Pursuant to Article 221 paragraph 3, Article 239 paragraph 6, Article 246 paragraphs 3 and 6 and Article 250 paragraph 8 of the Law on Medicinal Products ("Official Gazette of Montenegro", No 14/26"), the Management Board of the Institute for Medicines, with the with the approval of the Ministry of Agriculture, forestry and water management hereby adopts the following

RULEBOOK ON CONDITIONS FOR GRANTING MARKETING AUTHORISATION FOR VETERINARY MEDICINAL PRODUCT*

I GENERAL PROVISIONS

Article 1

This Rulebook lays down the detailed procedures for submission, the content of the application and the required documentation for granting a marketing authorisation for veterinary medicinal product, the content of the marketing authorisation for veterinary medicinal product, as well as the content of the summary of product characteristics, content and method of labelling, the list of abbreviations and pictograms, the rules on the size of small immediate packaging units, as well as the content of the package leaflet for the veterinary medicinal product, the list of variations not requiring assessment, more detailed conditions, classification, procedures and required documentation for the variation of a marketing authorisation for a veterinary medicinal product, as well as detailed procedure for the suspension and revocation of marketing authorisations for veterinary medicinal.

Article 2

Terms used in this Rulebook for natural persons in masculine gender shall include same terms in feminine gender.

Article 3

Terms used in this Rulebook shall have the following meaning:

1) **Reference Member State of the European Union** means a Member State which, in a decentralised or mutual recognition procedure, prepares and issues the Assessment Report;

2) **Assessment Report** means a document prepared by the European Medicines Agency (EMA) or by the competent authority of a Member State of the European Union, containing the analysis and conclusions regarding the quality, safety and efficacy of the medicinal product, based on expert assessment of the submitted documentation, including regulatory recommendations and the basis for decisions on the granting, variation or renewal of a marketing authorisation.

II CONDITIONS FOR THE ISSUANCE OF MARKETING AUTHORISATION FOR VETERINARY MEDICINAL PRODUCT

Article 4

Marketing authorisation for veterinary medicinal product may be issued to the applicant referred to in Article 220 paragraph 2 of the Law on Medicines (hereinafter: Law), based on the assessment of the documentation prescribed by this Rulebook.

Article 5

The application for granting a marketing authorisation for veterinary medicinal product shall be submitted to the Institute for Medicines and Medical Devices (hereinafter: the Institute) in accordance with the Law and this Rulebook.

An applicant may be a natural or a legal person seated in Montenegro.

An application referred to in paragraph 1 to this article shall contain the following information:

1) the name and address of the applicant;
2) information on veterinary medicinal product (brand name, international non-protected name (INN), pharmaceutical form, strength and packaging);
3) the name and address of the manufacturer of the veterinary medicinal product;
4) Anatomical-therapeutic-chemical veterinary (ATCvet) classification code;
5) the proposal for the dispensing classification of the veterinary medicinal product;
6) target animal species;
7) the type of application, i.e. the legal basis for granting a marketing authorisation (reference to the relevant Article of the Law);
8) information on whether the veterinary medicinal product has been granted a marketing authorisation in the European Union, and if so, the type and number of the procedure under which the authorisation was granted;
9) the date and signature of the responsible person for obtaining the marketing authorisation.

The application referred to in 1 of this Article shall be submitted for each pharmaceutical form, strength and packaging, using the application form published on the official website of the Institute.

Article 6

The following shall be submitted along with the application for granting a marketing authorisation:

1) the information set out in Annex I, which forms integral part of this rulebook;

2) technical documentation necessary for demonstrating the quality, safety and efficacy of the veterinary medicinal product in accordance with the requirements set out in Annex II, which forms integral part of this rulebook;

3) a summary of the pharmacovigilance system master file (hereinafter: PSMF);

4) proof that the prescribed fees have been paid.

Where the application concerns an antimicrobial veterinary medicinal product, the following shall be submitted in addition to the information, technical documentation and summary listed in paragraph 1 to this article:

1) documentation on direct or indirect risks to public or animal health or to the environment of use of the antimicrobial veterinary medicinal product in animals;

2) information about risk mitigation measures to limit antimicrobial resistance development related to the use of the veterinary medicinal product.

Article 7

The documentation required for the issuance of a marketing authorisation for veterinary medicinal product (hereinafter: documentation) shall be submitted in the form of the European dossier (hereinafter: EU dossier), which refers to veterinary medicines, in accordance with the European Commission guidelines.

The main parts of the EU dossier are as follows:

1) Part 1: Summary of the dossier
2) Part 2: Documentation on quality (physicochemical, biological or microbiological information)
3) Part 3: Documentation on safety (safety and residue tests)
4) Part 4: Documentation on efficacy (pre-clinical studies and clinical trials)

The content and structure of the documentation referred to in paragraph 1 of this Article are provided in Annex II of this Rulebook.

Article 8

Along with the application for granting a marketing authorisation for veterinary medicinal product, in addition to the information and documentation prescribed by the Law and this Rulebook, the applicant shall also submit a written authorisation issued by the marketing authorisation holder in the European Union or by the manufacturer of the medicinal product, confirming that the applicant is authorised to represent them in the procedure for granting a marketing authorisation in Montenegro.

The form of authorisation referred to in paragraph 1 of this Article shall be published on the official website of the Institute.

Article 9

The Institute shall, in the procedure for granting a marketing authorisation, assess the acceptability of the proposed name of the medicinal product.

The Institute may consider the proposed name of the medicinal product unacceptable if it is not in accordance with Article 7 paragraph 1 points 45) and 100) of the Law, as well as the provisions of this Rulebook.

A proposed name of a medicinal product shall not be accepted if it:

1) is misleading due to its similarity with the scientific/international non-proprietary name or commonly used name;

2) is misleading due to its similarity with the approved name of another medicinal product;

3) is misleading by implying therapeutic efficacy;
4) is misleading with regard to the composition of the medicinal product;
5) is misleading with regard to the safety of the medicinal product;
6) contains promotional wording;
7) is misleading with regard to the dispensing classification of the medicinal product.

Article 10

In the case of an application for a marketing authorisation under the accelerated procedure, in accordance with Article 232 of the Law, in addition to the documentation prescribed by this Rulebook, the following shall also be submitted:

1) identical documentation (a consolidated file covering Parts 1-4) that has been approved in the centralized procedure (hereinafter: CP), decentralized procedure (hereinafter: DC) or mutual recognition procedure (hereinafter: MRP);
2) a statement by the applicant confirming that the documentation submitted for the marketing authorization application in Montenegro is identical to the documentation on the basis of which the Assessment Report was prepared and issued, including all variations approved up to the date of submission of the application, and that the submitted documentation is valid in the Member States of the European Union. In cases where there are differences compared to the documentation approved in CP, DC or MRP, these must be clearly stated and explained;
3) a list of variations submitted and approved in the CP, DC or MRP up to the date of submission of the application to the Institute, including information on the status of each variation in the procedure, as well as whether they have been implemented in the dossier submitted to the Institute. For variations that have been approved and implemented, the relevant approvals from the CP, MRP or DC procedure shall be submitted;
4) the Assessment Report issued by the EMA or the Reference Member State in the DCP or MRP, as well as *Assessment of the responses to the outstanding questions raised by the RMS and CMSs*, as well as the preliminary reports from all stages of the MRP or DC procedure, if availlable;
5) a statement by the applicant undertaking to notify the Institute without delay, in the event of permanent or temporary withdrawal of the marketing authorisation in the European Union, as well as of any urgent safety restrictions.

III CONTENT OF MARKETING AUTHORISATION

Article 11

Marketing authorisation for a veterinary medicinal product shall contain the following:

1) the marketing authorisation number;
2) name and address of the marketing authorisation holder;
3) the name of the medicinal product;
4) the pharmaceutical form of the medicinal product;
5) the strength of the medicinal product;
6) the qualitative and quantitative composition of the active substance(s);
7) the type and pack size of the medicinal product;
8) the name and address of the manufacturer(s) responsible for batch release;
9) the Anatomical Therapeutic Chemical (ATC) classification code of the medicinal product;
10) the dispensing classification of the medicinal product;
11) the conditions and obligations in accordance with Article 233 of the Law;
12) the validity period of the marketing authorisation.

IV CONTENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS OF VETERINARY MEDICINAL PRODUCT

Summary of the product characteristics

Article 12

Summary of the product characteristics shall contain in the order indicated below, the following information:

1. Name of the veterinary medicinal product, strength and pharmaceutical form
2. Qualitative and quantitative composition of active substances and qualitative composition of excipients and other ingredients by stating their common name or chemical description and quantitative composition, if this information is necessary for the proper use of the veterinary medicinal product.
3. Clinical information:
   - 3.1. target species;
   - 3.2. indications for use, for each target species;
   - 3.3. contraindications;
   - 3.4. special warnings;
   - 3.5. special precautions for use, including in particular special precautions for safe use in the target species, special precautions to be taken by the person administering the veterinary medicinal product to the animals and special precautions for the protection of the environment;
   - 3.6. frequency and seriousness of adverse events;
   - 3.7. use during pregnancy, lactation and lay;
   - 3.8. interactions with other medicinal products and other forms of interactions;
   - 3.9. administration route and dosage;
   - 3.10. symptoms of overdose and, where applicable, emergency procedures and antidotes in the event of overdose;
   - 3.11. special restrictions for use;
   - 3.12. special conditions for use, including restrictions for use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance;
   - 3.13. if applicable, the withdrawal periods, even if such periods are zero;
4. Pharmacological information
   - 4.1. Anatomical Therapeutic Chemical Veterinary Code (‘ATCvet Code’);
   - 4.2. pharmacodynamics;
   - 4.3. pharmacokinetics;

   In case of an immunological veterinary medicinal product, instead of items 4.1., 4.2. and 4.3. immunological information shall be provided;
5. Pharmaceutical particulars:
   - 5.1. major incompatibilities;
   - 5.2. shelf life, where applicable after reconstitution of the medicinal product or after the immediate packaging has been opened for the first time;
   - 5.3. special precautions for storage;

5.4. nature and composition of immediate packaging;

5.5. requirement to use take-back schemes for veterinary medicinal products for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products and, if appropriate, additional precautions regarding hazardous waste disposal of unused veterinary medicinal products or waste materials derived from the use of such products;

6. Name of the marketing authorisation holder;
7. Marketing authorisation number;
8. Date of the first marketing authorisation;
9. Date of last revision of the summary of product characteristics;
10. If applicable, for veterinary medicinal products referred to in articles 227 or 228 of the Law, a statement:

-"marketing authorisation granted for a limited market and therefore assessment based on customised requirements for documentation"; or

- "marketing authorisation in exceptional circumstances and therefore assessment based on customised requirements for documentation";

11. information on the collection systems referred to in Article 310 of the Law applicable to the veterinary medicinal product concerned;
12. classification of the veterinary medicinal product i accordance with Article 237 paragraphs 1-3 of the Law.

In the case of generic veterinary medicinal products, parts of the summary of product characteristics of the reference veterinary medicine that relate to indications or pharmaceutical forms that are protected by patent law in Montenegro or a Member State of the European Union at the time of placing generic veterinary medicine on the market may be omitted.

Labelling of the immediate packaging of veterinary medicinal products

Article 13

The immediate packaging of a veterinary medicinal product shall contain the following information and shall, subject to Article 14 paragraph 4 of this Rulebook, contain no information other than:

1) name of the veterinary medicinal product, its strength and pharmaceutical form;
2) name of active substances expressed qualitatively and quantitatively per unit of individual dosage or according to the form of administration for a particular volume or weight, using their common names;
3) batch number;
4) name, or logo of the marketing authorization holder;
5) target species;
6) expiry date (month and year);
7) special storage precautions, if any;
8) route of administration; and
9) if applicable, the withdrawal period, even if such period is zero.

The information referred to in paragraph 1 of this Article shall appear in easily legible and clearly comprehensible characters, or in abbreviations or pictograms in accordance with the articles 18 and 19 of this Rulebook.

An identification code shall be added to the information required under paragraph 1.

Labelling of the outer packaging of veterinary medicinal products

Article 14

The outer packaging of a veterinary medicinal product shall contain the following information and shall contain no information other than:

1) information referred to in the Article 13 paragraph 1 of this Rulebook;
2) contents by weight, volume or number of immediate packaging units of the veterinary medicine;
3) warning that the veterinary medicinal product must be kept out of the sight and reach of children;
4) warning that the veterinary medicinal product is intended for animal treatment only;
5) recommendation to read the package leaflet;
6) in the case of homeopathic veterinary medicinal product, the statement 'homeopathic veterinary medicinal product;
7) in the case of veterinary medicinal product not subject to a veterinary prescription, the indication or indications;
8) the marketing authorisation number.

Identification code for a veterinary medicine may appear on the outer packaging instead of marketing authorisation number of the veterinary medicine.

The information referred to in paragraph 1 of this Article shall appear in easily legible and clearly comprehensible characters, or in abbreviations or pictograms in accordance with the articles 18 and 19 of this Rulebook.

Where there is no outer packaging, all the information referred to in paragraphs 1 and 2 to this article shall appear on the immediate packaging.

Labelling of small immediate packaging units of veterinary medicinal products

Article 15

By way of derogation from Article 13 of this Rulebook, immediate packaging units which are too small to contain in a readable form the information referred to in that Article shall contain the following information and shall contain no information other than:

1) the name of veterinary medicinal product;
2) the quantitative particulars of the active substances;
3) the batch number;
4) the expiry date (month and year).

The immediate packaging units referred to in paragraph 1 of this Article shall have an outer packaging containing information required in Article 14 paragraphs 1-3 of this Rulebook.

Article 16

The following types of immediate packaging shall be considered to be small immediate packaging units within the meaning of Article 15 of this rulebook:

1) blisters or strips;
2) ampoules and small single-dose containers other than ampoules;

3) a container or any other form of packaging that is in direct contact with the veterinary medicinal product and has a nominal volume of up to and including 50 ml.

By way of derogation from paragraph 1, point (c), multilingual immediate packaging units not exceeding a nominal volume of 100 ml to qualify are considered as small immediate packaging units where the following conditions are fulfilled:

1) the immediate packaging unit is too small or has a shape or configuration that makes it impossible to accommodate the information referred to in Article 13 paragraph 1 of this Rulebook in a readable manner, and
2) the veterinary medicinal product is classified as subject to veterinary prescription in accordance with Article 237 of the Law.

Additional information on the immediate packaging or outer packaging of veterinary medicinal products

Article 17

By way of derogation from Articles 13 paragraph 1, 14 paragraph 1 and 15 paragraph 1 of this Rulebook, Institute may, on request of the applicant, allow an applicant to include on the immediate packaging or outer packaging of a veterinary medicinal product additional useful information which is compatible with the summary of the product characteristics and which is not an advertisement for a veterinary medicinal product.

Abbreviations and pictograms to be used on the packaging of veterinary medicinal products

Article 18

The abbreviations and pictograms are set out in the Annex III and Annex IV to this Rulebook.

The abbreviations and pictograms may be used to replace the written information required on the labeling of immediate packaging and on the outer packaging of veterinary medicinal products referred to in Article 13 paragraph 1 and and Article 14 paragraph 1 of this Rulebook.

Abbreviations and pictograms not listed in the Annex III and Annex IV to this Rulebook shall not be used to replace that written information from paragraph 2 to this article.

Article 19

The abbreviations and pictograms shall only be used to replace the corresponding text as set out in the Annexes and shall not be used to replace any other information concerning the veterinary medicinal product.

Abbreviations and pictograms used on the labelling of a veterinary medicinal product must be explained in full text in the package leaflet of the veterinary medicinal product concerned.

Abbreviations shall be displayed in the format as laid down in Annex III to this Rulebook.

Pictograms:

1) shall be proportionate to the overall size of the labelling of immediate packaging or outer packaging of veterinary medicinal products;
2) shall be presented in a sufficiently readable format;
3) have a black symbol and no additional visual aspects such as shading;
4) stand out clearly on the color and presentation of the labeling of immediate packaging or outer packaging;
5) shall not negatively affect the readability of the rest of the information on the labeling of immediate or outer packaging due to their location.

Package leaflet of veterinary medicinal products

Article 20

The marketing authorisation holder shall make readily available a package leaflet for each veterinary medicinal product. That package leaflet shall contain at least the following information:

1) the name and permanent address of the marketing authorisation holder and of the manufacturer and, where applicable, of the representative of the marketing authorisation holder;
2) the name of the veterinary medicinal product, followed by its strength and pharmaceutical form;
3) qualitative and quantitative composition of the active substance or substances;
4) the target species, the dosage for each species, the method and route of administration and, if necessary, advice on correct administration;
5) the indications for use;
6) the contra-indications and adverse events;
7) if applicable, the withdrawal period, even if such period is zero;
8) special storage precautions, if any;
9) information essential for safety or health protection, including any special precautions relating to use and any other warnings;
10) information on the collection systems referred to in Article 310 applicable to the veterinary medicinal product concerned;
11) the marketing authorisation number;
12) contact details of the marketing authorisation holder or its representative, as appropriate, for the reporting of suspected adverse events;
13) classification of the veterinary medicinal product as referred to in Article 237 paragraphs 1-3 of the Law.

The package leaflet may bear additional information concerning distribution, possession or any necessary precaution in conformity with the marketing authorisation, provided that the information is not promotional. That additional information shall appear in the package leaflet clearly separated from the information referred to in paragraph 1.

The package leaflet shall be written and designed to be readable, clear and understandable, in terms that are comprehensible to the general public.

By derogation from paragraph 1 to this article, the information required in accordance with this Article may, alternatively, be provided on the packaging of the veterinary medicinal product.

General requirement regarding product information

Article 21

The information listed in Articles 13, 14, 15 and 17 shall comply with the summary of the product characteristics as set out in Article 12 to this Rulebook.

Package leaflet of registered homeopathic veterinary medicinal products

Article 22

By way of derogation from Article 20 paragraph 1 to this Rulebook, the package leaflet of homeopathic veterinary medicinal products registered in accordance with Article 229 of the Law shall contain at least the following information:

1) the scientific name of the stock or stocks followed by the degree of dilution, using the symbols of the European Pharmacopoeia or, in the absence thereof, of the pharmacopoeias used officially in Member States;
2) name or company name and permanent address or registered place of business of the registration holder and, where appropriate, of the manufacturer;
3) method of administration and, if necessary, route of administration;
4) pharmaceutical form;
5) special storage precautions, if any;
6) the target species and, where appropriate, dosage for each such species;
7) a special warning, if necessary, for the homeopathic veterinary medicinal product;
8) registration number;
9) withdrawal period, if applicable;
10) the statement ‘homeopathic veterinary medicinal product’.

Article 23

Institute may, in the marketing authorisation procedure and upon a duly justified request by the applicant, approve the use of outer packaging labelled in a foreign language, provided that such packaging has been approved in the country of origin, that the Institute has been provided with documentation identical to the one approved in the country of origin, and that the annual consumption of the medicinal product in Montenegro does not exceed 1000 packs. In such cases, Institute approves an additional label in the Montenegrin language, which must be affixed to the outer packaging.

An additional label from paragraph 1 to this Article shall contain the information from article 14 of this Rulebook, except the information which are easily legible and clearly visible on the original packaging (expiry date, batch number).

All information on medicinal product on the additional label must be readable, understudable and indelible.

Article 24

Institute may, during the marketing authorisation procedure and upon a duly justified request by the applicant, approve the use of outer packaging labelled in a language that is in official use in Montenegro, provided that such packaging has been approved in the country of origin and that the Institute has been provided with documentation identical to the one approved in the country of origin of the packaging. In such cases, Institute approves an additional label in the Montenegrin language, which must be affixed to the outer packaging.

An additional label from paragraph 1 to this Article shall contain the following information:

1) the name and address of the marketing authorisation holder in Montenegro;
2) the marketing authorisation number granted in Montenegro.

The additional label referred to in paragraph 1 of this Article may also include the name of the medicinal product, pharmaceutical form, strength, and pack size, if technically feasible.

Alternatively, the information required on the additional label referred to in paragraph 1 of this Article may be printed directly on the outer carton, provided that prior approval for such printing has been obtained from the competent authority in the country of origin of the packaging.

Article 25

The additional label referred to in Articles 23 and 24 of this Rulebook shall be provided by the manufacturer or the marketing authorisation holder for wholesale distribution of the medicinal product.

Article 36

The inclusion of the package leaflet, in the cases referred to in Articles 23 and 24 of this Rulebook, shall be ensured by the manufacturer or the holder of the wholesale distribution authorisation.

Article 27

A medicinal product for which the Institute has granted an import authorization in accordance with Article 219 of the Law shall be labelled with an additional sticker indicating the name of the importer and the number of the import authorization issued by the Institute.

V CONDITIONS, PROCEDURE AND DOCUMENTATION FOR THE VARIATION OF A MARKETING AUTHORISATION FOR VETERINARY MEDICINAL PRODUCT

Article 28

Marketing authorisation holder of veterinary medicinal product shall monitor scientific and technical developments in the field, pharmacovigilance data and other relevant information concerning the medicinal product and inform the Institute on any new findings related to the assessment of the quality, safety and efficacy of the medicinal product. The marketing authorisation holder shall submit an application for the variation in accordance with the new findings concerning the veterinary medicinal product.

Article 29

Variations referred to in Article 28 of this Rulebook shall be classified into variations not requiring assessment and variations requiring assessment, in accordance with the criteria referred to in Article 246 of the Law.

Variations not requiring assessment

Article 30

Variations listed in the Annex V to this Rulebook, which satisfy the requirements applicable to them as set out therein, shall not require assessment.

The marketing authorisation holder shall submit aplication for notification the Institute of a variation not requiring assessment in accordance with the Article 247 of the Law.

Together with the application reffered to in paragraph 2 to this Article, the marketing authorisation holder shall submit the following documentation:

1) a completed application form, published on the website of the Institute, signed by the authorised representative of the applicant;

2) documentation listed in the Annex V relating to the variation, providing sufficient information for its evaluation; and

3) proof of payment of the prescribed fees.

Variations requiring assessment

Article 31

Where a variation is not included in the list of the Annex V to this Rulebook,the marketing authorisation holder shall submit an application for a variation requiring assessment to the Institute in accordance with the Article 248 of the Law.

An application reffered to in paragraph 1 of this Article shall be submitted in the application form, published on the website of the Institute.

The application reffered to in the paragraph 1 of this Article shall contain:

1) a description of the variation;
2) data referred to in Article 6 to this Rulebook relevant to the variation;
3) details of the marketing authorisation affected by the application;
4) where the variation leads to consequential variations to the terms of the same marketing authorisation, a description of those consequential variations.

Together with the application reffered to in the paragraph 1 of this Article, the applicant shall submit the following documentation:

1) documentation relating to the variation, providing sufficient information for its evaluation, in accordance with the Guidance reffered to in Article 32 of this Rulebook; and

2) proof of payment of the prescribed fees.

Article 32

Variations requiring assessment shall be classified in accordance with Guidance EMA/CMDv/7381/2021 on the details of the classification of variations requiring assessment for veterinary medicinal products and on the documentation to be submitted pursuant to those variations.

Article 33

For a variation request concerning a veterinary medicinal product that has been granted marketing authorisation in Montenegro through the accelerated procedure in accordance with Article 232 of the Law**,** the applicant shall submit, in addition to the documentation prescribed by this Rulebook, the following**:**

1) the identical variation documentation (variation package) as approved under the Centralised Procedure (CP), Mutual Recognition Procedure (MRP), or Decentralised Procedure (DCP);
2) the variation approval in CP, MRP or DCP;
3) the assessment report issued by the EMA or by the reference Member State in the DCP or MRP, for variations.

Consequential changes to product information

Article 34

Where a variation entails consequential changes to the summary of the product characteristics, the labelling or the package leaflet, those changes shall be considered as part of that variation for the purposes of the examination of the application for a variation.

Groups of variations

Article 35

Marketing authorisation holder for veterinary medicine may submit an application containing multiple variations not included in the Annex Vreferred to in Article 30 paragraph 1 to this Rulebook in the following cases:

1) when several variations are submitted regarding the same marketing authorisation;
2) for one variation in respect of several different marketing authorisations.

VI TERMINATION OF THE MARKETING AUTHORISATION FOR A VETERINARY MEDICINAL PRODUCT

Article 36

The Marketing Authorisation Holder shall, in accordance with Article 250 of the Law, submit to the Institute a request for the termination of the marketing authorisation for a veterinary medicinal product, using the application form published on the Institute's website.

The request referred to in paragraph 1 of this Article shall be submitted separately for each pharmaceutical form, strength, and pack size of the medicinal product.

The request referred to in paragraph 1 of this Article shall be accompanied by proof of payment of the prescribed fees and any other documentation required by the Institute.

VII FINAL PROVISIONS

Article 37

Veterinary medicinal products for which a marketing authorisation has been issued or for which an application for a marketing authorisation has been submitted before the entry into force of this Rulebook may be used until 11 April 2029, even if the abbreviations and pictograms referred to the Articles 18 and 19 to this Rulebook do not comply with the provisions of this Rulebook.

Veterinary medicinal products for which a medicinal product authorisation has been issued or for which an application for a medicinal product authorisation has been submitted

before the entry into force of this Rulebook may be used until 11 April 2031, even if the information contained on the label as regards small immediate packaging units of veterinary medicinal product referred to in the Articles 15 and 16 to this Rulebook is not in compliance with this Rulebook.

Article 38

The provisions of Article 12 paragraph 1 item 5.5. on the requirement to use take-back schemes for veterinary medicinal products for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products shall apply from the date of accession of Montenegro to the European Union.

Article 39

On the date of entry into force of this Rulebook, the provisions of the Rulebook on more detailed conditions for issuance of marketing authorisation for a medicinal product ("Official Gazette of Montenegro" No 21/16 and 55/19) on the veterinary medicinal products shall cease to be valid.

Article 40

This Regulation shall enter into force on the eighth day from the day of its publication in the "Official Gazette of Montenegro ".

Done at Podgorica, 2026. godine CHAIRMAN OF THE BOARD OF DIRECTORS

Broj: dr Jovan Milić, spec. ophtalmology

*The provisions of the following regulations have been incorporated into these rulebook: **Regulation (EU) 2019/6 of the European Parliament and of the Council** of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, **Commission Delegated Regulation (EU) 2021/805** of 8 March 2021 amending Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council, **Commission Delegated Regulation (EU) 2023/183** of 23 November 2022 amending Regulation (EU) 2019/6 of the European Parliament and of the Council as regards the requirements on compliance with good laboratory practice for veterinary medicinal products set out in Annex II to that Regulation and **Commission Implementing Regulation (EU) 2021/17** establishing a list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council as amended by **Commission Implementing Regulation (EU) 2023/997** of 23 May 2023, **Commission Implementing Regulation (EU) 2024/916** of 26.03.2024 and **Commission Implementing Regulation (EU) 2025/163** amending Implementing Regulation (EU) 2021/17 establishing a list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council, **Commission Implementing Regulation (EU) 2024/875** of 21 March 2024 adopting a list of abbreviations and pictograms common throughout the Union to be used on the packaging of veterinary medicinal products for the purposes of Article 10(2) and Article 11(3) of Regulation (EU) 2019/6 of the European Parliament and of the Council and **Commission Implementing Regulation (EU) 2024/878** of 21 March 2024 adopting uniform rules on the size of small immediate packaging units of veterinary medicinal products as referred to in Article 12 of Regulation (EU) 2019/6 of the European Parliament and of the Council.

ANNEX I

INFORMATION REFERRED TO IN ARTICLE 6 PARAGRAPH 1 POINT (1) TO THIS RULEBOOK

1. Legal basis for the application for the marketing authorisation
2. Applicant:
   2.1. name and permanent address of the applicant
   2.2. name and permanent address of the manufacturer or importer of finished veterinary medicinal product and name and permanent address of the manufacturer of active substances;
   2.3. Name and address of the sites involved in the different stages of the manufacturing, importing, control and batch release (Flow chart for Montenegro)
3. Identification of the veterinary medicinal product
   3.1. Name of the veterinary medicinal product and Anatomical Therapeutic Chemical Veterinary code (ATCvet Code);
   3.2. Active substance(s) and, if applicable, diluent(s)
   3.3. Strength or, in case of immunological veterinary medicinal product, biological activity, potency or titre
   3.4. Pharmaceutical form
   3.5. Route of administration
   3.6. Target species
4. Manufacturing and pharmacovigilance information
   4.1 Proof of a manufacturing authorisation or certificate of good manufacturing practice
   4.2 Reference number of pharmacovigilance system master file
5. Veterinary medicinal product information
   5.1 Proposed summary of the product characteristics drawn up in accordance with Article 12 to this Rulebook
   5.2 Description of the final presentation of the veterinary medicinal product, including packaging and labelling
   5.3. Proposed text of the information to be provided on the immediate packaging, outer packaging and the package leaflet in accordance with Articles 13, 14, 15, 17, 20, 21 and 22 to this Rulebook
6. Other information
   6.1 List of countries in which a marketing authorisation has been granted or revoked for the veterinary medicinal product
   6.2 Copies of the summary of product characteristics as included in the terms of marketing authorisations granted by European union Member States
   6.3. List of countries in which an application has been submitted or refused
   6.4. List of European union Member States in which the veterinary medicinal product is to be placed on the market
   6.5 Critical expert reports on quality, safety and efficacy of the veterinary medicinal product.

ANNEX II

TECHNICAL DOCUMENTATION NECESSARY FOR DEMONSTRATING THE QUALITY, SAFETY AND EFFICACY OF THE VETERINARY MEDICINAL PRODUCT

Table of Contents

II.2E4. Microbiological controls
II.2E5. Batch-to-batch consistency
II.2E6. Other controls
II.2F. Stability test
II.2F1. Active substance(s)
II.2F2. Finished product
II.2G. Other information
II.3 Part 3: Safety documentation (safety and residues tests)
II.3A. Safety tests
II.3A1. Precise identification of the product and of its active substance(s)
II.3A2. Pharmacology
II.3A2.1. Pharmacodynamics
II.3A2.2. Pharmacokinetics
II.3A3. Toxicology
II.3A4. Other requirements
II.3A.4.1. Special studies
II.3A.4.2. Observations in humans
II.3A.4.3.Development of resistance and related risk in humans
II.3A5. User safety
II.3A6. Environmental risk assessment
II.3B. Residue tests
II.3B1. Identification of the product
II.3B2. Depletion of residues (metabolism and residue kinetics)
II.3B3. Residue analytical method
II.4. Part 4: Efficacy documentation (pre-clinical studies and clinical trial(s))
II.4A. Pre-clinical studies
II.4A1. Pharmacology
II.4A.1.1.Pharmacodynamics
II.4A.1.2.Pharmacokinetics
II.4A2. Development of resistance and related risk in animals
II.4A3. Dose determination and confirmation
II.4A4. Tolerance in the target animal species
II.4B. Clinical trial(s)
II.4B1. General principles
II.4B2. Documentation
II.4B2.1.Results of pre-clinical studies
II.4B2.2.Results of clinical trials

SECTION III

REQUIREMENTS FOR BIOLOGICAL VETERINARY MEDICINAL PRODUCTS

SECTION IIIa

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

IIIa.1. Part 1: Summary of the dossier

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

IIIa.2A. Product description

IIIa.2A1. Qualitative and quantitative composition

IIIa.2A2. Product development

IIIa.2A3. Characterisation

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

IIIa.2A3.2. Impurities

IIIa.2B. Description of the manufacturing method

IIIa.2C. Production and control of starting materials

IIIa.2C1. Starting materials listed in pharmacopoeias

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

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

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

IIIa.2D. Control tests during the manufacturing process

IIIa.2E. Control tests on the finished product

IIIa.2E1 Finish product specification

IIIa.2E2 Method descriptions and validation of release tests

IIIa.2E3. Reference standards or materials

IIIa.2F.Batch-to-batch consistency

IIIa.2F1. Active substance

IIIa.2F2. Finished product

IIIa.2G. Stability tests

IIIa.2H. Other information

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

IIIa.3A. Safety tests

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

IIIa.3A2.Pharmacology

IIIa.3A2.1. Pharmacodynamics

IIIa.3A2.2. Pharmacokinetics

IIIa.3A3. Toxicology

IIIa.3A3.1. Single-dose toxicity

IIIa.3A3.2. Repeat-dose toxicity

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

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

IIIa.3A3.5.Genotoxicity

IIIa.3A3.6. Carcinogenicity

IIIa.3A3.7.Exceptions

IIIa.3A4.Other requirements

IIIa.3A4.1.Special studies

IIIa.3A4.2.Observations in humans

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

IIIa.3A5.User safety

IIIa.3A6.Environmental risk assessment

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

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

IIIa.3B. Residue tests

IIIa.3B1.Identification of the product

IIIa.3B2.Depletion of residues

IIIa.3B3.Residue analytical method

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

IIIa.4A. Pre-clinical studies

IIIa.4A1.Pharmacology

IIIa.4A1.1.Pharmacodynamics

IIIa.4A1.2.Pharmacokinetics

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

IIIa.4A3.Dose determination and confirmation

IIIa.4A4.Tolerance in the target animal species

IIIa.4B. Clinical trials

IIIa.4B1.General principles

IIIa.4B2.Documentation

IIIa.4B2.1.Clinical trials

IIIa.4B2.2.Clinical trials

SECTION IIIb

REQUIREMENTS FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

IIIb.1.Part 1: Summary of the dossier

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

IIIb.2.A.Product description

IIIb.2A1.Qualitative and quantitative composition

IIIb.2A2.Product development

IIIb.2B. Description of the manufacturing method

IIIb.2C. Production and control of starting materials

IIIb.2C1.Starting materials listed in pharmacopoeias

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

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

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

IIIb.2D. Control tests during the manufacturing process

IIIb.2E. Control tests on the finished product

IIIb.2F. Batch-to-batch consistency

IIIb.2G. Stability tests

IIIb.2H. Other information

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

IIIb.3A. General requirements

IIIb.3B. Pre-clinical studies

IIIb.3C. Clinical trials

IIIb.3D. Environmental risk assessment

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

IIIb.3F. Residue tests to be included in the laboratory studies

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

IIIb.4A. General requirements

IIIb.4B. Pre-clinical studies

IIIb.4C. Clinical trials

SECTION IV

REQUIREMENTS FOR SPECIFIC MARKETING AUTHORISATION APPLICATIONS

IV.1.Applications for generic veterinary medicinal products

IV.2.Applications for hybrid veterinary medicinal products

IV.3.Applications for combination veterinary medicinal products

IV.4.Applications based on informed consent

IV.5.Applications based on bibliographic data

IV.6.Applications for limited markets

IV.7.Applications in exceptional circumstances

SECTION V

REQUIREMENTS FOR MARKETING AUTHORISATION APPLICATIONS FOR PARTICULAR VETERINARY MEDICINAL PRODUCTS

V.1. Novel therapies veterinary medicinal products

V.1.1 General requirements

V.1.2. Quality requirements

V.1.3. Safety requirements

V.1.4. Efficacy requirements

V.1.5. Specific data requirements for particular types of novel therapy products

V.1.5.1. Principles

V.1.5.2. Gene therapy veterinary medicinal products

V.1.5.3. Regenerative medicine, tissue engineering and cell therapy veterinary medicinal products

V.1.5.4. Veterinary medicinal product specifically designed for phage therapy

V.1.5.5. Veterinary medicinal product issued from nanotechnologies

V.1.5.6. RNA antisense therapy and RNA interference therapy products

V.2. Vaccine antigen master file

V.3. Multi-strain dossier
V.4. Vaccine platform technology
V.5. Authorised homeopathic veterinary medicinal products

SECTION I
GENERAL PRINCIPLES AND REQUIREMENTS

I.1. **General principles**

I.1.1. The documentation accompanying an application for a marketing authorisation shall be presented in accordance with the requirements set out in this Annex and the guidance documents published by the European Commission

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 safety studies shall be carried out in conformity with the provisions related to Good Laboratory Practice (GLP) laid down in Directives 2004/10/EC and 2004/9/EC of the European Parliament and of the Council.

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 in Montenegro or European Union.

I.2. **Dossier composition requirements**

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 to this rulabook, 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, 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, provided that:

1) the administration of the veterinary medicinal product is restricted to pharmaceutical forms requiring no particular knowledge or skill in using the products;

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

3) the summary of the product characteristics of the veterinary medicinal product does not contain any warnings of potential serious adverse events deriving from its correct use;

4) neither the veterinary medicinal product nor any other product containing the same active substance has previously been the subject of frequent adverse event reporting;

5) the summary of the product characteristics does not refer to contra-indications related to the use of the product concerned in combination with other veterinary medicinal products commonly used without prescription;

6) there is no risk for public health as regards residues in food obtained from treated animals even where the veterinary medicinal product is used incorrectly;

7) there is no risk to public or animal health as regards the development of resistance to substances even where the veterinary medicinal product containing those substances is used incorrectly.

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)**

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) statement of compliance with GLP for pre-clinical safety 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.

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 GLP for pre-clinical safety 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:

- Section IIIa describes the standardised requirements for applications for biological veterinary medicinal products other than immunological veterinary medicinal products;
- 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 221 paragraph 1 and 236 referred to the Law and article 6 of this Rulebook:

(a) in respect of substances which appear in the European Pharmacopoeia or, failing this, in the national pharmacopoeia of one of the Member States, 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 on the colouring matters which may be added to medicinal products.

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.

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 221 paragraph 1, 236 referred to the the Law and

article 6 of this Rulebook 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 221 paragraph 1 and 236 referred to the Law and Article 6 of this Rulebook. 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 221 paragraph 1, 236 referred to in the Law and Article 6 of this Rulebook. 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 on the colouring matters which may be added to medicinal products 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 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.

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 its closure 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 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, 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,
(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 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 Council2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (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 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin and acts adopted based on that Regulation 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**

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 Montenegro or European 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 Montenegro or European 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 Montenegro or European 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.4B2.1. **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 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;

(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, if applicable;

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

II.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:

- received no treatment,

- received a placebo, or

- 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

-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 23 to the Law, except products defined in Article 24 to the Law 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 221 paragraph 1, 236 referred to in the Law and article 6 of this Rulebook, 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 of the European Parliament and of the Council on the colouring matters which may be added to medicinal products.

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 221 paragraph 1 and 236 referred to in the Law and article 6 of this Rulebook 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 of the European Parliament and of the Council on the colouring matters which may be added to medicinal products.

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, Institute may require observance of its own national pharmacopoeia with regard to products manufactured in Montenegro.

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 of the European Parliament and of the Council on the deliberate release into the environment of genetically modified organisms.

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.2A14. 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.3.A.1. 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.3.A.2. 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.3.A.2.1. Pharmacodynamics

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

IIIa.3.A.2.2. 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.3.A.3. 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.3.A.3.1. 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.3.A.3.2. Repeat-dose toxicity

Repeat-dose toxicity tests are intended to reveal any physiological and/or pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how 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.3.A.3.3. Tolerance in the target species

A summary shall be provided of any signs of intolerance which have been observed during studies conducted, usually with the final formulation, in the target species in accordance with the requirements of Part 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.3.A.3.4. 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.3.A.3.5. 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.3.A.3.6. Carcinogenicity

The decision on whether carcinogenicity testing is required shall take into account the results of genotoxicity tests, structure-activity relationships and the findings in 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.3.A.3.7. Exceptions

Where a veterinary medicinal product is intended for topical use, systemic absorption shall be investigated in the target animal species. If it is proved that systemic absorption is negligible, the repeated dose toxicity tests, the tests for 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.3.A.4. Other requirements

IIIa.3.A.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, 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.3.A.4.2. 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.3.A.4.3. 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.3.A.5. 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.3.A.6. Environmental risk assessment

IIIa.3.A.6.1. 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.3.A.6.2. 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 on the deliberate release into the environment of genetically modified organisms.

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 on the deliberate release into the environment of genetically modified organisms.

IIIa.3.B. Residue tests

1. For the purposes of this point, the definitions of Regulation (EC) No 470/2009 on Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin and acts adopted based on that Regulation 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.3.B.1. 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.3.B.2. 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.3.B.3. 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.4.A. 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.4.A.1. Pharmacology

IIIa.4.A.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 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.

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

IIIa.4.A.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, particularly 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) 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.

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.

5. For fixed combinations, please refer to Section IV.

IIIa.4.A.2. 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.4.A.3. 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.4.A.4. 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.4.B. Clinical trials

IIIa.4.B.1. 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 Montenegro or European 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 Montenegrin or European 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 Montenegro or European 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.4.B.2. 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.4.B.2.1. 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 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.4.B.2.2. 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:

- received no treatment;

- received a placebo;

- 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

- 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 24 of the Law, 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.2.A.1. 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 221 paragraph 1 and 236 referred to the Law and article 6 of this Rulebook, 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 on the colouring matters which may be added to medicinal products.

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.2.A.2. 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.2.B. Description of the manufacturing method

1. The description of the manufacturing method accompanying the application for marketing authorisation pursuant to Article 221 paragraph 1 and 236 referred to in the Law and article 6 of this Rulebook 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.2.C. 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 on the colouring matters which may be added to medicinal products.

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.2.C.1. 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, Institute may require observance of its own national pharmacopoeia with regard to products manufactured in Montenegro.

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.2.C.2. Starting materials not listed in a pharmacopoeia

IIIb.2.C.2.1. 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 on the deliberate release into the environment of genetically modified organisms.

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.2.C.2.2. 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.2.D. 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.2.E. 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.2.F. Batch-to-batch consistency

In order to ensure that quality of the product is consistent from batch to batch and to demonstrate conformity with specifications a full protocol of three consecutive batches 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.2.G. 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.2.H. 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.3.A. 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 safety studies shall be carried out in compliance with 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.3.B. 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.3.C. 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.3.D. 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.3.E. 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 on the deliberate release into the environment of genetically modified organisms 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 on the deliberate release into the environment of genetically modified organism.

IIIb.3.F. 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.4.A. 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.4.B. 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;

(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 Montenegro i.e. the European 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.4.C. 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 222 of the Law (generic veterinary medicinal products) shall contain the data referred to in Parts 1 and 2 of Section II of this Annex. 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:

(a) evidence to demonstrate equivalent or differing depletion of residues from the administration site, which may be substantiated by appropriate residue depletion studies;

(b) 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 223 of the Law (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. 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 224 of the Law.

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 221 paragraph 1 and 236 referred to in the Law and article 6 of this Rulebook.

IV.3.2. For applications submitted under Article 224 of the Law, 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 225 of the Law 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 226 of the Law, 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 225 of the Law is not possible.

IV.5.3.5. The published documentation submitted by the applicant shall be freely available to 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 227 of the Law, 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 228 paragraphs 1 and 2 of the Law 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 25 of the Law, 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.1.5.1.3. 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 100 nm).

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:

- when physiological barriers are crossed, the impact of nanoparticles for drug delivery shall be investigated on the corresponding organ(s);
- 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;
- 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;
- 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 Montenegro and European 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 Montenegro and European 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 Montenegro and European 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 229 paragraph 2 of the Law 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 26 of the Law with the following specification, without prejudice to the provisions of Commission Regulation (EU) No 37/2010 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.

ANNEX III

When using abbreviations in accordance with Article 18 of this Rulebook, the following abbreviations shall be used to replace the following routes of administration on the labelling of immediate packaging or on the outer packaging of veterinary medicinal products:

ABBREVIATIONS

Route of administration	Abbreviations
Intramuscularly	**i.m.**
Intravenous	**i.v.**
Subcutaneously	**s.c.**

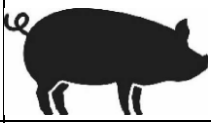
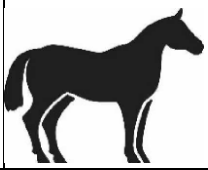
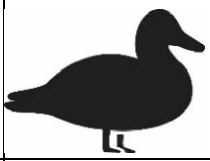
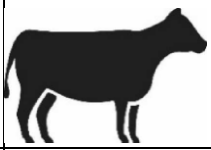
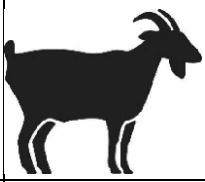
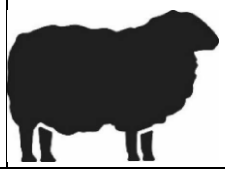
ANNEX IV

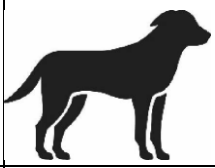
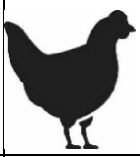
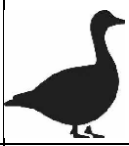
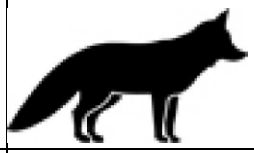
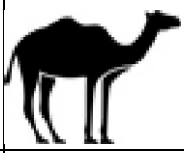
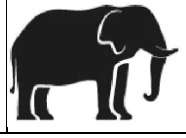
PICTOGRAMS

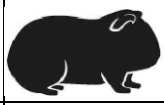
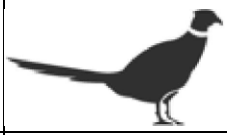
When using pictograms in accordance with Article 18 of this Rulebook, the pictograms included in this annex shall be used to replace the following particulars on the labelling of immediate packaging or on the outer packaging of veterinary medicinal products:

Section 1

Target species

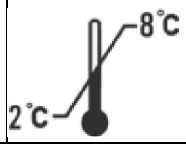
Target species	Pictogram
Pig	
Horse	
Duck	
Cattle	
Goat	
Fish	
Sheep	

Dog	
Chicken	
Rabbit	
Turkey	
Goose	
Cat	
Fox	
Camel	
Pigeon	
Elephant	

Guinea pig	
Snake	
Parrot	
Pheasant	
Bee	
Ornamental bird	

Section 2

Storage conditions

Storage precautions	Pictogram
Store in a refrigerator	

ANNEX V

VARIATIONS NOT REQUIRING ASSESSMENT

	Variation	**Requirements** **The requirements indicated in the line for the main section are valid for each sub-section of the given section. Any additional requirement specified in the sub-section should be read together with the requirements indicated in the main section.**	
Number		**Conditions**	**Documents to be provided**
A	**Administrative changes**		
1	Change in the name or address or contact details of:		
a)	— the marketing authorisation holder	The marketing authorisation holder shall remain the same legal entity. The marketing authorisation holder shall already be incorporated in the Montenegrin or European Union IT systems storing and providing organisational data.	
b)	— a manufacturer or supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance or a quality control testing site (where specified in the dossier) where no European Pharmacopoeia (Ph. Eur.) Certificate of Suitability (CEP) is part of the approved dossier.	The manufacturing or quality control site and all manufacturing operations shall remain the same. The manufacturer or supplier shall already be incorporated in the Montenegrin or European Union IT systems storing and providing organisational data (not applicable for starting material and reagent manufacturers/suppliers).	

c)	— an active substance master file (ASMF) holder	The manufacturing site and all manufacturing operations shall remain the same. The ASMF holder shall already be incorporated in the Montenegrin or European Union IT systems storing and providing organisational data.	Updated "letter of access" to the Active Substance Master File.'
d)	— a manufacturer of a [novel] excipient (where specified in the dossier)	The manufacturing site and all manufacturing operations shall remain the same.	
e)	— a manufacturer or importer of the finished product (including batch release or quality control testing sites)	The manufacturing or quality control site and all manufacturing operations shall remain the same. The manufacturer or supplier shall already be incorporated in the Montenegrin or European Union IT systems storing and providing organisational data.	
2	Change in the (invented) name of the veterinary medicinal product	The acceptability review of the new name by the Agency or the national competent authority, as applicable, shall be finalised and is positive.	
3	Change in name of the active substance or of an excipient	The substance shall remain the same. For veterinary medicinal products for food-producing species, the entry in Regulation (EC) No 470/2009 for this substance shall be amended before implementation of this change.	
4	Change in ATCvet Code	The change shall only be introduced following alteration to the index of the ATCvet Code.	
B	Changes to the quality part of the dossier		

1	Change in the name or address of a supplier of a packaging component or of a device of the finished product (where mentioned in the dossier):	The supplier shall already be incorporated in the Montenegrin or European Union IT systems storing and providing organisational data. The manufacturing site shall remain the same.’	
2	Change in the nomenclature [(2)] of the material for immediate packaging of the finished product	The change shall only be introduced following amendment to the name of the container in the standard terms database on the European Directorate for the Quality of Medicines and HealthCare (EDQM) website.	
3	Deletion of:		Amendment of the relevant section(s) of the dossier.
a)	a manufacturing site for an active substance, intermediate or finished product, packaging site, manufacturer responsible for importation, manufacturer responsible for batch release, site where batch control takes place, or supplier of (1) a starting material for an active substance, (2) a reagent or (3) an excipient (when mentioned in the dossier)	The deletion shall not be due to critical deficiencies concerning manufacturing. There shall at least remain one site or manufacturer, as previously authorised, performing the same function as the one(s) concerned by the deletion. There shall at least remain one site or manufacturer responsible for batch release within the European Union or the European Economic Area.’	
b)	a manufacturing process for the active substance or the finished product, including an intermediate used in the manufacture of the finished product when an alternative is already approved	The finished product, active substance, intermediates or in-process materials used in the manufacture of the finished product shall still conform to the approved specifications. The deletion shall not be due to critical deficiencies concerning manufacturing.	

c)	a non-significant in-process test during the manufacture of the active substance (e.g. deletion of an obsolete in-process test)	The change shall not relate to a commitment or to an unexpected event during manufacture. The change shall not concern a critical in-process test and shall not have the potential to affect the identity, quality, purity, potency or physical characteristics of the active substance, starting material, intermediate or reagent used in the manufacturing process of the active substance.	Comparative table of former and new in-process test.
d)	a non-significant specification parameter (e.g. deletion of an obsolete parameter) of — an active substance; — a starting material; — an intermediate or reagent used in the manufacturing process of the active substance	The change shall not relate to a commitment or to an unexpected event during manufacture. The change shall not concern a critical specification parameter or have the potential to affect the identity, quality, purity, potency or physical characteristics of the active substance, starting material, intermediate or reagent used in the manufacturing process of the active substance.	Comparative table of former and new specifications.
e)	a test procedure — for the active substance or a starting material, reagent or intermediate of the active substance; — for the immediate packaging of the active substance; — for an excipient or the finished product; — for the immediate packaging of the finished product	An alternative test procedure shall already be authorised by the national competent authority or the Agency and this test procedure has not been added through a variation procedure according to to Article 239 of the Law.	
f)	one of the authorised bulk or final containers (including packaging of an active substance) or immediate packaging of the finished product that	Where applicable, the remaining product presentations shall be adequate for the dosing	

	does not lead to the complete deletion of a strength or pharmaceutical form	instructions and treatment duration as defined in the summary of product characteristics.	
g)	a non-significant specification parameter (e.g. deletion of an obsolete parameter) in the specification parameters or limits of the immediate packaging of the active substance or the finished product	The change shall not relate to a commitment or to an unexpected event during manufacture of the immediate packaging material and storage of the active substance or the finished product. The change shall not concern a critical parameter or have the potential to affect the identity or quality of the immediate packaging.	Comparative table of former and new specifications.
h)	an approved change management protocol related to the active substance or the finished product	The change shall not be the result of an unexpected event or an out of specification result during the implementation of the change(s) described in the protocol.	
i)	a component or components of the flavouring or colouring system	The change shall not have the potential to affect the identity, strength, quality, purity, potency, safety or effectiveness of the finished product. For veterinary medicinal products for oral use, the change does not affect the uptake by target animal species. No change in functional characteristics of the pharmaceutical form, e.g. disintegration time, dissolution profile. Any minor adjustment to the formulation to maintain the total weight shall be made by an excipient which	

		currently makes up a major part of the finished product formulation. Stability studies have been started in line with conditions set out in the relevant guidelines, International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (ICH/VICH), Ph. Eur. etc., (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least 3 months satisfactory stability data are at the disposal of the applicant and the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). In addition, where relevant, photo-stability testing shall be performed.'	
j)	a solvent or diluent container from the pack	The pharmaceutical form shall remain unchanged. There shall be appropriate alternative means to obtain the solvent or diluent as required for the safe and effective use.	
k)	a non-significant in-process test (e.g. deletion of an obsolete test) during the manufacture of the finished product	The change shall not relate to a commitment or to an unexpected event during manufacture. The change shall not concern a critical parameter or have the potential to affect the identity, quality, purity,	Comparative table of former and new in-process tests and limits.

		potency or physical characteristics of the finished product or starting material, intermediate or reagent used in the manufacturing process of the finished product.	
l)	details on testing frequency by the finished product manufacturer of an excipient or an active substance or of packaging material for the immediate packaging of an active substance or the finished product, when mentioned in the dossier		
m)	a non-significant specification parameter (e.g. deletion of an obsolete parameter) in the specification parameters or limits of an excipient	The change shall not relate to a commitment or to an unexpected event during manufacture. The change shall not concern a critical parameter or have the potential to affect the identity, quality, purity, potency or physical characteristics of the excipient.	Comparative table of former and new specification parameters or limits.
n)	a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material) in the specification parameters or limits of the finished product	The change shall not relate to a commitment or to an unexpected event during manufacture. The change shall not concern a critical parameter or have the potential to affect the identity, strength, quality, purity, potency or physical characteristics of the finished product.	Comparative table of former and new specification parameters or limits.
o)	a measuring or administration device	The change shall not affect the delivery, use or safety of the finished product.	
p)	a non-significant specification parameter (e.g. deletion of an obsolete parameter) of a measuring or administration device	The change shall not relate to a commitment or to an unexpected event during manufacture. The change shall not concern a critical parameter or have the	Comparative table of former and new specifications.

		potential to affect the identity or quality of the measuring or administration device.	
q)	a test procedure of a measuring or administration device	An alternative test procedure shall already be authorised by the national competent authority or the Agency.	
r)	pack size(s) of the finished product	The remaining pack-sizes shall be consistent with the posology and treatment duration as approved in the summary of product characteristics.	
s)	a supplier of packaging components or devices (when mentioned in the dossier)	The change shall not include the deletion of a packaging component(s) or a device(s).	
t)	— a Ph. Eur. CEP — for an active substance; — for a starting material, reagent or intermediate used in the manufacturing process of the active substance; — for an excipient	At least one manufacturer for the same substance shall remain in the dossier.	
u)	— a Ph. Eur. Transmissible Spongiform Encephalopathy (TSE) CEP — for an active substance; — for a starting material, reagent or intermediate of an active substance; — for an excipient	At least one manufacturer for the same substance shall remain in the dossier.	
v)	— a pharmaceutical form or strength [(3)]	Remaining form(s) or strength(s) shall be suitable to allow accurate dosing of the product and treatment duration without the use of multiple presentations (e.g. several pipettes or tablets) or the use of	

		unapproved divided doses (e.g. half tablets that are not already authorised).	
4	Change in the manufacturer of a starting material, reagent or intermediate used in the manufacturing process of the active substance or change in the manufacturer of the active substance where no Ph. Eur. CEP is part of the approved dossier:		Amendment of the relevant section(s) of the dossier
a)	change in a manufacturer (including relevant quality control testing sites) that is part of the same pharmaceutical group as the currently approved manufacturer	The change shall not be applicable to a sterile active substance or a biological or immunological substance. The new manufacturer shall already be incorporated in the Union IT-systems storing and providing organisational data. For starting materials and reagents the specifications (including in-process controls, methods of analysis of all materials), shall be identical to those already approved. For intermediates and active substance(s) the specifications (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis shall be identical to those already approved. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current Note for Guidance on Minimising the Risk of Transmitting	TSE data as appropriate. Batch analysis data for at least two batches (minimum pilot scale). Qualified person (QP) declaration.

		Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.	
b)	changes to quality control testing arrangements for the active substance: replacement or addition of a site where batch control or testing of the active substance takes place	The change shall not be applicable to a sterile active substance or a biological or immunological substance. The new manufacturer or site shall already be incorporated in the Union IT-system storing and providing organisational data. Method transfer from the former to the new site shall have been successfully completed.	
c)	introduction of a new site of micronisation for the active substance	The change shall not be applicable to a sterile active substance or a biological or immunological substance. The new manufacturer or site shall already be incorporated in the Union IT-systems storing and providing organisational data. The change shall not provoke an adverse change in physico-chemical properties. The particle size specification for the active substance and the corresponding analytical method shall remain the same.	Batch analysis data for at least two comparative batches (minimum pilot scale). Qualified Person (QP) declaration.’
d)	new storage site of Master Cell Bank or Working Cell Banks	No change shall be made to the storage conditions, the shelf-life and the specifications.	

		The new site shall already be incorporated in the Union IT-systems storing and providing organisational data.	
5	Reduction of re-test period or storage period where no Ph. Eur. CEP covering the retest period is part of the approved dossier	The change shall not be the result of unexpected events arising during manufacture or because of stability concerns.	Amendment of the relevant section(s) of the dossier including specifications and stability confirmation, as appropriate.
6	Change to more restrictive storage conditions:	The change shall not be the result of unexpected events arising during manufacture or because of stability concerns.	Amendment of the relevant section(s) of the dossier including specifications and stability confirmation, as appropriate.
a)	of the reference standard (when mentioned in the dossier)		
b)	of the active substance		
7	Change to an approved stability protocol of an active substance (including starting material, reagent or intermediate)	The change shall not be the result of unexpected events arising during manufacture or because of stability concerns. The change shall not have the potential to affect the identity, strength, quality, purity, potency or physical characteristics of the active substance.	Amendment of the relevant section(s) of the dossier including results of appropriate real time stability studies.
8	Implementation of changes foreseen in an approved change management protocol (CMP) for the active substance	The change shall be in accordance with the approved CMP and the results of studies performed indicate that the predefined acceptance criteria specified in the protocol are met.	Amendment of the relevant section(s) of the dossier.

		The implementation of the change shall require no further supportive data to the CMP.	
9	Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance:	The change shall not be applicable to a biological or immunological substance. The change shall not adversely affect the reproducibility of the process. Changes to the manufacturing methods shall only be those necessitated by scale-up or downscaling, e.g. use of different-sized equipment.	Amendment of the relevant section(s) of the dossier. Test results of at least two batches in accordance with the specifications for the proposed batch size.'
a)	up to 10-fold increase compared to the originally approved batch size	The change shall not be applicable to a sterile active substance. The active substance and all intermediates, reagents, catalysts or solvents shall still conform to the approved specifications.	
b)	downscaling down to 10-fold	The change shall not be the result of unexpected events arising during manufacture or because of stability concerns.	
c)	more than 10-fold increase compared to the originally approved batch size	The change shall not be applicable to a sterile active substance. The intermediates, reagents, catalysts or solvents used in the process shall remain the same.	

		The active substance and all intermediates, reagents, catalysts or solvents shall still conform to the approved specifications. The change shall not provoke an adverse change in qualitative and quantitative impurity profile, or in physico-chemical properties of the active substance. The change shall not refer to the restricted part of an ASMF.	
10	Change to in-process tests or limits applied during the manufacture of the active substance	The change shall not be a consequence of any commitment from previous assessments to review specification limits. The change shall not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.	Amendment of the relevant section(s) of the dossier for the new test method, validation and batch data, as appropriate. Comparative table of former and new in-process tests and limits.
a)	tightening of in-process limits	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	
b)	addition of a new in-process test and limits	Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way. The new test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological active substance, except if this method is a standard pharmacopoeial microbiological method.	

11	Change in the specification parameters or limits of an active substance, starting material, intermediate or reagent used in the manufacturing process of the active substance or of the immediate packaging of the active substance:	The change shall not result from unexpected events arising during manufacture or storage (e.g. new unqualified impurity or change in total impurity). The change shall not be a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a variation approval procedure in accordance with Article 240 paragraph 1 of the Law and this rulebook) unless it has been previously assessed and agreed as part of a follow-up measure in a previous procedure in accordance with the law.	Amendment of the relevant section(s) of the dossier. Comparative table of former and new specification parameters and limits.'
a)	tightening of specification limits of an active substance, starting material, intermediate or reagent used in the manufacturing process of the active substance for all veterinary medicinal products including products subject to Official Control Authority Batch Release (OCABR);	The test procedure shall remain the same, or changes in the test procedure shall be minor. The change shall be within the range of currently approved limits.'	
c)	tightening of specification limits of the immediate packaging of the active substance	The test procedure shall remain the same, or changes in the test procedure shall be minor. The change shall be within the range of currently approved limits.	
d)	addition of a new specification parameter to the specification with its corresponding test method for an active substance, starting material, intermediate or reagent used in the manufacturing process of the active substance	The new test method shall not concern a novel non-standard technique or a standard technique used in a novel way. The new test method shall not be a biological, immunological or immunochemical method, or a	Details of any new analytical method and validation data, where relevant. Batch analysis data on two production batches (3

		method using a biological reagent for a biological active substance, except if this method is a standard pharmacopoeial microbiological method. The change shall not concern a genotoxic impurity. If it involves the final active substance, other than for residual solvents which shall be in line with ICH/VICH limits, any new impurity control shall be in line with the Ph. Eur. or National Pharmacopoeia of a Member State.	production batches for biologicals, unless otherwise justified) of the relevant substance for all specification parameters. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification. For herbal veterinary medicinal products, comparative disintegration data may be acceptable. Justification from the marketing authorisation holder (MAH) or ASMF Holder as appropriate of the new specification parameter and the limits.'
e)	addition of a new specification parameter to the specification with its corresponding test method for the immediate packaging of the active substance	The new test method shall not concern a novel non-standard technique or a standard technique used in a novel way.	Details of any new analytical method and validation data, where relevant. Batch analysis data on two batches of the immediate

			packaging for all specification parameters. Justification from the marketing authorisation holder or the ASMF Holder, as appropriate, of the new specification parameter and the limits.’
12	Minor changes:		
a)	— to an approved test procedure — for active substance or a starting material, reagent or intermediate used in the manufacturing process of the active substance; — for the finished product; — for an excipient	The test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods). Appropriate validation studies shall have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. There shall be no changes of the total impurity limits; no new unqualified impurities shall be detected. The method of analysis shall remain the same (e.g. a change in column length or temperature, but not a different type of column or method).	Amendment of the relevant section(s) of the dossier, including a description of the analytical methodology, a summary of validation data and revised specifications for impurities (if applicable). Comparative validation results, or if justified comparative analysis results showing that the current test and the proposed one are equivalent.
b)	— to an approved test procedure — for the immediate packaging of the active substance or the finished product	Appropriate validation studies shall have been performed in accordance with the relevant guidelines	Amendment of the relevant section(s) of the dossier, including a description of the

		and show that the updated test procedure is at least equivalent to the former test procedure. The method of analysis shall remain the same (e.g. a change in column length or temperature, but not a different type of column or method). Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way.	analytical methodology and a summary of validation data. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent.
c)	— to an approved test procedure for an in-process test — for active substance; — for the finished product	The test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological active substance. Appropriate validation studies shall have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. There shall be no changes of the total impurity limits; no new unqualified impurities shall be detected. The method of analysis shall remain the same (e.g. a change in column length or temperature, but not a different type of column or method).	Amendment of the relevant section(s) of the dossier.
d)	in the manufacturing process of an active substance	The change shall not be applicable to a biological or immunological active substance.	Amendment of the relevant section(s) of the dossier.

		The change shall not be a change in the geographical source, manufacturing route or production for a herbal veterinary medicinal substance. The change shall not provoke an adverse change in qualitative and quantitative impurity profile or in physico-chemical properties. The synthetic route remains the same, i.e. intermediates remain the same and there are no new reagents, catalysts or solvents used in the process. The specifications of the active substance or intermediates are unchanged. The change shall not refer to the restricted part of an ASMF.	Batch analysis data (in a comparative tabulated format) of at least two batches (minimum pilot scale) manufactured in accordance with the currently approved and proposed process.
e)	in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier) or a novel excipient	The excipients and all intermediates, reagents, catalysts, solvents or in-process controls shall still conform to the approved specifications (e.g. qualitative and quantitative impurity profile). Adjuvants and preservatives shall be excluded from the scope of this entry. Synthetic routes and specifications shall be identical, and there shall be no change in physico-chemical properties.	Amendment of the relevant section(s) of the dossier for batch data, comparative data, and specification, as appropriate.
f)	to an in-process limit range for the finished product	The change shall not be the result of unexpected events arising during manufacture or because of stability concerns.	Amendment of the relevant section(s) of the dossier. Comparative table of former and new in-process limits.

		The change shall concern an in-process test, which is also part of the finished product specification at release, and the new in-process limit range shall be within the approved release limit.	
g)	to an approved change management protocol of the active substance that does not change the strategy defined in the protocol	The intermediates, reagents, catalysts or solvents used in the process shall remain the same. The active substance and all intermediates, reagents, catalysts or solvents shall still conform to the approved specifications. There shall be no adverse change in qualitative and quantitative impurity profile or in physico-chemical properties. The change shall not refer to the restricted part of an ASMF. The changes shall be within the range of currently approved limits. In case of biological veterinary medicinal products, this change shall be only possible if comparability is not required. Changes in the geographical source, manufacturing route or production of a herbal substance or herbal preparation of a herbal veterinary medicinal product shall be excluded.	Amendment of the relevant section(s) of the dossier.
h)	to production equipment (when described in the dossier) including processes related to the equipment	The change shall not result in any changes or modifications of the production process or quality of the product.	Amendment of the relevant section(s) of the dossier.
i)	to an approved test procedure	Appropriate validation studies shall have been performed in accordance with the relevant guidelines	Amendment of the relevant section(s) of the dossier,

	— of a measuring or administration device	and show that the updated test procedure is at least equivalent to the former test procedure. The method of analysis shall remain the same.	including a description of the analytical methodology and a summary of validation data. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent.
j)	— in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product	The change relates only to an immediate release solid oral dosage form/oral solution and the veterinary medicinal product concerned is not a biological/immunological or herbal veterinary medicinal product. The manufacturing steps remain the same. The finished product / intermediates / in-process materials used in the manufacture of the finished product shall still conform to the approved specifications. No adverse change in qualitative and quantitative impurity profile or in physico-chemical properties. The new process shall lead to an identica product regarding all aspects of quality, safety and efficacy. Relevant stability studies in accordance with the relevant guidelines shall have been started with at least one pilot scale or industrial scale batch and at least 3 months stability data shall be at the disposal of the applicant.	Amendment of the relevant section(s) of the dossier. For solid dosage forms: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process; data on the next two full production batches shall be available on request or reported if outside specification (with proposed action). Justification for not submitting a new bioequivalence study in accordance with the relevant guidance on Bioavailability/Bioequivalence .

			Batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured in accordance to both the currently approved and the proposed process.’
13	Changes to a test procedure (including replacement or addition):	The active substance/finished product shall not be biological or immunological. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. The new test method shall not concern a novel non-standard technique or a standard technique used in a novel way.	Amendment of the relevant section(s) of the dossier and comparative validation data, as appropriate. In the absence of comparative validation data, if justified, comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.’
a)	— for a reagent used in the manufacturing process of the active substance but which does not have a significant effect on the overall quality of the active substance	There shall be no changes to the total impurity limits; no new unqualified impurities shall be detected. The method of analysis shall remain the same (e.g. a change in column length or temperature, but not a different type of column or method).	
b)	— for the immediate packaging of the active substance		

14	Change in qualitative or quantitative composition of the immediate packaging for the active substance	Sterile, liquid, biological or immunological active substances shall be excluded. The new packaging material shall be at least equivalent to the approved material in respect of its relevant properties. Relevant stability studies have been started under VICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least 3 months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging, the 3 months' stability data do not yet have to be available. These studies shall be finalised and the data shall be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the shelf-life/retest period (with proposed action).	Amendment of the relevant section(s) of the dossier. Appropriate data on the new packaging (e.g. comparative data on permeability, e.g. for O_2, CO_2 moisture), including a confirmation that the material complies with relevant pharmacopoeial requirements or Union legislation on plastic materials and objects in contact with foodstuffs. Where appropriate, proof shall be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack). Comparative table of former and new immediate packaging specifications, permeability data and interaction data, as appropriate.'
15	Addition of or change to a calendar package for a pack size already registered in the dossier	The primary packaging material shall remain the same.	

16	Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking of the finished product	The change shall not affect the delivery, use or safety of the finished product. The finished product release and shelf life specifications shall not have been changed except for appearance. The ink shall comply with the relevant pharmaceutical legislation. The change shall not relate to a scored tablet that is intended to be divided into equal doses.	Amendment of the relevant section(s) of the dossier.
17	Change in the shape or dimensions of the pharmaceutical form for immediate release tablets, capsules, suppositories and pessaries	The dissolution profile of the product shall remain unchanged. For herbal medicinal products, where dissolution testing may not be feasible the new disintegration time of the product shall be comparable to the former one. The release and end of shelf-life specifications of the product shall not have been changed. The qualitative or quantitative composition and mean mass shall remain unchanged. The change shall not relate to a scored tablet that is intended to be divided into equal doses.	Amendment of the relevant section(s) of the dossier.
18	Change(s) in the composition (excipients) of the finished product:	The change shall not be applicable to a biological or immunological veterinary medicinal product. The change shall not have the potential to affect the identity, strength, quality, purity, potency, physical characteristics, safety or effectiveness of the finished product.	Amendment of the relevant section(s) of the dossier including stability confirmation.

		Any minor adjustment to the formulation to maintain the total weight shall be made by an excipient which currently makes up a major part of the finished product formulation. The change shall not affect the functional characteristics of the pharmaceutical form (e.g. disintegration time, dissolution profile). Stability studies shall have been started under International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) conditions; relevant stability parameters shall have been assessed in at least two pilot scale or industrial scale batches, and at least three months satisfactory stability data shall be at the disposal of the applicant. The stability profile shall be similar to the currently registered situation. In addition, where relevant, photo-stability testing shall be performed.	
a)	— increase or reduction of a component or components of the flavouring or colouring system	Quantitative change(s) shall not exceed +/- 10 % of the existing concentration of the component. The finished product specification shall only have been updated in respect of appearance, odour or taste and, if relevant, deletion of an identification test.	

		For veterinary medicinal products for oral use, the change shall not negatively affect the uptake by target animal species.	
b)	— any minor adjustment of the quantitative composition of the finished product with respect to excipients	Quantitative change(s) shall not exceed +/- 10 % of the existing concentration of the component. Where relevant, the dissolution profile of the changed product shall be determined on a minimum of two pilot scale batches and shall be comparable to the former one. No significant differences regarding comparability shall occur. For herbal veterinary medicinal products, where dissolution testing may not be feasible, the disintegration time of the changed product shall be comparable to the former one. The change shall not be the result of stability issues and shall not result in potential safety concerns, e.g. differentiation between strengths.	
c)	— addition or replacement of a component or components of the flavouring or colouring system	The finished product specification has only been updated in respect of appearance/odour/taste and if relevant, deletion of an identification test. Any new proposed components shall comply with the relevant applicable Regulations. A new component shall not include the use of materials of human or animal origin.	Either a Ph. Eur. Certificate of Suitability for any new component of animal origin susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by the competent authority and shown to comply with the scope of the current Note for Guidance on Minimising the

		Where applicable, the change does not affect the differentiation between strengths and does not have a negative impact on taste acceptability. For veterinary medicinal products for oral use, the change does not affect the uptake by target animal species. For veterinary medicinal products for food-producing species, the component or components of the flavouring or colouring system shall be allowed in accordance with Regulation (EC) No° 470/2009 and the acts adopted on the basis thereof before implementation of this change. The change shall not be the result of stability issues and shall not result in potential safety concerns (e.g. differentiation between strengths).	Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products. The following information shall be included for each such material: name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate.
19	Change in coating weight of oral dosage forms or change in weight of capsule shells for a solid oral pharmaceutical form	The change shall not be the result of stability issues and shall not result in potential safety concerns (e.g. differentiation between strengths). For veterinary medicinal products for oral use, the coating shall not be a critical factor for the release mechanism and the change shall not affect the uptake by target animal species. The finished product specification shall only be updated in respect of weight and dimensions, if applicable.	Amendment of the relevant section(s) of the dossier including stability confirmation.

		The dissolution profile of the changed product shall be determined on a minimum of two pilot scale batches and shall be comparable to the former one. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the changed product shall be comparable to the former one. Relevant stability studies shall have been started under VICH conditions and relevant stability parameters shall have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data shall be at the disposal of the applicant at time of implementation.	
20	Replacement or addition of a primary packaging site of a non-sterile finished product	The change shall not be applicable to a biological or immunological medicinal product. The primary packaging site shall already be introduced in the Montenegrin or European Union IT systems storing and providing organisational data. The site shall be appropriately authorised to manufacture the pharmaceutical form or product concerned and satisfactorily inspected. The validation scheme shall be available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches, as appropriate.	Amendment of the relevant section(s) of the dossier.

		If the manufacturing site and the primary packaging site are different, conditions of transport and bulk storage shall be specified and validated.	
21	Replacement or addition of a secondary packaging site of a finished product	The secondary packaging site shall already be introduced in the Montenegrin or European Union IT systems storing and providing organisational data. The site shall be appropriately authorised to manufacture the pharmaceutical form or product concerned and satisfactorily inspected.	Amendment of the relevant section(s) of the dossier.
22	Change to importer, batch control arrangements and quality testing (replacement or addition of a site) for a finished product	The site shall be already introduced in the Montenegrin or European Union IT systems storing and providing organisational data. The site shall be appropriately authorised and satisfactorily inspected. The change shall not be applicable to a biological or immunological medicinal product. Method transfer from the former to the new site shall have been successfully completed.	
23	Replacement or addition of a manufacturer of a finished product responsible for importation	The site shall already be introduced in the Montenegrin or European Union IT systems storing and providing organisational data. The site shall be appropriately authorised and satisfactorily inspected	
24	Replacement or addition of a manufacturer responsible for:	The manufacturer or the site shall already be introduced in the Montenegrin or European Union IT systems storing and providing organisational data.	Amendment of the relevant section(s) of the dossier, including revised product information, as appropriate.

		The site shall be appropriately authorised and satisfactorily inspected.	Qualified person (QP) declaration.
a)	batch release including batch control or testing of a sterile or non-sterile finished product	The change shall not be applicable to a biological or immunological medicinal product. Method transfer from the former to the new site shall have been successfully completed.	
b)	batch release not including batch control or testing of a sterile or non-sterile finished product	At least one batch control/testing site remains within the EEA or in a country where an operational and suitably scoped GMP mutual recognition agreement (MRA) exists between the country concerned and the EU, that is able to carry out product testing for the purpose of batch release within the EEA.	
25	Change in the packaging material of bulk product (intermediate product) not in contact with the bulk product formulation (including replacement or addition)	The manufacturing steps shall remain the same. The finished product, intermediates or in-process controls used in the manufacture of the finished product shall still conform to the approved specifications. The secondary packaging shall not play a functional role on the stability of the bulk product, or if it does, it shall not be less protective than the approved one.	Amendment of the relevant section(s) of the dossier.
26	Change in the batch size (including batch size ranges) of the finished product:	The change shall not be applicable to a biological or immunological medicinal product. The change shall not be the result of unexpected events arising during manufacture or because of stability concerns. The change shall not affect reproducibility or consistency of the product. The changes to the manufacturing method or to the in-process controls shall be only those necessitated by	Amendment of the relevant section(s) of the dossier. Where relevant, the batch numbers, corresponding batch size, the manufacturing date of batches (3) used in the validation study and the validation data or the validation

		the change in batch-size, e.g. use of different sized equipment. A validation scheme shall be available or a validation of the manufacture shall have been successfully carried out according to the current protocol with at least three batches of the new batch size in accordance with the relevant guidelines.	protocol (scheme) shall be provided.
a)	up to 10-fold increase compared to the originally approved batch size of an immediate release oral pharmaceutical forms or of a non-sterile liquid based pharmaceutical form	The batch size shall be within the 10-fold range of the batch size foreseen when the marketing authorisation was granted.	
b)	up to 10-fold increase compared to the originally approved batch size for the pharmaceutical form medicinal gas	The batch size shall be within the 10-fold range of the batch size foreseen when the marketing authorisation was granted.	
c)	downscaling down to 10-fold compared to the originally approved batch size of an immediate release oral pharmaceutical forms or to non-sterile liquid based pharmaceutical form	The batch size shall be within the 10-fold range of the batch size foreseen when the marketing authorisation was granted.	
d)	downscaling down to 10-fold (for the pharmaceutical form medicinal gas	The batch size shall be within the 10-fold range of the batch size foreseen when the marketing authorisation was granted.	
e)	more than 10-fold increase compared to the originally approved batch size for an immediate release, solid oral pharmaceutical form		3 months stability data for at least one pilot batch under VICH condition.
27	Change to in-process tests or limits applied during the manufacture of the finished product:	The change shall not relate to a commitment or to an unexpected event during manufacture.	Comparative table of former and new in-process tests or limits.

		The change shall not have the potential to affect the identity, strength, quality, purity, potency or physical characteristics of the finished product, intermediates or in-process materials.	
a)	tightening of in-process limits	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	Amendment of the relevant section(s) of the dossier.
b)	addition of a new in-process test and limits	Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way. The new test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological active substance, except if this method is a standard pharmacopoeial microbiological method.	Amendment of the relevant section(s) of the dossier for method and validation data, where relevant, batch data and relevant comparative data.’
28	Change in the specification parameters or limits of an excipient	The change shall not be a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a variation procedure according to Article 240 paragraph 1 of the Law and this rulebook). The change shall not be a result of unexpected events arising during manufacture, e.g. new unqualified impurity or change in total impurity limits.	

a)	tightening of specification limits	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	
b)	addition of a new specification parameter to the specification with its corresponding test method	Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way. The new test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological active substance, except if this method is a standard pharmacopoeial microbiological method. The change shall not concern a genotoxic impurity.	Amendment of the relevant section(s) of the dossier for method and validation, batch data and relevant comparative data.
29	Change in source of an excipient or reagent with TSE risk from material with TSE risk to vegetable or synthetic origin	The excipient, finished product release and end of shelf life specifications shall remain the same. The change shall not concern an excipient or reagent used in the manufacture of a biological or immunological active substance or in a biological or immunological medicinal product.	Amendment of the relevant section(s) of the dossier. Declaration from the manufacturer or the marketing authorisation holder of the material that it is purely of vegetable or synthetic origin.
30	Change in the specification parameters or limits of the finished product:	The change shall not be a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a variation procedure according to according to Article 240 paragraph 1 of the Law and and Article 31 paragraph 1 of this Rulebook), unless the supporting documentation has already been assessed and	Amendment of the relevant section(s) of the dossier. Comparative table of former and new specification parameters and limits.

		approved within the context of another procedure under the Law. The change shall not result from unexpected events arising during manufacture, e.g. new unqualified impurity or change in total impurity limits.	
a)	tightening of specification limits	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	
b)	tightening of specification limits for finished products subject to Official Control Authority Batch Release	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	
c)	addition of a new specification parameter to the specification with its corresponding test method	Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way. The test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological active substance except if this method is a standard pharmacopoeial microbiological method. The change shall not concern any impurities (including genotoxic) or dissolution.	Amendment of the relevant section(s) of the dossier for method and validation, batch data and relevant comparative data.
d)	update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur. for the finished product	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	

		The change shall not concern any impurities (including genotoxic) or dissolution.	
31	Uniformity of dosage units is introduced to replace the currently registered method	The change shall follow changes to the Ph. Eur. Standard 2.9.5. Uniformity of mass or Ph. Eur. Standard 2.9.6 Uniformity of content.	Amendment of the relevant section(s) of the dossier. Comparative table of former and new specification parameters and limits.
32	Change in the specification parameters or limits of the finished product to describe more accurately the appearance of the product	The change shall not be a result of any unexpected events arising during manufacture or testing of the finished product.	Amendment of the relevant section(s) of the dossier. Comparative table of former and new specification parameters and limits.
33	Change in test procedure for the finished product to comply with Ph. Eur.:	The change shall not concern changes of the total impurity limits; no new unqualified impurities shall be detected. The method of analysis shall remain the same (e.g. a change in column length or temperature, but not a different type of column or method). The test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological active substance, except if this method is a standard pharmacopoeial microbiological method.	Amendment of the relevant section(s) of the dossier.
a)	update of the test procedure to comply with the updated general monograph in the Ph. Eur.		

b)	update of the test procedure to reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number		
34	Change in qualitative and quantitative composition of the immediate packaging for a solid pharmaceutical form for a finished product	For solid pharmaceutical forms, the change shall only concern the same packaging or container type (e.g. blister to blister). The finished product shall not be sterile. The change shall not affect the delivery, use, safety or stability of the finished product. Relevant stability studies shall have been started under VICH conditions and relevant stability parameters shall have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data shall be at the disposal of the applicant at time of implementation. However, if the new packaging is more resistant than the existing packaging, the three months' stability data do not yet have to be available. The new packaging material shall be at least equivalent to the approved material in respect of its relevant properties.	Amendment of the relevant section(s) of the dossier. Comparative table of former and new immediate packaging specifications, permeability data and interaction data, as appropriate.
35	Change in the specification parameters or limits of the immediate packaging of the finished product:	The changes shall not be a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a variation procedure according to Article 240	Comparative table of former and new specifications or limits.

		paragraph 1 of the Law and Article 31 of this Rulebook), unless the supporting documentation has already been assessed and approved within the context of another procedure under the Law. The change shall not result from unexpected events arising during manufacture.	
a)	tightening of specification limits	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	
b)	addition of a new specification parameter to the specification with its corresponding test method	Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way.	Amendment of the relevant section(s) of the dossier for method and validation and batch data, as appropriate.
36	Change in test procedure for the immediate packaging of the finished product (including replacement or addition)	The change shall not be applicable to a biological or immunological medicinal product. Appropriate validation studies shall have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way.	Amendment of the relevant section(s) of the dossier for method and validation and batch data, as appropriate.
37	Change in shape or dimensions of the container or closure (immediate packaging) of a non-sterile finished product	The change shall not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.	Amendment of the relevant section(s) of the dossier.

		The change shall not concern the qualitative or quantitative composition of the container. In case of a change in the headspace or a change in the surface/volume ratio, stability studies in accordance with the relevant guidelines shall have been started, relevant stability parameters shall have been assessed in at least two pilot scale or industrial scale batches, and at least three months stability data shall be at the disposal of the applicant.	
38	Change in pack size (number of units e.g. tablets, ampoules, etc. in a pack) within the range of the currently approved pack size (4)	The new pack size shall be consistent with the posology and treatment duration as approved in the Summary of Product Characteristics. The primary packaging material shall remain the same.	
39	Change in any part of the primary packaging material not in contact with the finished product formulation (such as change of colour due to different plastic used for flip-off caps, colour code rings on ampoules or change of needle shield)	The change shall not concern a part of the packaging material that affects the delivery, use, safety or stability of the finished product.	Amendment of the relevant section(s) of the dossier.
40	Replacement or addition of a supplier of packaging components or devices (when mentioned in the dossier)	The qualitative and quantitative composition of the packaging components or device and design specifications shall remain the same. The change shall not have the potential to affect the identity, quality or purity of the packaging component or devices.	Amendment of the relevant section(s) of the dossier.
41	Change in the shelf-life or to an approved stability protocol of the finished product:	The change shall not be the result of unexpected events arising during manufacture or because of stability concerns.	Amendment of the relevant section(s) of the dossier.

a)	reduction of the shelf life of the finished product as packaged for sale, after first opening or after dilution or reconstitution		
b)	change to an approved stability protocol	The change shall not have the potential to affect the identity, strength, quality, purity, potency or physical characteristics of the finished product. The change shall not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.	
42	Implementation in practice of changes already foreseen in an approved change management protocol (CMP) for the finished product	The change shall be in accordance with the approved CMP and the results of studies performed indicate that the predefined acceptance criteria specified in the protocol are meet. The implementation of the change shall require no further supportive data to the CMP.	
43	Editorial changes to part 2 of the dossier if inclusion in an upcoming procedure concerning part 2 is not possible		Comparative table of the changes to the dossier.
44	Submission of a Ph. Eur. CEP for: — active substance; — starting material, reagent or intermediate used in the manufacturing process of the active substance; — excipient	The finished product release and end of shelf life specifications shall remain the same. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (e.g.	Amendment of the relevant section(s) of the dossier, including a copy of the updated Ph. Eur. CEP and QP declaration, as appropriate.’

		particle size profiles, polymorphic form), if applicable. For active substance only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier. For a herbal substance or a herbal preparation, the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) shall remain the same. The manufacturer shall already be approved and incorporated in the Montenegrin or European Union IT systems storing and providing organisational data (not applicable for starting material, reagent and excipient manufacturers/suppliers).	
a)	Updated certificate	The manufacturing process of the active substance, starting material, reagent, intermediate or excipient shall not include the use of material from human or animal origin, or if it does, any information in relation to material from human or animal origin shall remain unchanged. If the active substance is not a sterile substance but is to be used in a sterile veterinary medicinal product, in accordance with the CEP, the manufacturing process shall not include the use of water during the last steps	

		of the synthesis, or if it does, the quality of water used in the last step of the synthesis shall be unchanged compared to the previous version of the CEP submitted.	
b)	New certificate	The manufacturing process of the active substance, starting material, reagent, intermediate or excipient shall not include the use of material from human or animal origin. The active substance/starting material/reagent/intermediate/excipient is not sterile. If the active substance is not a sterile substance but is to be used in a sterile veterinary medicinal product, in accordance with the CEP the manufacturing process shall not include the use of water during the last steps of the synthesis, or if it does, the active substance shall be free from bacterial endotoxins.	
46	Submission of an updated Ph. Eur. TSE CEP of an already approved manufacturer for: — active substance; — starting material, reagent, intermediate used in the manufacturing process of the active substance; — excipient	There has been no change in the source of material. The viral risk assessment is unchanged. If gelatine manufactured from bones is to be used in a veterinary medicinal product for parenteral use, it shall only be manufactured in compliance with the relevant requirements. The manufacturer shall already be approved and incorporated in the Montenegrin or European Union IT systems storing and providing organisational data	Amendment of the relevant section(s) of the dossier, including a copy of the updated Ph. Eur. CEP and QP declaration, as appropriate. Where applicable, a document providing information of any materials falling within the scope of the Note for Guidance on Minimising the Risk of Transmitting Animal

		(not applicable for starting material, reagent and excipient manufacturers/suppliers).	Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products including those which are used in the manufacture of the active substance/excipient. The following information shall be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. That information shall be included in an updated TSE table A (and B, if relevant).
47	Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State:	The change shall be made exclusively to fully comply with the pharmacopoeia. All the tests in the specification shall correspond to the pharmacopoeial standard after the change, except any additional tests. Additional validation of a new or changed pharmacopoeial method shall not be required. For a herbal substance or a herbal preparation the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) shall remain the same.	Amendment of the relevant section(s) of the dossier . Comparative table of the former and new specifications, if applicable.
a)	change of specification(s) of a former non EU Pharmacopoeial active substance, excipient or	Additional specifications to the pharmacopoeia for product specific properties shall be unchanged (e.g.	Batch data and data demonstrating the suitability of

	active substance starting material to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State	particle size profiles, polymorphic form, bioassays or aggregates). The change shall not concern significant changes in qualitative and quantitative impurities profile unless the specifications are tightened.	the monograph to control the substance.
b)	change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	Additional specifications to the pharmacopoeia for product specific properties shall be unchanged (e.g. particle size profiles, polymorphic form, bioassays or aggregates).	
c)	change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.		Amendment of the relevant section(s) of the dossier, including batch data and data demonstrating the suitability of the monograph to control the substance.
d)	to reflect compliance with the Ph. Eur. by removing reference to the internal test method and test method number		
48	Addition or replacement of a measuring or administration device which is not an integrated part of the primary packaging	The change shall not affect the delivery, use, safety or stability of the finished product. The change shall be only applicable to a device with CE marking. The new measuring or administration device shall accurately deliver the required dose for the product concerned in line with the approved posology, and results of such studies shall be available.	Amendment of the relevant section(s) of the dossier.

		The new device shall be compatible with the veterinary medicinal product. The change shall not lead to substantial amendments of the product information.	
49	Change in specification parameters or limits of a measuring or administration device:	The change shall not be a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a variation procedure according to Article 240 paragraph 1 of the Law and Article 31 paragraph 1 to this Rulebook), unless the supporting documentation has already been assessed and approved within the context of another procedure under the Law. The change shall not be the result of unexpected events arising during manufacture.	Amendment of the relevant section(s) of the dossier. Comparative table of former and new specification parameters and limits.
a)	tightening of specification limits	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	
b)	addition of a new specification parameter to the specification with its corresponding test method	Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way.	Amendment of the relevant section(s) of the dossier for method and validation and batch data.
50	Change in test procedure (including replacement or addition) of a measuring or administration device	Appropriate validation studies shall have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.	Amendment of the relevant section(s) of the dossier for method and validation and batch data.

		Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way.	
51	Update of the quality dossier intended to implement the outcome of a Union interest referral procedure according to Article 257 of the Law:	This change shall only be applicable when no new or additional data is required for an assessment.	Amendment of the relevant section(s) of the dossier.
a)	the finished product is covered by the defined scope of the procedure		
b)	the finished product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure		
C	Changes to the safety, efficacy and pharmacovigilance part of the dossier		
1	Change(s) in the name or address or contact details of a qualified person for pharmacovigilance (QPPV)		
2	Change(s) in the Summary of Product Characteristics (SPC), labelling or package leaflet intended to implement the outcome of a Union interest referral procedure according to Article 257 of the Law	The veterinary medicinal product shall be covered by the defined scope of the referral. This change shall only be applicable when no new or additional data is required for an assessment. The proposed Summary of Product Characteristics, Labelling and Package Leaflet shall be identical for the concerned sections to that annexed to the Commission Decision on the referral procedure for the reference medicinal product.	

3	Change(s) in the SPC, labelling or package leaflet of a generic or hybrid medicinal product following assessment of the same change(s) for the reference product	This change shall only be applicable when no new or additional data is required for an assessment. The proposed changes to Summary of Product Characteristics, Labelling and Package Leaflet shall be identical to those changes approved for the reference medicinal product. The reference product shall be approved in the Member State concerned.	
4	Change(s) in the SPC, labelling or package leaflet intended to implement the outcome of a procedure or recommendation from the competent authority or the Agency concerning risk management measures in pharmacovigilance related to veterinary medicinal products	This change shall only be applicable when no new or additional data is required for an assessment. The proposed changes to Summary of Product Characteristics, Labelling and Package Leaflet shall be identical to wording agreed by the competent authority or the Agency.	Reference to the agreement/assessment of the competent authority or the Agency.'
5	Change in the pharmacovigilance system master file (PSMF) location		
6	Introduction of a summary of the PSMF or changes to the summary of the PSMF not already covered elsewhere in this Annex		Summary of pharmacovigilance system master file according to Article 213 paragraph 1 point 6 of the Law and article 6 paragraph 1 point c) to this rulebook.
7	Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan	The wording shall be limited to that agreed by the competent authority or the Agency.	Reference to the agreement/assessment of the competent authority or the Agency.

8	Implementation of changes in the SPC not already covered elsewhere in this Annex	This change shall only be applicable when no new or additional data is required for an assessment. The changes shall not affect the quality, safety or efficacy of the product. Changes shall be minor in nature and shall be consistent with the information currently included in the SPC.	
9	Editorial changes to SPC, package leaflet or labelling if inclusion in an upcoming procedure is not possible	The changes shall not affect the quality, safety or efficacy of the medicinal product.	
10	Changes to the labelling or the package leaflet which shall not be connected with the SPC:		
a)	administrative information concerning the holder's representative		
b)	other changes	Changes shall be minor in nature and shall be consistent with the information included in the SPC. The change shall not include the introduction of new batch release sites. Changes shall not be promotional in nature and shall not have a negative impact on the legibility of the product information.	
c)	inclusion of traceability stickers in or on product carton	Addition shall not have a negative impact on the legibility of the product information.	
d)	— replacement of information on the immediate or outer packaging by an abbreviation or pictogram (including initial addition)	The new abbreviation or pictogram is included in the annex III or Annex IV to this rulebook.	

	— replacement of an existing abbreviation or pictogram on the immediate or outer packaging that is not compliant with the legal act regulates list of abbreviation and pictograms by another abbreviation or pictogram	The addition does not have a negative impact on the readability of the labelling.	
e)	Alignment of the labelling of the immediate packaging with the requirements laid down in Article 15 of this rulebook	The packaging qualifies as a small immediate packaging unit according to article 16 to this rulebook	
f)	Alignment of the product information with the requirements laid down in separate legal act laying down rules on appropriate measures to ensure the effective and safe use of veterinary medicinal products authorised and prescribed for oral administration via routes other than medicated feed and administered by the animal keeper to food-producing animals	This change shall only be applicable when no new or additional data is required for an assessment.	
D	Changes to the vaccine antigen master file (VAMF) part of the dossier		
1	Change in the name or address of the VAMF certificate holder for biological products	The VAMF certificate holder shall remain the same legal entity.	Amendment of the relevant section(s) of the dossier, as appropriate.’
2	Inclusion of an already certified VAMF in the marketing authorisation dossier of a veterinary medicinal product. (VAMF 2 nd step procedure)	Changes shall not affect the properties of the finished product.	Amendment of the relevant section(s) of the dossier.
(2) As per EDQM standard terms the system of names and terms published by the EDQM for marketing authorisation applications.			

(3) In cases where a given pharmaceutical form or strength has received an individual marketing authorisation which is separate to the marketing authorisation for other pharmaceutical forms or strengths of the same product, the deletion of the former will not be a variation but the withdrawal of the marketing authorisation.

(4) In cases where a given pack size has received an individual marketing authorisation which is separate to the marketing authorisation for other pack sizes of the same product, the change of the former will not be a variation nor requiring assessment, but a variation requiring assessment.