positive or negative, shall be reported.

(6) Established statistical principles in accordance with the relevant guidance published by the Agency shall be used in protocol design, analysis and evaluation of clinical trials, unless otherwise justified.

IIIa.4B2. Documentation

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

IIIa.4B2.1. Results of pre-clinical studies

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

(a) tests demonstrating pharmacological activity;

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

(c) tests demonstrating the main pharmacokinetic profile;

(d) tests demonstrating target animal safety;

(e) tests to determine and confirm the dose (including dose interval, duration of treatment and any re-treatment interval);

(f) tests and investigations on resistance, if applicable.

In the case where unexpected results occur during the course of the tests, those results shall be sufficiently detailed. Additionally, the following particulars shall be provided in all pre-clinical study reports.

(a) a summary;

(b) a study protocol;

(c) a detailed description of the objectives, design and conduct to include methods, apparatus and materials used, details such as species, age, weight, sex, number, breed or strain of animals, identification of animals, dose, route and schedule of administration;

(d) a statistical analysis of the results;

(e) an objective discussion of the results obtained, leading to conclusions on the efficacy and target animal safety of the veterinary medicinal product.

Omission of any of those data shall be justified.

IIIa.4B2.2. Results of clinical trials

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

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

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

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

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

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

(i) received no treatment;

(ii) received a placebo;

(iii) received another veterinary medicinal product authorised in the Union that has demonstrated an acceptable level of efficacy and been approved for the proposed indication(s) for use in the same target animal species; or

(iv) received the same active substance under investigation in a different formulation or by a different route;

(d) the frequency of observed adverse reactions;

(e) observations as to the effect on animal performance, if appropriate;

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

animals the physiological or pathological condition of which requires special consideration;

(g) a statistical evaluation of the results.

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

SECTION IIIb
REQUIREMENTS FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

The following requirements shall apply to immunological veterinary medicinal products as defined in Article 4(5), except where otherwise set out in Section IV.

IIIb.1. PART 1: Summary of the dossier

Please refer to Section I.

IIIb.2. PART 2: Quality documentation (physicochemical, biological and microbiological information)

IIIb.2.A. Product description

IIIb.2A1. Qualitative and quantitative composition

(1) Qualitative composition of all the constituents of the immunological veterinary medicinal product shall mean the designation or description of:

(a) the active substance(s);

(b) the constituents of the adjuvants;

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

(d) accompanying reconstitution solvents.

(2) Those data in point (1) shall be supplemented by any relevant data concerning the immediate packaging and if relevant the outer packaging and, where appropriate, its manner of closure, together with details of devices with which the immunological veterinary medicinal product will be used or administered and which will be delivered with the medicinal product. If the device is not delivered together with the immunological veterinary medicinal product, relevant information about the device shall be provided, where necessary for the assessment of the product.

(3) The usual terminology to be used in describing the constituents of immunological veterinary medicinal products, notwithstanding the application of the other provisions of Article 8, means:

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

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

(c) in respect of colouring matter designation by the 'E' code assigned to them in Directive 2009/35/EC.

(4) In order to give the quantitative composition of the active substances of an immunological veterinary medicinal product, it is necessary to specify whenever possible the number of organisms, the specific protein content, the mass, the number of International Units (IU) or units of biological activity, either per dosage-unit or volume, and with regard to the adjuvant and to the constituents of the excipients, the mass or the volume of each of them, with due allowance for the details provided in Part IIb.2B.

(5) Where an international unit of biological activity has been defined, this shall be used.

(6) The units of biological activity for which no published data exist shall be expressed in such a way as to provide unambiguous information on the activity of the ingredients, for example, by stating the amount as determined by titration or potency testing of the final product.

(7) The composition shall be given in terms of minimum quantities and, if appropriate, with maximum quantities.

IIIb.2A2. Product development

(1) Explanation shall be provided with regard to, but may not be limited to:

(a) the choice of composition and the choice of the constituents, in particular relative to their intended functions and their respective concentrations;

(b) the inclusion of a preservative in the composition shall be justified;

(c) the immediate packaging and the suitability of the container and its closure system used for the storage and use of the finished product. A study of the interaction between finished product and the primary packaging shall be submitted wherever the risk of such interaction is regarded as possible, especially where injectable preparations are concerned;

(d) the possible further packaging, outer packaging if relevant;

(e) the proposed pack sizes related to the proposed route of administration, the posology and the target species;

(f) any overage(s) in the formulation to guarantee minimum potency/antigen content at end of shelf life with justification;

(g) the selection of the manufacturing process of the active substance and the finished product;

(h) differences between the manufacturing process(es) used to produce batches used in clinical trials and the process described in the application for marketing authorisation shall be discussed;

(i) when an accompanying test is recommended to be used with the finished product (e.g. diagnostic test), relevant information about the test shall be provided.

(2) This explanation shall be supported by scientific data on product development.

IIIb.2B. Description of the manufacturing method

(1) The description of the manufacturing method accompanying the application for marketing authorisation pursuant to Article 8 shall be drafted in such a way as to give an adequate description of the nature of the operations employed, including the identification of the key stages in the production process.

(2) The description of the manufacturing process shall include at least:

(a) the various stages of manufacture (including production of the antigen and purification procedures) accompanied by a process flow chart so that an assessment may be made of the reproducibility of the manufacturing procedure and of the risks of adverse effects on the finished products, such as microbiological contamination;

(b) in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity and consistency of each batch of the finished product. Information on how a batch is defined and on the proposed commercial batch size(s) shall be provided;

(c) listing of all the substances at the appropriate steps where they are used, including those which cannot be recovered in the course of manufacturing;

(d) the details of the blending, with the quantitative particulars of all the substances used, including an example for a representative production batch;

(e) list of in-process controls including the stage of manufacture at which they are conducted;

(f) for sterile products, where non-pharmacopoeial sterilisation conditions are used, details of the sterilisation processes and/or aseptic procedures used.

(3) Validation of all the methods of control used in the manufacturing process shall be described, documented and the results provided, unless otherwise justified. The validation of key stages in the production process shall be demonstrated and the validation of the production process as a whole shall be demonstrated with provision of results of three consecutive batches produced using the method described.

IIIb.2C. Production and control of starting materials

(1) For the purposes of this Part, ‘starting materials’ means all components used in the production of the immunological veterinary medicinal product.

(2) Commercially available ready-to-use adjuvant systems designated by a brand name as well as culture media used for production of the active substance consisting of several components shall be regarded as one starting material. Nevertheless, the qualitative and quantitative composition shall be presented insofar as the authorities consider that this information is relevant to the quality of the finished product and any risks that might be posed.

(3) If materials of animal origin are used for preparation of those culture media or adjuvant systems, the animal species and the tissue used have to be included and compliance with the relevant monographs including general monographs and general chapters of the European Pharmacopoeia shall be demonstrated.

(4) The applicant shall supply documentation to demonstrate that the starting materials, including seed materials, cell seeds, batches of serum and other material originating from animal species relevant for the transmission of TSE and the manufacturing of

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

(5) The dossier shall include the specifications, information on the tests to be conducted for the quality control of all batches of starting materials and results for a batch for all components used and shall be submitted in accordance with the requirements of this Part.

(6) Certificates of analysis shall be presented for the starting materials in order to demonstrate compliance with the defined specification.

(7) Colouring matter shall, in all cases, satisfy the requirements of Directive 2009/35/EC.

(8) The use of antibiotics during production and the inclusion of preservatives in the composition of the finished product shall be justified and in compliance with the European Pharmacopoeia.

(9) For novel excipients, that is to say excipient(s) used for the first time in the Union in a veterinary medicinal product or by a new route of administration, details of manufacture, characterisation, and controls, with cross references to supporting safety data, both clinical and non- clinical, shall be provided. For colouring matters the declarations of compliance as mentioned under Part II.2C2, points (3) and (4) shall be considered sufficient.

IIIb.2C1. Starting materials listed in pharmacopoeias

(1) The monographs of the European Pharmacopoeia shall be applicable to all starting materials appearing in it, unless proper justification is provided.

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

(3) The description of the analytical methods may be replaced by a detailed reference to the pharmacopoeia in question.

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

(5) In cases where a specification or other provisions contained in a monograph of the European Pharmacopoeia or in the pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the applicant for marketing authorisation. The alleged insufficiency shall be reported to the authorities responsible for the pharmacopoeia in question.

IIIb.2C2. Starting materials not listed in a pharmacopoeia

IIIb.2C2.1. Starting materials of biological origin

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

(2) Vaccine production shall be based on a seed lot system and on established cell seeds, whenever possible. For the production of immunological veterinary medicinal products consisting of serum, the origin, general health and immunological status of the producing animals shall be indicated and defined pools of source materials shall be used.

(3) The origin, including geographical region, and history of starting materials shall be described and documented.

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

(5) In the case of veterinary medicinal products containing or consisting of genetically modified organisms (GMO), the quality part of the application shall also be accompanied by the documents required in accordance with Directive 2001/18/EC.

(6) Seed materials, including cell seeds and raw serum for anti-serum production shall be tested for identity and the absence of extraneous agents shall be demonstrated according to the European Pharmacopoeia.

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

(a) details of the source of the materials;

(b) details of any processing, purification and inactivation applied, with data on the validation of those processes and controls during production;

(c) details of any tests for contamination carried out on each batch of the substance.

(8) If the presence of extraneous agents is detected or suspected, the corresponding material shall be discarded or processed to reduce the risk of presence with a validated treatment. If after treatment presence is detected or suspected, the corresponding material shall be used only when further processing of the product ensures their elimination and/or inactivation; elimination and/or inactivation of such extraneous agents shall be demonstrated.

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

(10) For live attenuated vaccines, confirmation of the stability of the attenuation characteristics of the seed shall be provided. Unless a specific characteristic is associated with the attenuation (e.g. genetic marker, thermal stability), this is typically achieved through absence of reversion to virulence in the target animal species.

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

IIIb.2C2.2. Starting materials of non-biological origin

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

(a) the name of the starting material meeting the requirements of point (3) of Part IIIb.2A1. shall be supplemented by any trade or scientific synonyms;

(b) the description of the starting material, set down in a form similar to that used in a descriptive item in the European Pharmacopoeia;

(c) the function of the starting material;

(d) methods of identification;

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

IIIb.2D. Control tests during the manufacturing process

(1) The dossier shall include particulars relating to the control tests, which are carried out on intermediate stages of manufacture with a view to verifying the consistency of the manufacturing process and the final product. Specifications shall be set for each control test and the analytical methods shall be described. Validation of the control tests for parameters considered critical to the manufacturing process shall be provided unless otherwise justified.

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

(3) In accordance with the provisions of Directive 2010/63/EU and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, tests shall be carried out in such a way as to use the minimum number of animals and to cause the least pain, suffering, distress or lasting harm. If available, an alternative in vitro test shall be used when this leads to replacement or reduction of animal use or reduction of suffering.

IIIb.2E. Control tests on the finished product

(1) For all tests, the description of the techniques for analysing the finished product shall be set out in sufficient detail for a quality assessment.

(2) Where appropriate monographs exist, if test procedures and limits other than those mentioned in the monographs of the European Pharmacopoeia, or failing this, in the pharmacopoeia of a Member State, are used, proof shall be supplied that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned. The application for marketing authorisation shall list those tests, which are carried out on representative samples of each batch of finished product. The frequency of the tests carried out on the final bulk vaccine instead of on the batch or batches prepared from it, shall be stated. Release limits shall be indicated and justified. Validation of the control tests carried out on the finished product shall be provided.

(3) Information regarding the establishment and replacement of reference material shall be provided. If more than one reference standard has been used, a qualification history shall be provided describing how the relationship between the different standards was maintained.

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

(5) In accordance with the provisions of Directive 2010/63/EU and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, tests shall be carried out in such a way as to use the minimum number of animals and to cause the least pain, suffering, distress or lasting harm. If available, an alternative *in vitro* test shall be used when this leads to replacement or reduction of animal use or reduction of suffering.

(6) General characteristics of the finished product

The tests of general characteristics shall, wherever applicable, relate to the appearance and to physical or chemical tests, such as, conductivity, pH, viscosity, etc. For each of those characteristics, specifications, with appropriate acceptance limits, shall be established by the applicant.

(7) Identification of active substance(s)

Where necessary, a specific test for identification shall be carried out. When appropriate, the identification test may be combined with the batch titre or potency test.

(8) Batch titre or potency

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

(9) Identification and assay of adjuvants

The quantity and nature of the adjuvant and its components shall be verified on the finished product, unless otherwise justified.

(10) Identification and assay of excipient components

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

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

(11) Sterility and purity test

Freedom from extraneous agents (bacteria, mycoplasma, fungi and bacterial endotoxin when relevant) shall be demonstrated for parenterally administered products in compliance with the European Pharmacopoeia. For non-liquid, non-parenterally administered products, where adequately justified, compliance to a maximum bioburden limit instead of sterility test may be acceptable.

Appropriate tests to demonstrate the absence of contamination by extraneous agents or other substances, shall be carried out according to the nature of the immunological veterinary medicinal product, the method and the conditions of manufacture. A risk-based approach to demonstrate the absence of extraneous agents as described in the European Pharmacopoeia shall be used.

(12) Residual humidity

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

(13) Filling volume

Appropriate tests to demonstrate the correct filling volume shall be carried out.

IIIb.2F. Batch-to-batch consistency

In order to ensure that quality of the product is consistent from batch to batch and to demonstrate conformity with specifications a full protocol of three consecutive batches representative of the routine production giving the results for all tests performed during production and on the finished product shall be provided. Consistency data obtained from combined products may be used for derivative products containing one or more of the same components.

IIIb.2G. Stability tests

(1) Stability tests cover stability of the active substance and the finished product, including solvent(s), if relevant.

(2) A description shall be given of the tests undertaken to support the shelf life, the recommended storage conditions and the specifications at the end of the shelf life proposed for the active substance and the finished product. Those tests shall always be real-time studies.

If intermediate products obtained at various stages of the manufacturing process are stored, the intended conditions and duration of storage shall be adequately justified on the basis of the stability data available.

(3) Stability tests for the finished product shall be carried out on not fewer than three representative batches produced according to the described production process and on products stored in the final container(s); those tests include biological and physicochemical stability tests carried out at regular intervals, for the finished product until 3 months beyond the claimed end of the shelf life.

(4) The conclusions shall contain the results of analyses, justifying the proposed shelf life under all proposed storage conditions. The results obtained during the stability study shall be taken into account when defining appropriate formulation and release specifications to ensure the conformity of the product with the claimed shelf life

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

(6) Where a finished product requires reconstitution prior to administration or is administered in drinking water, details of the proposed shelf life are required for the product reconstituted as recommended. Data in support of the proposed shelf life for the reconstituted product shall be submitted.

(7) Stability data obtained from combined products may be used where adequately justified for derivative products containing one or more of the same components.

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

(9) The efficacy of any preservative system shall be demonstrated.

(10) Information on the efficacy of preservatives in other similar immunological veterinary medicinal products from the same manufacturer may be sufficient.

(11) If active substances are stored, the intended conditions and duration of storage shall be defined on the basis of stability data. Those data may be obtained either through

testing of the active substances themselves or through appropriate testing of the finished product.

IIIb.2H. Other information

Information relating to the quality of the immunological veterinary medicinal product not covered by this Section may be included in the dossier.

***IIIb.3. PART 3: Safety documentation (safety and residues tests*)**

IIIb.3A. General requirements

(1) The safety documentation shall be adequate for the assessment of:

(a) the safety of the immunological veterinary medicinal product when administered to the target species and any undesirable effects which may occur under the proposed conditions of use; those undesirable effects shall be evaluated in relation to potential benefits of the product;

(b) the potential harmful effects to man of residues of the veterinary medicinal product or substance in foodstuffs obtained from treated animals;

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

(d) the potential risks to the environment resulting from the use of the veterinary medicinal product.

(2) Pre-clinical studies shall be carried out in compliance with good laboratory practice (GLP) requirements.

Non-GLP studies may be accepted for non-target species studies as well as studies evaluating immunological, biological or genetic properties of the vaccine strains, under adequately controlled conditions. Other deviations shall be justified.

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

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

(5) Clinical trials (field trials) shall be conducted in compliance with established principles of good clinical practice (GCP). Deviations shall be justified.

(6) The safety studies shall be in line with the relevant European Pharmacopeia requirements. Deviations shall be justified.

(7) The safety studies shall be carried out in the target species. The dose to be used shall be the quantity of the product to be recommended for use and the batch used for safety testing shall be taken from a batch or batches produced according to the manufacturing process described in Part 2 of the application.

(8) For laboratory tests described in Sections B.1, B.2 and B.3, the dose of the veterinary medicinal product shall contain the maximum titre, antigen content or potency. If necessary, the concentration of the antigen may be adjusted to achieve the required dose.

(9) The safety of an immunological veterinary medicinal product shall be demonstrated for each category of target animal species in which its use is recommended, by each recommended route and method of administration and using the proposed schedule of administration. A worst-case scenario for route and method of administration may be used if scientifically justified.

(10) In the case of immunological veterinary medicinal products consisting of live organisms, special requirements are included under B.6.

(11) The particulars and documents which shall accompany the application for marketing authorisation shall be submitted in accordance with the requirements for pre-clinical studies and clinical trials described in Parts IIIb.4B, point (4), and IIIb.4C, point (3). .

IIIb.3B. Pre-clinical studies

(1) Safety of the administration of one dose

The immunological veterinary medicinal product shall be administered at the recommended dose and by each recommended route and method of administration to animals of each species and each relevant category (e.g. minimum age, pregnant animals, as appropriate) in which it is intended for use.

The animals shall be observed and examined daily for signs of systemic and local reactions until reactions may no longer be expected, but in all cases, at least 14 days after administration. Where appropriate, those studies shall include detailed post-mortem macroscopic and microscopic examinations of the injection site. Other objective criteria shall be recorded, such as rectal temperature and performance measurements.

This study may be part of the repeated dose study required under point 3 or omitted if the results of the overdose study required under point 2 have revealed no major signs of systemic or local reactions. If omitted, the systemic or local reactions seen in the overdose study shall be taken as the basis for describing safety of the product in the Summary of Product Characteristics.

(2) Safety of one administration of an overdose

Only live immunological veterinary medicinal products require overdose testing.

An overdose of the immunological veterinary medicinal product, normally consisting of ten doses, shall be administered by each recommended route(s) and method(s) of administration to animals of the most sensitive categories of the target species, unless the selection of the most sensitive of several similar routes is justified. In the case of immunological veterinary medicinal products administered by injection, the doses and route(s) and method(s) of administration shall be chosen to take account of the maximum volume, which can be administered at any one single injection site.

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

Where appropriate, those studies shall include detailed post-mortem macroscopic and microscopic examinations of the injection site if this has not been done under point 1.

(3) Safety of the repeated administration of one dose

In the case of immunological veterinary medicinal products to be administered more than once, as part of the basic administration scheme, a study of the repeated administration of one dose shall be required to reveal any adverse effects induced by such administration.

The test shall be carried out on the most sensitive categories of the target species (such as certain breeds, age groups), using each recommended route and method of administration.

The number of administrations shall not be less than the maximum number recommended; for vaccines, this shall take account of the number of administrations for primary vaccination and the first re-vaccination.

The interval between administrations may be shorter than the one claimed in the Summary of Product Characteristics. The chosen interval shall be justified with respect to the proposed conditions of use.

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

(4) Examination of reproductive performance

Examination of reproductive performance shall be considered when the immunological veterinary product is intended for use or may be used in pregnant animals or laying birds and when data suggest that the starting material from which the product is derived may be a potential risk factor.

Reproductive performance of males and non-pregnant and pregnant females shall be investigated with the recommended dose and by the most sensitive route and method of administration.

For immunological veterinary medicinal products that are recommended for use in pregnant animals, examination of the reproductive performance shall address safety of administration during the entire gestation period or during specific period of gestation taking into account the intended use of the product.

The observation period shall be extended to parturition to investigate possible harmful effects on the progeny, including teratogenic and abortifacient effects.

Those studies may form part of the safety studies described in points 1, 2, 3 or of the field trials provided for in Section IIIb.3C.

(5) Examination of immunological functions

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

(6) Special requirements for live vaccines

(6)(1) Spread of the vaccine strain

Spread of the vaccine strain from vaccinated to unvaccinated target animals shall be investigated, using the recommended route of administration most likely to result in the spread. Moreover, it may be necessary to investigate the spread to non-target animal species which could be highly susceptible to a live vaccine strain. An assessment of the number of animal-to-animal passages likely to occur under normal conditions of use and potential consequences shall be provided.

(6)(2) Dissemination in the vaccinated animal

Faeces, urine, milk, eggs, oral, nasal and other secretions shall be tested for the presence of the organism as appropriate. Moreover, studies may be required of the dissemination of the vaccine strain in the body, with particular attention being paid to the predilection sites for replication of the organism. In the case of live vaccines for zoonoses within the meaning of

Directive 2003/99/EC of the European Parliament and of the Council to be used for food producing animals, those studies shall take particularly into account the persistence of the organism at the injection site.

(6)(3) Increase in virulence

Increase in or reversion to virulence shall be investigated with the master seed. If the master seed is not available in sufficient quantity the lowest passage seed used for the production shall be examined. Use of another passage option shall be justified. The initial vaccination shall be carried out using the route and method of administration most likely to lead to an increase in virulence indicative of reversion to virulence. Serial passages shall be made in target animals through five groups of animals, unless there is justification to make more passages or the organism disappears from the test animals sooner. Where the organism fails to replicate adequately, as many passages as possible shall be carried out in the target species.

(6)(4) Biological properties of the vaccine strain

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

For vaccines containing live genetically modified organism(s), where the product of a foreign gene is incorporated into the strain as a structural protein, the risk of changing the tropism or virulence of the strain shall be addressed and, where necessary, specific tests shall be conducted.

(6)(5) Recombination or genomic reassortment of strains

The probability of recombination or genomic reassortment with field or other strains shall be evaluated and the consequences of such events discussed.

(7) User safety

This section shall include a discussion of the effects found in Part IIIb.3A to IIIb.3B and relate those effects to the type and extent of human exposure to the product with a view to formulating appropriate user warnings and other risk management measures.

User safety shall be addressed in accordance with relevant guidance published by the Agency.

(8) Interactions

If there is a compatibility statement with other veterinary medicinal products in the summary of product characteristics the safety of the association shall be investigated. Any other known interactions with veterinary medicinal products shall be described.

IIIb.3C. Clinical trials

Unless otherwise justified, results from pre-clinical studies shall be supplemented with data from clinical trials, using batches representative of the manufacturing process described in the marketing authorisation application. Both safety and efficacy may be investigated in the same clinical trials.

IIIb.3D. Environmental risk assessment

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

(2) This assessment consists of two phases. The first phase of the assessment shall always be performed. The details of the assessment shall be provided in accordance

with guidance published by the Agency. It shall indicate the potential exposure of the environment to the product and the level of risk associated with any such exposure, taking into account in particular the following items:

(a) the target animal species and the proposed pattern of use;

(b) the route and method of administration, in particular the likely extent to which the product will enter directly into the environmental system;

(c) the possible excretion or secretion of the product, its active substances into the environment by treated animals, persistence in such excreta or secreta;

(d) the disposal of unused or waste product.

(3) In the case of live vaccine strains which may be zoonotic, the risk to humans shall be assessed.

(4) Where the conclusions of the first phase indicate a relevant potential risk for the environment of the product, the applicant shall proceed to the second phase and evaluate the potential risk(s) that the veterinary medicinal product might pose to the environment. Where necessary, further investigations on the impact of the product (soil, water, air, aquatic systems, non-target organisms) shall be carried out.

(5) For DNA vaccines, a specific safety concern is the potential risk of migration of the DNA to gonadal tissues and potential DNA transfer into germ line cells of vaccinated male and female animals and thus potential transmission to offspring. The applicant shall evaluate and discuss potential risk(s) such immunological veterinary medicinal products might pose on human health and the environment (including plants and animals). If potential risk(s) are identified, investigations on the impact of the vaccine depending on its use in companion animals or in food producing animals shall be carried out to provide information on this point.

IIIb.3E. Assessment required for veterinary medicinal products containing or consisting of genetically modified organisms

(1) In the case of veterinary medicinal products containing or consisting of genetically modified organisms (GMOs) the application shall also be accompanied by the documents required under Article 2 and Part C of Directive 2001/18/EC and the specific guidance dealing with GMOs.

(2) Potential adverse effects on human health and the environment, which may occur through gene transfer from GMOs to other organisms or arise from genetic modifications, shall be accurately assessed on a case-by-case basis. The objective of such an environmental risk assessment is, to identify and evaluate potential direct and indirect, immediate or delayed adverse effects of the GMO on human health and the environment (including plants and animals) and shall be carried out in accordance with the principles of Annex II to Directive 2001/18/EC.

IIIb.3F. Residue tests to be included in the pre-clinical studies

(1) For immunological veterinary medicinal products, it will normally not be necessary to undertake a study of residues.

(2) Where antibiotics, adjuvants, preservatives or any other excipient are used in the manufacture of immunological veterinary medicinal products intended for food producing animals and/or are included in the final formulation, consideration shall be given to the possibility of consumer exposure to residues in foodstuffs derived from treated animals and compliance with MRLs legislation. Consumer safety

implications arising from their potential presence in the finished product shall be addressed.

(3) In the case of live vaccines for well-established zoonotic diseases, in addition to the studies of dissemination, the determination of residual vaccine organisms at the injection site may be required. If necessary, the effects of such residues shall be investigated.

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

IIIb.4. PART 4: Efficacy documentation (pre-clinical studies and clinical trial(s))

IIIb.4A. General requirements

(1) The following general requirements shall be complied with:

(a) the efficacy studies shall be in line with the general European Pharmacopeia requirements; Deviations shall be justified.

(b) the primary parameter on which determination of efficacy is based needs to be defined by the investigator at the time of study design and shall not be changed after the study is completed;

(c) the planned statistical analysis shall be described in detail in the study protocols;

(d) the choice of antigens or vaccine strains shall be justified on the basis of epizoological data;

(e) efficacy trials carried out in the laboratory shall be controlled trials, including untreated control animals unless this is not justified for animal welfare reasons and efficacy can be otherwise demonstrated.

(2) In general, pre-clinical studies shall be supported by trials carried out in field conditions.

When pre-clinical studies fully support the claims made in the summary of product characteristics, trials carried out in field conditions are not required.

Unless otherwise justified, results from pre-clinical studies shall be supplemented with data from clinical trials, using batches representative of the manufacturing process described in the marketing authorisation application. Both safety and efficacy may be investigated in the same clinical trials.

(3) All trials shall be described in sufficient detail so as to be properly assessed by the competent authorities. The validity of all techniques used in the trial shall be demonstrated.

(4) All results obtained, whether favourable or unfavourable, shall be reported:

(a) The efficacy of an immunological veterinary medicinal product shall be demonstrated for each category of target animal species in which its use is recommended, by each recommended route and method of administration and using the proposed schedule of administration. Unless otherwise justified, the onset and duration of immunity shall be established and supported by data from trials.

(b) The influence of passively acquired maternally derived antibodies on the efficacy of vaccines when administered to animals at an age at which maternally acquired immunity is still present shall be adequately evaluated, if appropriate.

(c) The efficacy of each of the components of multivalent and combined immunological veterinary medicinal products shall be demonstrated. If the product is recommended for administration in combination with or at the same time as another veterinary medicinal product, to the efficacy of the association shall be demonstrated by appropriate studies. Any known interactions with any other veterinary medicinal products shall be described.

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

(e) The dose to be used shall be the quantity of the product to be recommended for use and the batch used for efficacy testing shall be taken from a batch or batches produced according to the manufacturing process described in Part 2 of the application.

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

(g) For vaccines intended to allow a distinction between vaccinated and infected animals (marker vaccines), where the efficacy claim is reliant on *in vitro* diagnostic tests, sufficient data on the diagnostic tests shall be provided to allow adequate assessment of the claims related to the marker properties.

IIIb.4B. Pre-clinical studies

(1) In principle, demonstration of efficacy shall be undertaken under well-controlled laboratory conditions by challenge after administration of the immunological veterinary medicinal product to the target animal under the recommended conditions of use. Insofar as possible, the conditions under which the challenge is carried out shall reflect the natural conditions for infection. Details of the challenge strain and its relevance shall be provided.

(2) For live vaccines, the product used for efficacy testing shall be taken from a batch or batches containing the minimum titre or potency. For other products, product from batches containing the minimum active content or potency expected at the end of the period of validity shall be used, unless otherwise justified.

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

(4) The following shall be provided for all pre-clinical studies:

(a) a summary;

(b) a statement of compliance with good laboratory practice for pre-clinical studies, where applicable;

(c) the name of the body having carried out the studies;

(d) a detailed experimental protocol giving a description of the methods, apparatus and materials used, details such as species or breed of animals, categories of animals, where they were obtained, their identification and number, the conditions under which they were housed and fed (stating, inter alia, whether they were free from any

specified pathogens and/or specified antibodies, the nature and quantity of any additives contained in the feed), dose, route, schedule and dates of administration, a description and a justification of the statistical methods used;

(e) in the case of control animals, whether they received a placebo or no treatment;

(f) in the case of treated animals and, where appropriate, whether they received the test product or another product authorised in the Union;

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

(h) the nature, frequency and duration of observed adverse reactions;

(i) the number of animals withdrawn prematurely from the studies and reasons for such withdrawal;

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

(k) occurrence and course of any intercurrent disease;

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

(m) any other observations and deviations from the protocol and possible impact on the results;

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

IIIb.4C. Clinical trials

(1) Unless otherwise justified, results from pre-clinical studies shall be supplemented with data from field trials, using batches representative of the manufacturing process described in the marketing authorisation application. Both safety and efficacy may be investigated in the same field trial.

(2) Where pre-clinical studies cannot be supportive of efficacy, the performance of field trials alone may be acceptable.

(3) Particulars concerning field trials shall be sufficiently detailed to enable an objective judgement to be made. They shall include the following:

(a) a summary;

(b) a statement of compliance with good clinical practice;

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

(d) place and date of administration, identity code that may be linked to the name and address of the owner of the animal(s);

(e) details of the trial protocol, giving a description of the methods, apparatus and materials used, details such as the route and method of administration, the schedule of administration, the dose, the categories of animals, the duration of observation, the

serological response and other investigations carried out on the animals after administration;

(f) in the case of control animals, whether they received a placebo, a competitor product or no treatment;

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

(h) a brief description of the method of rearing and feeding, stating the nature and quantity of any additives contained in the feed;

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

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

(k) all observations and results of the trials, whether favourable or unfavourable, with a full statement of the observations and the results of the objective tests of activity required to evaluate the product; the techniques used shall be specified and the significance of any variations in the results explained;

(l) effects on the animals' performance;

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

(n) the nature, frequency and duration of observed adverse reactions;

(o) occurrence and course of any intercurrent disease;

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

(q) any other observations and deviations for the protocol and possible impact on the results;

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

SECTION IV
REQUIREMENTS FOR SPECIFIC MARKETING AUTHORISATION APPLICATIONS

IV.1. Applications for generic veterinary medicinal products

IV.1.1. Applications based on Article 18 (generic veterinary medicinal products) shall contain the data referred to in Parts 1 and 2 of Section II of this Annex. If required, pursuant to Article 18(7) an environmental risk assessment shall be included. In addition, the dossier shall contain data demonstrating that the product has the same qualitative and quantitative composition in active substance(s) and the same pharmaceutical form as the reference medicinal product; and data, showing bioequivalence with the reference medicinal product or a justification as to why such studies were not performed with reference to established

guidance. All immediate-release oral pharmaceutical forms shall be considered to be the same pharmaceutical form.

For biological (including immunological) veterinary medicinal products, the standard generic approach is in principle not considered appropriate, and a hybrid approach shall be followed (see Part IV.2.).

IV.1.2. For generic veterinary medicinal products, the critical expert reports on safety and efficacy shall particularly focus on the following elements:

(a) the grounds for claiming bioequivalence;

(b) a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) together with an evaluation of those impurities;

(c) an evaluation of the bioequivalence studies or other information that may provide support for claiming bioequivalence in accordance with relevant guidance published by the Agency;

(d) any additional data in order to demonstrate the equivalence of safety and efficacy properties of different salts, esters or derivatives of an authorised active substance;

(e) a review of the user safety risk assessment focusing on differences between the generic and reference veterinary medicinal products (for example, composition in excipients);

(f) a review of environmental risk assessment, where relevant.

IV.1.3. For a generic veterinary medicinal product application containing an antimicrobial substance, information about the level of resistance, as known from bibliographic data, shall be provided.

IV.1.4. For a generic veterinary medicinal product containing an antiparasitic substance, information about the level of resistance, as known from bibliographic data, shall be provided.

IV.1.5. For generic veterinary medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes, the following additional data shall be provided:

evidence to demonstrate equivalent or differing depletion of residues from the administration site, which may be substantiated by appropriate residue depletion studies;

(a) evidence to demonstrate target animal tolerance at the administration site, which may be substantiated by appropriate target animal tolerance studies.

IV.2. Applications for hybrid veterinary medicinal products

IV.2.1. Applications based on Article 19 (hybrid veterinary medicinal products) concern veterinary medicinal products, which are similar to a reference veterinary medicinal product, but which do not meet the conditions in the definition of generic veterinary medicinal product.

IV.2.2. For such applications, the following information shall be supplied:

(a) all the data referred to in Parts 1 and 2 of Sections II or III, as appropriate, of this Annex;

(b) for Parts 3 and 4 of the dossier, hybrid applications may rely in part on the results of the appropriate safety, residue, pre-clinical studies and clinical trials for an already authorised reference veterinary medicinal product, and in part on new data. New data shall include a user safety risk assessment and an environmental risk assessment in

accordance with Article 18 (7), if applicable. In addition, for relevant products (for example, antimicrobials, antiparasitics) the risk of development of resistance shall be addressed, if applicable.

IV.2.3. In the case of biological (including immunological) veterinary medicinal products, a comprehensive comparability review, addressing the quality, safety and efficacy part shall be provided.

IV.2.4. Where reference is made to data originating from another authorised veterinary medicinal product, a justification for the use and relevance of those data for the new product shall be provided.

IV.2.5. The extent of new data required to support safety and efficacy will depend on the specific characteristics of the individual new product, and its differences to the reference veterinary medicinal product, and shall be determined on a case-by-case basis. New pre-clinical and clinical data for the new product shall be presented for all aspects where the reference veterinary medicinal product does not provide relevant support.

IV.2.6. If new studies are conducted with batches of a reference veterinary medicinal product authorised in a third country, the applicant shall demonstrate that the reference veterinary medicinal product has been authorised in accordance with requirements equivalent to those established in the Union, and are so highly similar that they may substitute each other in the pre-clinical studies or clinical trials.

IV.3. Applications for combination veterinary medicinal products

IV.3.1. An application for a fixed combination product with individual active substances, which have already been the object of a marketing authorisation for a veterinary medicinal product in the EEA, shall be submitted under Article 20.

A fixed combination product containing at least one new active substance which has not yet been authorised for a veterinary medicinal product in the EEA, shall be submitted under Article 8.

IV.3.2. For applications submitted under Article 20, a full dossier containing Parts 1, 2, 3 and 4 shall be provided.

IV.3.3. A sound scientific justification based on valid therapeutic principles for the combination of active substances, including clinical data, shall be provided, which demonstrates the need for and contribution of all active substances at the moment of treatment.

IV.3.4. In general, all the data on the safety and efficacy shall be provided for the fixed combination product, and safety and efficacy data for the individual active substances alone are not required, except to clarify their individual pharmacological properties.

IV.3.5. If data on the safety and efficacy of an individual known active substance are available to the applicant with sufficient amount of detail, those data could be provided to obviate the need for some studies with the fixed combination, or contributing relevant information. In that case, possible interaction between active substances shall also be investigated.

IV.3.6. User safety assessment, environmental risk assessment, residues depletion studies, and clinical studies shall be conducted with the fixed combination product.

IV.3.7. Unless the omission is justified, a target animal safety study with the final formulation shall be provided.

IV.4. Applications based on informed consent

IV.4.1. Applications based on Article 21 concern products with identical composition, pharmaceutical form and manufacturing process (including raw and starting materials, process parameters and manufacturing sites) as the already authorised veterinary medicinal products.

IV.4.2. The dossier for such applications shall only include data for Part 1A and 1B, as described in Annex I (points 1 to 6.4), provided that the marketing authorisation holder for the already authorised veterinary medicinal product has given the applicant his written consent to refer to the content of Parts 1C, 2, 3 and 4 of the dossier of that product. In that case, there is also no need to submit quality, safety and efficacy critical expert reports. The applicant shall provide proof of the written consent with their application.

IV.5. Applications based on bibliographic data

IV.5.1. For veterinary medicinal products for which the active substance(s) has or have been in well-established veterinary use as referred to in Article 22, with recognised efficacy and an acceptable level of safety, the following specific rules shall apply.

IV.5.2. A full dossier (containing Parts 1, 2, 3 and 4) shall be provided. The applicant shall submit Parts 1 and 2 as described in this Annex. For Parts 3 and 4, a detailed scientific bibliography together with information demonstrating the appropriate bridging between bibliographic references and the veterinary medicinal product shall be submitted to address safety and efficacy. The bibliographic data may need to be complemented by some documentation specific to the product, for example, user safety and environmental risk assessments, or residue study data to justify any proposed withdrawal period(s).

IV.5.3. The specific rules set out in Part IV.5.3.1 to IV.5.3.12 shall apply in order to demonstrate well-established veterinary use.

IV.5.3.1. In order to establish a well-established veterinary medicinal use of constituents of veterinary medicinal products, the following factors shall be taken into account:

(a) the time over which an active substance has been regularly used in the target species using the proposed route of administration and dosage regimen;

(b) quantitative aspects of the use of the active substance(s), taking into account the extent to which the substance(s) has or have been used in practice, and the extent of use on a geographical basis;

(c) the degree of scientific interest in the use of the active substance(s) (reflected in the published scientific literature);

(d) the coherence of scientific assessments.

IV.5.3.2. Different periods of time may be necessary for establishing well-established use of different active substances. In any case, the period of time required for establishing a well-established veterinary use of a constituent of a medicinal product shall not be less than 10 years from the first systematic and documented use of that substance as a veterinary medicinal product in the Union.

IV.5.3.3. Veterinary use does not exclusively mean use as an authorised veterinary medicinal product. Well-established veterinary use refers to the use for a specific therapeutic purpose in the target species.

IV.5.3.4. If a substance in well-established use is proposed for entirely new therapeutic indications, it is not possible to solely refer to a well-established veterinary use. Additional data on the new therapeutic indication, together with appropriate safety and residue tests and

preclinical and clinical data shall be provided and, in such a case, applications based on Article 21 is not possible.

IV.5.3.5. The published documentation submitted by the applicant shall be freely available to the the public and published by a reputable source, preferably peer-reviewed.

IV.5.3.6. The documentation shall contain sufficient details to allow an independent assessment.

IV.5.3.7. The documentation shall cover all aspects of the safety and/or efficacy assessment of the product for the proposed indication in the target species using the proposed route of administration and dosage regimen. It 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 the form of epidemiological studies and, in particular, of comparative epidemiological studies.

IV.5.3.8. All documentation, both favourable and unfavourable, shall be communicated. With respect to the provisions on well-established veterinary use, it is in particular necessary to clarify that bibliographic reference to other sources of evidence (post-marketing studies, epidemiological studies etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if the applicant explains and justifies the use of those sources of evidence satisfactorily.

IV.5.3.9. Public assessment reports or freedom of information summaries cannot be considered to supply sufficient information, apart from the assessment report published by the Agency following the evaluation of an application for the establishment of maximum residue limits, which may be used in an appropriate manner as literature, particularly for the safety tests.

IV.5.3.10. Particular attention shall be paid to any missing information, and justification shall be given as to why demonstration of an acceptable level of safety and/or efficacy may be supported although some information is lacking.

IV.5.3.11. The critical expert reports regarding safety and efficacy shall explain the relevance of any data submitted, which concern a product different from the product intended for marketing. A judgement shall be made whether or not the product studied in the bibliography may be satisfactorily or scientifically bridged to the product, for which the application for a marketing authorisation has been made in spite of the existing differences.

IV.5.3.12. Post-marketing experience with other products containing the same constituents is of particular importance and applicants shall put a special emphasis on this issue.

IV.6. Applications for limited markets

IV.6.1. A marketing authorisation may be granted for a limited market in the absence of comprehensive safety and/or efficacy data when, as provided for in Article 23, the applicant demonstrates that the product is intended for use in a limited market and that the benefit of availability of the new product outweighs the risk associated with the omission of some of the safety or efficacy data required by this Annex.

IV.6.2. For such applications, the applicant shall submit Parts 1 and 2 as described in this Annex.

IV.6.3. For Parts 3 and 4, some of the safety or efficacy data required by this Annex may be omitted. As regards the extent of safety and efficacy data that may be omitted, the relevant guidance published by the Agency shall be taken into account.

IV.7. Applications in exceptional circumstances

IV.7.1. In exceptional circumstances related to animal or public health, a marketing authorisation may be granted under Article 25 for a veterinary medicinal product, subject to certain specific obligations, conditions and/or restrictions.

IV.7.2. For such applications, the applicant shall submit Part 1 as described in this Annex, together with a justification as to why the benefit of the immediate availability on the market of the veterinary medicinal product concerned outweighs the risk inherent in the fact that certain quality, safety or efficacy documentation has not been provided.

IV.7.3. For Parts 2, 3 and 4, certain quality, safety or efficacy data required by this Annex may be omitted, if the applicant justifies that those data cannot be provided at the time of submission. For the identification of the essential requirements for all such applications, the relevant guidance published by the Agency shall be taken into account.

IV.7.4. Post-authorisation studies may be requested as part of the conditions for marketing authorisation, and shall be designed, conducted, analysed and presented according to the general principles for quality, safety and efficacy tests set out in this Annex, and relevant guidance documents, as applicable depending on the issue to be addressed in the study.

SECTION V
REQUIREMENTS FOR MARKETING AUTHORISATION APPLICATIONS FOR PARTICULAR VETERINARY MEDICINAL PRODUCTS

This Section lays down specific requirements for identified veterinary medicinal products related to the nature of the active substances contained therein.

V.1. Novel therapies veterinary medicinal products

V.1.1 General requirements

V.1.1.1. Depending on the active substance and the mode of action, a novel therapy veterinary medicinal product could fall under any of the three product categories:

(a) veterinary medicinal products other than biological veterinary medicinal products;

(b) biological veterinary medicinal products other than immunological veterinary medicinal products;

(c) immunological veterinary medicinal products.

V.1.1.2. In general, marketing authorisation applications for novel therapy veterinary medicinal products, as defined in Article 4 (43), shall follow the format and data requirements described in Section II or III of this Annex depending on how the novel therapy is categorised. A full dossier containing Parts 1, 2, 3 and 4 shall normally be provided in accordance with the requirements described in Section II or III and any relevant guidance published by the Agency. Deviations from the requirements of this Annex may be possible when justified. Where appropriate and taking into account the specificities of novel therapy products, additional requirements may be relevant for particular types of products.

V.1.1.3. The manufacturing processes for novel therapy veterinary medicinal products shall comply with the principles of Good Manufacturing Practice (GMP) adapted where necessary, to reflect the specific nature of those products. Guidelines specific to novel therapy veterinary products shall be drawn up, to properly reflect the particular nature of their manufacturing process.

V.1.1.4. According to the specific nature of a novel therapy product the use of the product may potentially be associated with specific risks. Those risks shall be identified applying a

risk profiling methodology to identify the risks inherent to the specific product and the risk factors contributing to those risks. In this context, risks would be any potential unfavourable effects that may be attributed to the use of the novel therapy product which are of concern to the target population and/or the user, the consumer, and/or the environment. The risk analysis may cover the entire development. Risk factors that may be considered include the origin of the starting material (cells etc.), the mode of action in the animal (proliferation, initiation of an immune response, permanence in the body, etc.), the level of cell manipulation (for example, the manufacturing process), the combination of the active substance with bioactive molecules or structural materials, the extent of replication competence of viruses or micro-organisms used *in vivo*, the level of integration of nucleic acids sequences or genes into the genome, the long-time functionality, the risk of oncogenicity, the off-target effects and the mode of administration or use.

V.1.1.5. Based on the evaluation of the information on the identified risks and risk factors a specific profile of each individual risk associated with a specific product shall be established and may be used to determine and justify how the data set provided gives the necessary assurances for quality, safety and efficacy and is adequate to support a marketing authorisation application, especially for those aspects of novel therapy products that are beyond current knowledge.

V.1.1.6. To address data gaps or uncertainties at the time of product authorisation, implementation of post-authorisation measures or studies may be considered on a case-by-case basis. In order to detect early or delayed signals of adverse reactions, to prevent clinical consequences of such reactions and to ensure timely treatment and to gain information on the long-term safety and efficacy of novel therapy veterinary medicinal products a risk management plan shall detail the measures envisaged to ensure such follow up.

V.1.1.7. For any novel therapy product, in particular those considered as a nascent field in veterinary medicine, it is recommended to seek the advice of the Agency in a timely manner before submission of the marketing authorisation dossier in order to classify the product, determine the applicable dossier structure and to receive relevant information about the additional data set which may be necessary to support quality, safety and efficacy.

V.1.2. Quality requirements

V.1.2.1. In general, description of the composition, the manufacturing method, consistency of production, controls of starting materials, controls implemented during the manufacturing process, finished product testing including implementation of an activity test or a quantification of the active substance and stability data shall be submitted.

V.1.2.2. The data requirements for manufacturing and testing for novel therapy veterinary medicinal products of biological origin and classified as a biological product or as an immunological product shall in general be in accordance with those for biological or immunological medicinal products (as described in Section III of this Annex) including the need for a relevant potency test. There may be cases where additional requirements are applicable, for example, cells and vector gene constructs.

V.1.2.3. For novel therapy veterinary medicinal products constructed by chemical synthesis, data requirements as for veterinary medicinal products other than biological products (as described in Section II of this Annex) are generally applicable. There may be cases where additional requirements are applicable, for example, a relevant potency test.

V.1.3. Safety requirements

V.1.3.1. Depending on the nature of the product and its intended use, further data to evaluate safety for the target animal, the user, the consumer or the environment could be relevant as determined by a risk analysis in each case.

V.1.3.2. The requirements of Directive 2001/18/EC shall be taken into consideration when the treated animal itself could become a genetically modified organism. While Directive 2001/18/EC applies to finished products containing genetic modified organisms, it remains the best technical guide currently available for listing the necessary data. In particular, a main issue is the integration rate of DNA into germ cells (thus transmissible to offspring) or the potential transmission of the genetically modified cells to offspring. It shall also be noted that this problem is not completely the same when considering companion animals and food-producing animals (human consumption of products containing genetic modified organisms).

V.1.3.3. For substances intended for integration into or editing of the genome, appropriate tests shall be performed to evaluate the risk of off-target modifications and/or insertional mutagenesis.

V.1.4. Efficacy requirements

V.1.4.1. Efficacy data requirements differ primarily depending on the intended indications for use in the target species. Depending on the novel therapy product categorisation and the intended use in the target species, the efficacy requirements set out in Sections II or III may be applicable for a novel therapy veterinary medicinal product.

V.1.4.2. The indications claimed shall be supported by appropriate data in the target species.

V.1.5. Specific data requirements for particular types of novel therapy products

V.1.5.1. Principles

V.1.5.1.1. Taking into account the specificities of novel therapy products, specific requirements additional to the standard requirements for evaluation of quality, safety and efficacy may be appropriate.

V.1.5.1.2. The following sections highlight specific requirements to be considered for particular type of novel therapy products. Those specific requirements established for a particular type of novel therapy product represent a non-exhaustive list of requirements that may need to be adapted to the specific product concerned on a case-by-case basis and based on a risk analysis.

V.1.5.13. In all cases and especially for novel therapies that are considered nascent in the field of veterinary medicine, applicants will need to take into account the current state of veterinary medicinal knowledge and the scientific guidance published by the Agency and the Commission, consistent with Section I of this Annex.

V.1.5.2. Gene therapy veterinary medicinal products

V.1.5.2.1. Gene therapy products are biological veterinary medicinal products that contain an active substance which contains or consists of a recombinant nucleic acid used in or administered to animals with a view to regulating, repairing, replacing, adding or deleting a genetic sequence. Their therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence they contain, or to the product of genetic expression of this sequence.

V.1.5.2.2. In addition to the data requirements set out in Sections II or III the following requirements shall apply:

(a) information shall be provided on all the starting materials used for the manufacture of the active substance, including the products necessary for the genetic modification of cells, as applicable, subsequent culture and preservation of the genetically modified cells, taking into consideration the possible absence of purification steps;

(b) for products containing a microorganism or a virus, data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the microorganism or virus, pathogenicity and characteristics of the parental strain shall be provided;

(c) process-related impurities and product-related impurities shall be described in the relevant sections of the dossier and in particular replication competent virus contaminants if the vector is designed to be replication incompetent;

(d) for plasmids, quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product;

(e) for genetically modified cells, the characteristics of the cells before and after the genetic modification, as well as before and after any subsequent freezing/storage procedures, shall be tested. For genetically modified cells, in addition to the specific requirements for gene therapy medicinal products, the quality requirements for cell therapy medicinal products and tissue engineered products shall apply;

(f) off-target insertions (leading, for example, to tumours/cancer, metabolic dysfunctions) and insertional mutagenesis and genotoxicity (insertion of genetic elements and the expression of DNA-modifying proteins as mediators of genotoxic side effects) in target species need to be considered;

(g) germline transmission studies shall be provided, unless otherwise justified.

V.1.5.3. Regenerative medicine, tissue engineering and cell therapy veterinary medicinal products

V.1.5.3.1. Regenerative medicines are considered to encompass a wide area of products and therapies with a general purpose of restoring functions. Those medicines include cell-based therapies in which tissue engineered products are included.

V.1.5.3.2. Cell therapy veterinary medicinal products are biological veterinary medicinal products that contain or consist of cells or tissues that have been subject to substantial manipulation in either nature or function so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor. They are presented as having properties for, or are used in or administered to animals with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues or to regenerating, repairing or replacing a tissue.

V.1.5.3.3. In addition to the data requirements set out in Sections II or III the following requirements shall apply:

(a) summary information shall be provided on procurement and testing of the animal tissue and cells used as starting materials. If non-healthy cells or tissues are used as starting materials, their use shall be justified;

(b) the potential variability introduced through the animal tissues and cells shall be addressed as part of the validation of the manufacturing process, characterisation of

the active substance and the finished product, development of assays, setting of specifications and stability;

(c) for the genetic modification of the cells, the technical requirements specified for gene therapy products shall apply;

(d) relevant information shall be provided on the characterisation of the cell population or cell mixture in terms of identity, purity (for example, extraneous agents and cellular contaminants), viability, potency, karyology, tumourigenicity and suitability for the intended medicinal use. The genetic stability of the cells shall be demonstrated;

(e) the impact and interactions of any components likely to interact (directly or as a result of degradation or metabolism) with the active substance shall be investigated;

(f) where a three-dimensional structure is part of the intended function, the differentiation state, structural and functional organisation of the cells and, where applicable, the extracellular matrix generated shall be part of the characterisation for those cell-based products.

V.1.5.4. Veterinary medicinal product specifically designed for phage therapy

V.1.5.4.1. Bacteriophages are viruses that depend on bacterial hosts for proliferation and act very specifically on certain bacterial strains. Phage therapy may be used, for example, as an alternative to antibiotics. Generally, bacteriophages consist of a genome, comprised of single or double stranded DNA or RNA, encapsulated by a protein capsid. Due to the diversity of the intended targets for treatment and the specificity of the bacteriophages, it will be necessary to choose the suitable bacteriophage strain against the disease-causing bacterial strain on a case-by-case basis for the individual outbreak of the disease.

V.1.5.4.2 The quality and quantity of the bacteriophages to be used in the finished product are normally variable. Therefore, a fixed qualitative and quantitative composition of bacteriophages will not be the usual situation as the phages need to be adapted on an ongoing basis. Based on this a seed stock of bacteriophages strains need to be established and maintained (comparable with a multi-strain approach).

V.1.5.4.3. Bacteriophages as well as host bacteria / master cell banks for manufacturing shall preferably be produced based on a master seed system. Confirmation shall be provided that the bacteriophage used is lytic.

V.1.5.4.4. The absence of resistance gene(s) and the absence of genes coding for virulence factors shall be shown on all master seeds.

V.1.5.4.5. The indication shall be for prophylactic, metaphylactic and/or therapeutic treatment of one or several specific infection(s) or infectious disease(s). Efficacy of treatment is linked to the lytic activity of phages that confers bactericidal activity on those bacteriophages with specificity for the bacterial strain concerned.

V.1.5.4.6. For genetically modified phages, the genetic modification shall be described.

V.1.5.5. Veterinary medicinal product issued from nanotechnologies

V.1.5.5.1. Nanotechnologies are seen primarily as a technology to generate carriers for chemically synthesised substances but may also be carriers for biological substances. The use of nanoparticles may be a way of controlling delivery of substances with low solubility or toxic compounds.

V.1.5.5.2. 'Nanotechnology' corresponds to the design, characterisation, and production of nanomaterials by controlling shape and size at the nanoscale (up to around 100nm).

V.1.5.5.3. 'Nanoparticles' are considered to have two or more dimensions at the nanoscale.

V.1.5.5.4. Within the veterinary field, nanoparticles for drug delivery system are relevant as 'products issued from nanotechnologies': nanoparticles are conjugated with substances in order to change the pharmacokinetic and/or pharmacodynamic properties. mRNA drugs are rather encapsulated in nanoparticle delivery systems.

V.1.5.5.5. In addition to the quality data requirements set out in Sections II or III the following requirements shall apply:

(a) size distribution of particles shall be determined;

(b) a suitable *in vitro* test for their function and possible delivery capacity (if used as drug delivery system) shall be used.

V.1.5.5.6. With regard to safety, the kind of hazards that are introduced by using nanoparticles for drug delivery may be beyond conventional hazards imposed by chemicals in classical delivery matrices. Therefore, the following aspects shall be considered with regard to safety:

(a) The nanoparticles for drug delivery could influence the toxicity of the medicinal product. The toxicity of the active substance is pivotal to the product but the toxicity of the nanoparticle for drug delivery shall also be considered, as they may introduce specific risks (agglomerates, cytotoxicity), may convey impurities by adsorption, may generate toxic materials by degradation or solubilisation, or may be transferred through physiological barrier (haemato-encephalic, foeto-placental, cell and nuclear membranes, etc.). In this context:

(i) when physiological barriers are crossed, the impact of nanoparticles for drug delivery shall be investigated on the corresponding organ(s);

(ii) the impact of agglomerates shall be investigated in the different targeted organs, focusing in particular on the risk of embolism in the smaller blood vessels;

(iii) safety issues of the nanoparticles for drug delivery may be linked to a cumulative effect, a degradation profile or persistence in the body with negative effects on the functions of the targeted organs;

(iv) safety issues might also be perceived at the cell level. Cells might not always be able to eliminate the nanoparticles conveyed through the cell membrane, leading to cytotoxicity especially via the induction of an oxidative stress. The toxicological assays to be implemented shall be able to assess this cytotoxicity and the related aspects, such as the generation of toxic free radicals and biopersistence.

(b) The toxicology profile of the active substances contained in nanoparticles for drug delivery may differ as they may be distributed differently into various internal organs (different solubility in biological matrices), or as they may unexpectedly cross various biological barriers within the body, such as the brain barrier.

(c) The side effects linked to the active substances may be exacerbated when they are delivered by nanoparticles.

(d) Immunosafety issues such as immunotoxicity (direct damage to immune cells), immunostimulation, immunosuppression and immunomodulation (such as

complement activation, inflammation, activation of the innate or adaptive immunity), were already identified for nanomedicines.

(e) The capacity of nanoparticles to create inflammatory or allergic reactions shall be considered. The capacity to penetrate into the blood stream and to induce inflammatory reactions may lead to disseminated intravascular coagulation or fibrinolysis with further consequences such as thrombosis. The haemocompatibility of the nanoparticles shall therefore be checked.

V.1.5.6. RNA antisense therapy and RNA interference therapy products

V.1.5.6.1. Antisense therapy and interference therapy products may be generated by synthesis or through recombinant techniques.

V.1.5.6.2. Antisense RNA is a single stranded RNA that is complementary to a protein coding messenger RNA with which it hybridises, and thereby blocks its translation into protein.

V.1.5.6.3. RNA interference is a biological process in which RNA molecules inhibit gene expression or translation, by neutralising targeted mRNA molecules.

V.1.5.6.4. In addition to the data requirements set out in Sections II or III the following requirements shall apply:

(a) the minimum amount of RNA segments per volume needs to be established as part of control tests of the finished product, as well as the confirmation that the RNA segments present the correct sequence;

(b) for certain antisense therapy products falling under Section II of this Annex a potency bioassay may be needed for their release testing;

(c) stability studies shall include a test to monitor the degradation rate of the RNA segments over time;

(d) for RNA antisense therapy products, the possible harmful effects due to on- or off-target binding shall be addressed as well as possible non-antisense harmful effects due to, for example, accumulation, pro-inflammatory responses and aptamer binding;

(e) for RNAi therapy products, the possible harmful effects of off-target interference (due to the positive RNAi strand) shall be addressed, as well as the possibility of crossing the blood-brain barrier and causing central nervous system disorders;

(f) for RNA antisense therapy and RNA interference therapy products intended for gene therapy the requirements for gene therapy veterinary medicinal product shall be considered.

V.2. Vaccine Antigen Master File

For particular immunological veterinary medicinal products and by derogation from Section IIIb, Part 2, the concept of a Vaccine Antigen Master File is introduced.

V.2.1. Principles

V.2.1.1. For the purpose of this Annex, a Vaccine Antigen Master File means a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information on quality concerning each of the active substances, which are part of the veterinary medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.

V.2.1.2. The use of Vaccine Antigen Master Files is optional. For combined vaccines, the vaccine antigen(s) to be included in Vaccine Antigen Master File(s) shall be specified and a separate Vaccine Antigen Master File shall be required for each of them.

V.2.1.3. The submission and approval of a Vaccine Antigen Master File shall comply with the relevant guidance published by the Agency.

V.2.2. Content

The Vaccine Antigen Master File dossier shall contain the information in Parts V.2.2.1 to V.2.3.3 extracted from the relevant sections of Part 1 (Summary of the dossier) and Part 2 (Quality documentation) as set out in Section IIIb of this Annex:

V.2.2.1. Summary of the dossier (Part 1)

The name and address of the manufacturer(s) and the site(s) involved in the different stages of manufacture and control of the active substance, accompanied by copies of the corresponding manufacturing authorisations, shall be given.

V.2.2.2. Qualitative and quantitative particulars of the constituents (Part 2.A)

The complete and exact name of the active substance (for example, virus or bacteria strain, antigen) shall be provided, in the same way as mentioned in any finished product. Information on product development relevant to the active substance shall be provided.

V.2.2.3. Description of the manufacturing method (Part 2.B)

The description of the manufacturing method for the active substance shall be provided including validation of the key stages of production and justification, if relevant, of any intermediate storage proposed. For inactivated vaccines, data relevant to the inactivation of the active substance, including the validation of the inactivation process shall be provided.

V.2.2.4. Production and control of starting materials (Part 2.C)

V.2.2.4.1. The standard requirements described in Section IIIb.2C and relevant to the active substance shall apply.

V.2.2.4.2. Information on the active substance (for example, virus/bacteria strain), the substrate/s (cells, culture medium) and all the raw materials (pharmacopoeia or non-pharmacopoeia, biological or non-biological) used in the production of the active substance shall be provided.

V.2.2.4.3. The dossier shall include the specifications, information on the processes implemented and on the tests to be conducted for the quality control of all batches of starting materials and results for a batch for all components used.

V.2.2.4.4. TSE and extraneous agents (EA) risk assessment shall be provided, where applicable. It is to be noted that the target species retained for the finished products making reference to the Vaccine Antigen Master File shall be considered for the TSE and EA risk assessment. Warnings or restrictions of use may be brought in at the Vaccine Antigen Master File level depending on the information presented, which may be mitigated during the risk analysis at the level of the finished product.

V.2.2.4.5. If the active substance is obtained by recombinant techniques, all corresponding relevant data on the genetically modified virus/bacteria shall be provided.

V.2.2.5. Control tests during the manufacturing process (Part 2.D)

The standard requirements described in Section IIIb.2D shall apply for the in-process control tests carried out during the manufacture of the active substance, including validations of key control tests and, if relevant, any intermediate storage proposed (prior to blending).

V.2.2.6. Batch-to-batch consistency (Part 2.F)

The standard requirements described in Section IIIb.2F shall apply for the demonstration of consistency in the manufacture of the antigen.

V.2.2.7. Stability (Part 2.G)

The standard requirements described in Section IIIb.2G to demonstrate the stability of the antigen and, where relevant any intermediate storage, shall apply.

V.2.3. Evaluation and certification

V.2.3.1. For vaccines containing new vaccine antigen(s) where no Vaccine Antigen Master File already exists, the applicant shall submit to the Agency a full marketing authorisation application dossier including all the Vaccine Antigen Master Files corresponding to each single vaccine antigen for which the use of a Vaccine Antigen Master File is intended. A scientific and technical evaluation of each Vaccine Antigen Master File shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance with Union legislation for each Vaccine Antigen Master File, which shall be accompanied by the evaluation report. The certificate shall apply throughout the Union.

V.2.3.2. Part V.2.3.1 shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of those vaccine antigens are part of vaccines already authorised in the Union.

V.2.3.3. Changes to the content of a Vaccine Antigen Master File for a vaccine authorised in the Union shall be subject to a scientific and technical evaluation carried out by the Agency. In the case of a positive evaluation, the Agency shall issue a certificate of compliance with Union legislation for the Vaccine Antigen Master File. The certificate issued shall apply throughout the Union.

V.3. Multi-strain dossier

V.3.1. For certain immunological veterinary medicinal products and by derogation from the provisions of Section IIIb, Part 2, the concept of the use of a multi-strain dossier is introduced.

V.3.2. A multi-strain dossier means a single dossier containing the relevant data for a unique and thorough scientific assessment of the different options of strains/combinations of strains permitting the authorisation of inactivated vaccines against antigenically variable viruses or bacteria for which rapid or frequent change in the composition of vaccine formulations is needed to ensure efficacy with regard to the epidemiological situation in the field. According to the epidemiological situation where the vaccine is intended to be used, a number of strains could be selected from those included in the dossier to formulate a final product.

V.3.3. Each multi-strain dossier is applicable only to one virus species, bacteria genus or vector for a given disease; mixtures of various viruses belonging to different families, genera, species or bacteria belonging to different families or genera cannot be approved in the context of a multi-strain dossier.

V.3.4. For new applications to multi-strain dossier marketing authorisations where no authorised multi-strain vaccine already exists for a particular virus/bacterium/disease, eligibility for the multi-strain dossier approach shall be confirmed by the Agency before submission of the application.

V.3.5. The submission of multi-strain dossiers shall comply with relevant guidance published by the Agency.

V.4. Vaccine platform technology

V.4.1. Principles

V.4.1.1. Vaccine platform technology is a collection of technologies that have in common the use of a 'backbone' carrier or vector that is modified with a different antigen or set of antigens for each vaccine derived from the platform. This includes, but may not be limited to, protein-based platforms (virus-like particles), DNA vaccine platforms, mRNA based platforms, replicons (self-replicating RNA) and viral and bacterial vector vaccines.

V.4.1.2. Applications for marketing authorisations of immunological veterinary medicinal products manufactured based on vaccine platform technologies are considered to be eligible for reduced data requirements. A full dossier is required for the first product from a manufacturer based on a particular platform technology for a particular target species. At the time of submission of the first (full) dossier based on the platform technology, the applicant may submit in parallel a 'Platform Technology Master File' comprising all data relative to the platform for which there is reasonable scientific certainty that will remain unchanged regardless of the antigen(s)/gene(s) of interest added to the platform. The nature of the data to be included in the Platform Technology Master File will depend on the type of platform.

V.4.1.3. Once a Platform Technology Master File is certified, the certificate may be used to fulfil the relevant data requirements in subsequent applications for marketing authorisations based on the same platform and intended for the same target species.

V.4.2. Evaluation and certification

V.4.2.1. The submission of Platform Technology Master Files shall comply with relevant guidance published by the Agency. A scientific and technical evaluation of a Platform Technology Master File shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance with Union legislation for the Platform Technology Master File, which shall be accompanied by the evaluation report. The certificate shall apply throughout the Union.

V.4.2.2. Changes to the content of a Platform Technology Master File for a vaccine authorised in the Union shall be subject to a scientific and technical evaluation carried out by the Agency.

V.4.2.3. In the case of a positive evaluation the Agency shall issue a certificate of compliance with Union legislation for the Platform Technology Master File.

V.5. Authorised homeopathic veterinary medicinal products

V.5.1 Quality (Part 2)

The provisions of Section II.2. PART 2 shall apply to the documents for authorisation of homeopathic veterinary medicinal products referred to in Article 85(2) with the following modifications.

V.5.2 Terminology

The Latin name of the homeopathic stock described in the marketing authorisation application dossier shall be in accordance with the Latin title of the European Pharmacopoeia or, in absence thereof, of an official pharmacopoeia of a Member State. Where relevant the traditional name(s) used in each Member State shall be provided.

V.5.3 Control of starting materials

The particulars and documents on the starting materials, that is to say, all of the materials used including raw materials and intermediates up to the final dilution to be incorporated into the finished authorised homeopathic veterinary medicinal product, accompanying the application, shall be supplemented by additional data on the homeopathic stock.

The general quality requirements shall apply to all of the starting and raw materials as well as intermediate steps of the manufacturing process up to the final dilution to be incorporated into the finished homeopathic product. Where a toxic component is present, this shall be controlled, if possible, in the final dilution. If this is not possible because of the high dilution, the toxic component shall normally be controlled at an earlier stage. Every step of the manufacturing process from the starting materials up to the final dilution to be incorporated into the finished product shall be fully described.

Where dilutions are involved, those dilution steps shall be done in accordance with the homeopathic manufacturing methods laid down in the relevant monograph of the European Pharmacopoeia or, in absence thereof, in an official pharmacopoeia of a Member State.

V.5.4 Control tests on the finished medicinal product

The general quality requirements shall apply to the homeopathic finished veterinary medicinal products. Any exception shall be duly justified by the applicant.

Identification and assay of all the toxicologically relevant constituents shall be carried out. If justified that identification and/or an assay on all the toxicologically relevant constituents is not possible, for example, due to their dilution in the finished medicinal product the quality shall be demonstrated by complete validation of the manufacturing and dilution process.

V.5.5 Stability tests

The stability of the finished product shall be demonstrated. Stability data from the homeopathic stocks are generally transferable to dilutions/potentisations obtained thereof. If no identification or assay of the active substance is possible due to the degree of dilution, stability data of the pharmaceutical form may be considered.

V.5.6 Safety documentation (Part 3)

Part 3 shall apply to homeopathic veterinary medicinal products referred to in Article 4(10) of this Regulation with the following specification, without prejudice to the provisions of Commission Regulation (EU) No 37/2010[7] on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin.

Any missing information shall be justified, for example, justification shall be given as to why demonstration of an acceptable level of safety may be supported, even where some studies are lacking.'

[7] Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin (OJ L 15, 20.1.2010, p. 1).