Consolidated text of the Rulebook on more detailed conditions for issuance of marketing authorization for a medicinal product includes the following regulations:

1. Rulebook on more detailed conditions for issuance of marketing authorization for a medicinal product ("Official Gazette of Montenegro" No 021/16 from 25.03.2016.)
2. Rulebook on amendments to the Rulebook more detailed conditions for issuance of marketing authorization for a medicinal product ("Official Gazette of Montenegro" No 055/19 from 27.09.2019) in which their date of entry into force is indicated.

RULEBOOK
ON MORE DETAILED CONDITIONS FOR ISSUANCE OF MARKETING AUTHORISATION FOR A MEDICINAL PRODUCT

("Official Gazette of Montenegro", No 021/16 from 25 March 2016, 055/19 from 27 September 2019)

I. GENERAL PROVISIONS

Article 1

This Rulebook determines in more details conditions for issuance of the authorisation for placing human and veterinary medicinal products onto the market (hereinafter: marketing authorisation), contents of the application and required documentation for issuance of marketing authorisation, contents of the marketing authorisation, conditions, manner and documentation for amendments, renewal and transfer of the authorisation.

Article 2

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

Aricle 3

Terms used in this Rulebook shall have the following meaning:

1) reference country is an EU Member State which prepares and issues Assessment Report in the decentralised procedure or in the mutual recognition procedure

2) Assessment Report is a document in which European Medicines Agency (EMA) or competent authority of EU Member State reports based on expert reports about quality, safety and efficacy of the medicinal product, and based on that suggests issuance of marketing authorisation for a medicinal product or rejection of issuance.

II. CONDITIONS FOR ISSUANCE OF MARKETING AUTHORISATION

Article 4

Marketing authorisation may be issued to the applicant referred to in Article 30 paragraph 2 of the Law on Medicinal products (hereinafter: Law), based on the documentation assessment stipulated by this Rulebook.

Article 5

Application for issuance of marketing authorisation for a medicinal product, shall contain:

1) logo, name and address of the applicant;

2) data on a medicinal product (brand name, international non-protected name (INN) or generic name, pharmaceutical form, strength);

3) proposal of packaging of the medicinal product and/or information on packaging of the medicinal product;

4) data on the manufacturer of the medicinal product (name, address and manufactiring site);

5) proposal of ATC (Anatomical-Therapeutic-Chemical) classification code, or ATC veterinary classification code for a veterinary medicinal product;

6) proposal of dispensing mode;

7) type of application for issuance of marketing authorisation;

8) information on weather a medicinal product has been authorised for marketing in the European Union, as well as type and number of the procedure under which marketing authorisation was issued; and

9) date and signature of the responsible person for the procedure of issuance of marketing authorisation.

Application from paragraph 1 of this Article refers to each pharmaceutical form, strength and packaging.

Article 6

The application for marketing authorisation shall be submitted to the Agency for Medicines and Medical Devices (hereinafter: Agency).

The application from paragraph 1 of this Article shall be submitted on the form published on the portal of the Agency.

The Agency conducts formal evaluation in accordance with Article 38 of the Law.

Article 7

The application for marketing authorisation shall be accompanied by:

- documentation on the medicinal product; and
- evidence that fees have been paid.

Article 8

Required documentation for issuance of marketing authorisation (hereinafter: documentation) shall be submitted on the form of:

1) common technical document (hereinafter: CTD dossier), for a medicinal product for human use; and

2) european (hereinafter: EU dossier), for veterinary medicinal products and immunological veterinary medicinal products.

Documentation for paragraph 1 of this Article shall be prepared in accordance with directives of European Parliament and European Council.

Content and the structure of the documentation referred to in paragraph 1 of this Article are laid down in the Annexes 2 and 3, which is an integral part of this Rulebook.

Article 9

CTD dossier contains:

- Module 1 – Administrative and regional data;
- Module 2 - Concise expert presentations of Modules 3, 4 and 5;

- Module 3 - Data on quality (pharmaceutical-chemical-biological data);
- Module 4 – Pre-clinical (pharmacological-toxicological) examination, and;
- Module 5 – Clinical trials.

In addition to modules referred to in paragraph 1 of this Article, when all the information on active substances necessary for the evaluation of the dossier is not provided, the Agency may request the dossier on active substance (hereinafter: ASMF), both open (Applicants Part ASMF) and restricted part (Restricted Part ASMF).

Article 10

EU contains:
- 1st part: administrative data;
- 2nd part: pharmaceutical (physico-chemical, biological or microbiological information (quality));
- 3rd part: pharmacological-toxicological documentation:
    1) documentation on safety and residue tests of veterinary medicinal products, or
    2) documentation on the safety tests of immunological veterinary medicinal products;
- 4th part:
    1) documentation on pre-clinical and clinical trials of efficiency of veterinary medicinal products, or
    2) documentation on examination of efficiency of immunological veterinary medicinal products.

Article 11

Module 1 referred to in Article 9 of this Rulebook shall be submitted either in paper or electronic form.
Modules 2, 3, 4 and 5 referred to in Article 9
of this Rulebook shall be submitted in electronic form, and upon request of the Agency some parts shall be submitted in the paper form.
Parts of the EU dossier may be submitted either in paper or electronic form.

Article 12

Application for marketing authoriosation having own data shall be accompanied by the documentation on quality, safety and efficacy of a medicinal product which contains the following:
- administrative data;
- own data on pharmaceutical-chemical-biological testing of a medicinal product;
- own data on pre-clinical, i.e. pharmacological-toxicological testing of a medicinal product; and
- own data on clinical trial of a medicinal product.

By way of exception to paragraph 1 indents 3 and 4 of this Article, application with own data may contain data from the literature complementing and confirming submitted data on own testings (application with combined data).

Article 13

Application for marketing authoriosation having bibliographical data on safety and efficacy of a medicinal product shall be accompanied by the documentation which contains the following:
- administrative data;
- own data on pharmaceutical-chemical-biological testing of a medicinal product;
- bibliographical data on pre-clinical, i.e. pharmacological-toxicological testing of a medicinal product; and
- bibliographical data on clinical trial of a medicinal product.

Bibliographical data referred to in paragraph 1 of this Article from published scientific literature or results of pre and post marketing studies, may be used only with the proof that the active substance is being used as a medicinal product for at least ten years in Montenegro or other countries having the same standards for issuance of marketing authorisation and for which there is published coherent professionally acknowledged literature, which contains all necessary data from requested pharmacological-toxicological documentation or clinical documentation proving safety and efficacy of a medicinal product.

Bibliographical data from paragraph 1 of this Article refer to therapeutic indications which application has been submitted for and include both positive and negative published data.

If certain bibliographical data are missing, the applicant shall in the Module 2 of the CTD dossier explain that a conclusion on safety and efficacy of the medicinal product may nonetheless be brought.

Article 14

Application for marketing authorisation referring to documentation of a reference medicinal product shall be accompanied by the documentation containing the following:

- administrative data;
- references to documentation about pharmaceutical-chemical-biological testing of the reference medicinal product, about pre-clinical i.e. pharmacological-toxicological examination of the reference medicinal product and on clinical trial of the reference medicinal product;
- proof that the marketing authorisation holder of the reference medicinal product agrees with reference to his documentation regarding the pharmaceutical-chemical-biological testing of the reference medicinal product, about pre-clinical i.e. pharmacological-toxicological examination of the reference medicinal product and on clinical trial of the reference medicinal product;
- proof that reference medicinal product possesses valid marketing authorisation in Montenegro.

Reference medicinal product from paragraph 1 of this Article has a different brand name from a medicinal product which application has been submitted for.

Article 15

Application for marketing authorisation for generic medicinal product shall be accompanied by the documentation containing:

- administrative data;
- own data on pharmaceutical-chemical-biological testing of a medicinal product;
- reference to data on pre-clinical i.e. pharmacological-toxicological examination of the reference medicinal product;
- reference to data on clinical trial of the reference medicinal product;
- proof of essential similarity of reference medicinal product and medicinal product for which the application for marketing authorisation is being submitted;
- proof that the reference medicinal product is at least eight years marketed in Montenegro or in other countries having the same professional requests for obtaining marketing authorisation for a medicinal product; and
- proof that there are no significant differences in terms of safety and/or efficacy, i.e. confirmation of equal safety and/or efficacy in relation to reference medicinal product, if active substance in generic medicinal product (salt, ester, ether, isomer, mixture of isomers, complex or derivative) differ from active substance in reference medicinal product.

Article 16

Application for marketing authorisation for generic medicinal product with combined data shall be submitted along with documentation on safety and efficacy that contains the following:

- administrative data;
- own data on pharmaceutical-chemical-biological testing of a medicinal product;

- reference to data on pre-clinical i.e. pharmacological-toxicological examination of the reference medicinal product and own data on safety which are required in relation to the difference between reference medicinal product and medicinal product which application has been applied for; and
- reference to data on clinical trial of a reference medicinal product and own data, i.e. results of appropriate clinical trials referring to differences from reference medicinal product.

Article 17

Application for marketing authorisation for biologically similar medicinal product shall be submitted along with documentation that contains the following:

- administrative data;
- own data on pharmaceutical-chemical-biological testing of a medicinal product;
- reference to data on pre-clinical i.e. pharmacological-toxicological examination of the reference biological medicinal product and own data, i.e. results of appropriate pre-clinical i.e. pharmacological-toxicological examination of a medicinal product relating to differences from reference biological medicinal product; and/or
- reference to data on clinical trial of a reference biological medicinal product and own data, i.e. results of appropriate clinical trials relating to differences from reference biological medicinal product.

Own data from paragraph 1 indents 2 and 3 of this Article refer in particular to the differences in relation to raw materials and the manufacturing process in relation to the reference biological medicinal product, in accordance with the requirements of Annex I of Directive 2001/82/EC of the European Parliament and the Council of Europe.

Article 18

Application for marketing authorisation for a medicinal product with fixed combination of active substances shall be submitted along with the documentation which contains the following:

- administrative data;
- own data on pharmaceutical-chemical-biological testing of a medicinal product relating to fixed combination of active substances in a medicinal product;
- data on pre-clinical i.e. pharmacological-toxicological examination of the medicinal product relating to fixed combination of active substances in a medicinal product; and
- data on clinical trial of a medicinal product relating to fixed combination of active substances in a medicinal product.

III. CONTENTS OF MARKETING AUTHORISATION

Article 19

Marketing authorisation shall contain the following:

1) logo, name and address of the Agency;
2) data on marketing authorisation holder;
3) name of a medicinal product (brand name, INN or generic name);
4) qualitative and quantitative composition of active substance;
5) strength of a medicinal product;
6) pharmaceutical form;
7) packaging of a medicinal product;
8) data on manufacturer;
9) anatomical-therapeutical-chemical classification code for a medicinal product (ATC), or anatomical- therapeutical-chemical veterinary classification code for a medicinal product (ATC-vet);
10) EAN identification code of a medicinal product (13 or 8 digits);

11) dispensing mode;
12) information on contents of narcotic or psychotropic substances and stipulated mark for that type of medicinal products;
13) number and date of issuance of marketing authorisation;
14) period for which marketing authorisation is being issued;
15) signature of responsible person in the Agency; and
16) legal remedy.

Integral part of the authorisation referred to in paragraph 1 of this Article is the following:

- approved summary of product characteristics with the dispensing mode and date of the last approved revision;
- approved patient information leaflet or packaging leaflet with the dispensing mode and date of the last approved revision, in accordance with regulations determining labeling of medicinal products; and
- approved immediate and outer packaging or its approved conceptual design or sticker, in accordance with regulations determining labeling of medicinal products.

Contents of summary of product characteristics from paragraph 2 indent 1 of this Article is provided in the Annex 1 which is an integral part of this Rulebook.

Article 20

Conditional marketing authorisation issued under special circumstances, beside information from article 19 of this Rulebook, may also contain information on:

- measures taken to ensure safe use of medicinal product and which are included in the risk management system, in accordance with regulations governing pharmacovigilance;
- post-marketing study of safe use of medicinal product i.e. efficacy of the medicinal product, after issuance of marketing authorisation;
- fullfillment of additional obligations on suspected adverse reactions monitoring and reporting;
- having appropriate system of pharmacovigilance.

Marketing authorisation from paragraph 1 of this Article also contains a time-limit for fulfillment of conditions from paragraph 1 indents 1 to 4 of this Article.

IV. CONDITIONS, MANNER AND DOCUMENTATION FOR AMENDMENT TO THE MARKETING AUTHORISATION

Article 21

Marketing authorisation holder, according to the Law, shall follow scientific and technical development, pharmacovigilance and other data on medicinal product and inform Agency about the evaluation of quality, safety and efficacy of the medicinal product and shall submit an application for amendment to the marketing authorisation (hereinafter: variations), in accordance with new findings about the medicinal product.

Article 22

Variations referred to in Article 21of this Rulebook are as follows:

- minor variations – variations of type I which may be variations type IA, IAIN and variations type IB;
- major variations – variations type II; and
- variations for which a new marketing authorisation should be issued, which is an extension of the existing marketing authorisation, based on the new application.

Variations referred to in paragraph 1 of this Article are classified in accordance with Regulation 1234/2008/EC and Guideline 2013/C 223/01 on variations of European Commission.

Article 23

Type IA variations either do not have at all, or have minimum impact on quality, safety or efficacy of the medicinal product and are submitted to the Agency within 12 months of their use (Do and Tell procedure).

Within time-limit referred to in paragraph 1 of this Article, marketing authorisation holder may submit several type IA variations used in previous 12 months - Annual Reporting.

Type IAIN are submitted to the Agency by the marketing authorisation holder right after their use.

Article 24

Type IA variations refer to:

- administrative changes in relation to the identity and information about marketing authorisation holder, the manufacturer or supplier of any starting material, reagent, intermediate, active substance used in the manufacturing process or medicinal product;
- removing any manufacturing site, including manufacturing site of active substance, intermediate or a medicinal product, site where packaging takes place, the manufacturer responsible for batch release, site where batch control takes place;
- minor changes of the approved process of physical-chemical testing where it is proven that new process is either identical or improved compared to the previous testing process; conducted appropriate validations and results showing that new process is identical or improved compared to the previous testing process;
- amendments to specifications of the active substance or excipients in order to comply with the updated monograph of the European Pharmacopoeia or national pharmacopoeia of the Member States of the European Union, where the change has been made solely to comply with the pharmacopoeia, and specifications of the medicinal product remain unchanged;
- changes of packaging material that does not come into contact with the medicinal product, which does not affect the delivery, use, safety or stability of the medicinal product;
- establishment of stricter specification limits, where the change is not a consequence of the obligation of previous assessment to review specification limits and does not result from unexpected events arised during the manufacture.

Article 25

Type IB variations are variations that are not type IA, IAIN, type II variations, or variations that need issuance of new marketing authorisation.

If the variation may not be classified under terms of Article 22 of this Rulebook, the Agency, in an agreement with marketing authorisation holder shall consider it as a variation of type IB (unforeseen).

For type IB variations, the marketing authorization holder shall submit to the Agency an application for approval before the use.

"Tell, Wait and Do" procedure shall be applied to the variation referred to in paragraph 1 of this Article, in accordance with the Regulation and the Directive of the European Commission under Article 22 paragraph 2 of this Rulebook.

Article 26

Type II variations are variations which may have a significant impact to quality, safety or efficacy of a medicinal product.

Variations from paragraph 1 of this Article shall refer to:

- addition of new therapeutic indications, or modification of existing ones;

- significant changes of summary of product characteristics of a medicinal product as a result of new information related to quality, preclinical and clinical findings or findings related to pharmacovigilance;
- dispensing mode change;
- changes outside the scope of approved specifications, limits or eligibility criteria;
- significant changes in the manufacturing process, formulation, specifications or impurity profile of the active substance or medicinal products that may have a significant impact on quality, safety or efficacy of a medicinal product;
- modification of the manufacturing process or the manufacturing sites of active substances for biological medicinal products;
- introduction of a new Design Space (changes relating to the development of a medicinal product) or extension of the approved one, where the Design Space made in accordance with relevant European and international scientific guidelines;
- change or addition of target species of animals whose products are not used in human nutrition;
- replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue;
- replacement of the strain in veterinary vaccines against influenza in horses;
- changes to the active substance of seasonal, pre-pandemic or pandemic vaccine against human influenza;
- change of the waiting period veterinary medicinal product.

For type II variations, the marketing authorization holder shall submit to the Agency an application for approval before the use.

Article 27

Marketing authorisation holder shall submit to the Agency new application for issuance of marketing authorisation for the following variations:

- which refer to the active substanve;
- which refer to a change of strength, pharmaceutical form and route of administration; and
- which are specific for veterinary medicinal products administered in animals used in human nutrition.

Article 28

Variations that refer to active substance from Article 27 paragraph 1 indent 1 of this Rulebook are as follows:

1) replacement of chemical active substance by other salt or ester, a complex, or a derivative which has the same therapeutic functional group, where characteristics of the efficacy and safety are not significantly different;
2) replacement by a different isomer, different mixture of isomers, replacement of mixture by isolated isomer (e.g. replacement of the racemic mixture by a single enantiomer), where characteristics of the efficacy and safety are not significantly different;
3) replacement of biologically active substances by a biological substance of slightly different molecular structure, where characteristics of efficacy and safety are not significantly different, except in the case of:
    - replacement of the active principle in seasonal pre-pandemic or pandemic vaccine against human influenza
    - replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue, and
    - replacement of the strain in veterinary vaccines against influenza in horses;

4) modification of the vector used for the production of antigens or replacing of starting material, including a new main bank of cells of other origin, where the characteristics of efficacy and safety have not been substantially altered;
5) a new ligand or coupling mechanism for radiopharmaceuticals where characteristics of the efficacy and safety are not significantly different
6) change in solvent for extraction or in relation of a substance of plant origin and plant product, where the characteristics of efficacy and safety have not been significantly altered.

Article 29

Variations concerning a change in strength, pharmaceutical form or route of administration from Article 27, paragraph 1, indent 2 of this Rulebook are as follows:

- change of biological availability;
- change in pharmacokinetics, i.e. change of the releasing speed of active substance;
- change or addition of a new strength (potency);
- change or addition of a new pharmaceutical form; and
- change or addition of a new route of administration.

In variations from paragraph 1 indent 4 of this Article, it is necessary to establish a distinction between intra-arterial, intravenous, intramuscular, subcutaneous and other routes of administration in medicinal products for parenteral use. When medicinal products are administered in poultry, respiratory, oral and ocular (nebulization) route of application when applying vaccines are considered to be equivalent.

Article 30

Variations specific to veterinary medicinal products that are administered to animals, or to animals whose products are used in human nutrition referred to in Article 27, paragraph 1, indent 3 of this Rulebook are change or addition of target species.

Article 31

If variations referred to in Article 22 of this Rulebook cause amendments in integral parts of marketing authorisation from Article 19 paragraph 2 of this Rulebook, they may be considered part of the same variation.

Article 32

Application for variation may contain more variations in following cases:

- where same variations of type IA to the terms of one or several marketing authorisations owned by the same holder, are submitted at the same time;
- where several variations to the terms of the same marketing authorisation are submitted at the same time.

Application from paragraph 1 indent 2 of this Article may be submitted if:

1) one of the variations in the group require issuance of a new marketing authorisation;
2) one of the variations in the group is a variation of type II and all other variations in the group are variations which are consequential variations;
3) one of the variations in the group is a variation of type IB and all other variations in the group are variations which are consequential variations;
4) all variations in the group relate solely to changes of administrative nature to the summary of product characteristics, package leaflet and labelling;
5) all variations in the group are changes to an Active Substance Master File, Plasma Master File or Vaccine Antigen Master File;

6) all variations in the group relate to improvement of the manufacturing process and the quality of the medicinal product concerned or its active substance;
7) all variations in the group are changes affecting the quality of a human pandemic influenza vaccine;
8) all variations in the group are changes to the pharmacovigilance system;
9) all variations in the group are consequential to a given urgent safety measure;
10) all variations in the group relate to the implementation of a given class labelling;
11) all variations in the group are consequential to the assessment of a given periodic safety update report.;
12) all variations in the group are consequential to a given post-authorisation study conducted under the supervision of the holder;
13) all variations in the group are consequential to specific obligations of the conditional marketing authorisation holder;
14) all variations in the group are consequential to specific obligations of the holder under specific conditions.

Article 33

An application submitted for issuance of approval of the variation(s) contains the following:
1) logo, name and address of the applicant;
2) data on a medicinal product (brand name, international non-protected name (INN) or generic name, pharmaceutical form and strength);
3) information on the packaging of a medicinal product;
4) data on the manufacturer of the medicinal product;
5) estimated date of introducing the variation; and
6) date and signature of the person responsible for the procedure for issuance of marketing authorisation.

Application from paragraph 1 of this Article is submitted on the form published on the portal of the Agency.

Article 34

Application for issuance of approval of the variation(s) is accompanied by:
- documentation relating to the variation and gives enough information for its assessment; and
- evidence that fees have been paid.

Article 35

Marketing authorisation holder shall immediately notify the Agency on the urgent safety restrictions to be introduced in the event of a risk to public health, animal health, or the environment.

Urgent safety restriction is a variation of type II which involves change of information on the medicinal product due to new information affecting safety of the medicinal product's use, and particularly refers to one or more parts of the summary of product characteristics and packaging leaflet (indications, posology, contraindications, warnings, target species and waiting period).

If no objections have been raised by the Agency to urgent safety measures from paragraph 1 of this Article, or if it does not respond to the holder, the holder shall introduce the variation within 24 hours from the time of notifying the Agency.

In the event of a risk from paragraph 1 of this Article, the Agency may require introducing urgent safety restrictions.

Marketing authorisation holder shall submit the completed form for appropriate variation with the necessary documentation immediately upon the introduction of restrictions measures referred to in paragraph 1 of this Article, and at latest within 15 days.

Article 36

For the purpose of this Rulebook, transfer of the authorisation to a new holder is also considered amendment to the authorisation.

Application for the approval of the transfer of the authorisation shall contain the following:

1) logo, name and address of the applicant;
2) data on a medicinal product (brand name, international non-protected name (INN) or generic name, pharmaceutical form and strength);
3) packaging(s) of a medicinal product;
4) data on the manufacturer of the medicinal product (full name, address, information on the manufacturing site);
5) date and number of the issued authorisation;
6) name and address of the new authorisation holder and evidence on fullfillment of requirements for the marketing authorisation prescribed by the law;
7) statement of the new holder on acceptance of the requirements of the marketing authorisation holder;
8) statement of former new holder to pass on all the documentation necessary for the fullfillment of requirements for the marketing authorisation to a new holder; and
9) date and signature of the responsible person.

Application from paragraph 1 of this article shall be submitted on the form published on the portal of the Agency.

Article 37

Application for obtaining of approval of the authorisation transfer is accompanied by:

- evidence that fees have been paid, and
- other necessary documentation upon the request of the Agency.

V. RENEWAL OF THE AUTHORISATION

Article 38

Marketing authorisation holder shall, within the time-frame defined by the Law, submit to the Agency an application for the renewal of the authorisation that contains the following:

1) logo, name and address of the marketing authorisation holder;
2) data on a medicinal product (brand name, international non-protected name (INN) or generic name, pharmaceutical form and strength);
3) packaging(s) of a medicinal product;
4) data on the manufacturer of the medicinal product (full name, address, information on the manufacturing site);
5) date and number of the issued authorisation;
6) updated administrative data; and
7) date and signature of the responsible person.

Upon the request of the Agency, an applicant is obliged to submit medicinal products samples and reference standards necessary for the laboratory quality control of the medicinal product.

Application from paragraph 1 of this article shall be submitted on the form published on the portal of the Agency.

Article 39

Application for obtaining of approval of the renewal of the authorisation is accompanied by:

- documentation on the medicinal product; and

- evidence that fees have been paid.

Article 40

Documentation from Article 39 paragraph 1 indent 1 of this Rulebook shall contain the following:

- complemented/updated summary of product characteristics;
- complemented/updated packaging leaflet;
- proposal of the conceptual design, or already made immediate and outer packaging;
- latest periodic safety update report (PSUR) or other appropriate document with updated information on post-marketing safety;
- updated PSMF; and
- list of approved and reported variations in the validity period of the authorisation.

Documentation from paragraph 1 of this Article shall be prepared in accordance with guidelines of European Commission.

Article 41

Updated administrative data from Article 38 paragraph 1 item 6 of this Rulebook shall include the following:

- certificates on the implementation of Good Manufacturing Practice for the manufacturing site specified in the documentation that are not older than three years and a statement that updated certificates shall be submitted to the Agency every three years; and
- other updated information upon the request of the Agency.

Article 42

Application for obtaining authorisation, transfer and renewal of the authorisation, and amendment to the authorisation within the fast-track procedure in accordance with Article 41 of the Law, shall, beside documentation prescribed by this Rulebook, also be accompanied by:

- assessment report by EMA or reference member state for medicinal products approved within centralised procedure, decentralised procedure, or mutual reckognition procedure;
- list of other countries that were involved in the decentralised procedure, or mutual reckognition procedure;
- statement of the applicant that the documentation based on which marketing authorisation is applied for in Montenegro is identical to the documentation based on which Assessment report is made and issued, including all amendments approved by the date of submission of the application, i.e. that the submitted documentation is valid European Union Member States; and
- statement of the applicant to notify the Agency without delay on the event of temporary or permanent revocation of the marketing authorization in the European Union, as well as on all urgent safety restrictions.

Article 43

For cessation of validity of the marketing authorisation a holder shall submit an application that contains the following:

1) logo, name and address of the marketing authorisation holder;
2) data on a medicinal product (brand name, international non-protected name (INN) or generic name, pharmaceutical form and strength);
3) packaging(s) of a medicinal product;
4) data on the manufacturer of the medicinal product (full name, address, information on the manufacturing site);
5) date and number of the issued authorisation;

6) reason for cessation of validity of the marketing authorisation; and
7) date and signature of the responsible person.

Application from paragraph 1 of this Article shall be submitted on the form published on the portal of the Agency.

Article 44

Application for obtaining of approval of cessation of validity of the marketing authorisation is accompanied by:

- evidence that fees have been paid; and
- other necessary information upon the request of the Agency.

VI. FINAL PROVISIONS

Article 45

Upon the entry into force of this Rulebook, Rulebook on more detailed conditions for issuance of marketing authorisation for a medicinal product ("Official Gazette of Montenegro", No 30/09) shall cease to be valid.

Article 46

This Law shall enter into force eight days from the day of its publication in "Official Gazette of Montenegro".

Annex 1

A) CONTENTS OF SUMMARY OF PRODUCTS FOR HUMAN USE CHARACTERISTICS

1. Name of the medicinal product:
   Name, strength and pharmaceutical form
2. Qualitative and quantitative composition
   Expressed as the content of active substance and excipients (with confirmed effect) that are important for the adequate use of the medicine, stated as INN or generic name.
3. Pharmaceutical form
4. Clinical details
   4.1. therapeutic indications;
   4.2. posology and route of administration;
   4.3. contraindications;
   4.4. special warnings and precautionary measures for use of the medicine, and in the case of immunology medicines, special precautions for patients and personnel handling and administering the medicines to patients
   4.5. clinically significant intreactions;
   4.6. use during pregnancy and breastfeeding;
   4.7. affecting the ability to drive vehicles and use machines;
   4.8. adverse reactions to a medicinal product;
   4.9. overdose (symptoms, emergency measures to be taken, antidotes)
5. Pharmacological properties
   5.1. pharmacdinamic properties;
   5.2. pharmacokinetic properties;
   5.3. preclinical data on safety;

6. Pharmaceutical details
    6.1. list of excipients;
    6.2. incompatibilities;
    6.3. expiry date; if necessary, the expiry date after reconstitution of the medicinal product, or after first opening the inner packaging shall be stated
    6.4. special storage warnings;
    6.5. type and contents of the container;
    6.6. special precautions for disposal of the material that needs to be disposed after use of the medicinal product (and other instructions for handling)
7. Marketing authorisation holder (name, address, contact details)
8. Number of the authorisation
9. Date of the first marketing authorization, or the renewal
10. Date of the last revision of the text
11. Dosimetric data (for radiopharmaceuticals only)
12. Instructions for the preparation of a radiopharmaceutical (additional detailed instructions for immediate preparation and quality control of such preparation and where necessary the longest shelf life for which intermediates, such as eluate or ready-to-use form, meet the prescribed specifications (for radiopharmaceuticals only).

B) CONTENTS OF SUMMARY OF PRODUCT CHARACTERISTICS FOR MEDICINAL PRODUCTS FOR VETERINARY USE

1. Name of the medicinal product:
    Name, strength and pharmaceutical form
2. Qualitative and quantitative composition
    Expressed as the content of active substance and excipients (with confirmed effect) that are important for the adequate use of the medicine, stated as INN or generic name.
3. Pharmaceutical form
4. Clinical particulars:
    4.1. target species,
    4.2. indications for use, specifying the target species,
    4.3. contra-indications,
    4.4. special warnings for each target species,
    4.5. special precautions for use, including special precautions to be taken by the person administering the medicinal product to the animals,
    4.6. adverse reactions (frequency and seriousness),
    4.7. use during pregnancy, lactation or lay,
    4.8. interaction with other medicinal products and other forms of interaction,
    4.9. dosage and administration route,
    4.10. overdose (symptoms, emergency procedures, antidotes), if necessary,
    4.11. waiting periods for the various foodstuffs, including those for which the waiting period is zero;
5. Pharmacological properties
    5.1. pharmacdinamic properties;
    5.2. pharmacokinetic particulars;
6. Pharmaceutical details
    6.1. list of excipients,
    6.2. incompatibilities,
    6.3. shelf life, when necessary after reconstitution of the medicinal product or when the inner packaging is opened for the first time,
    6.4. special precautions for storage,
    6.5. nature and composition of packaging,

6.6. special precautions for disposal of the material that needs to be disposed after use of the veterinary medicinal product (and other instructions for handling)
7. Marketing authorisation holder;
8. Marketing authorisation number;
9. Date of the first authorisation or date of renewal of the authorisation;
10. Date of revision of the text.

Annex 2

ANALYTICAL, PHARMACO-TOXICOLOGICAL AND CLINICAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS

TABLE OF CONTENTS

3.2.2.3. Manufacturing process of the finished medicinal product
3.2.2.4. Control of excipients
3.2.2.5. Control of the finished medicinal product
3.2.2.6. Reference standards or materials
3.2.2.7. Container and closure of the finished medicinal product
3.2.2.8. Stability of the finished medicinal product

4. Module 4: Non-clinical reports

4.1. Format and Presentation
4.2. Content: basic principles and requirements
4.2.1. Pharmacology
4.2.2. Pharmaco-kinetics
4.2.3. Toxicology

5. Module 5: Clinical study reports

5.1. Format and Presentation
5.2. Content: basic principles and requirements
5.2.1. Reports of bio-pharmaceutics studies
5.2.2. Reports of studies pertinent to pharmaco-kinetics using human bio-materials
5.2.3. Reports of human pharmaco-kinetic studies
5.2.4. Reports of human pharmaco-dynamic studies
5.2.5. Reports of efficacy and safety studies
5.2.5.1. Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
5.2.5.2. Study reports of uncontrolled clinical studies reports of analyses of data from more than one study and other clinical study reports
5.2.6. Reports of post-marketing experience
5.2.7. Case reports forms and individual patient listings

Part II Specific marketing authorisation dossiers and requirements

1. Well-established medicinal use
2. Essentially similar medicinal products
3. Additional data required in specific situations
4. Similar biological medicinal products
5. Fixed combination medicinal products
6. Documentation for applications in exceptional circumstances
7. Mixed marketing authorisation applications

Part III Particular medicinal products

1. Biological medicinal products
1.1. Plasma-derived medicinal product
1.2. Vaccines
2. Radio-pharmaceuticals and precursors
2.1. Radio-pharmaceuticals
2.2. Radio-pharmaceutical precursors for radio-labelling purposes
3. Homeopathic medicinal products
4. Herbal medicinal products
5. Orphan Medicinal Products

Part IV Advanced therapy medicinal products

1. Introduction
2. Definitions
2.1. Gene therapy medicinal product
2.2. Somatic cell therapy medicinal product
3. Specific requirements regarding Module 3

3.1. Specific requirements for all advanced therapy medicinal products
3.2. Specific requirements for gene therapy medicinal products
3.2.1. Introduction: finished product, active substance and starting materials
3.2.1.1. Gene therapy medicinal product containing recombinant nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es)
3.2.1.2. Gene therapy medicinal product containing genetically modified cells
3.2.2. Specific requirements
3.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products
3.3.1. Introduction: finished product, active substance and starting materials
3.3.2. Specific requirements
3.3.2.1. Starting materials
3.3.2.2. Manufacturing process
3.3.2.3. Characterisation and control strategy
3.3.2.4. Excipients
3.3.2.5. Developmental studies
3.3.2.6. Reference materials
3.4. Specific requirements for advanced therapy medicinal products containing devices
3.4.1. Advanced therapy medicinal product containing devices as referred to in Article 7 of Regulation (EC) No 1394/2007
3.4.2. Combined advanced therapy medicinal products as defined in Article 2 paragraph 1 item d of Regulation (EC) No 1394/2007
4. Specific requirements regarding module 4
4.1. Specific requirements for all advanced therapy medicinal products
4.2. Specific requirements for gene therapy medicinal products
4.2.1. Pharmacology
4.2.2. Pharmacokinetics
4.2.3. Toxicology
4.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products
4.3.1. Pharmacology
4.3.2. Pharmacokinetics
4.3.3. Toxicology
5. Specific requirements regarding module 5
5.1. Specific requirements for all advanced therapy medicinal products
5.2. Specific requirements for gene therapy medicinal products
5.2.1. Human pharmacokinetic studies
5.2.2. Human pharmacodynamic studies
5.2.3. Safety studies
5.3. Specific requirements for somatic cell therapy medicinal products
5.3.1. Somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s)
5.3.2. Biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components
5.3.3. Safety studies
5.4. Specific requirements for tissue engineered products
5.4.1. Pharmacokinetic studies
5.4.2. Pharmacodynamic studies
5.4.3. Safety studies

Introduction and general principles

1) The particulars and documents accompanying an application for marketing authorisation shall be in accordance with the Law on Medicinal products as well as with the requirements set out in this Rulebook

and shall follow the guidance published by the Commission in The rules governing medicinal products in the European Community, Volume 2 B, Notice to applicants, Medicinal products for human use, Presentation and content of the dossier, Common Technical Document (CTD).
2) The particulars and documents shall be presented as five modules: Module 1 provides European Community specific administrative data; Module 2 provides quality, non-clinical and clinical summaries, Module 3 provides chemical, pharmaceutical and biological information, Module 4 provides non-clinical reports and Module 5 provides clinical study reports. This presentation implements a common format for all ICH regions (European Community, United States of America, Japan). These five Modules shall be presented in strict accordance with the format, content and numbering system delineated in details in Volume 2 B of the Notice to Applicants referred to above.
3) The European Community-CTD-presentation is applicable for all types of marketing authorisation applications irrespective of the procedure to be applied (i.e. centralised, mutual recognition or national) and of whether they are based on a full or abridged application. It is also applicable for all types of products including new chemical entities (NCE), radio-pharmaceuticals, plasma derivatives, vaccines, herbal medicinal products, etc.
4) In assembling the dossier for application for marketing authorisation, applicants shall also take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use as adopted by the Committee for Human Medicinal Products (HMP) and published by the European Medicines Agency (EMA) and the other pharmaceutical E guidelines published by the Commission in the different volumes of The rules governing medicinal products in the European Community.
5) With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.
6) The manufacturing process shall comply with the requirements of Commission Directive 91/356/EEC laying down the principles and guidelines of Good Manufacturing Practice (GMP) for medicinal products for human use and with the principles and guidelines on GMP, published by the Commission in The rules governing medicinal products in the European Community, Volume 4.
7) All information, which is relevant to the evaluation of the medicinal product concerned, shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned pharmaco-toxicological or clinical test or trial relating to the medicinal product and/or completed trials concerning therapeutic indications not covered by the application.
8) All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. To be taken into account during the assessment of an application, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.
9) Non-clinical (pharmaco-toxicological) studies shall be carried out in conformity with the provisions related to Good Laboratory Practice laid down in Council Directives 87/18/EEC on the harmonisation of regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their application for tests in chemical substances and 88/320/EEC on the inspection and verification of good laboratory practice (GLP).
10) Member States shall also ensure that all tests on animals are conducted in accordance with Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulation and administrative provisions of the Member States regarding the protection of animals for experimental and other scientific purposes.
11) In order to monitor the benefit/risk assessment, any new information not in the original application and all pharmaco-vigilance information shall be submitted to the Agency. After marketing authorisation has

been granted, any change to the data in the dossier shall be submitted in accordance with the requirements of Commission Regulations (EC) No 1084/2003 and (EC) No 1085/2003 of the Commission or, if relevant, in accordance with national provisions, as well as the requirements in Volume 9 of Commission publication The rules governing medicinal products in the European Community.

This Annex is divided in four different parts:

Part I describes the application format, the summary of product characteristics, the labelling, the leaflet and presentation requirements for standard applications (Modules 1 to 5).

Part II provides derogation for 'Specific applications', i.e. well-established medicinal use, essentially similar products, fixed combinations, similar biological products, exceptional circumstances and mixed applications (part bibliographic and part own studies).

Part III deals with 'Particular application requirements' for biological medicinal products (Plasma Master File; Vaccine Antigen Master File), radio-pharmaceuticals, homeopathic medicinal products, herbal medicinal products and orphan medicinal products.

Part IV deals with 'Advanced therapy medicinal products' and concerns specific requirements for gene therapy medicinal products (using human autologous or allogeneic system, or xenogeneic system) and cell therapy medicinal products both of human or animal origin and xenogeneic transplantation medicinal products.

PART I

Standardised marketing authorisation dossier requirements

1. Module 1: Administrative information

1.1. Table of contents

A comprehensive table of contents of Modules 1 to 5 of the dossier submitted for marketing authorisation application shall be presented.

1.2. Application form

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

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

The applicant shall identify the type of application and indicate what samples, if any, are also provided.

Annexed to the administrative data shall be copies of the manufacturing authorisation as defined in Article 31, together with a list of countries in which authorisation has been granted, copies of all the summaries of product characteristics approved by Member States and a list of countries in which an application has been submitted.

As outlined in the application form, the applicants shall provide, inter alia, details of the medicinal product subject of the application, the legal basis of the application, the proposed marketing authorisation holder and manufacture(s), information on orphan medicinal product status, scientific advice and paediatric development program.

1.3. Summary of product characteristics, labelling and package leaflet

1.3.1. Summary of product characteristics

The applicant shall propose a summary of the product characteristics, in accordance with the Law and this Rulebook.

1.3.2. Labelling and package leaflet

A proposed labelling text for immediate and outer packaging as well as for the package leaflet shall be provided. These shall be in accordance with Rulebook on the contents and method of labelling the outer

and immediate packaging of a medicine and contents of the package leaflet ("Official Gazette of Montenegro" No 21/16 and 67/18).

1.3.3. Mock-ups and specimens

The applicant shall provide specimen and/or mock-ups of the immediate and outer packaging, labels and package leaflets for the medicinal product concerned

1.3.4. Summaries of product characteristics already approved in the Member States

Annexed to the administrative data of the application form shall be copies of all the summaries of product characteristics approved by Member States, where applicable and a list of countries in which an application has been submitted.

1.4. Information about the experts

Experts must provide detailed reports of their observations on the documents and particulars which constitute the marketing authorisation dossier and in particular on Modules 3, 4 and 5 (chemical, pharmaceutical and biological documentation, non-clinical documentation and clinical documentation, respectively). The experts are required to address the critical points related to the quality of the medicinal product and of the investigations carried out on animals and human beings and bring out all the data relevant for evaluation.

These requirements shall be met by providing a quality overall summary, a non-clinical overview (data from studies carried out in animals) and a clinical overview that shall be located in Module 2 of the marketing authorisation application dossier. A declaration signed by the experts together with brief information on their educational background, training and occupational experience shall be presented in Module 1. The experts shall have suitable technical or professional qualifications. The professional relationship of the expert to the applicant shall be declared.

1.5. Specific requirements for different types of applications

Specific requirements for different types of applications are addressed in Part II of the present Annex.

1.6. Environmental risk assessment

Where applicable, applications for marketing authorisations shall include a risk assessment overview evaluating possible risks to the environment due to the use and/or disposal of the medicinal product and make proposals for appropriate labelling provisions. Environmental risk connected with the release of medicinal products containing or consisting of GMOs (Genetically Modified Organisms) within the meaning of Article 2 of Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of modified organisms and repealing Council Directive 90/220/EEC (1) shall be addressed.

Information pertaining to the environmental risk shall appear as an appendix to Module 1.

The information shall be presented in accordance with the provisions of Directive 2001/18/EC, taking into account any guidance documents published by the Commission in connection with the implementation of the said Directive.

The information shall consist of:

1) an introduction;

2) a copy of any written consent or consents to the deliberate release into the environment of the GMO(s) for research and development purposes according to Part B of Directive 2001/18/EC;

3) the information requested in Annexes II to IV of the Directive 2001/18/EC, including detection and identification methods as well as unique code of the GMO, plus any additional information on the GMO or the product of relevance to evaluating the environmental risk;

4) an environment risk assessment (ERA) report prepared on basis of the information specified in Annexes III and IV of Directive 2001/18/EC and in accordance with Annex II of Directive 2001/18/EC;

5) taking into account the above information and the ERA, a conclusion which proposes an appropriate risk management strategy which includes, as relevant to the GMO and product in question, a post-market

monitoring plan and the identification of any special particulars which need to appear in the Summary of Product Characteristics, labelling and package leaflet;
6) appropriate measures in order to inform the public.
A dated signature of the author, information on the author's educational, training and occupational experience, and a statement of the author's relationship with the applicant, shall be included.

2. Module 2: Summaries
This Module aims to summarise the chemical, pharmaceutical and biological data, the non-clinical data and the clinical data presented in Modules 3, 4 and 5 of the dossier for marketing authorisation, and to provide the reports/overviews described in Article 9 of this Rulebook.
Critical points shall be addressed and analysed. Factual summaries including tabular formats shall be provided. Those reports shall provide cross-references to tabular formats or to the information contained in the main documentation presented in Module 3 (chemical, pharmaceutical and biological documentation), Module 4 (non-clinical documentation) and Module 5 (clinical documentation).
Information contained in Module 2 shall be presented in accordance with the format, content and numbering system delineated in the Volume 2 of the Notice to Applicants. The overviews and summaries shall comply with the basic principles and requirements as laid down herewith:

2.1. Overall table of contents
Module 2 shall contain a table of contents for the scientific documentation submitted in Modules 2 to 5.

2.2. Introduction
Information on the pharmacological class, mode of action and proposed clinical use of the medicinal product for which a marketing authorisation is requested shall be supplied.

2.3. Quality overall summary
A review of the information related to the chemical, pharmaceutical and biological data shall be provided in a quality overall summary.
Key critical parameters and issues related to quality aspects shall be emphasised as well as justification in cases where the relevant guidelines are not followed. This document shall follow the scope and outline of the corresponding detailed data presented in Module 3.

2.4. Non-clinical overview
An integrated and critical assessment of the non-clinical evaluation of the medicinal product in animals/in vitro shall be required. Discussion and justification of the testing strategy and of deviation from the relevant guidelines shall be included.
Except for biological medicinal products, an assessment of the impurities and degradation products shall be included along with their potential pharmacological and toxicological effects. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the non-clinical studies and the product to be marketed shall be discussed.
For biological medicinal products, comparability of material used in non-clinical studies, clinical studies, and the medicinal product for marketing shall be assessed.
Any novel excipient shall be the subject of a specific safety assessment.
The characteristics of the medicinal product, as demonstrated by the non-clinical studies shall be defined and the implications of the findings for the safety of the medicinal product for the intended clinical use in human shall be discussed.

2.5. Clinical overview
The clinical overview is intended to provide a critical analysis of the clinical data included in the clinical summary and Module 5. The approach to the clinical development of the medicinal product, including critical study design, decisions related to and performance of the studies shall be provided.

A brief overview of the clinical findings, including important limitations as well as an evaluation of benefits and risks based on the conclusions of the clinical studies shall be provided. An interpretation of the way the efficacy and safety findings support the proposed dose and target indications and an evaluation of how the summary of product characteristics and other approaches will optimise the benefits and manage the risks is required.
Efficacy or safety issues encountered in development and unresolved issues shall be explained.

2.6. Non-clinical summary
The results of pharmacology, pharmaco-kinetics and toxicology studies carried out in animals/in vitro shall be provided as factual written and tabulated summaries which shall be presented in the following order:

1) Introduction
2) Pharmacology Written Summary
3) Pharmacology Tabulated Summary
4) Pharmaco-kinetics Written Summary
5) Pharmaco-kinetics Tabulated Summary
6) Toxicology Written Summary
7) Toxicology Tabulated Summary.

2.7. Clinical Summary
A detailed, factual summary of the clinical information on the medicinal product included in Module 5 shall be provided. This shall include the results of all bio-pharmaceutics studies, of clinical pharmacology studies, and of clinical efficacy and safety studies. A synopsis of the individual studies is required.
Summarised clinical information shall be presented in the following order:

1) Summary of Bio-pharmaceutics and Associated Analytical Methods
2) Summary of Clinical Pharmacology Studies
3) Summary of Clinical Efficacy
4) Summary of Clinical Safety
5) Synopses of Individual Studies

3. Module 3: Chemical, pharmaceutical and biological information for medicinal products containing chemical and/or biological active substances

3.1. Format and presentation
The general outline of Module 3 is as follows:

1) Table of contents
2) Body of data
3) Active substance

General information

1) Nomenclature
2) Structure
3) General Properties

Manufacture

1) Manufacturer(s)
2) Description of Manufacturing Process and Process Controls
3) Control of Materials
4) Controls of Critical Steps and Intermediates
5) Process Validation and/or Evaluation
6) Manufacturing Process Development

Characterisation

1) Elucidation of Structure and other Characteristics
2) Impurities
3) Specification

4) Analytical Procedures
5) Validation of Analytical Procedures
6) Batch Analyses
7) Justification of Specification

Referentni standardi i materijali

Container closure system

Stability

1) Stability Summary and Conclusions
2) Post-approval Stability Protocol and Stability Commitment
3) Stability Data
4) Finished Medicinal Product

Description and composition of the medicinal product

Pharmaceutical development

1) Components of the Medicinal Product
2) Active Substance
3) Excipients
4) Medicinal Product
5) Formulation Development
6) Overages
7) Physicochemical and Biological Properties
8) Manufacturing Process Development
9) Container Closure System
10) Microbiological Attributes
11) Compatibility

Manufacture

1) Manufacturer(s)
2) Batch Formula
3) Description of Manufacturing Process and Process Controls
4) Controls of Critical Steps and Intermediates
5) Process Validation and/or Evaluation

Control of excipients

1) Specifications
2) Analytical Procedures
3) Validation of Analytical Procedures
4) Justification of Specifications
5) Excipients of Human or Animal Origin
6) Novel Excipients

Control of Finished medicinal product

1) Specification(s)
2) Analytical Procedures
3) Validation of Analytical Procedures
4) Batch Analyses
5) Characterisation of Impurities
6) Justification of Specification(s)

Reference standards or materials

Container closure system

Stability

1) Stability Summary and Conclusion
2) Post-approval Stability Protocol and Stability Commitment
3) Stability Data
4) Appendices
5) Facilities and Equipment (Biological Medicinal Products only)

6) Adventitious Agents Safety Evaluation
7) Excipients
8) European Community Additional Information
9) Process Validation Scheme for the Medicinal Product
10) Medical Device
11) Certificate(s) of Suitability
12) Medicinal products containing or using in the manufacturing process materials of animal and/or human origin (TSE procedure)
13) Literature References

3.2. Content: basic principles and requirements

1) The chemical, pharmaceutical and biological data that shall be provided shall include for the active substance(s) and for the finished medicinal product all of relevant information on: the development, the manufacturing process, the characterisation and properties, the quality control operations and requirements, the stability as well as a description of the composition and presentation of the finished medicinal product.

2) Two main sets of information shall be provided, dealing with the active substance(s) and with the finished medicinal product, respectively.

3) This Module shall in addition supply detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s) and on the excipients incorporated in the formulation of the finished medicinal product.

4) All the procedures and methods used for manufacturing and controlling the active substance and the finished medicinal product shall be described in sufficient details to enable them to be repeated in control tests, carried out at the request of the competent authority. All test procedures shall correspond to the state of scientific progress at the time and shall be validated. Results of the validation studies shall be provided. In the case of test procedures included in the European Pharmacopoeia, this description shall be replaced by the appropriate detailed reference to the monograph(s) and general chapters.

5) The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia.

However, where a material in the European Pharmacopoeia or in the pharmacopoeia of a Member State has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described. In cases where a specification contained in a monograph of the European Pharmacopoeia or in the national 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 marketing authorisation holder. The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorisation holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.

In the case of analytical procedures included in the European Pharmacopoeia, this description shall be replaced in each relevant section by the appropriate detailed reference to the monograph(s) and general chapters.

6) In case where starting and raw materials, active substances or excipients are described neither in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia can be accepted. In such cases, the applicant shall submit a copy of the monograph accompanied by the validation of the analytical procedures contained in the monograph and by a translation where appropriate.

7) Where the active substance and/or a raw and starting material or excipients are the subject of a monograph of the European Pharmacopoeia, the applicant can apply for a certificate of suitability that, where granted by the European Directorate for the Quality of Medicines, shall be presented in the relevant section of this Module. Those certificates of suitability of the monograph of the European Pharmacopoeia are deemed to replace the relevant data of the corresponding sections described in this Module. The manufacturer shall give the 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.
8) For a well-defined active substance, the active substance manufacturer or the applicant may arrange for the

- detailed description of the manufacturing process,
- quality control during manufacture, and
- process validation

to be supplied in a separate document directly to the Agency by the manufacturer of the active substance as an Active Substance Master File.
In this case, the manufacturer shall, however, provide the applicant with all of the data, which may be necessary for the latter to take responsibility for the medicinal product. The manufacturer shall confirm in writing to the applicant that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing the applicant. Documents and particulars supporting the application for such a change shall be supplied to the Agency; these documents and particulars will be also supplied to the applicant when they concern the open part of the active substance master file.
9) Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies (materials from ruminant origin): at each step of the manufacturing process, the applicant must demonstrate the compliance of the materials used with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.
Demonstration of compliance with the said Note for Guidance can be done by submitting either, preferably a certificate of suitability to the relevant monograph of the European Pharmacopoeia that has been granted by the European Directorate for the Quality of Medicines or by the supply of scientific data to substantiate this compliance.
10) For adventitious agents, information assessing the risk with respect to potential contamination with adventitious agents, whether they are non-viral or viral, as laid down in relevant guidelines as well as in relevant general monograph and general chapter of the European Pharmacopoeia, shall be provided
11) Any special apparatus and equipment, which may be used at any stage of the manufacturing process and control operations of the medicinal product, shall be described in adequate details.
12) Where applicable and if needed, a CE marking which is required by Community legislation on medical devices shall be provided.
Special attention shall be paid to the following selected elements.

3.2.1. Active substance(s)
3.2.1.1. General information and information related to the starting and raw materials
1) Information on the nomenclature of the active substance shall be provided, including recommended International Non-proprietary Name (INN), European Pharmacopoeia name if relevant,
chemical name(s).
The structural formula, including relative and absolute stereo-chemistry, the molecular formula, and the relative
molecular mass shall be provided. For biotechnological medicinal products if appropriate, the schematic amino acid sequence and relative molecular mass shall be provided.
A list shall be provided of physicochemical and other relevant properties of the active substance, including biological activity for biological medicinal products.
2) For the purposes of this Annex, starting materials shall mean all the materials from which the active substance is manufactured or extracted.
For biological medicinal products, starting materials shall mean any substance of biological origin such as micro-organisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells).
A biological medicinal product is a product, the active substance of which is a biological substance.

A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing,
together with the production process and its control. The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma, in accordance with the Law, advanced therapy medicinal products as defined in Part IV of this
Annex, as well as medicinal products falling within the scope of Part A of the Annex to Regulation (EEC) No 2309/93;
Any other substances used for manufacturing or extracting the active substance(s) but from which this active substance is not directly derived, such as reagents, culture media, foetal calf serum, additives, and buffers involved in chromatography, etc.are known as raw materials.

3.2.1.2. Manufacturing process of the active substance (s)
1) The description of the active substance manufacturing process represents the applicant's commitment for the manufacture of the active substance. To adequately describe the manufacturing process and process controls, appropriate information as laid down in guidelines published by the EMA shall be provided.
2) All materials needed in order to manufacture the active substance shall be listed, identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.
Raw materials shall be listed and their quality and controls shall also be documented.
The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.
3) For biological medicinal products, the following additional requirements shall apply.
The origin and history of starting materials shall be described and documented.
Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate that the active substance complies with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.
When cell banks are used, characteristics of the cells used for the production and beyond shall be shown to have remained unchanged.
Seed materials, cell banks, pools of serum or plasma and other materials of biological origin and, whenever possible, the materials from which they are derived shall be tested for adventitious agents.
If the presence of potentially pathogenic adventitious agents is inevitable, the corresponding material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated.
Whenever possible, vaccine production shall be based on a seed lot system and on established cell banks.
For bacterial and viral vaccines, the characteristics of the infectious agent shall be demonstrated on the seed. In addition, for live vaccines, the stability of the attenuation characteristics shall be demonstrated on the seed; if this proof is not sufficient, the attenuation characteristics shall also be demonstrated at the production stage.
For medicinal products derived from human blood or plasma, the origin and the criteria and procedures for collection, transportation and storage of the starting material shall be described and documented in accordance with provisions laid down in Part III of this Annex.
The manufacturing facilities and equipment shall be described.
4) Tests and acceptance criteria carried out at every critical step, information on the quality and control of intermediates and process validation and/or evaluation studies shall be provided as appropriate.
5) If the presence of potentially pathogenic adventitious agents is inevitable, the correspondent material shall be used only when further processing ensures their elimination and/or inactivation and this shall be validated in the section dealing with viral safety evaluation.

6) A description and discussion of the significant changes made to the manufacturing process during development and/or manufacturing site of the active substance shall be provided.

3.2.1.3. Characterisation of the active substance(s)
Data highlighting the structure and other characteristics of the active substance(s) shall be provided.
Confirmation of the structure of the active substance(s) based on any physico-chemical and/or immuno-chemical and/or biological methods, as well as information on impurities shall be provided.

3.2.1.4. Control of active substance(s)
Detailed information on the specifications used for routine control of active substance(s), justification for the choice of these specifications, methods of analysis and their validation shall be provided.
The results of control carried out on individual batches manufactured during development shall be presented.

3.2.1.5. Reference standards or materials
Reference preparations and standards shall be identified and described in detail. Where relevant, chemical and biological reference material of the European Pharmacopoeia shall be used.

3.2.1.6. Container and the closure system of the active substance
A description of the container and the closure system and their specifications shall be provided.

3.2.1.7. Stability of the active substance(s)
1) The types of studies conducted, protocols used, and the results of the studies shall be summarized.
2) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format
3) The post authorisation stability protocol and statement on planned stability tests shall be provided.

3.2.2. Finished medicinal product
3.2.2.1. Description and composition of the finished medicinal product
A description of the finished medicinal product and its composition shall be provided. The information shall include the description of the pharmaceutical form and composition with all the constituents of the finished medicinal product, their amount on a per-unit basis, the function of the constituents of:
1) the active substance(s),
2) the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,
3) the constituents, intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products (hard capsules, soft capsules, rectal capsules, coated tablets, films-coated tablets, etc.),
4) these particulars shall be supplemented by any relevant data concerning the type of container and, where appropriate, its manner of closure, together with details of devices with which the medicinal product will be used or administered and which will be delivered with the medicinal product.

The usual terminology shall be used in describing the constituents of medicinal products:
1) in respect of substances which appear in the European Pharmacopoeia or, failing this, in the national pharmacopoeia of one of the Member States, the main title at the head of the monograph in question, with reference to the pharmacopoeia concerned,
2) in respect of other substances, the international non-proprietary name (INN) recommended by the World Health Organisation, or, failing this, 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,

3) in respect of colouring matter, designation by the 'E' code assigned to them in Council Directive 78/25/EEC of 12 December 1977 on the approximation of the rules of the Member States concerning the colouring matters authorised for use in medicinal products and/or European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuffs.

In order to give the quantitative composition of the active substance(s) of the finished 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.
Active substances present in the form of compounds or derivatives shall be designated quantitatively by their total mass, and if necessary or relevant, by the mass of active entity or entities of the molecule.
For medicinal products containing a new active substance, quantitative statement of an active substance, which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity or entities in the molecule. All subsequently authorised medicinal products shall have their quantitative composition stated in the same way for the same active substance.
Units of biological activity shall be used for substances, which cannot be defined molecularly. Where an International Unit of biological activity has been defined by the World Health Organisation, this shall be used. Where no International Unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances by using where applicable the European Pharmacopoeia Units.

3.2.2.2. Pharmaceutical development

This chapter shall be devoted to information on the development studies conducted to establish that the pharmaceutical form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the intended use specified in the marketing authorisation application dossier.
The studies described in this chapter are distinct from routine control tests conducted according to specifications. Critical parameters of the formulation and process attributes that can influence batch reproducibility, medicinal product performance and medicinal product quality shall be identified and described. Additional supportive data, where appropriate, shall be referenced to the relevant chapters of Module 4 (Non Clinical Study Reports) and Module 5 (Clinical Study Reports) of the marketing authorisation application dossier.
1) The compatibility of the active substance with excipients as well as key physicochemical characteristics of the active substance that can influence the performance of the finished product or the compatibility of different active substances with each other in the case of combination products, shall be documented.
2) The choice of excipients, in particular relative to their respective functions and concentration shall be documented.
3) A description of the development of the finished product shall be provided, taking into consideration the proposed route of administration and usage.
4) Any overages in the formulation(s) shall be justified.
5) As far as the physicochemical and biological properties are concerned, any parameter relevant to the performance of finished product shall be addressed and documented.
6) The selection and optimisation of the manufacturing process as well as differences between the manufacturing process(es) used to produce clinical batches and the process used for manufacturing the proposed finished medicinal product shall be provided.
7) The suitability of the container and closure system used for the storage, shipping and use of the finished product shall be documented. A possible interaction between medicinal product and container may need to be considered.
8) The microbiological attributes of the dosage form in relation with non-sterile and sterile products shall be in accordance with and documented as prescribed in the European Pharmacopoeia.
9) In order to provide appropriate and supportive information for the labelling the compatibility of the finished product with reconstitution diluent(s) or dosage devices shall be documented.

3.2.2.3. Manufacturing process of the finished medicinal product

1) The description of the manufacturing method accompanying the application for Marketing Authorisation pursuant to Article 31 of the Law, shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.
For this purpose it shall include at least:
— mention of the various stages of manufacture including process controls and corresponding acceptance criteria, so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced an adverse change in the constituents,
— in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished product,
— experimental studies validating the manufacturing process, where a non-standard method of manufacture is used or where it is critical for the product,
— for sterile medicinal products, details of the sterilisation processes and/or aseptic procedures used,
— a detailed batch formula.
The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.
2) Particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the production process shall be included. These tests are essential for checking the conformity of the medicinal product with the formula in case of using an analytical method for testing the finished product which does not include the assay of all the active substances (or of all the excipient constituents subject to the same requirements as the active substances).
The same applies where the quality control of the finished product depends on in-process control tests, particularly if the medicinal product is essentially defined by its method of preparation.
3) Description, documentation, and results of the validation studies for critical steps or critical assays used in the manufacturing process shall be provided.

3.2.2.4. Control of excipients
1) All the materials needed in order to manufacture the excipient(s) shall be listed identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.
Colouring matter shall, in all cases, satisfy the requirements of Directives 78/25/EEC and/or 94/36/EC. In addition, colouring matter shall meet purity criteria as laid down in Directive 95/45/EC, as amended.
2) For each excipient, the specifications and their justifications shall be detailed. The analytical procedures shall be described and duly validated.
3) Specific attention shall be paid to excipients of human or animal origin.
Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate also for excipients that the medicinal product is manufactured in accordance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.
Demonstration of compliance with the aforementioned Note for Guidance can be done by submitting either preferably a certificate of suitability to the relevant monograph on Transmissible Spongiform Encephalopathies of the European Pharmacopoeia, or by the supply of scientific data to substantiate this compliance.
4) Novel excipients:
For excipient(s) used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data, both non-clinical and clinical, shall be provided according to the active substance format previously described.
A document containing the detailed chemical, pharmaceutical and biological information shall be presented. This information shall be formatted in the same order as the chapter devoted to Active Substance(s) of Module 3.

Information on novel excipients may be presented as a stand-alone document following the format described in the former paragraphs. Where the applicant differs from the novel excipient manufacturer the said stand-alone document shall be made available to the applicant for submission to the Agency.
Additional information on toxicity studies with the novel excipient shall be provided in Module 4 of the dossier.
Clinical studies shall be provided in Module 5.

3.2.2.5. Control of the finished medicinal product
For the control of the finished medicinal product, a batch of a medicinal product is an entity which comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time.
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.
Detailed information on the specifications, (release and shelf life) justification for their choice, methods of analysis and their validation shall be provided.

3.2.2.6. Reeference standards or materials
Reference materials and standards used for testing of the finished medicinal product shall be identified and described in detail, if not previously provided in the section related to the active substance.

3.2.2.7. Container and closure of the finished medicinal product
A description of the container and the closure system(s) including the identity of each immediate packaging material and their specifications shall be provided. The specifications shall include description and identification. Non-pharmacopoeial methods (with validation) shall be included where appropriate.
For non-functional outer packaging materials only a brief description shall be provided. For functional outer packaging materials additional information shall be provided.

3.2.2.8. Stability of the finieshed medicinal product
1) The types of studies conducted, protocols used, and the results of the studies shall be summarised;
2) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format; in case of vaccines, information on cumulative stability shall be provided where appropriate;
3) The post authorisation stability protocol and statement on planned stability tests shall be provided.

4. Module 4: Non-clinical reports
4.1. Format and Presentation
The general outline of Module 4 is as follows:
1) Table of contents
2) Study reports
3) Pharmacology
   - Primary Pharmaco-dynamics
   - Secondary Pharmaco-dynamics
   - Safety Pharmacology
   - Pharmaco-dynamic Interactions
4) Pharmaco-kinetics
   - Analytical Methods and Validation Reports
   - Absorption
   - Distribution
   - Metabolism
   - Excretion
   - Pharmaco-kinetic Interactions (non-clinical)

- Other Pharmaco-kinetic Studies

5) Toxicology
    - Single-Dose Toxicity
    - Repeat-Dose Toxicity
    - Genotoxicity
    - In vitro
    - In vivo (including supportive toxico-kinetics evaluations)
    - Carcinogenicity
    - Long-term studies
    - Short- or medium-term studies
    - Other studies
    - Reproductive and Developmental Toxicity
    - Fertility and early embryonic development
    - Embryo-fetal development
    - Prenatal and postnatal development
    - Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
    - Local Tolerance
    - Other Toxicity Studies
    - Antigenicity
    - Immuno-toxicity
    - Mechanistic studies
    - Dependence
    - Metabolites
    - Impurities
    - Other
    - Literature references

4.2. Content: basic principles and requirements

Special attention shall be paid to the following selected elements.

1. The pharmacological and toxicological tests must show:

1) the potential toxicity of the product and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human beings; these should be evaluated in relation to the pathological condition concerned;

2) the pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in human beings. All results must be reliable and of general applicability. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results.

Additionally, it is necessary for clinicians to be given information about the therapeutic and toxicological potential of the product.

2. For biological medicinal products such as immunological medicinal products and medicinal products derived from human blood or plasma, the requirements of this Module may have to be adapted for individual products; therefore the testing program carried out shall be justified by the applicant.

In establishing the testing program, the following shall be taken into consideration:

1) all tests requiring repeated administration of the product shall be designed to take account of the possible induction of, and interference by, antibodies;

examination of reproductive function, of embryo/foetal and peri-natal toxicity shall be considered, as well as of mutagenic potential and of carcinogenic potential. Where constituents other than the active substances are the reason for adverse reactions, validation of their removal may replace the study.

3. The toxicology and pharmaco-kinetics of an excipient used for the first time in the pharmaceutical field shall be investigated.

4. Where there is a possibility of significant degradation during storage of the medicinal product, the toxicology of degradation products must be considered.

4.2.1. Pharmacology

Pharmacology study shall follow two distinct lines of approach.

1) Firstly, the actions relating to the proposed therapeutic use shall be adequately investigated and described. Where possible, recognised and validated assays, both in vivo and in vitro, shall be used. Novel experimental techniques must be described in such detail as to allow them to be reproduced. The results shall be expressed in quantitative terms using, for example, dose-effect curves, time-effect curves, etc. Wherever possible, results shall be compared with data relating to a substance or substances with a similar therapeutic action.

2) Secondly, the applicant shall investigate the potential undesirable pharmaco-dynamic effects of the substance on physiological functions. These investigations shall be performed in the anticipated therapeutic range and above. The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and the investigator must establish their validity. Any suspected modification of responses resulting from repeated administration of the substance shall be investigated.

For the pharmaco-dynamic medicinal product interaction, tests on combinations of active substances may be prompted either by pharmacological premises or by indications of therapeutic effect. In the first case, the pharmaco-dynamic study shall demonstrate those interactions, which might be of value in therapeutic use. In the second case, where scientific justification for the combination is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and the importance of any collateral effects shall be investigated.

4.2.2. Pharmaco-kinetics

Pharmaco-kinetics means the study of the fate of the active substance, and its metabolites, within the organism, and covers the study of the absorption, distribution, metabolism (bio-transformation) and excretion of these substances.

The study of these different phases may be carried mainly by means of physical, chemical or possibly by biological methods, and by observation of the actual pharmaco-dynamic activity of the substance itself.

Information on distribution and elimination shall be necessary in all cases where such data are indispensable to determine the dosage for humans, and in respect of chemo-therapeutic substances (antibiotics, etc.) and substances whose use depends on their non-pharmaco- dynamic effects (e.g. numerous diagnostic agents, etc.).

In vitro studies also can be carried out with the advantage of using human material for comparison with animal material (i.e. protein binding, metabolism, drug-drug interaction).

Pharmaco-kinetic investigation of all pharmacologically active substances is necessary. In the case of new combinations of known substances, which have been investigated in accordance with the provisions of this Directive, pharmaco-kinetic studies may not be required, if the toxicity tests and therapeutic experimentation justify their omission.

The pharmaco-kinetic program shall be design to allow comparison and extrapolation between animal and human.

4.2.3. Toxicology

1) Single-dose toxicity

A single-dose toxicity test shall mean a qualitative and quantitative study of the toxic reactions, which may result from a single administration of the active substance or substances contained in the medicinal product, in the proportions and physico-chemical state in which they are present in the actual product.

The acute dose toxicity test must be carried out in accordance with the relevant guidelines published by EMA.

2) Repeat-dose toxicity

Repeated dose toxicity tests are intended to reveal any physiological and/or anatomo-pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.
Generally, it is desirable that two tests be performed: one short term, lasting two to four weeks, the other long-term. The duration of the latter shall depend on the conditions of clinical use. Its purpose is to describe potential adverse effects to which attention should be paid in clinical studies. The duration is defined in the relevant guidelines published by EMA.
3) Geno-toxicity
The purposes of the study of mutagenic and clastogenic potential is to reveal the changes which a substance may cause in the genetic material of individuals or cells. Mutagenic substances may present a hazard to health since exposure to a mutagen carries the risk of inducing germ-line mutation, with the possibility of inherited disorders, and the risk of somatic mutations including those leading to cancer. These studies are obligatory for any new substance.
4) Carcino-genicity
Tests to reveal carcinogenic effects shall normally be required:
- These studies shall be performed for any medicinal product whose expected clinical use is for a prolonged period of a patient's life, either continuously or repeatedly in an intermittent manner.
- These studies are recommended for some medicinal products if there is concern about their carcinogenic potential, e.g. from product of the same class or similar structure, or from evidence in repeated dose toxicity studies
- Studies with unequivocally geno-toxic compounds are not needed, as they are presumed to be trans-species carcinogens, implying a hazard to humans. If such a medicinal product is intended to be administered chronically to humans a chronic study may be necessary to detect early tumorigenic effects.
5) Reproductive and developmental toxicity
Investigation of possible impairment of male or female reproductive function as well as harmful effects on progeny shall be performed by appropriate tests.
These tests comprise studies of effect on adult male or female reproductive function, studies of the toxic and teratogenic effects at all stages of development from conception to sexual maturity as well as latent effects, when the medicinal product under investigation has been administered to the female during pregnancy.
Omission of these tests must be adequately justified.
Depending on the indicated use of the medicinal product, additional studies addressing development when administering the medicinal product of the offspring may be warranted.
Embryo/foetal toxicity studies shall normally be conducted on two mammalian species, one of which shall be other than a rodent. Peri- and postnatal studies shall be conducted in at least one species. If the metabolism of a medicinal product in particular species is known to be similar to that in man, it is desirable to include this species. It is also desirable that one of the species is the same as in the repeated dose toxicity studies.
The state of scientific knowledge at the time when the application is lodged shall be taken into account when determining the study design.
6) Local tolerance
The purpose of local tolerance studies is to ascertain whether medicinal products (both active substances and excipients) are tolerated at sites in the body, which may come into contact with the medicinal product as a result of its administration in clinical use. The testing strategy shall be such that any mechanical effects of administration or purely physico-chemical actions of the product can be distinguished from toxicological or pharmaco-dynamic ones.
Local tolerance testing shall be conducted with the preparation being developed for human use, using the same constituents and/or excipients in treating the control group(s). Control groups with positive control shall be included where necessary.
The design of local tolerance tests (choice of species, duration, frequency and route of administration, doses) will depend upon the subject to be investigated and the proposed conditions of administration in clinical use. Reversibility of local lesions shall be performed where relevant.

Studies in animals can be substituted by validated in vitro tests provided that the test results are of comparable quality and usefulness for the purpose of safety evaluation.
For chemicals applied to the skin (e.g. dermal, rectal, vaginal) the sensitising potential shall be evaluated in at least one of the test systems currently available (the guinea pig assay or the local lymph node assay).

5. Module 5: Clinical study reports

5.1. Format and Presentation

The general outline of Module 5 is as follows:

1) Table of contents for clinical study reports
2) Tabular listing of all clinical studies
3) Clinical study reports
4) Reports of Bio-pharmaceutical Studies
5) Bio-availability Study Reports
6) Comparative Bio-availability and Bio-equivalence Study Reports
7) In vitro — In vivo Correlation Study Report
8) Reports of Bio-analytical and Analytical Methods
9) Reports of Studies Pertinent to Pharmaco-kinetics Using Human Bio-materials
10) Plasma Protein Binding Study Reports
11) Reports of Hepatic Metabolism and Interaction Studies
12) Reports of Studies Using Other Human Bio-materials
13) Reports of Human Pharmaco-kinetic Studies
14) Healthy subjects Pharmaco-kinetics and Initial Tolerability Study Reports
15) Patient Pharmaco-kinetics and Initial Tolerability Study Reports
16) Intrinsic Factor Pharmaco-kinetics Study Reports
17) Extrinsic Factor Pharmaco-kinetics Study Reports
18) Population Pharmaco-kinetics Study Reports
19) Reports of Human Pharmaco-dynamic Studies
20) Healthy Subject Pharmaco-dynamic and Pharmaco-kinetics/ Pharmaco-dynamic Study Reports
21) Patient Pharmaco-dynamic and Pharmaco-kinetics/ Pharmaco-dynamic Studies Study Reports
22) Reports of Efficacy and Safety Studies
23) Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
24) Study Reports of Uncontrolled Clinical Studies
25) Reports of Analyses of Data from More than One Study including any formal integrated analyses, meta-analyses and bridging analyses
26) Other Study Reports
27) Reports of Post-marketing Experience
28) Literature references
29)

5.2. Content: basic principles and requirements

Special attention shall be paid to the following selected elements.

1) The clinical particulars to be provided pursuant to Articles 31 and 34 of the Law must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorisation. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.

2) Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of Module 4 of this Annex. The investigator must acquaint himself with the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide him at least with the investigator's brochure, consisting of all the relevant information known prior to the onset of a clinical trial including chemical, pharmaceutical and biological

data, toxicological, pharmaco-kinetic and pharmaco-dynamic data in animals and the results of earlier clinical trials, with adequate data to justify the nature, scale and duration of the proposed trial; the complete pharmacological and toxicological reports shall be provided on request. For materials of human or animal origin, all available means shall be employed to ensure safety from transmission of infectious agents prior to the commencement of the trial.

3) Marketing authorisation holders must arrange for essential clinical trial documents (including case report forms) other than subject's medical files, to be kept by the owners of the data:

- for at least 15 years after completion or discontinuation of the trial,
- or for at least two years after the granting of the last marketing authorisation in the European Community and when there are no pending or contemplated marketing applications in the European Community,
- or for at least two years after formal discontinuation of clinical development of the investigational product.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor. It is the responsibility of the sponsor to inform the hospital, institution or practice as to when these documents no longer need to be retained.

The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the product is authorised. This documentation shall include: the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product, the reference medicinal product and/or the placebo used; standard operating procedures; all written opinions on the protocol and procedures; the investigator's brochure; case report forms on each trial subject; final report; audit certificates, if available. The final report shall be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorised.

In addition for trials conducted within the European Community, the marketing authorisation holder shall make any additional arrangements for archiving of documentation in accordance with the provisions of Directive 2001/20/EC and implementing detailed guidelines.

Any change of ownership of the data shall be documented.

All data and documents shall be made available if requested by the Agency.

4) The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made:

- the protocol, including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational medicinal product used
- audit certificate(s), if available
- the list of investigator(s), and each investigator shall give his name, address, appointments, qualifications and clinical duties, state where the trial was carried out and assemble the information in respect of each patient individually, including case report forms on each trial subject
- final report signed by the investigator and for multi-centre trials, by all the investigators or the co-ordinating (principal) investigator.

5) The particulars of clinical trials referred to above shall be forwarded to the competent authorities. However, in agreement with the competent authorities, the applicant may omit part of this information. Complete documentation shall be provided forthwith upon request.

The investigator shall, in his conclusions on the experimental evidence, express an opinion on the safety of the product under normal conditions of use, its tolerance, its efficacy and any useful information relating to indications and contra-indications, dosage and average duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of over dosage. In reporting the results of a multi-centre study, the principal investigator shall, in his conclusions, express an opinion on the safety and efficacy of the investigational medicinal product on behalf of all centres

6) The clinical observations shall be summarised for each trial indicating:

- the number and sex of subjects treated;

- the selection and age-distribution of the groups of patients being investigated and the comparative tests;
- the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal;
- where controlled trials were carried out under the above conditions, whether the control group:

a) received no treatment
b) received a placebo
c) received another medicinal product of known effect
d) received treatment other than therapy using medicinal products

- the frequency of observed adverse reactions;
- details concerning patients who may be at increased risk, e.g. elderly people, children, women during pregnancy or menstruation, or whose physiological or pathological condition requires special consideration;
- parameters or evaluation criteria of efficacy and the results in terms of these parameters;
- a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.

7) In addition, the investigator shall always indicate his observations on:

- any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;
- any interactions that have been observed with other medicinal products administered concomitantly;
- the criteria determining exclusion of certain patients from the trials;
- any deaths which occurred during the trial or within the follow-up period.

8) Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and efficacy of the combination.
9) Total or partial omission of data must be explained. Should unexpected results occur during the course of the trials, further pre clinical toxicological and pharmacological tests must be undertaken and reviewed.
10) If the medicinal product is intended for long-term administration, particulars shall be given of any modification of the pharmacological action following repeated administration, as well as the establishment of long-term dosage.

5.2.1. Reports of bio-pharmaceutics studies
Bio-availability study reports, comparative bio-availability, bio-equivalence study reports, reports on in vitro and in vivo correlation study, and bio-analytical and analytical methods shall be provided.
In addition, an assessment of bio-availability shall be undertaken where necessary to demonstrate bio-equivalence for the medicinal products referred to in Article 34 of the Law.

5.2.2. Reports of studies pertinent to pharmaco-kinetics using human bio-materials
For the purposes of this Annex, human bio-materials shall mean any proteins, cells, tissues and related materials derived from human sources that are used in vitro or ex vivo to assess pharmaco-kinetics properties of drug substances.
In this respect, reports of plasma protein binding study, hepatic metabolism and active substance interaction studies and studies using other human bio-materials shall be provided.

5.2.3. Reports of human pharmaco-kinetic studies
1) The following pharmaco-kinetic characteristics shall be described:

- absorption (rate and extent),
- distribution,
- metabolism,
- excretion.

Clinically significant features including the implication of the kinetic data for the dosage regimen especially for patients at risk, and differences between man and animal species used in the pre clinical studies, shall be described.

In addition to standard multiple-sample pharmaco-kinetics studies, population pharmaco-kinetics analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose- pharmaco-kinetics response relationship. Reports of pharmaco-kinetic and initial tolerability studies in healthy subjects and in patients, reports of pharmaco-kinetic studies to assess effects of intrinsic and extrinsic factors, and reports of population pharmaco-kinetic studies shall be provided.
2) If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.
Pharmaco-kinetic interactions between the active substance and other medicinal products or substances shall be investigated.

5.2.5. Reports of efficacy and safety studies

5.2.5.1. Study reports of controlled clinical sludies pertinent to the claimed indication
In general, clinical trials shall be done as 'controlled clinical trials' if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.
1. As far as possible, and particularly in trials where the effect of the product cannot be objectively measured, steps shall be taken to avoid bias, including methods of randomisation and blinding.
2. The plan of the trial must include a thorough description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomisation, shall be documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.
The safety data shall be reviewed taking into account guidelines published by the European Commission, with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal, and deaths. Any patients or patient groups at increased risk shall be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, frail elderly, people with marked abnormalities of metabolism or excretion etc. The implication of the safety evaluation for the possible uses of the medicinal product shall be described.

5.2.5.2. Study reports of uncontrolled clinical studies reports of analzses of data from more than one study and other clinical study reports
These reports shall be provided.

5.2.6. Reports of post-marketing experience
If the medicinal product is already authorised in third countries, information shall be given in respect of adverse reactions of the medicinal product concerned and medicinal products containing the same active substance(s), in relation to the usage rates if possible.

5.2.7. Case reports forms and individual patient listings
When submitted in accordance with the relevant Guideline published by the EMA, case report forms and individual patient data listings shall be provided and presented in the same order as the clinical study reports and indexed by study.

PART II
SPECIFIC MARKETING AUTHORISATION DOSSIERS AND REQUIREMENTS

Some medicinal products present specific features which are such that all the requirements of the marketing authorisation application dossier as laid down in Part I of this Annex need to be adapted. To take account of these particular situations, an appropriate and adapted format of the dossier shall be followed by applicants.

1. WELL-ESTABLISHED MEDICINAL USE

For medicinal products the active substance(s) of which has/have a 'well-established medicinal use' as referred to Article 32 of the Law, with recognised efficacy and an acceptable level of safety, the following specific rules shall apply.

The applicant shall submit Modules 1, 2 and 3 as described in part I of this Annex.

For Modules 4 and 5, a detailed scientific bibliography shall address non-clinical and clinical characteristics.

The following specific rules shall apply in order to demonstrate the well-established medicinal use:

1) Factors which have to be taken into account in order to establish a well-established medicinal use of constituents of medicinal products are:

- the time over which a substance has been used,
- quantitative aspects of the use of the substance,
- the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and
- the coherence of scientific assessments.

Therefore different periods of time may be necessary for establishing well-established use of different substances. In any case, however, the period of time required for establishing a well established medicinal use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the European Union..

2) The documentation submitted by the applicant should cover all aspects of the safety and/or efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, must be communicated. With respect to the provisions on 'well-established medicinal use' it is in particular necessary to clarify that 'bibliographic reference' to other sources of evidence (post marketing studies, epidemiological studies, etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.

3) Particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking.

4) The non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences.

5) Post-marketing experience with other products containing the same constituents is of particular importance and applicants should put a special emphasis on this issue.

2. ESSENTIALLY SIMILAR MEDICINAL PRODUCTS

1) Applications based upon Article 32 paragraph 4 of the Law shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex provided the applicant has been granted the consent of the holder of the original marketing authorisation to cross refer to the content of his Modules 4 and 5.

2) Applications based upon Article 34 of the Law (essentially similar products i.e. generics) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex together with data showing bio-availability and bio-equivalence with the original medicinal product provided the latter is not a biological medicinal product (see Part II, 4 Similar biological medicinal products).

For these products the non-clinical/clinical overviews/summaries shall particularly focus on the following elements:

- the grounds for claiming essential similarity;
- a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed together with an evaluation of these impurities;
- an evaluation of the bio-equivalence studies or a justification why studies were not performed with respect to the guideline on 'Investigation of Bio-availability and Bio-equivalence';
- an update of published literature relevant to the substance and the present application. It may be acceptable for articles in expert journals to be annotated for this purpose;
- every claim in the summary of product characteristics not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.
- if applicable, additional data in order to demonstrate evidence on the equivalence of safety and efficacy properties of different salts, esters or derivatives of an authorised active substance should be provided by the applicant when he claims essential similarity.

3. ADDITIONAL DATA REQUIRED IN SPECIFIC SITUATIONS

Where the active substance of an essentially similar medicinal product contains the same active part of the molecule as the original authorised product associated with a different salt/ester complex/derivative evidence that there is no change in the pharmaco-kinetics, pharmaco-dynamics and/or in toxicity of the molecule which could change the safety/ efficacy profile shall be demonstrated. Should this not be the case, this substance shall be considered as a new active substance.

Where a medicinal product is intended for a different therapeutic use or presented in a different pharmaceutical form or to be administered by different routes or in different doses or with a different posology, the results of appropriate toxicological and pharmacological tests and/or of clinical trials shall be provided.

4. SIMILAR BIOLOGICAL MEDICINAL PRODUCTS

The provisions of Article 34 of the Law may not be sufficient in the case of biological medicinal products. If the information required in the case of essentially similar products (generics) are not enough for the demonstration similarity between two biological medicinal products, additional data, in particular, the toxicological and clinical profile shall be provided.

When a biological medicinal product as defined in Part I, paragraph 3.2 of this Annex, which refers to an original medicinal product having been granted a marketing authorisation in the European Union, is submitted for a marketing authorisation by an independent applicant after the expiry of data protection period, the following approach shall be applied.

1) Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.

2) Due to the diversity of biological medicinal products, the need for identified studies foreseen in Modules 4 and 5, shall be required by the competent authority, taking into account the specific characteristic of each individual medicinal product.

The general principles to be applied are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by EMA. In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.

5. FIXED COMBINATION MEDICINAL PRODUCTS

Applications based upon 32 paragraph 1 of the Law) shall relate to new medicinal products made of at least two active substances not previously authorised in that combination.

For applications for fixed combination medicinal products a full dossier (Modules 1 to 5) shall be provided for. Where applicable, information regarding the manufacturing sites and safety evaluation of the contamination by adventitious agents shall be provided.

6. DOCUMENTATION FOR APPLICATIONS IN EXCEPTIONAL CIRCUMSTANCES

When, as provided for in Article 43 of the Law, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

1) the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
2) in the present state of scientific knowledge, comprehensive information cannot be provided, or
3) it would be contrary to generally accepted principles of medical ethics to collect such information,

marketing authorisation may be granted subject to certain specific obligations.

These obligations may include the following:

1) the applicant shall complete an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile,
2) the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorised person,
3) the package leaflet and any medical information shall draw the attention of the doctor to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

7. MIXED MARKETING AUTHORISATION APPLICATIONS

Mixed marketing-authorisation applications shall mean marketing-authorisation application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references. All other Modules are in accordance with the structure described in Part I of this Annex. The Agency authority shall decide on accepting the proposed format presented by the applicant on a case by case basis.

PART III

PARTICULAR MEDICINAL PRODUCTS

This Part lays down specific requirements related to the nature of identified medicinal products.

1. BIOLOGICAL MEDICINAL PRODUCTS

1.1. Plasma-derived medicinal product

For medicinal products derived from human blood or plasma and by derogation from the provisions of Module 3, the dossier requirements mentioned in ‘Information related to the starting and raw materials’, for starting materials made of human blood/plasma may be replaced by a Plasma Master File certified in accordance with this Part.

1) Principles

For the purposes of this Annex:

— Plasma Master File shall mean a stand-alone documentation, which is separate from the dossier for marketing authorisation which provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipient and active substance(s), which are part of medicinal products or medical devices referred to in Directive 2000/70/EC amending Council Directive 93/42/EC as regards medical devices incorporating stable derivatives of human blood or human plasma

- Every centre or institution for fractionation/processing of human plasma shall prepare and keep updated the set of detailed relevant data from the documentation on plasma.
- The Plasma Master File shall be submitted to EMA, or the Agency. Where the applicant for a marketing authorisation or the marketing authorisation holder differs from the holder of the Plasma Master File,

the Plasma Master File shall be made available to the applicant or marketing authorisation holder for submission to the competent authority. In any case, the applicant or marketing authorisation holder shall take responsibility for the medicinal product.

- The competent authority that is evaluating the marketing authorisation shall await for EMA to issue the certificate before deciding on the application.
- Any marketing authorisation dossier containing a human plasma-derived constituent shall refer to the Plasma Master File corresponding to the plasma used as a starting/raw material.

2) Content

In accordance with the provisions of the Directive 2002/98/EC, which refers to the requirements for donors and the testing of donations, the Plasma Master File shall include information on the plasma used as starting/raw material, in particular:

1. Plasma origin
   1) information on centres or institutions in which blood/plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections.
   2) information on centres or institutions in which testing of donations and plasma pools is carried out, including inspection and approval status.
   3) selection/exclusion criteria for blood/plasma donors.
   4) system in place which enables the path taken by each donation to be traced from the blood/plasma collection institution through to finished products and vice versa.
2. Plasma quality and safety
   1) compliance with European Pharmacopoeia Monographs.
   2) testing of blood/plasma donations and pools for infectious agents, including information on test methods and, in the case of plasma pools, validation data on the tests used.
   3) technical characteristics of bags for blood and plasma collection, including information on anticoagulants solutions used.
   4) conditions of storage and transport of plasma
   5) procedures for any inventory hold and/or quarantine period.
   6) characterisation of the plasma pools.
3. System in place between the plasma-derived medicinal product manufacturer and/or plasma fractionator/processor on the one hand, and blood/plasma collection and testing centres or institutions on the other hand, which defines the conditions of their interaction and their agreed specifications.

In addition, the Plasma Master File shall provide a list of the medicinal products for which the Plasma Master File is valid, whether the medicinal products have been granted a marketing authorisation or are in the process of being granted such an authorisation, including medicinal products referred to in Article 2 of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

3) Evaluation and Certification

- For medicinal products not yet authorised, the marketing authorisation applicant shall submit a full dossier to a competent authority, which shall be accompanied by a separate Plasma Master File where one does not already exist.
- The Plasma Master File is subject to a scientific and technical evaluation carried out by EMA. A positive evaluation shall result in a certificate of compliance with legislation of the European Union for the Plasma Master File, which shall be accompanied by the evaluation report. The certificate issued shall apply throughout the EU.
- The Plasma Master File shall be updated and re-certified on an annual basis.
- Subsequently introduced changes (variations) of the documentation on plasma that are subject of the Regulation (EEC) No 2309/93 must follow evaluation procedure laid down by the Regulation (EC) No 542/95. Conditions for the assessment of these changes are laid down by Regulation (EC) No 1085/2003.
- As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Plasma Master File on the concerned medicinal product(s).

– By derogation from the provisions of the second indent of the present item (evaluation and certification), where a Plasma Master File corresponds only to blood/plasma-derived medicinal products the marketing authorisation of which is restricted to a single Member State, the scientific and technical evaluation of the said Plasma Master File shall be carried out by the national competent authority of that Member State.

1.2. Vaccines

For vaccines for human use and by derogation from the provisions of Module 3 on active substances, the following requirements when based on the system of the documentation on vaccine antigen system shall apply.

The marketing authorisation application dossier of a vaccine other than human influenza vaccine, shall be required to include a vaccine vntigen documentation for every vaccine antigen that is an active substance of this vaccine.

1) Principles

For the purposes of this Annex:

— Vaccine Antigen documentation shall mean a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information of biological, pharmaceutical and chemical nature concerning each of the active substances, which are part of this 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.

– A vaccine may contain one or several distinct vaccine antigens. There are as many active substances as vaccine antigens present in a vaccine.
– A combined vaccine contains at least two distinct vaccine antigens aimed at preventing a single or several infectious diseases.
– A monovalent vaccine is a vaccine, which contains one vaccine antigen aimed at preventing a single infectious disease.

2) Content

The Vaccine Antigen documentation shall contain the following information extracted from the relevant part (Active substance) of Module 3 on quality data as delineated in Part I of this Annex:

Active Substance

1. General Information, including compliance with the relevant monographs of the European Pharmacopoeia.

2. Information on the manufacture of the active substance: this heading must cover the manufacturing process, information on the starting and raw materials, specific measures on TSEs and safety evaluation of the contamination by adventitious agents and facilities and equipment.

3. Characterisation of the active substance

4. Quality control of the active substance

5. Reference standard and materials

6. Container and closure system of the active substance

7. Stability of the active substance.

3) Evaluation and Certification

– For novel vaccines, which contain a novel vaccine antigen, the applicant shall submit to a competent authority a full marketing-authorisation application dossier including all the Vaccine Antigen documentation corresponding to each single vaccine antigen that is part of the novel vaccine where no documentation already exists for the single vaccine antigen. A scientific and technical evaluation of each Vaccine Antigen documentation shall be carried out by EMA. A positive evaluation shall result in a certificate of compliance to the European legislation for each Vaccine Antigen documentation, which shall be accompanied by the evaluation report. The certificate shall apply throughout the European Union.
– The provisions of the first indent shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of these vaccine antigens are part of vaccines already authorised in the European Union.

- Changes to the content of a Vaccine Antigen documentation for a vaccine authorised in the European Union shall be subject to a scientific and technical evaluation carried out by the EMA in accordance with the procedure laid down in Regulation (EC) No 1085/2003.
  In the case of a positive evaluation EMA shall issue a certificate of compliance with European Community legislation for the Vaccine Antigen documentation. The certificate issued shall apply throughout the European Community.
- By derogation from the provisions of the first, second and third indents of the present item (evaluation and certification), where a Vaccine Antigen documentation corresponds only to a vaccine which is the subject of a marketing authorisation which has not been/will not be granted according to a European Union procedure, and, provided the authorised vaccine includes vaccine antigens which have not been evaluated through a European Union procedure, the scientific and technical evaluation of the said Vaccine Antigen documentation and its subsequent changes, shall be carried out by the national competent authority that has granted the marketing authorisation.
- As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Vaccine Antigen documentation on the concerned medicinal product(s).

2. RADIO-PHARMACEUTICALS AND PRECURSORS

2.1. Radio-pharmaceuticals

For the purposes of this chapter, applications based upon Article 21 of the Law shall provide a full dossier in which the following specific details shall be included:

Module 3

1) In the context of a radio-pharmaceutical kit, which is to be radio-labelled after supply by the manufacturer, the active substance is considered to be that part of the formulation which is intended to carry or bind the radio-nuclide. The description of the manufacturing method of radio-pharmaceutical kits shall include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product. The necessary specifications of the radio-nuclide shall be described in accordance, where relevant, with the general monograph or specific monographs of the European Pharmacopoeia. In addition, any compounds essential for the radio-labelling shall be described. The structure of the radio-labelled compound shall also be described.
For radio-nuclides, the nuclear reactions involved shall be discussed.
In a generator, both mother and daughter radio-nuclides shall be considered as active substances.
2) Details of the nature of the radio-nuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be provided.
3) Starting materials include irradiation target materials.
4) Considerations on chemical/radiochemical purity and its relationship to bio-distribution shall be provided.
5) Radio-nuclide purity, radiochemical purity and specific activity shall be described.
6) For generators, details on the testing for mother and daughter radio-nuclides are required. For generator-eluates, tests for mother radio-nuclides and for other constituents of the generator system shall be provided.
7) The requirement to express the content of active substances in terms of the mass of active entities shall only apply to radio-pharmaceutical kits. For radio-nuclides, radioactivity shall be expressed in Becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated.
8) For kits, the specifications of the finished product shall include tests on performance of products after radio-labelling. Appropriate controls on radiochemical and radio-nuclidic purity of the radio-labelled compound shall be included. Any material essential for radio-labelling shall be identified and assayed.
9) Information on stability shall be given for radio-nuclide generators, radio-nuclide kits and radio-labelled products. The stability during use of radio-pharmaceuticals in multi-dose vials shall be documented.

Module 4

It is appreciated that toxicity may be associated with a radiation dose. In diagnosis, this is a consequence of the use of radio-pharmaceuticals; in therapy, it is the property desired. The evaluation of safety and efficacy of radio-pharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects. Organ/tissue exposure to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognised system by a particular route of administration.

Module 5
The results of clinical trials shall be provided where applicable otherwise justified in the clinical overviews.

2.2. Radio-pharmaceutical precursors for radio-labelling purposes
In the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes, the primary objective shall be to present information which would address the possible consequences of poor radio-labeling efficiency or in vivo dissociation of the radio-labeled conjugate, i.e. questions related to the effects produced in the patient by free radio-nuclide. In addition, it is also necessary to present relevant information relating to occupational hazards, i.e. radiation exposure to hospital staff and to the environment. In particular, the following information where applicable shall be provided:

Module 3
The provisions of Module 3 shall apply to the registration of radio-pharmaceutical precursors as defined in Chapter 2.1. indents 1 to 9 where applicable.

Module 4
Concerning single dose and repeat dose toxicity, the results of studies carried out in conformity with the provisions related to good laboratory practice laid down in Council Directives 87/18/EEC and 88/320/EEC shall be provided, unless otherwise justified.
Mutagenicity studies on the radio-nuclide are not considered to be useful in this particular case.
Information relating to the chemical toxicity and disposition of the relevant 'cold' nuclide shall be presented.

Module 5
Clinical information generated from clinical studies using on the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes.
However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented.

3. HOMEOPATHIC MEDICINAL PRODUCTS
This section sets out specific provisions on the application of Modules 3 and 4 to homeopathic medicinal products as defined in Article 24 of the Law.

Module 3
The provisions of Module 3 shall apply to the documents submitted in accordance with Article 24 of the Law in the simplified registration of homeopathic medicinal products as well as to the documents for authorisation of other homeopathic medicinal products with the following modifications.
1) Terminology
The Latin name of the homeopathic stock described in the marketing authorisation application dossier must be in accordance with the Latin title of the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State. Where relevant the traditional name(s) used in each Member State shall be provided.
2) Control of starting materials

The particulars and documents on the starting materials, i.e. all of the materials used including raw materials and intermediates up to the final dilution to be incorporated into the finished 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 medicinal product. If possible, an assay is required if toxic components are present and if the quality cannot be controlled on final dilution to be incorporated because of the high dilution degree. Every step of the manufacturing process from the starting materials up to the final dilution to be incorporated into the finished medicinal product must be fully described.
In case dilutions are involved, these dilution steps should be done in accordance with the homeopathicmanufacturing methods laid down in the relevant monograph of the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State.
3) Control tests on the finished medicinal product
The general quality requirements shall apply to the homeopathic finished medicinal products, any exception needs to be duly justified by the applicant.
Identification and assay of all the toxicologically relevant constituents shall be carried out. If it can be justified that an identification and/or an assay on all the toxicologically relevant constituents is not possible e.g. due to their dilution in the finished medicinal product the quality shall be demonstrated by complete validation of the manufacturing and dilution process.
d) Stability tests
The stability of the finished medicinal product must be demonstrated. Stability data from the homeopathic stocks are generally transferable to dilutions/triturations 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.
Module 4
The provisions of Module 4 shall apply to the simplified registration of homeopathic medicinal products referred to in Article 24 of the Law with the following specifications.
Any missing information must be justified, e.g., justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking.

4. HERBAL MEDICINAL PRODUCTS
Applications for herbal medicinal products shall provide a full dossier in which the following specific details shall be included.
Module 3
The provisions of Module 3, including compliance with monograph(s) of the European Pharmacopoeia, shall apply to the authorisation of herbal medicinal products. The state of scientific knowledge at the time when the application is lodged shall be taken into account.
The following aspects specific to herbal medicinal products shall be considered:
(1) Herbal substances and herbal preparations
For the purposes of this Annex the terms ‘herbal substances and preparations’ shall be considered equivalent to the terms ‘herbal drugs and herbal drug preparations’, as defined in the European Pharmacopoeia.
With respect to the nomenclature of the herbal substance, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal substance, the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.
With respect to the nomenclature of the herbal preparation, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal preparation, the ratio of the herbal substance to the herbal preparation, the extraction solvent(s), the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.
To document the section of the structure for herbal substance(s) and herbal preparation(s) where applicable, the physical form, the description of the constituents with known therapeutic activity or markers (molecular

formula, relative molecular mass, structural formula, including relative and absolute stereo-chemistry) as well as other constituents shall be provided.
To document the section on the manufacturer of the herbal substance, the name, address, and responsibility of each supplier, including contractors, and each proposed site or facility involved in production/collection and control of the herbal substance shall be provided, where appropriate.
To document the section on the manufacture of the herbal preparation, the name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation shall be provided, where appropriate.
With respect to the description of manufacturing process and process controls for the herbal substance, information shall be provided to adequately describe the plant production and plant collection, including the geographical source of the medicinal plant and cultivation, harvesting, drying and storage conditions.
With respect to the description of manufacturing process and process controls for the herbal preparation, information shall be provided to adequately describe the manufacturing process of the herbal preparation, including description of the processing, solvents and reagents, purification stages and standardisation.
With respect to the manufacturing process development, a brief summary describing the development of the herbal substances and herbal preparation(s) where applicable shall be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the herbal substances and herbal preparation(s) where applicable used in supporting bibliographic data and the herbal substances and herbal preparation(s), where applicable, contained as active substance(s) in the herbal medicinal product applied for shall be discussed, where appropriate.
With respect to the elucidation of the structure and other characteristics of the herbal substance, information on the botanical, macroscopical, microscopical, phyto-chemical characterisation, and biological activity if necessary, shall be provided.
With respect to the elucidation of the structure and other characteristics of the herbal preparation, information on the phyto- and physicochemical characterisation, and biological activity if necessary, shall be provided.
The specifications for the herbal substances and herbal preparation(s) where applicable shall be provided.
The analytical procedures used for testing the herbal substances and herbal preparation(s) where applicable shall be provided.
With respect to the validation of analytical procedures, analytical validation information, including experimental data for the analytical procedures used for testing the herbal substances and herbal preparation(s) where applicable shall be provided.
With respect to batch analyses, description of batches and results of batch analyses for the herbal substances and herbal preparation(s) where applicable shall be provided, including those for pharmacopoeial substances.
Justification for the specifications of the herbal substances and herbal preparation(s) where applicable shall be provided.
Information on the reference standards or reference materials used for testing of the herbal substances and herbal preparation(s) where applicable shall be provided.
Where the herbal substance or the herbal preparation is the subject of a monograph, the applicant can apply for a certificate of suitability that was granted by the European Directorate for the Quality of Medicines.
2) Herbal medicines
With respect to the formulation development, a brief summary describing the development of the herbal medicinal product should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the products used in supporting bibliographic data and the herbal medicinal product applied for shall be discussed, where appropriate.

5. ORPHAN MEDICINAL PRODUCTS
- In the case of an orphan medicinal product in the meaning of Regulation (EC) No 141/2000, general provisions of Part II-6 (exceptional circumstances) can be applied. The applicant shall then justify in the non-clinical and clinical summaries the reasons for which it is not possible to provide the complete

information and shall provide a justification of the benefit/risk balance for the orphan medicinal product concerned.
- When an applicant for an marketing authorisation for an orphan medicinal product invokes the provisions of Article 32 of the Law and Part II-1 of this Annex (well-established medicinal use), the systematic and documented use of the concerned substance can refer — as way of derogation — to the use of that substance in accordance with the provisions of Article 5 of the Directive 2001/83.

PART IV
ADVANCED THERAPY MEDICINAL PRODUCTS
1. INTRODUCTION
Marketing authorisation applications for advanced therapy medicinal products, as defined in item (a) of Article 2(1) of Regulation (EC) No 1394/2007, shall follow the format requirements (Modules 1, 2, 3, 4 and 5) described in Part I of this Annex.
The technical requirements for Modules 3, 4 and 5 for biological medicinal products, as described in Part I of this Annex, shall apply. The specific requirements for advanced therapy medicinal products described in sections 3, 4 and 5 of this part explain how the requirements in Part I apply to advanced therapy medicinal products. In addition, where appropriate and taking into account the specificities of advanced therapy medicinal products, additional requirements have been set.
Due to the specific nature of advanced therapy medicinal products, a risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorisation application, in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products referred to in item 4 of the 'Introduction and general principles'.
The risk analysis may cover the entire development. Risk factors that may be considered include: the origin of the cells (autologous, allogeneic, xenogeneic), the ability to proliferate and/or differentiate and to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the nature of the gene therapy medicinal products, 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 and the mode of administration or use.
Relevant available non-clinical and clinical data or experience with other, related advanced therapy medicinal products may also be considered in the risk analysis.
Any deviation from the requirements of this Annex shall be scientifically justified in Module 2 of the application dossier. The risk analysis described above, when applied, shall also be included and described in Module 2. In this case, the methodology followed, the nature of the identified risks and the implications of the risk based approach for the development and evaluation program shall be discussed and any deviations from the requirements of this Annex resulting from the risk analysis shall be described.

2. DEFINITIONS
For the purposes of this Annex, in addition to the definitions laid down in Regulation (EC) No 1394/2007, the definitions set out in sections 2.1 and 2.2 shall apply.
2.1. Gene therapy medicinal product
Gene therapy medicinal product means a biological medicinal product which has the following characteristics:
1) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;
2) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.
Gene therapy medicinal products shall not include vaccines against infectious diseases.
2.2. Somatic cell therapy medicinal product
Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

1) contains or consists of cells or tissues that have been subject to substantial manipulation 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;
2) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.
For the purposes of item (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.

3. SPECIFIC REQUIREMENTS REGARDING MODULE 3

3.1. Specific requirements for all advanced therapy medicinal products

A description of the traceability system that the marketing authorisation holder intends to establish and maintain to ensure that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used, shall be provided.
The traceability system shall be complementary to, and compatible with, the requirements established in Directive 2004/23/EC of the European Parliament as regards human cells and tissues other than blood cells, and Directive 2002/98/EC, as regards human blood cells.

3.2. Specific requirements for gene therapy medicinal products

3.2.1. Introduction: finished product, active substance and starting materials

3.2.1.1. Gene therapy medicinal product containing recombinant nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es)

The finished medicinal product shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es) formulated in their final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.
The active substance shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es).

3.2.1.2. Gene therapy medicinal product containing genetically modified cells

The finished medicinal product shall consist of genetically modified cells formulated in the final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.
The active substance shall consist of cells genetically modified by one of the products described in section 3.2.1.1 above.

3.2.1.3. In the case of products consisting of viruses or viral vectors, the starting materials shall be the components from which the viral vector is obtained, i.e. the master virus vector seed or the plasmids used to transfect the packaging cells and the master cell bank of the packaging cell line.

3.2.1.4. In the case of products consisting of plasmids, non-viral vectors and genetically modified microorganism(s) other than viruses or viral vectors, the starting materials shall be the components used to generate the producing cell, i.e. the plasmid, the host bacteria and the master cell bank of recombinant microbial cells.

3.2.1.5. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the

human or animal cells. The principles of good manufacturing practice shall apply from the bank system used to produce the vector onwards.

3.2.2. Specific requirements
In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Annex, the following requirements shall apply:
1) 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 human or animal cells and, as applicable, subsequent culture and preservation of the genetically modified cells, taking into consideration the possible absence of purification steps;
2) 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;
3) 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;
4) for plasmids, quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product;
5) 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 somatic cell therapy medicinal products and tissue engineered products (see section 3.3) shall apply.

3.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products

3.3.1. Introduction: finished product, active substance and starting materials
The finished medicinal product shall consist of the active substance formulated in its immediate container for the intended medical use, and in its final combination for combined advanced therapy medicinal products.
The active substance shall be composed of the engineered cells and/or tissues.
Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) which are combined with manipulated cells of which they form an integral part shall be considered as starting materials, even if not of biological origin.
Materials used during the manufacture of the active substance (e.g. culture media, growth factors) and that are not intended to form part of the active substance shall be considered as raw materials.

3.3.2. Specific requirements
In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Annex, the following requirements shall apply:

3.3.2.1. Starting materials
1) Summary information shall be provided on donation, procurement and testing of the human tissue and cells used as starting materials and made in accordance with Directive 2004/23/EC. If non-healthy cells or tissues (e.g. cancer tissue) are used as starting materials, their use shall be justified.
2) If allogeneic cell populations are being pooled, the pooling strategies and measures to ensure traceability shall be described.
3) The potential variability introduced through the human or 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.
4) For xenogeneic cell-based products, information on the source of animals (such as geographical origin, animal husbandry, age), specific acceptance criteria, measures to prevent and monitor infections in the

source/donor animals, testing of the animals for infectious agents, including vertically transmitted micro-organisms and viruses, and evidence of the suitability of the animal facilities shall be provided.
5) For cell-based products derived from genetically modified animals, the specific characteristics of the cells related to the genetic modification shall be described. A detailed description of the method of creation and the characterisation of the transgenic animal shall be provided.
6) For the genetic modification of the cells, the technical requirements specified in section 3.2 shall apply.
7) The testing regimen of any additional substance (scaffolds, matrices, devices, biomaterials, biomolecules or other components), which are combined with engineered cells of which they form an integral part, shall be described and justified.
8) For scaffolds, matrices and devices that fall under the definition of a medical device or active implantable medical device, the information required under section 3.4 for the evaluation of the combined advanced therapy medicinal product shall be provided.

3.3.2.2. Manufacturing process
1) The manufacturing process shall be validated to ensure batch and process consistency, functional integrity of the cells throughout manufacturing and transport up to the moment of application or administration, and proper differentiation state.
2) If cells are grown directly inside or on a matrix, scaffold or device, information shall be provided on the validation of the cell culture process with respect to cell-growth, function and integrity of the combination.
3.3.2.3. Characterisation and control strategy
1) Relevant information shall be provided on the characterisation of the cell population or cell mixture in terms of identity, purity (e.g. adventitious microbial agents and cellular contaminants), viability, potency, karyology, tumourigenicity and suitability for the intended medicinal use. The genetic stability of the cells shall be demonstrated.
2) Qualitative and, where possible, quantitative information on product- and process-related impurities, as well as on any material capable of introducing degradation products during production, shall be provided. The extent of the determination of impurities shall be justified.
3) If certain release tests cannot be performed on the active substance or finished product, but only on key intermediates and/or as in-process testing, this shall be justified.
4) Where biologically active molecules (such as growth factors, cytokines) are present as components of the cell-based product, their impact and interaction with other components of the active substance shall be characterised.
5) 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 these cell-based products. Where needed, non-clinical investigations shall complement the physicochemical characterisation.

3.3.2.4. Excipients
For excipients used in cell or tissue-based medicinal products (e.g. the components of the transport medium), the requirements for novel excipients, as laid down in Part I of this Annex, shall apply, unless data exists on the interactions between the cells or tissues and the excipients.

3.3.2.5. Developmental studies
The description of the development program shall address the choice of materials and processes. In particular, the integrity of the cell population as in the final formulation shall be discussed.

3.3.2.6. Reference materials
A reference standard, relevant and specific for the active substance and/or the finished product, shall be documented and characterised.

3.4. Specific requirements for advanced therapy medicinal products containing devices

3.4.1. Advanced therapy medicinal product containing devices as referred to in Article 7 of Regulation (EC) No 1394/2007
A description of the physical characteristics and performance of the product and a description of the product design methods shall be provided.
The interaction and compatibility between genes, cells and/or tissues and the structural components shall be described.

3.4.2. Combined advanced therapy medicinal products as defined in Article 2 paragraph 1 item d of Regulation (EC) No 1394/2007
For the cellular or tissue part of the combined advanced therapy medicinal product, the specific requirements for somatic cell therapy medicinal products and tissue engineered products set out in section 3.3 shall apply and, in the case of genetically modified cells, the specific requirements for gene therapy medicinal products set out in section 3.2 shall apply.
The medical device or the active implantable medical device may be an integral part of the active substance.
Where the medical device or active implantable medical device is combined with the cells at the time of the manufacture or application or administration of the finished products, they shall be considered as an integral part of the finished product.
Information related to the medical device or the active implantable medical device (which is an integral part of the active substance or of the finished product) which is relevant for the evaluation of the combined advanced therapy medicinal product shall be provided. This information shall include:
1) information on the choice and intended function of the medical device or implantable medical device and demonstration of compatibility of the device with other components of the product;
2) evidence of conformity of the medical device part with the essential requirements laid down in Annex I to Council Directive 93/42/EEC, or of conformity of the active implantable device part with the essential requirements laid down in Annex 1 to Council Directive 90/385/EEC;
3) where applicable, evidence of compliance of the medical device or implantable medical device with the BSE/TSE requirements laid down in Commission Directive 2003/32/EC;
4) where available, the results of any assessment of the medical device part or the active implantable medical device part by a notified body in accordance with Directive 93/42/EEC or Directive 90/385/EEC.
The notified body which has carried out the assessment referred to in item 4 of this section shall make available on request of the competent authority assessing the application, any information related to the results of the assessment in accordance with Directive 93/42/EEC or Directive 90/385/EEC. This may include information and documents contained in the conformity assessment application concerned, where necessary for the evaluation of the combined advanced therapy medicinal product as a whole.

4. SPECIFIC REQUIREMENTS REGARDING MODULE 4

4.1. Specific requirements for all advanced therapy medicinal products
The requirements of Part I, Module 4 of this Annex on the pharmacological and toxicological testing of medicinal products may not always be appropriate due to unique and diverse structural and biological properties of advanced therapy medicinal products. The technical requirements in sections 4.1, 4.2 and 4.3 below explain how the requirements in Part I of this Annex apply to advanced therapy medicinal products. Where appropriate and taking into account the specificities of advanced therapy medicinal products, additional requirements have been set.
The rationale for the non-clinical development and the criteria used to choose the relevant species and models (in vitro and in vivo) shall be discussed and justified in the non-clinical overview. The chosen animal model(s) may include immuno-compromised, knockout, humanised or transgenic animals. The use of homologous models (e.g. mouse cells analysed in mice) or disease mimicking models shall be considered, especially for immunogenicity and immunotoxicity studies.
In addition to the requirements of Part I, the safety, suitability and biocompatibility of all structural components (such as matrices, scaffolds and devices) and any additional substances (such as cellular products, biomolecules, biomaterials, and chemical substances), which are present in the finished product,

shall be provided. Their physical, mechanical, chemical and biological properties shall be taken into account.

4.2. Specific requirements for gene therapy medicinal products
In order to determine the extent and type of non-clinical studies necessary to determine the appropriate level of non-clinical safety data, the design and type of the gene therapy medicinal product shall be taken into account.

4.2.1. Pharmacology
1) In vitro and in vivo studies of actions relating to the proposed therapeutic use (i.e. pharmacodynamic 'proof of concept' studies) shall be provided using models and relevant animal species designed to show that the nucleic acid sequence reaches its intended target (target organ or cells) and provides its intended function (level of expression and functional activity). The duration of the nucleic acid sequence function and the proposed dosing regimen in the clinical studies shall be provided.
2) Target selectivity: When the gene therapy medicinal product is intended to have a selective or target-restricted functionality, studies to confirm the specificity and duration of functionality and activity in target cells and tissues shall be provided.

4.2.2. Pharmacokinetics
1) Biodistribution studies shall include investigations on persistence, clearance and mobilisation. Biodistribution studies shall additionally address the risk of germline transmission.
2) Investigations of shedding and risk of transmission to third parties shall be provided with the environmental risk assessment, unless otherwise duly justified in the application on the basis of the type of product concerned.

4.2.3. Toxicology
1) Toxicity of the finished gene therapy medicinal product shall be assessed. In addition, depending on the type of product, individual testing of active substance and excipients shall be taken into consideration, the in vivo effect of expressed nucleic acid sequence-related products which are not intended for the physiological function shall be evaluated.
2) Single-dose toxicity studies may be combined with safety pharmacology and pharmacokinetic studies, e.g. to investigate persistence.
3) Repeated dose toxicity studies shall be provided when multiple dosing of human subjects is intended. The mode and scheme of administration shall closely reflect the planned clinical dosing. For those cases where single dosing may result in prolonged functionality of the nucleic acid sequence in humans, repeated toxicity studies shall be considered. The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. A justification for the duration shall be provided.
4) Genotoxicity shall be studied. However, standard genotoxicity studies shall only be conducted when they are necessary for testing a specific impurity or a component of the delivery system.
5) Carcinogenicity shall be studied. Standard lifetime rodent carcinogenicity studies shall not be required. However, depending on the type of product, the tumourigenic potential shall be evaluated in relevant in vivo/in vitro models.
6) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, unless otherwise duly justified in the application on the basis of the type of product concerned.
7) Additional toxicity studies
— Integration studies: integration studies shall be provided for any gene therapy medicinal product, unless the lack of these studies is scientifically justified, e.g. because nucleic acid sequences will not enter into the cell nucleus. For gene therapy medicinal products not expected to be capable of integration, integration studies shall be performed, if biodistribution data indicate a risk for germline transmission.

— Immunogenicity and immunotoxicity: potential immunogenic and immunotoxic effects shall be studied.

4.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products

4.3.1. Pharmacology

1) The primary pharmacological studies shall be adequate to demonstrate the proof of concept. The interaction of the cell-based products with the surrounding tissue shall be studied.

2) The amount of product needed to achieve the desired effect/the effective dose, and, depending on the type of product, the frequency of dosing shall be determined.

3) Secondary pharmacological studies shall be taken into account to evaluate potential physiological effects that are not related to the desired therapeutic effect of the somatic cell therapy medicinal product, of the tissue engineered product or of additional substances, as biologically active molecules besides the protein(s) of interest might be secreted or the protein(s) of interest could have unwanted target sites.

4.3.2. Pharmacokinetics

1) Conventional pharmacokinetic studies to investigate absorption, distribution, metabolism and excretion shall not be required. However, parameters such as viability, longevity, distribution, growth, differentiation and migration shall be investigated, unless otherwise duly justified in the application on the basis of the type of product concerned.

2) For somatic cell therapy medicinal products and tissue engineered products, producing systemically active biomolecules, the distribution, duration and amount of expression of these molecules shall be studied.

4.3.3. Toxicology

1) The toxicity of the finished product shall be assessed. Individual testing of active substances, excipients, additional substances and any process-related impurities shall be taken into consideration.

2) The duration of observations may be longer than in standard toxicity studies and the anticipated lifespan of the medicinal product, together with its pharmacodynamic and pharmacokinetic profile, shall be taken into consideration. A justification of the duration shall be provided.

3) Conventional carcinogenicity and genotoxicity studies shall not be required, except with regard to the tumourigenic potential of the product.

4) Potential immunogenic and immunotoxic effects shall be studied.

5) In the case of cell-based products containing animal cells, the associated specific safety concerns such as transmission to humans of xenogeneic pathogens shall be addressed.

5. SPECIFIC REQUIREMENTS REGARDING MODULE 5

5.1. Specific requirements for all advanced therapy medicinal products

5.1.1. The specific requirements in this section of Part IV are additional requirements to those set in Module 5 in Part I of this Annex.

5.1.2. Where the clinical application of advanced therapy medicinal products requires specific concomitant therapy and involve surgical procedures, the therapeutic procedure as a whole shall be investigated and described. Information on the standardisation and optimisation of those procedures during clinical development shall be provided.

Where medical devices used during the surgical procedures for application, implantation or administration of the advanced therapy medicinal product may have an impact on the efficacy or safety of the advanced therapy product, information on these devices shall be provided.

Specific expertise required to carry out the application, implantation, administration or follow-up activities shall be defined. Where necessary, the training plan of health care professionals on the use, application, implantation or administration procedures of these products shall be provided.

5.1.3. Given that, due to the nature of advanced therapy medicinal products, their manufacturing process may change during clinical development, additional studies to demonstrate comparability may be required.

5.1.4. During clinical development, risks arising from potential infectious agents or the use of material derived from animal sources and measures taken to reduce such risk shall be addressed.

5.1.5. Dose selection and schedule of use shall be defined by dose-finding studies.

5.1.6. The efficacy of the proposed indications shall be supported by relevant results from clinical studies using clinically meaningful endpoints for the intended use. In certain clinical conditions, evidence of long-term efficacy may be required. The strategy to evaluate long-term efficacy shall be provided.

5.1.7. A strategy for the long-term follow-up of safety and efficacy shall be included in the risk management plan.

5.1.8. For combined advanced therapy medicinal products, the safety and efficacy studies shall be designed for and performed on the combined product as a whole.

5.2. Specific requirements for gene therapy medicinal products

5.2.1. Human pharmacokinetic studies
Human pharmacokinetic studies shall include the following aspects:
1) shedding studies to address the excretion of the gene therapy medicinal products;
2) biodistribution studies;
3) pharmacokinetic studies of the medicinal product and the gene expression moieties (e.g. expressed proteins or genomic signatures).

5.2.2. Human pharmacodynamic studies
Human pharmacodynamic studies shall address the expression and function of the nucleic acid sequence following administration of the gene therapy medicinal product.

5.2.3. Safety studies
Safety studies shall address the following aspects:
1) emergence of replication competent vector;
2) emergence of new strains;
3) reassortment of existing genomic sequences;
(4) neoplastic proliferation due to insertional mutagenicity.
5.3. Specific requirements for somatic cell therapy medicinal products

5.3.1. Somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s)
For somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s), the pharmacokinetic profile (in particular distribution, duration and amount of expression) of those molecules shall be addressed, if feasible.

5.3.2. Biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components
The biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components shall be addressed during the clinical development.

5.3.3. Safety studies
Safety studies shall address the following aspects:
1) distribution and engrafting following administration;
2) ectopic engraftment;

3) oncogenic transformation and cell/tissue lineage fidelity.

5.4. Specific requirements for tissue engineered products

5.4.1. Pharmacokinetic studies
Where conventional pharmacokinetic studies are not relevant for tissue engineered products, the biodistribution, persistence and degradation of the tissue engineered product components shall be addressed during the clinical development.

5.4.2. Pharmacodynamic studies
Pharmacodynamic studies shall be designed and tailored to the specificities of tissue engineered products. The evidence for the 'proof of concept' and the kinetics of the product to obtain the intended regeneration, repairing or replacement shall be provided. Suitable pharmacodynamic markers, related to the intended function(s) and structure shall be taken into account.

5.4.3. Safety studies
Section 5.3.3 shall apply.

Annex 3

CHEMICAL, PHARMACEUTICAL AND ANALYTICAL STANDARDS, SAFETY AND RESIDUE TESTS, PRE-CLINICAL AND CLINICAL TRIALS IN RESPECT OF TESTING OF VETERINARY MEDICINAL PRODUCTS

TABLE OF CONTENTS

1.1.3. Physico-chemical characteristics liable to affect bioavailability
1.2.Excipients
1.3.Container-closure systems
1.3.1. Active substance
1.3.2. Finished Product
1.4.Substances of biological origin

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

E.TESTS ON THE FINISHED PRODUCT

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

F.STABILITY TEST

1. Active substances(s)
2. Finished product

G.OTHER INFORMATION

PART 3:Safety and residues tests

A. Safety tests
CHAPTER I: PERFORMANCE OF TESTS

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

2.1.Pharmacodynamics
2.2.Pharmacokinetics

3. Toxicology

3.1.Single-dose toxicity
3.2.Repeat-dose toxicity
3.3.Tolerance in the target species
3.4.Reproductive toxicity including developmental toxicity
3.4.1. Study of the effects on reproduction
3.4.2. Study of developmental toxicity
3.5.Genotoxicity
3.6.Carcinogenicity
3.7.Exceptions

4. Other requirements

4.1.Special studies
4.2.Microbiological properties of residues
4.2.1. Potential effects on the human gut flora
4.2.2. Potential effects on the microorganisms used for industrial food processing
4.3.Observations in humans
4.4.Development of resistance

5. User safety
6. Environmental risk assessment

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

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

CHAPTER II: PRESENTATION OF PARTICULARS AND DOCUMENTS

B. Residue tests
CHAPTER I: PERFORMANCE OF TESTS
1. Introduction
2. Metabolism and residue kinetics
2.1.Pharmacokinetics (absorption, distribution, metabolism, excretion)
2.2.Depletion of residues
3. Residue analytical method

CHAPTER II:PRESENTATION OF PARTICULARS AND DOCUMENTS
1. Identification of the product

PART 4: Pre-clinical and clinical trial

CHAPTER I: PRE-CLINICAL REQUIREMENTS
A. Pharmacology
A.1. Pharmacodynamics
A.2. Development of resistance
A.3. Pharmacokinetics

B. Tolerance in the target animal species

CHAPTER II:CLINICAL REQUIREMENTS
1. General principles
2. Conduct of clinical trials

CHAPTER III:PARTICULARS AND DOCUMENTS
1. Results of pre-clinical trials
2. Results of clinical trials

TITLE II- Requirements for immunological veterinary medicinal products

PART 1:Summary of the dossier
A. ADMINISTRATIVE INFORMATION
B. SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET
C. DETAILED AND CRITICAL SUMMARIES

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

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS
1. Qualitative particulars
2. ‘Usual terminology’
3. Quantitative particulars
4. Product development

B.DESCRIPTION OF MANUFACTURING METHOD

C.PRODUCTION AND CONTROL OF STARTING MATERIALS

1. Starting materials listed In Pharmacopoeias
2. Starting materials not listed in a pharmacopoeia

2.1.Starting materials of biological origin

2.2.Starting materials of non-biological origin

D.CONTROL TESTS DURING THE MANUFACTURING PROCESS

E.CONTROL TESTS ON THE FINISHED PRODUCT

1. General characteristics of the finished product
2. Identification of active substance(s)
3. Batch titre or potency
4. Identification and assay of adjuvants
5. Identification and assay of excipient components
6. Safety tests
7. Sterility and purity test
8. Residual humidity
9. Inactivation

F. BATCH TO BATCH CONSISTENCY

G. STABILITY TESTS

H. OTHER INFORMATION

PART 3:SAFETY TESTS

A. INTRODUCTION AND GENERAL REQUIREMENTS

B. LABORATORY TESTS

1.Safety of the administration of one dose
2.Safety of one administration of an overdose
3.Safety of the repeated administration of one dose
4.Examination of reproductive performance
5.Examination of immunological functions
6.Special requirements for live vaccines
6.1.Spread of the vaccine strain
6.2.Dissemination in the vaccinated animal
6.3.Reversion to virulence of attenuated vaccines
6.4.Biological properties of the vaccine strain
6.5.Recombination or genomic reassortment of strains
7.User safety
8.Study of residues
9.Interactions

C.FIELD STUDIES

D.ENVIRONMENTAL RISK ASSESSMENT

E.ASSESSMENT REQUIRED FOR VETERINARY MEDICINAL PRODUCTS CONTAINING OR CONSISTING OF GENETICALLY MODIFIED ORGANISMS

PART 4: EFFICACY TESTS

CHAPTER I
1. General principles
2. Performance of trials

CHAPTER II
A.General requirements
B.Laboratory trials
C.Field trials

PART 5: PARTICULARS AND DOCUMENTS
A.INTRODUCTION
B.LABORATORY STUDIES
C.FIELD STUDIES

PART 6:BIBLIOGRAPHICAL REFERENCES

TITLE III - Requirements for specific marketing authorisation applications
1. Generic veterinary medicinal products
2. Similar biological veterinary medicinal products
3. Well-established veterinary use
4. Combination veterinary medicinal products
5. Informed consent applications
6. Documentation for applications in exceptional circumstances
7. Mixed marketing authorisation applications

TITLE IV - Requirements for marketing authorisation applications for particular veterinary medicinal products
1.Immunological veterinary medicinal products
2.Homeopathic veterinary medicinal products

INTRODUCTION AND GENERAL PRINCIPLES

1)The particulars and documents accompanying an application for marketing authorisation pursuant to Articles 12 to 18 of this rulebook shall be presented in accordance with the requirements set out in this Annex and the guidance of the European Commission (The rules governing medicinal products in the European Union, Volume 6 B, Notice to applicants, Veterinary medicinal products, Presentation and Contents of the Dossier).

2) In assembling the dossier for application for marketing authorisation, applicants shall also take into account the current state of veterinary medicinal knowledge and the scientific guidelines relating to the quality, safety and efficacy of veterinary medicinal products published by the EMA and the other pharmaceutical guidelines of the European Union published by the European Commission.

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

quality, safety and efficacy parts of the dossier, all relevant monographs including general monographs and the general chapters of the European Pharmacopoeia are applicable.

4) The manufacturing process shall comply with the requirements of the European Commission Directive on Good Manufacturing Practice and guidance of the Good Manufacturing Practice published by the European Commission (EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines).

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

6) Pharmacological, toxicological, residue and safety tests shall be carried out in conformity with the provisions related to Good Laboratory Practice (GLP) laid down in legislation on chemical substances.

7) Member States shall ensure that all experiments on animals are conducted in accordance with European Union legislation on the protection of animals used for scientific purposes.

8) In order to monitor the risk/benefit assessment, any new information not in the original application and all pharmacovigilance information shall be submitted. After marketing authorisation has been granted, any change to the content of the dossier shall be submitted as defined in article 21 to 37 of this Rulebook.

9) The environmental risk assessment for veterinary medicinal products containing or consisting of Genetically Modified Organisms (GMOs) in accordance with the legislation regulates Genetically Modified Organisms shall be provided in the dossier.

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

This Annex is divided in four titles:

Title I describes the standardised requirements for applications for veterinary medicinal products other than immunological veterinary medicinal products
Title II describes the standardised requirements for applications for immunological veterinary medicinal products
Title III describes specific types of marketing authorisation dossiers and requirements
Title IV describes the dossier requirements for particular types of veterinary medicinal products.

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

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

PART 1: SUMMARY OF THE DOSSIER

A. ADMINISTRATIVE INFORMATION

The veterinary medicinal product, which is the subject of the application, shall be identified by its name and by the name of the active substance(s), the strength, the pharmaceutical form, the route and method of

administration and a description of the final presentation of the product, including packaging, labelling and package leaflet.

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

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

Annexed to the administrative information shall be a document showing that the manufacturer is authorised to produce the veterinary medicinal products concerned, together with a list of countries in which authorisation has been granted, copies of all the summaries of product characteristics as approved by European Union member states and a list of countries in which an application has been submitted or refused.

B. SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The applicant shall propose a summary of the product characteristics, in accordance with the Annex 1 B) of this Rulebook.

A proposed labelling text for the immediate and outer packaging shall be provided in accordance with the separate legal act regulates the contents and manner of labelling packaging of a veterinary medicinal product, together with a package leaflet where one is required pursuant the separate legal act regulates the contents and manner of labelling packaging of a veterinary medicinal product. In addition the applicant shall provide one or more specimens or mock-ups of the final presentation(s) of the veterinary medicinal product in at least one of the official languages in Montenegro. The mock-up may be provided in black and white and electronically where prior agreement from the Agency has been obtained.

C. DETAILED AND CRITICAL SUMMARIES

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

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

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

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

Where the active substance has been included in a medicinal product for human use authorised in accordance with the requirements of Annex 2 to this rulebook, the overall quality summary provided for in

Module 2, section 2.3 of that Annex may replace the summary regarding the documentation related to the active substance or the product, as appropriate.

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

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

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

Basic principles and requirements

The particulars and documents on the results on pharmaceutical (physico-chemical, biological or microbiological) tests which shall accompany the application for marketing authorisation shall be submitted in accordance with the requirements below.

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

All monographs, including general monographs and general chapters of the European Pharmacopoeia, or failing that, of a European Union Member State are applicable.

All test procedures shall fulfill the criteria for analysis and control of the quality of the starting materials and the finished product and should take account of established guidance and requirements. The results of the validation studies shall be provided.

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

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

In cases where the active substance has been included in a medicinal product for human use authorised in accordance with the requirements of Annex 2 to this rulebook the chemical, pharmaceutical and biological/microbiological information provided for in Module 3 of that Annex may replace the documentation related to the active substance or the finished product, as appropriate.

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

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

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

1. Qualitative particulars

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

1) the active substance(s),

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

3) the constituents, intended to be ingested or otherwise administered to animals, of the outer covering of the veterinary medicinal products, such as capsules, gelatine capsules.

These particulars shall be supplemented by any relevant data concerning the immediate packaging and if relevant the secondary packaging and, where appropriate, its manner of closure, together with details of devices with which the medicinal product will be used or administered and which will be supplied with the medicinal product.

2. Usual terminology

The usual terminology to be used in describing the constituents of veterinary medicinal products means:

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

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

3) in respect of colouring matter, designation by the 'E' code assigned to them by separate legal act regulates food additives.

3. Quantitative particulars

3.1. In order to give "quantitative particulars" of all the active substances of the veterinary medicinal products, it is necessary, depending on the pharmaceutical form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active substance.

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

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

1) 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,

2) 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,

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

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

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

4. Development of the medicinal product

An explanation shall be provided with regard to the choice of composition, constituents, immediate packaging, possible further packaging, outer packaging if relevant, the intended function of the excipients in the finished product and the method of manufacture of the finished product. This explanation shall be supported by scientific data on development pharmaceutics. The overage, with justification thereof, shall be stated. The microbiological characteristics (microbiological purity and antimicrobial activity) and usage instructions shall be proven to be appropriate for the intended use of the veterinary medicinal product as specified in the marketing authorisation application dossier.

B. DESCRIPTION OF THE MANUFACTURING METHOD

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

The description of the manufacturing method accompanying the application for marketing authorization, shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.

For this purpose it shall include at least:

1) mention of the various stages of manufacture, so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced an adverse change in the constituents,

2) in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished product,

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

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

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

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

C. CONTROL OF STARTING MATERIALS

1. General requirements

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

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

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

Where a Certificate of Suitability (hereinafter: CEP) has been issued by the European Directorate for the Quality of Medicines and Health Care (hereinafter: EDQM) for a starting material, active substance or excipient, this Certificate constitutes the reference to the relevant monograph of the European Pharmacopoeia.

Where a CEP 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 EDQM.

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

1.1. Active substances

The name, address, and responsibility of each manufacturer and each proposed production site or facility involved in manufacturing and testing of an active substance shall be indicated.
For a well-defined active substance, the active substance manufacturer or the applicant may arrange for the following information to be supplied in a separate document directly to the Agency by the manufacturer of the active substance as an Active Substance Master File, containing the following information:

1) a detailed description of the manufacturing process,
2) a description of the quality control during manufacture,
3) a description of the process validation.

In this case, the manufacturer shall however provide the applicant with all the data which may be necessary for the latter to take responsibility for the veterinary medicinal product. The manufacturer shall confirm in writing to the applicant that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing the applicant. Documents and particulars supporting the application for such a change shall be supplied to the Agency and to the applicant where they concern the applicant's part of the Active Substance Master File.

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

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

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

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

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

1.1.1. Active substances listed in pharmacopoeias

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

Constituents fulfilling the requirements of the European Pharmacopoeia or the pharmacopoeia of one of the European Union Member States shall be deemed to comply sufficiently for the description of the testing methods employed by the manufacturer. In this case the description of the analytical methods and procedures shall be replaced in each relevant section by an appropriate reference to the pharmacopoeia in question.

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

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

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

In cases where an active substance is described neither in the European Pharmacopoeia nor in the pharmacopoeia of a European Union Member State, compliance with the monograph of a country who is not the Member of the European Union pharmacopoeia may be accepted if its suitability is demonstrated; in such cases, the applicant shall submit a copy of the monograph accompanied by a translation where appropriate. Data to demonstrate the ability of the monograph to adequately control the quality of the active substance shall be presented.

1.1.2. Active substances not in a pharmacopoeia

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

1) the name of the constituent, meeting the requirements of Section A item 2, shall be supplemented by any trade or scientific synonyms;

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

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

4) 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;

5) tests and limits to control parameters relevant to the finished product, such as particle size and sterility shall be described and methods shall be validated where relevant;

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

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

1.1.3. Physico-chemical characteristics liable to affect bioavailability

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

1) crystalline form and solubility coefficients,

2) particle size, where appropriate after pulverisation,

3) state of hydration,

4) oil/water coefficient of partition,

5) pK/pH values.

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

1.2. Excipients

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

Excipients shall comply with the requirements of the appropriate European Pharmacopoeia monograph. Where such a monograph does not exist reference may be made to the pharmacopoeia of a European Union Member State. In the absence of such a monograph reference may be made to the pharmacopoeia of a country who is not the Member of the European Union, in this case the suitability of this monograph shall be demonstrated. Where appropriate, additional tests to control parameters such as particle size, sterility, residual solvents shall supplement the requirements of the monograph. In the absence of a pharmacopoeial monograph a specification shall be proposed and justified. The requirements for specifications as set out in section 1.1.2 (1 to 5) for the active substance shall be followed. The proposed methods and their supporting validation data shall be presented.

Colouring matters for inclusion in veterinary medicinal products shall satisfy the requirements of the separate legal act on colours for use in foodstuffs, except for certain veterinary medicinal products for topical use, such as insecticidal collars and ear tags, where the use of other colouring matters is justified.

Colouring matters shall meet the purity criteria as laid down in the separate legal act on food additives.

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

1.3. Container-closure systems

1.3.1. Active substance

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

1.3.2. Finished product

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

Packaging materials shall comply with the requirements of the appropriate European Pharmacopoeia monograph. Where such a monograph does not exist reference may be made to the pharmacopoeia of a European Union Member State. In the absence of such a monograph reference may be made to the Pharmacopoeia of a a country who is not the Member of the European Union, and the suitability of this monograph shall be demonstrated.
In the absence of a pharmacopoeial monograph, a specification shall be proposed and justified for the packaging material.

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

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

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

1.4. Substances of biological origin

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

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

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

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

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

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

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

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

The dossier shall include particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the technical characteristics and the production process.

The tests referred to in paragraph 1 are essential for checking the conformity of the veterinary medicinal product with the formula when, exceptionally, an applicant proposes an analytical method for testing the finished product which does not include the assay of all the active substances (or of all the excipient components subject to the same requirements as the active substances).

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

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

E. TESTS ON THE FINISHED PRODUCT

For the control of the finished product, a batch of a finished product comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time.

The application for marketing authorisation shall list those tests, which are carried out routinely on each batch of finished product. The frequency of the tests which are not carried out routinely shall be stated. Release limits shall be indicated.

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

The provisions of the relevant monographs and general chapters of the European Pharmacopoeia, or failing that, of a Member State, shall be applicable to all products defined therein.

If test procedures and limits other than those mentioned in the relevant monographs and general chapters of the European Pharmacopoeia, or failing this, in the pharmacopoeia of a country who is not the Member of the European Union are used, this shall be justified by providing proof that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned.

1. General characteristics of the finished product

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

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

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

2. Identification and assay of active substance(s)

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

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

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

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

An in vivo or in vitro biological assay shall be obligatory when physico-chemical methods cannot provide adequate information on the quality of the product. Such an assay shall, whenever possible, include reference materials and statistical analysis allowing calculation of confidence limits. Where these tests

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

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

Where the particulars given in Section B show that a significant overage of an active substance is employed in the manufacture of the medicinal product or where the stability data show that the assay of the active substance declines on storage, the description of the control tests on the finished product shall include, where appropriate, the chemical and, if necessary, the toxico-pharmacological investigation of the changes that this substance has undergone, and possibly the characterisation and/or assay of the degradation products.

3. Identification and assay of excipient components

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

4. Safety tests

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

F. STABILITY TEST

1. Active substances(s)

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

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

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

2. Finished product

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

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

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

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

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

The conclusions shall contain the results of analyses, justifying the proposed shelf life and if appropriate, the in-use shelf life, under the recommended storage conditions and the specifications of the finished product at the end of the shelf life, and in-use shelf life if appropriate, of the finished product under these recommended storage conditions.
The maximum acceptable level of individual and total degradation products at the end of shelf life shall be indicated.

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

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

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

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

PART 3: SAFETY AND RESIDUES TESTS
The particulars and documents which shall accompany the application for marketing authorisation shall be submitted in accordance with the requirements referred to in this Part.

A. Safety tests

CHAPTER I: PERFORMANCE OF TESTS

The safety documentation shall show:
1) the potential toxicity of the veterinary medicinal product and any dangerous or undesirable effects which may occur under the proposed conditions of use in animals; these should be evaluated in relation to the severity of the pathological condition concerned;

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

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

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

All results shall be reliable and valid generally. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results. Additionally,

information shall be provided regarding the therapeutic potential of the product and about the hazards connected with its use.

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

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

1. Precise identification of the product and of its active substance(s)
1) international non-proprietary name (INN),
2) International Union of Pure and Applied Chemistry Name (IUPAC),
3) Chemical Abstract Service (CAS) number,
4) therapeutic, pharmacological and chemical classification,
5) synonyms and abbreviations,
6) structural formula,
7) molecular formula,
8) molecular weight,
9) degree of impurity,
10) qualitative and quantitative composition of impurities,
11) description of physical properties,
12) melting point,
13) boiling point,
14) vapour pressure,
15) solubility in water and organic solvents expressed in g/l, with indication of temperature,
16) density,
17) spectra of refraction, rotation, etc,
18) formulation of the product.

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

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

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

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

2.2. Pharmacokinetics
Data on the fate of the active substance and its metabolites in the species used in the toxicological studies shall be provided, covering absorption, distribution, metabolism and excretion (ADME). The data shall be related to the dose/effect findings in the pharmacological and toxicological studies, to determine adequate exposure. Comparison with the pharmacokinetic data obtained in the studies on the target species, Part 4,

Chapter I, Section A.2, shall be included in Part 4 in order to determine the relevance of the results obtained in the toxicology studies for the toxicity to the target species.

3. Toxicology

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

1) basic tests required for all new veterinary medicinal products for use in food-producing animals in order to assess the safety of any residues present in food for human consumption;

2) additional tests that may be required depending on specific toxicological concerns such as those associated with the structure, class, and mode of action of the active substance(s);

3) special tests which might assist in the interpretation of data obtained in the basic or additional tests.

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

3.1. Single-dose toxicity

Single-dose toxicity studies may be used to predict:

1) the possible effects of acute overdosage in the target species,

2) the possible effects of accidental administration to humans,

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

Single-dose toxicity studies should reveal the acute toxic effects of the substance and the time course for their onset and remission.
The studies to be carried out shall be selected with a view to providing information on user safety, e.g. if substantial exposure by inhalation or dermal contact of the user of the veterinary medicinal product is anticipated, those routes of exposure shall be studied.

3.2. Repeat-dose toxicity

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

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

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

The investigator shall give his reasons for the choice of species, having regard to the available knowledge of the metabolism of the product in animals and man. The test substance shall be administered orally. The investigator shall clearly state and give his reasons for the method and frequency of administration and the length of the trials.

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

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

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

3.3. Tolerance in the target species

A summary shall be provided of any signs of intolerance which have been observed during studies conducted, usually with the final formulation, in the target species in accordance with the requirements of Part 4, Chapter I, Section B. The studies concerned, the dosages at which the intolerance occurred and the species and breeds concerned shall be identified. Details of any unexpected physiological changes shall also be provided. The full reports of these studies shall be included in Part 4.

3.4. Reproductive toxicity and teratogenicity

3.4.1. Study of the effects on reproduction

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

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

3.4.2. Study of embyo-fetal toxicity and teratogenicity

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

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

3.5. Genotoxicity

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

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

3.6. Carcinogenicity

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

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

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

3.7. Exceptions

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

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

2) under the intended conditions of use laid down, exposure of the user of the veterinary medicinal product by other routes than the dermal route is to be expected, or

3) the active substance or metabolites may enter foodstuffs obtained from the treated animal.

4. Other requirements

4.1. Special studies

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

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

4.2. Microbiological properties of residues

4.2.1. Potential effects on the human gut flora

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

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

In certain cases, it may be necessary to carry out tests to determine whether microbiologically active residues may interfere in technological processes in the industrial processing of foodstuff.

4.3. Observations in humans

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

4.4. Development of resistance

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

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

5. User safety

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

6. Environmental risk assessment

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

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

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

1) the target animal species, and the proposed pattern of use,

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

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

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

In the second phase, further specific investigation of the fate and effects of the product on particular ecosystems shall be conducted, in accordance with established guidance. The extent of exposure of the product to the environment, and the available information about the physical/chemical, pharmacological and/or toxicological properties of the substance 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 Rulebook, shall be taken into consideration.

6.2. Environmental risk assessment for veterinary medicinal products containing or consisting of genetically modified organisms
In the case of a veterinary medicinal product containing or consisting of genetically modified organisms the application shall also be accompanied by the documents required under separate legal act regulates genetically modified organisms.

CHAPTER II: PRESENTATION OF PARTICULARS AND DOCUMENTS

The dossier of safety tests shall include the following:
1) an index of all studies included in the dossier,

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

3) a justification for the omission of any type of study,

4) an explanation of the inclusion of an alternative type of study,

5) a discussion of the contribution that any study that pre-dates studies performed in line with good laboratory practice (GLP) can make to the overall risk assessment.

Each study report shall include:

1) a copy of the study plan (protocol),

2) a statement of compliance with good laboratory practice, where applicable,

3) a description of the methods, apparatus and materials used,

4) a description and justification of the test system,

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

6) a statistical analysis of the results where appropriate,

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

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

B. Residue tests

CHAPTER I: PERFORMANCE OF TESTS

1. Introduction

For the purposes of this Annex, the following definitions shall apply:

1) residues of pharmacologically active substances means means all pharmacologically active substances, expressed in mg/kg or μg/kg on a fresh weight basis, whether active substances, excipients or degradation products, and their metabolites which remain in food obtained from animals;

2) food-producing animals means animals bred, raised, kept, slaughtered or harvested for the purposes of producing food.

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

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

1) to what extent, and how long, do residues of the veterinary medicinal product or its metabolites persist in the edible tissues of the treated animal or in milk, eggs and/or honey obtained therefrom,

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

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

2. Metabolism and residue kinetics

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

A summary of the pharmacokinetic data shall be submitted with cross reference to the pharmacokinetic studies in target species submitted in Part 4. The full study report does not need to be submitted.

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

The final product, or a formulation, which has comparable characteristics in terms of bioavailability as the final product, shall be administered to the target animal species at the maximum recommended dose.

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

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

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

2.2. Depletion of residues

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

At a sufficient number of times after the test animal has received the final dose of the veterinary medicinal product, the quantities of residues present shall be determined by validated analytical methods; the technical procedures and the reliability and sensitivity of the methods employed shall be specified.

3. Residue analytical method

The analytical method(s) used in the residues depletion study (studies) and its (their) validation shall be described in detail.

The following characteristics shall be described:

1) specificity,

2) accuracy,

3) precision,

4) limit of detection,

5) limit of quantification,

6) practicability and applicability under normal laboratory conditions,

7) susceptibility to interference,

8) stability of incurred residues.

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

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

CHAPTER II: PRESENTATION OF PARTICULARS AND DOCUMENTS

1. Identification of the product

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

1) composition,

2) the physical and chemical (potency and purity) test results for the relevant batch(es),

3) batch identification,

4) relationship to the final product,

5) specific activity and radio-purity of labelled substances,

6) position of labelled atoms in the molecule.

The dossier of residue tests shall include:

1) an index of all studies included in the dossier,

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

3) a justification for the omission of any type of study,

4) an explanation of the inclusion of an alternative type of study,

5) a discussion of the contribution that any study that pre-dates GLP can make to the overall risk assessment,

6) a withdrawal period proposal.

Each study report shall include:

1) a copy of the study plan (protocol),

2) a statement of compliance with good laboratory practice, where applicable,

3) a description of the methods, apparatus and materials used,
4) a description of the results obtained, in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author,

5) a statistical analysis of the results where appropriate,

6) a discussion of the results,

7) an objective discussion of the results obtained, and proposals concerning the withdrawal periods necessary to ensure that no residues which might constitute a hazard for consumers are present in foodstuffs obtained from treated animals.

PART 4: PRE-CLINICAL AND CLINICAL TRIAL

The particulars and documents, which shall accompany applications for marketing authorisations shall be submitted in accordance with the requirements below.

CHAPTER I: PRE-CLINICAL REQUIREMENTS

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

A. Pharmacology

A.1. Pharmacodynamics

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

First, the mechanism of action and the pharmacological effects on which the recommended application in practice is based shall be adequately described. The results shall be expressed in quantitative terms (using, for example, dose-effect curves, time-effect curves, etc.) and, wherever possible, in comparison with a

substance the activity of which is well known. Where a higher efficacy is being claimed for an active substance, the difference shall be demonstrated and shown to be statistically significant.

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

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

The investigations shall be intensified where the recommended dose approaches a dose likely to produce adverse reactions.

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

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

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

A.2. Development of resistance

Where relevant, data on the potential emergence of resistant organisms of clinical relevance are necessary for veterinary medicinal products. The mechanism of the development of such resistance is particularly important in this regard. Measures to limit resistance development from the intended use of the veterinary medicinal product shall be proposed by the applicant.

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

A.3. Pharmacokinetics

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

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

1) descriptive pharmacokinetics leading to the determination of basic parameters;

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

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

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

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

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

Appropriate bioavailability studies shall be undertaken to establish bioequivalence:
1) when comparing a reformulated veterinary medicinal product with the existing one,
2) where necessary for the comparison of a new method or route of administration with an established one.

B. Tolerance in the target animal species

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

CHAPTER II: CLINICAL REQUIREMENTS

1. General principles

The purpose of clinical trials is to demonstrate or substantiate the effect of the veterinary medicinal product after administration at the proposed dosage regimen via the proposed route of administration and to specify its indications and contra-indications according to species, age, breed and sex, its directions for use as well as any adverse reactions which it may have.

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

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

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

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

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

3) nutritional efficiency and growth of target animal species,

4) general health status of the target animal species.

2. Conduct of clinical trials

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

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

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

Unless the field trial is conducted with a blind design, the provisions of the separate legal act regulates the contents and manner of labelling packaging of a veterinary medicinal product shall apply by analogy to the labelling of formulations intended for use in veterinary field trials. In all cases, the words 'for veterinary field trial use only' shall appear prominently and indelibly upon the labelling.

CHAPTER III: PARTICULARS AND DOCUMENTS

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

1. Results of pre-clinical trials

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

1) tests demonstrating pharmacological actions;

2) tests demonstrating the pharmacodynamic mechanisms underlying the therapeutic effect;

3) tests demonstrating the main pharmacokinetic profile;

4) tests demonstrating target animal safety;

5) tests investigating resistance.

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

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

1) a summary;

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

3) a statistical analysis of the results, where relevant;

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

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

2. Results of clinical trials

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

The particulars supplied shall take the following form:

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

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

3) details of the clinical trial protocol giving a description of the methods used, including methods of randomisation and blinding, details such as the route of administration, schedule of administration, the dose, identification of trial animals, species, breeds or strains, age, weight, sex, physiological status;

4) method of animal management and feeding, stating the composition of the feed and the nature and quantity of any feed additives;

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

6) diagnosis and means used to make it;

7) clinical signs, if possible according to conventional criteria;

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

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

10) duration of treatment and period of subsequent observation;

11) all details concerning other veterinary medicinal products which have been administered during the period of examination, either prior to or concurrently with the test product and, in the latter case, details of any interactions observed;

12) all results of the clinical trials, fully describing the results based on the efficacy criteria and end points specified in the clinical trial protocol and including the results of the statistical analyses, if appropriate;

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

14) effect on animals' performance if appropriate;

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

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

Omission of one or more items 1 to 16 shall be justified.

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

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

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

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

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

- received no treatment, or

- received a placebo, or

- received another veterinary medicinal product authorised in the Community for the same indication for use in the same target animal species, or

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

4) the frequency of observed adverse reactions;

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

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

7) a statistical evaluation of the results.

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

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

TITLE II
REQUIREMENTS FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS
Without prejudice to specific requirements regulates the control and eradication of specific infectious animal diseases, the following requirements shall apply to immunological veterinary medicinal products,

except when the products are intended for use in some species or with specific indications as defined in Title III and in relevant guidelines.

PART 1: SUMMARY OF THE DOSSIER

A. ADMINISTRATIVE INFORMATION

The immunological veterinary medicinal product, which is the subject of the application, shall be identified by name and by name of the active substance(s), together with the biological activity, potency or titre, the pharmaceutical form, the route and method if appropriate of administration and a description of the final presentation of the product, including packaging, labelling and leaflet. Diluents may be packed together with the vaccine vials or separately.

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

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

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

Annexed to the administrative information shall be copies of a document showing that the manufacturer is authorised to produce immunological veterinary medicinal products. Moreover, the list of organisms handled at the production site shall be given.

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

B. SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The applicant shall propose a summary of the product characteristics, in accordance with the Annex 1 B to this Rulebook.

A proposed labelling text for the immediate and outer packaging shall be provided in accordance with the separate legal act regulates the contents and manner of labelling packaging of a veterinary medicinal product, together with a package leaflet where one is required pursuant to the legal act regulates the contents and manner of labelling packaging of a veterinary medicinal product. In addition the applicant shall provide one or more specimens or mock-ups of the final presentation(s) of the veterinary medicinal product in Montenegrin language. The mock-up may be provided in black and white and electronically where prior agreement from the Agency has been obtained.

C. DETAILED AND CRITICAL SUMMARIES

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

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

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

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

All test procedures shall fulfill the necessary criteria for analysis and control of the quality of the starting materials and the finished product and shall be validated procedures. The results of the validation studies shall be provided. Any special apparatus and equipment which may be used shall be described in adequate detail, possibly accompanied by a diagram. The formulae of the laboratory reagents shall be supplemented, if necessary, by the manufacturing method.

In the case of test procedures included in the European Pharmacopoeia or the pharmacopoeia of an European Union Member State, this description may be replaced by a detailed reference to the pharmacopoeia in question.

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

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

1. Qualitative particulars

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

1) the active substance(s),

2) the constituents of the adjuvants,

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

4) the constituents of the pharmaceutical form administered to animals.

These particulars shall be supplemented by any relevant data concerning the container and, where appropriate, its manner of closure, together with details of devices with which the immunological veterinary medicinal product will be used or administered and which will be delivered with the medicinal product. If the device is not delivered together with the immunological veterinary medicinal product, relevant information about the device shall be provided, where necessary for the assessment of the product.

2. Usual terminology

The 'usual terminology', to be used in describing the constituents of immunological veterinary medicinal products, shall mean:

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

2) in respect of other substances, the international non-proprietary name recommended by the World Health Organisation, which may be accompanied by another non-proprietary name or, failing these, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,
3) in respect of colouring matter, designation by the 'E' code assigned to them by separate legal act regulates food additives.

3. Quantitative particulars

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

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

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

4. Product development

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

B. DESCRIPTION OF MANUFACTURING METHOD

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

For this purpose the description shall include at least:

1) the various stages of manufacture (including production of the antigen and purification procedures) so that an assessment can be made of the reproducibility of the manufacturing procedure and of the risks of adverse effects on the finished products, such as microbiological contamination; the validation of key stages in the production process shall be demonstrated and the validation of the production process as a whole shall be demonstrated with provision of results of three consecutive batches produced using the method described;

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

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

4) the details of the blending, with the quantitative particulars of all the substances used;

5) a statement of the stages of manufacture at which sampling is carried out for control tests during production.

C. PRODUCTION AND CONTROL OF STARTING MATERIALS

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

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

1. Starting materials listed in pharmacopoeias

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

In respect of other substances, Agency may require observance of pharmacopoeia of one of the European Union Member States with regard to products manufactured in its territory.

Constituents fulfilling the requirements of the European Pharmacopoeia or the pharmacopoeia of one of the European Union Member States, it is not necessary to submit the description of the analytical methods. In this case the description of the analytical methods may be replaced by a detailed reference to the pharmacopoeia in question.

Colouring matter shall, in all cases, satisfy the requirements of the separate legal act regulates food additives.
The routine tests carried out on each batch of starting materials must be as stated in the application for marketing authorisation. If tests other than those mentioned in the pharmacopoeia are used, proof must be supplied that the starting materials meet the quality requirements of that pharmacopoeia.

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

In cases where a starting material is described neither in the European Pharmacopoeia nor in the pharmacopoeia of a European Union Member State, compliance with the monograph of a country who is not the Member of the European Union pharmacopoeia can be accepted; in such cases, the applicant shall submit a copy of the monograph accompanied where necessary by the validation of the test procedures contained in the monograph and by a translation where appropriate.

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

The applicant shall supply documentation to demonstrate that the starting materials and the manufacturing of the veterinary medical product is in comply with the requirements of the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, as well as with the requirements of the corresponding monograph of the European

Pharmacopoeia. CEP issued by the EDQM, with reference to the relevant monograph of the European Pharmacopoeia, may be used to demonstrate compliance.

2. Starting materials not listed in a pharmacopoeia

2.1. Starting materials of biological origin
The description shall be given in the form of a monograph.

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

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

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

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

1) details of the source of the materials,

2) details of any processing, purification and inactivation applied, with data on the validation of these process and controls during production,

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

If the presence of extraneous agents is detected or suspected, the corresponding material shall be discarded or used in very exceptional circumstances only when further processing of the product ensures their elimination and/or inactivation; elimination and/or inactivation of such extraneous agents shall be demonstrated.

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

For live attenuated vaccines, proof of the stability of the attenuation characteristics of the seed has to be given.
Documentation shall be supplied to demonstrate that the seed materials, cell seeds, batches of serum and other material originating from animal species relevant for the transmission of TSE comply with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products published by European Commission, as well as with the corresponding monograph of the European Pharmacopoeia. CEP issued by the EDQM, with reference to the relevant monograph of the European Pharmacopoeia, can be used to demonstrate compliance.

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

2.2. Starting materials of non-biological origin
The description shall be given in the form of a monograph under the following headings:

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

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

3) the function of the starting material,

4) methods of identification,
5) any special precautions which may be necessary during storage of the starting material and, if necessary, its storage life shall be given.

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

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

E. CONTROL TESTS ON THE FINISHED PRODUCT
For all tests, the description of the techniques for analysing the finished product shall be set out in sufficiently precise detail for quality assessment.

The dossier shall include particulars relating to control tests on the finished product. Where appropriate monographs exist, if test procedures and limits other than those mentioned in the monographs of the European Pharmacopoeia, or failing this, in the pharmacopoeia of a European Union Member State, are used, proof must be supplied that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned. The application for marketing authorisation shall list those tests, which are carried out on representative samples of each batch of finished product. The frequency of the tests, which are not carried out on each batch, shall be stated. Release limits shall be indicated.

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

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

2. Identification of active substance(s)
Where necessary, a specific test for identification shall be carried out.

3. Batch titre or potency

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

4. Identification and assay of adjuvants

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

5. Identification and assay of excipient components

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

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

6. Safety tests

Apart from the results of tests submitted in accordance with Part 3 of this Title (Safety Tests), particulars of the batch safety tests shall be submitted. These tests shall preferably be overdosage studies carried out in at least one of the most sensitive target species and by at least the recommended route of administration posing the greatest risk. Routine application of the batch safety test may be waived in the interests of animal welfare when a sufficient number of consecutive production batches have been produced and been found to comply with the test.

7. Sterility and purity test

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

8. Residual humidity

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

9. Inactivation

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

F. BATCH-TO-BATCH CONSISTENCY

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

G. STABILITY TESTS

The particulars and documents on the dosage for the various species of animal for which the veterinary medicinal product is intended, its pharmaceutical form, method and route of administration and proposed shelf life, and on description of the testing methods employed by the manufacturer, accompanying the application for marketing authorisation shall be submitted in accordance with the following requirements.

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

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

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

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

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

The proposed in-use shelf life shall be justified.

The efficacy of any preservative system shall be demonstrated.

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

H. OTHER INFORMATION

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

PART 3: SAFETY TESTS

A.INTRODUCTION AND GENERAL REQUIREMENTS

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

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

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

In the case of an immunological veterinary medicinal products containing a live organism, the dose to be used in the laboratory tests described in Sections B.1 and B.2 of this Part shall be the quantity of the product containing the maximum titre. If necessary the concentration of the antigen may be adjusted to achieve the required dose. For inactivated vaccines the dose to be used shall be that quantity recommended for use containing the maximum antigen content unless justified.

The safety documentation shall be used for assessment of the potential risks which may result from the exposure of human beings to the veterinary medicinal product, for example during its administration to the animal.

B. LABORATORY TESTS

1. Safety of the administration of one dose

The immunological veterinary medicinal product shall be administered at the recommended dose and by each recommended route of administration to animals of each species and category in which it is intended

for use, including animals of the minimum age of administration. The animals shall be observed and examined for signs of systemic and local reactions. Where appropriate, these studies shall include detailed post-mortem macroscopic and microscopic examinations of the injection site. Other objective criteria shall be recorded, such as rectal temperature and performance measurements.

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

This study may be part of the repeated dose study required under item 3 or omitted if the results of the overdose study required under item 2 have revealed no signs of systemic or local reactions.

2. Safety of one administration of an overdose

Only live immunological veterinary medicinal products require overdose testing.

An overdose of the immunological veterinary medicinal product shall be administered by each recommended route(s) of administration to animals of the most sensitive categories of the target species, unless the selection of the most sensitive of several similar routes is justified. In the case of immunological veterinary medicinal products administered by injection, the doses and route(s) of administration shall be chosen to take account of the maximum volume, which can be administered at any one single injection site. The animals shall be observed and examined for at least 14 days after administration for signs of systemic and local reactions. Other criteria shall be recorded, such as rectal temperature and performance measurements.

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

3. Safety of the repeated administration of one dose

In the case of immunological veterinary medicinal products to be administered more than once, as part of the basic vaccination scheme, a study of the repeated administration of one dose shall be required to reveal any adverse effects induced by such administration. These tests shall be carried out on the most sensitive categories of the target species (such as certain breeds, age groups), using each recommended route of administration.

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

4. Examination of reproductive performance

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

These studies may form part of the safety studies described in item 1, 2, 3 or of the field studies provided for in Section C.

5. Examination of immunological functions

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

6. Special requirements for live vaccines

6.1. Spread of the vaccine strain

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

6.2. Dissemination in the vaccinated animal

Faeces, urine, milk, eggs, oral, nasal and other secretions shall be tested for the presence of the organism as appropriate. Moreover, studies may be required of the dissemination of the vaccine strain in the body, with particular attention being paid to the predilection sites for replication of the organism. In the case of live vaccines for zoonoses within the meaning of the separate legal act regulates the monitoring of zoonoses and zoonotic agents to be used for food producing animals, these studies must shall take particularly into account the persistence of the organism at the injection site.

6.3. Reversion to virulence of attenuated vaccines

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

6.4. Biological properties of the vaccine strain

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

6.5. Recombination or genomic reassortment of strains

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

7. User safety

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

8. Study of residues

For immunological veterinary medicinal products, it will normally not be necessary to undertake a study of residues. However, where adjuvants and/or preservatives are used in the manufacture of immunological veterinary medicinal products, consideration shall be given to the possibility of any residue remaining in the foodstuffs. If necessary, the effects of such residues shall be investigated.

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

9. Interactions

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

C. FIELD STUDIES

Unless justified, results from laboratory studies shall be supplemented with data from field studies, using batches according to the manufacturing process described in the marketing authorisation application. Both safety and efficacy may be investigated in the same field studies.

D.ENVIRONMENTAL RISK ASSESSMENT

The purpose of the environmental risk assessment is to assess the potential harmful effects, which the use of the product may cause to the environment and to identify any precautionary measures, which may be necessary to reduce such risks.

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

1) the target animal species and the proposed pattern of use,

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

3) the possible excretion of the product, its active substances into the environment by treated animals, persistence in such excreta,

4) the disposal of unused or waste product.

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

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

E. ASSESSMENT REQUIRED FOR VETERINARY MEDICINAL PRODUCTS CONTAINING OR CONSISTING OF GENETICALLY MODIFIED ORGANISMS

In the case of veterinary medicinal products containing or consisting of genetically modified organisms the application shall also be accompanied by the documents required under separate legal act regulates genetically modified organisms.

PART 4: EFFICACY TESTS

CHAPTER I

1. General principles

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

2. Performance of trials

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

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

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

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

Unless the field trial is conducted with a blind design, the provisions of the separate legal act regulates the contents and manner of labelling packaging of a veterinary medicinal product shall apply by analogy to the labelling of formulations intended for use in veterinary field trials. In all cases, the words ‘for veterinary field trial use only’ shall appear prominently and indelibly upon the labelling.

CHAPTER II

A. General requirements

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

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

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

All trials shall be described in sufficiently precise details so as to be reproducible in controlled trials, carried out at the request of the Agency. The investigator shall demonstrate the validity of all the techniques involved.

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

3. The efficacy of an immunological veterinary medicinal product shall be demonstrated for each category of target animal species recommended for vaccination, by each recommended route of administration and using the proposed schedule of administration. The influence of passively acquired and maternally derived antibodies on the efficacy of a vaccine shall be adequately evaluated, if appropriate. Unless justified, the onset and duration of immunity shall be established and supported by data from trials.

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

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

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

7. If there is a compatibility statement with other immunological products in the summary of product characteristics, the efficacy of the association shall be investigated. Any other known interactions with any other veterinary medicinal products shall be described. Concurrent or simultaneous use may be allowed if supported by appropriate studies.

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

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

B. Laboratory trials

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

For live vaccines, batches containing the minimum titre or potency shall be used unless justified. For other products, batches containing the minimum active content shall be used unless otherwise justified.

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

C. Field trials

1. Unless justified, results from laboratory trials shall be supplemented with data from field trials, using batches representative of the manufacturing process described in the marketing authorisation application. Both safety and efficacy may be investigated in the same field study.

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

PART 5: PARTICULARS AND DOCUMENTS

A. INTRODUCTION

The dossier of the safety and efficacy studies shall include an introduction defining the subject and indicating the tests which have been carried out in compliance with Parts 3 and 4 as well as a summary, with detailed references to the published literature. This summary shall contain an objective discussion of all the results obtained and lead to a conclusion on the safety and efficacy of the immunological veterinary medicinal product. Omission of any tests or trials listed shall be indicated and discussed.

B. LABORATORY STUDIES

The following shall be provided for all studies:

1) a summary;

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

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

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

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

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

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

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

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

10) occurrence and course of any intercurrent disease;

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

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

C. FIELD STUDIES

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

1) a summary;

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

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

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

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

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

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

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

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

10) effects on the animals' performance;

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

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

13) occurrence and course of any intercurrent disease;

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

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

PART 6: BIBLIOGRAPHICAL REFERENCES

The bibliographical references cited in the summary mentioned under Part 1 shall be listed in detail and copies shall be provided.

TITLE III

REQUIREMENTS FOR SPECIFIC MARKETING AUTHORISATION APPLICATIONS

1. Generic veterinary medicinal products

Applications for generic veterinary medicinal products shall contain the data referred to in Parts 1 and 2 of Title I of this Annex together with an environmental risk assessment and data demonstrating that the product has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product and data showing bio-equivalence with the reference medicinal product. If the reference veterinary medicinal product is a biological medicinal product, the documentation requirements in Section 2 of this Title for similar biological veterinary medicinal products shall be fulfilled.

For generic veterinary medicinal products the detailed and critical summaries on safety and efficacy shall particularly focus on the following elements:

1) the grounds for claiming essential similarity,

2) a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed together with an evaluation of these impurities,

3) an evaluation of the bio-equivalence studies or a justification as to why studies were not performed with reference to established guidance,

4) if applicable, additional data in order to demonstrate the equivalence of safety and efficacy properties of different salts, esters or derivatives of an authorised active substance shall be provided by the applicant; those data shall include evidence that there is no change in the pharmacokinetic or pharmacodynamic properties of the therapeutic moiety and/or in toxicity, which could influence the safety/efficacy profile.

Every claim in the summary of product characteristics not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non-clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.

For generic veterinary medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes, the following additional data shall be provided:

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

2) evidence to demonstrate target animal tolerance at the administration site, which may be substantiated by appropriate target animal tolerance studies.

2. Similar biological veterinary medicinal products

Where a biological veterinary medicinal product which is similar to a reference biological veterinary medicinal product does not meet the conditions in the definition of generic medicinal product, information to be supplied shall not be limited to Parts 1 and 2 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bioavailability data. In such cases, additional data shall be provided, in particular on the safety and efficacy of the product.

1) The type and amount of additional data (i.e. toxicological and other safety studies and appropriate clinical studies) shall be determined on a case-by-case basis in accordance with relevant scientific guidelines.

2) Due to the diversity of biological veterinary medicinal products, the Agency shall determine the necessary studies foreseen in Parts 3 and 4, taking into account the specific characteristic of each individual biological veterinary medicinal product.

The general principles to be applied are listed in EMA guideline, taking into account the characteristics of the concerned biological veterinary medicinal product. If the reference biological veterinary medicinal product has more than one indication, the efficacy and safety of the biological veterinary medicinal product claimed to be similar shall be justified or, if necessary, demonstrated separately for each of the claimed indications.

3. Well-established veterinary use

For veterinary medicinal products the active substance(s) of which has/have been in “well-established veterinary use”, with recognised efficacy and an acceptable level of safety, the following specific rules shall apply.

The applicant shall submit Parts 1 and 2 as described in Title I of this Annex.

For Parts 3 and 4, a detailed scientific bibliography shall address all aspects of the safety and efficacy.

The following specific rules shall apply in order to demonstrate the well-established veterinary use:

3.1. The following factors shall be taken into account in order to establish a well-established veterinary medicinal use of constituents of veterinary medicinal products:

1) the time over which an active substance has been used;

2) quantitative aspects of the use of the active substance;

3) the degree of scientific interest in the use of the active substance (reflected in the published scientific literature);

4) the coherence of scientific assessments.

Different periods of time may be necessary for establishing well-established use of different substances. In any case, however, the period of time required for establishing a well-established veterinary use of a constituent of a medicinal product shall not be less than ten years from the first systematic and documented use of that substance as a veterinary medicinal product in the European Union.

3.2. The documentation submitted by the applicant shall cover all aspects of the safety and/or efficacy assessment of the product for the proposed indication in the target species using the proposed route of administration and dosage regimen. It must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, shall be communicated. With respect to the provisions on well-established veterinary use, it is in particular necessary to clarify that bibliographic reference to other sources of evidence (post-marketing studies, epidemiological studies etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.

3.3. Particular attention must be paid to any missing information and justification must be given as to why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking.

3.4. The detailed and critical summaries regarding safety and efficacy must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether or not the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences.

3.5. Post-marketing experience with other products containing the same constituents is of particular importance and applicants shall put a special emphasis on this issue.

4. Combination veterinary medicinal products

A dossier containing Parts 1, 2, 3 and 4 shall be provided for the combination veterinary medicinal product. It shall not be necessary to provide studies on the safety and efficacy of each active substance. It shall nevertheless be possible to include information on the individual substances in the application for a fixed combination. The submission of data on each individual active substance, in conjunction with the required user safety studies, residues depletion studies and clinical studies on the fixed combination product, may be considered a suitable justification for omitting data on the combination product, based on animal welfare grounds and unnecessary testing on animals, unless there is suspected interaction leading to added toxicity.

Where applicable, information regarding the manufacturing sites and the safety evaluation of adventitious agents shall be provided.

5. Informed consent applications

Informed consent applications shall contain the data described in Part 1 of Title 1 of this Annex, provided that the marketing authorisation holder for the original veterinary medicinal product has given the applicant his consent to refer to the content of Parts 2, 3 and 4 of the dossier of that product. In this case, there is no need to submit quality, safety and efficacy detailed and critical summaries.

6. Documentation for applications in exceptional circumstances

A marketing authorisation may be granted subject to certain specific obligations requiring the applicant to introduce specific procedures, in particular concerning the safety and efficacy of the veterinary medicinal product, when, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use.

The identification of essential requirements for all applications mentioned in this section should be subject to EMA guidelines.

7. Mixed marketing authorisation applications

Mixed marketing authorisation applications are applications where Part(s) 3 and/or 4 of the dossier consist of safety and efficacy studies carried out by the applicant as well as bibliographical references. All other part(s) are in accordance with the structure described in Part I of Title I of this Annex. The Agency shall accept the proposed format presented by the applicant on a case-by-case basis.

TITLE IV
REQUIREMENTS FOR MARKETING AUTHORISATION APPLICATIONS FOR PARTICULAR VETERINARY MEDICINAL PRODUCTS

This part lays down specific requirements for identified veterinary medicinal products related to the nature of the active substances contained therein.

1. IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

A. VACCINE ANTIGEN MASTER FILE

For particular immunological veterinary medicinal products and by derogation from the provisions of Title II, Part 2 Section C on active substances, the concept of a Vaccine Antigen Master File is introduced.

For the purpose of this 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 this veterinary medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.

Scientific guidelines for the submission and evaluation of a vaccine antigen master file shall be adopted by the Agency. The procedure for the submission and evaluation of a vaccine antigen master file shall follow the guidance published by the Commission in The rules governing medicinal products in the European Union, Volume 6B, Notice to Applicants.

B. MULTI-STRAIN DOSSIER

For certain immunological veterinary medicinal products (foot-and-mouth disease, avian influenza and bluetongue) and by derogation from the provisions of Title II, Part 2 Section C on active substances the concept of the use of a multi-strain dossier is introduced.

A multi-strain dossier means a single dossier containing the relevant data for a unique and thorough scientific assessment of the different options of strains/combinations of strains permitting the authorisation of vaccines against antigenically variable viruses.
Scientific guidelines for the submission and evaluation of multi-strain dossiers shall be adopted by the Agency. The procedure for the submission and evaluation of multi-strain dossiers shall follow the guidance published by the Commission in The rules governing medicinal products in the European Union, Volume 6B, Notice to Applicants.

2. HOMEOPATHIC VETERINARY MEDICINAL PRODUCTS

This section sets out specific provisions on the application of Title I, Parts 2 and 3 to homeopathic veterinary medicinal products as defined in the Law on medicinal products.

Implementation of the provisions of the Title 1 Part 2 to this Annex

The provisions of Part 2 shall apply to the documents submitted in the simplified registration of homeopathic veterinary medicinal products as well as to the documents for authorisation of other homeopathic veterinary medicinal products with the following modifications.

1) 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 European Union Member State shall be provided.

2) Control of starting materials

The particulars and documents on the starting materials, i.e. all of the materials used including raw materials and intermediates up to the final dilution to be incorporated into the finished homeopathic veterinary medicinal product, accompanying the application shall be supplemented by additional data on the homeopathic stock.
The general quality requirements shall apply to all of the starting and raw materials as well as intermediate steps of the manufacturing process up to the final dilution to be incorporated into the finished homeopathic product. Where a toxic component is present, this should be controlled if possible in the final dilution. However, if this is not possible because of the high dilution, the toxic component shall normally be controlled at an earlier stage. Every step of the manufacturing process from the starting materials up to the final dilution to be incorporated into the finished product must be fully described.

In case dilutions are involved, these dilution steps shall be done in accordance with the homeopathic manufacturing methods laid down in the relevant monograph of the European Pharmacopoeia or, in absence thereof, in an official pharmacopoeia of a European Union Member State.

3) Control tests on the finished medicinal product

The general quality requirements shall apply to the homeopathic finished veterinary medicinal products. Any exception shall be duly justified by the applicant.

Identification and assay of all the toxicologically relevant constituents shall be carried out. If it can be justified that identification and/or an assay on all the toxicologically relevant constituents is not possible e.g. due to their dilution in the finished medicinal product the quality shall be demonstrated by complete validation of the manufacturing and dilution process.

4) 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.

Implementation of the provisions of the Title 1 Part 3 to this Annex

The provisions of Part 3 shall apply to the simplified registration of homeopathic veterinary medicinal products with the following specification, without prejudice to the provisions of the European Union legislation on establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin for substances included in the homeopathic stocks intended for administration to food-producing animal species.

Any missing information must be justified, e.g. justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking.