

Status: Point in time view as at 31/12/2020.

Changes to legislation: There are currently no known outstanding effects for the Regulation (EU) 2019/6 of the European Parliament and of the Council, TITLE I. (See end of Document for details)

ANNEX II

REQUIREMENTS REFERRED TO IN POINT (B) OF ARTICLE 8(1)⁽¹⁾

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.

PART I

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), together with the strength, the pharmaceutical form, the route and method of administration (see Article 12(3)(f) of Directive) and a description of the final presentation of the product, including packaging, labelling and package leaflet (see Article 12(3)–(l) of Directive).

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 in support of the application 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, as defined in Article 44, together with a list of countries in which authorisation has been granted, copies of all the summaries of product characteristics in accordance with Article 14 as approved by 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 Article 14 of this Directive.

A proposed labelling text for the immediate and outer packaging shall be provided in accordance with Title V of this Directive, together with a package leaflet where one is required pursuant to Article 61. 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 of the European Union; the mock-up may be provided in black and white and electronically where prior agreement from the competent authority has been obtained.

C. DETAILED AND CRITICAL SUMMARIES

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In accordance with Article 12(3), detailed and critical summaries shall be provided 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.

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 I to Directive 2001/83/EC of the European Parliament and of the Council⁽²⁾ 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 competent authority has publicly announced that the chemical, pharmaceutical and biological/microbiological information for the finished product may be included in the dossier in the Common Technical Document (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 competent authorities.

PART 2

Pharmaceutical (physico-chemical, biological or microbiological information (quality))

Basic principles and requirements

The particulars and documents which shall accompany the application for marketing authorisation pursuant to the first indent of Article 12(3)(j) shall be submitted in accordance with the requirements below.

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

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

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All test procedures shall fulfil 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 competent authority; any special apparatus and equipment, which may be used shall be described in adequate detail, possibly accompanied by a diagram. The formulae of the laboratory reagents shall be supplemented, if necessary, by the method of preparation. In the case of test procedures included in the *European Pharmacopoeia* or the pharmacopoeia of a Member State, this description may be replaced by a detailed reference to the pharmacopoeia in question.

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 I to Directive 2001/83/EC the chemical, pharmaceutical and biological/microbiological information provided for in Module 3 of that Directive 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 the competent authority 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 competent authorities.

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:

- active substance(s),
- the constituents of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances,
- 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, notwithstanding the application of the other provisions of Article 12(3)(c):

- in respect of constituents 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,

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- in respect of other constituents, the international non-proprietary name (INN) recommended by the World Health Organisation (WHO), which may be accompanied by another non-proprietary name, or, failing these, the exact scientific designation; 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,
- in respect of colouring matter, designation by the 'E' code assigned to them by Council Directive 78/25/EEC⁽³⁾.

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:

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

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

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

4. Development pharmaceuticals

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 pharmaceuticals. The overage, with justification thereof, shall be stated. The microbiological characteristics (microbiological purity and antimicrobial activity) and usage instructions shall be proven to be

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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 authorisation pursuant to Article 12(3)(d), shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.

For this purpose it shall include at least:

- mention of the various stages of manufacture, so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced an adverse change in the constituents,
- in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished product,
- 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,
- 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,
- experimental studies validating the manufacturing process and where appropriate a process validation scheme for production scale batches,
- 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, point 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 has been issued by the European Directorate for the Quality of Medicines and HealthCare for a starting material, active substance or excipient, this Certificate constitutes the reference to the relevant monograph of the *European Pharmacopoeia*.

Where a Certificate of Suitability is referred to, the manufacturer shall give an assurance in writing to the applicant that the manufacturing process has not been modified since the granting

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of the certificate of suitability by the European Directorate for the Quality of Medicines and HealthCare.

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 competent authorities by the manufacturer of the active substance as an Active Substance Master File:

- (a) a detailed description of the manufacturing process;
- (b) a description of the quality control during manufacture;
- (c) 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 competent authorities those documents and particulars shall also be supplied 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 Certificate of Suitability 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

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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 Member States shall be deemed to comply sufficiently with Article 12(3)(i). 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 Member State is insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the applicant, including limits for specific impurities with validated test procedures.

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 absence of a *European Pharmacopoeia* monograph for an active substance, and where the active substance is described in the pharmacopoeia of a 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 Member State, compliance with the monograph of a third country pharmacopoeia may be accepted if its suitability is demonstrated; in such cases, the applicant shall submit a copy of the monograph accompanied by a translation where appropriate. Data to demonstrate the ability of the monograph to adequately control the quality of the 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:

- (a) the name of the constituent, meeting the requirements of Section A point 2, shall be supplemented by any trade or scientific synonyms;
- (b) the definition of the substance, set down in a form similar to that used in the *European Pharmacopoeia*, shall be accompanied by any necessary explanatory evidence, 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;
- (c) methods of identification may be described in the form of complete techniques as used for production of the substance, and in the form of tests which ought to be carried out as a routine matter;
- (d) purity tests shall be described in relation to each individual predictable impurity, especially those which may have a harmful effect, and, if necessary, those which, having regard to the combination of substances to which the application refers, might adversely affect the stability of the medicinal product or distort analytical results;
- (e) tests and 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;
- (f) 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

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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:

- crystalline form and solubility coefficients,
- particle size, where appropriate after pulverisation,
- state of hydration,
- oil/water coefficient of partition,
- 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 Member State. In the absence of such a monograph reference may be made to the pharmacopoeia of a third country. 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 (a to e) 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 Directive 78/25/EEC, 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 Commission Directive 95/45/EC⁽⁴⁾.

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

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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 Member State. In the absence of such a monograph reference may be made to the Pharmacopoeia of a third country. In this case 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⁽⁵⁾, as well as with the corresponding monograph of the *European Pharmacopoeia*. Certificates of Suitability issued by the European Directorate for the Quality of Medicines and HealthCare, with reference to the relevant monograph of the *European Pharmacopoeia*, may be used to demonstrate compliance.

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

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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.

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

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

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 Member State 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

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otherwise justified. Those studies shall also be carried out where administration is by another means if the competent authorities of the Member State concerned consider 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 $\pm 5\%$ 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 competent authority to have the conformity of the medicinal product with its specification verified after it has been placed on the market.

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

Where 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 toxicopharmacological 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 toxicopharmacological 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.

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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 Certificate of Suitability for the active substance from the proposed source is available and specifies a retest period and storage conditions, stability data for the active substance from that source 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 breached 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

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Changes to legislation: There are currently no known outstanding effects for the Regulation (EU) 2019/6 of the European Parliament and of the Council, TITLE I. (See end of Document for details)

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 pursuant to the second and fourth indents of Article 12(3)(j) shall be submitted in accordance with the requirements below.

A. SAFETY TESTS

Chapter I

Performance of tests

The safety documentation shall show:

- (a) 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;
- (b) 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;
- (c) the potential risks which may result from the exposure of human beings to the veterinary medicinal product, for example during its administration to the animal;
- (d) the potential risks to the environment resulting from the use of the veterinary medicinal product.

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)**
 - international non-proprietary name (INN),
 - International Union of Pure and Applied Chemistry Name (IUPAC),
 - Chemical Abstract Service (CAS) number,
 - therapeutic, pharmacological and chemical classification,
 - synonyms and abbreviations,
 - structural formula,

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Changes to legislation: There are currently no known outstanding effects for the Regulation (EU) 2019/6 of the European Parliament and of the Council, TITLE I. (See end of Document for details)

- molecular formula,
- molecular weight,
- degree of impurity,
- qualitative and quantitative composition of impurities,
- description of physical properties,
- melting point,
- boiling point,
- vapour pressure,
- solubility in water and organic solvents expressed in g/l, with indication of temperature,
- density,
- spectra of refraction, rotation, etc.,
- 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;

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- (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:

- the possible effects of acute overdosage in the target species,
- the possible effects of accidental administration to humans,
- the doses which may usefully be employed in the repeat dose studies.

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

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 Directive, the repeat-dose tests may, except where

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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 including developmental toxicity*

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 developmental toxicity

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.

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Changes to legislation: There are currently no known outstanding effects for the Regulation (EU) 2019/6 of the European Parliament and of the Council, TITLE I. (See end of Document for details)

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:

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

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Changes to legislation: There are currently no known outstanding effects for the Regulation (EU) 2019/6 of the European Parliament and of the Council, TITLE I. (See end of Document for details)

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:

- the target animal species, and the proposed pattern of use,
- the method of administration, in particular the likely extent to which the product will enter directly into environmental systems,
- the possible excretion of the product, its active substances or relevant metabolites into the environment by treated animals; persistence in such excreta,
- 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(s) concerned, including metabolites in case of an identified risk, which has been obtained during the conduct of the other tests and trials required by this Directive, shall be taken into consideration.

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

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Changes to legislation: There are currently no known outstanding effects for the Regulation (EU) 2019/6 of the European Parliament and of the Council, TITLE I. (See end of Document for details)

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

Chapter II

Presentation of particulars and documents

The dossier of safety tests shall include the following:

- an index of all studies included in the dossier,
- a statement confirming that all data known by the applicant at the time of submission, whether favourable or unfavourable, are included,
- a justification for the omission of any type of study,
- an explanation of the inclusion of an alternative type of study,
- a discussion of the contribution that any study that pre-dates studies performed in line with good laboratory practice (GLP) according to Directive 2004/10/EC can make to the overall risk assessment.

Each study report shall include:

- a copy of the study plan (protocol),
- a statement of compliance with good laboratory practice, where applicable,
- a description of the methods, apparatus and materials used,
- a description and justification of the test system,
- a description of the results obtained, in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author,
- a statistical analysis of the results where appropriate,
- a discussion of the results, with comment on observed and no-observed-effect levels, and on any unusual findings,
- 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 definitions of Council Regulation (EEC) No 2377/90⁽⁶⁾ shall apply.

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:

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Changes to legislation: There are currently no known outstanding effects for the Regulation (EU) 2019/6 of the European Parliament and of the Council, TITLE I. (See end of Document for details)

- (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:

- specificity,

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- accuracy,
- precision,
- limit of detection,
- limit of quantification,
- practicability and applicability under normal laboratory conditions,
- susceptibility to interference,
- 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:

- composition,
- the physical and chemical (potency and purity) test results for the relevant batch(es),
- batch identification,
- relationship to the final product,
- specific activity and radio-purity of labelled substances,
- position of labelled atoms in the molecule.

The dossier of residue tests shall include:

- an index of all studies included in the dossier,
- a statement confirming that all data known by the applicant at the time of submission, whether favourable or unfavourable, are included,
- a justification for the omission of any type of study,
- an explanation of the inclusion of an alternative type of study,
- a discussion of the contribution that any study that pre-dates GLP can make to the overall risk assessment,
- a withdrawal period proposal.

Each study report shall include:

- a copy of the study plan (protocol),
- a statement of compliance with good laboratory practice, where applicable,
- a description of the methods, apparatus and materials used,
- a description of the results obtained, in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author,
- a statistical analysis of the results where appropriate,
- a discussion of the results,
- 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.

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Changes to legislation: There are currently no known outstanding effects for the Regulation (EU) 2019/6 of the European Parliament and of the Council, TITLE I. (See end of Document for details)

PART 4

Pre-clinical and clinical trial

The particulars and documents, which shall accompany applications for marketing authorisations pursuant to the third indent of Article 12(3)(j) 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.

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Changes to legislation: There are currently no known outstanding effects for the Regulation (EU) 2019/6 of the European Parliament and of the Council, TITLE I. (See end of Document for details)

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:

- (i) descriptive pharmacokinetics leading to the determination of basic parameters;
- (ii) use of these parameters to investigate the relationships between dosage regimen, plasma and tissue concentration over time and pharmacological, therapeutic or toxic effects;
- (iii) 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:

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

Status: Point in time view as at 31/12/2020.

Changes to legislation: There are currently no known outstanding effects for the Regulation (EU) 2019/6 of the European Parliament and of the Council, TITLE I. (See end of Document for details)

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 Articles 55, 56 and 57 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.

Status: Point in time view as at 31/12/2020.

Changes to legislation: There are currently no known outstanding effects for the Regulation (EU) 2019/6 of the European Parliament and of the Council, TITLE I. (See end of Document for details)

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:

- (a) tests demonstrating pharmacological actions;
- (b) tests demonstrating the pharmacodynamic mechanisms underlying the therapeutic effect;
- (c) tests demonstrating the main pharmacokinetic profile;
- (d) tests demonstrating target animal safety;
- (e) tests 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:

- (a) a summary;
- (b) a detailed experimental protocol giving a description of the methods, apparatus and materials used, details such as species, age, weight, sex, number, breed or strain of animals, identification of animals, dose, route and schedule of administration;
- (c) a statistical analysis of the results, where relevant;
- (d) an objective discussion of the results obtained, leading to conclusions on the 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:

- (a) name, address, function and qualifications of investigator in charge;
- (b) place and date of treatment; name and address of owner of the animals;
- (c) details of the 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;
- (d) method of animal management and feeding, stating the composition of the feed and the nature and quantity of any feed additives;

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Changes to legislation: There are currently no known outstanding effects for the Regulation (EU) 2019/6 of the European Parliament and of the Council, TITLE I. (See end of Document for details)

- (e) case history (as full as possible), including occurrence and course of any intercurrent diseases;
- (f) diagnosis and means used to make it;
- (g) clinical signs, if possible according to conventional criteria;
- (h) 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);
- (i) dosage of the veterinary medicinal product, method, route and frequency of administration and precautions, if any, taken during administration (duration of injection, etc.);
- (j) duration of treatment and period of subsequent observation;
- (k) all details concerning 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;
- (l) 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;
- (m) 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;
- (n) effect on animals' performance if appropriate;
- (o) effects on the quality of foodstuffs obtained from treated animals, particularly in the case of veterinary medicinal products intended for use as performance enhancers;
- (p) 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 (a) to (p) shall be justified.

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

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

- (a) the number of control and test animals treated either individually or collectively, with a breakdown according to species, breed or strain, age and sex;
- (b) the number of animals withdrawn prematurely from the trials and the reasons for such withdrawal;
- (c) in the case of control animals, whether they have:
 - received no treatment,
 - received a placebo, or
 - received another veterinary medicinal product authorised in the Community for the same indication for use in the same target animal species, or

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- received the same active substance under investigation in a different formulation or by a different route;
- (d) the frequency of observed adverse reactions;
- (e) observations as to the effect on animal performance, if appropriate;
- (f) details concerning test animals which may be at increased risk owing to their age, their mode of rearing or feeding, or the purpose for which they are intended, or animals the physiological or pathological condition of which requires special consideration;
- (g) a statistical evaluation of the results.

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.

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- (1) This Annex will be amended by the Commission in accordance with Articles 146 and 153. All references to Articles or to 'this Directive' in this Annex, unless otherwise specified, are to be understood as references to Directive 2001/82/EC.
- (2) [OJ L 311, 28.11.2001, p. 67.](#)
- (3) [OJ L 11, 14.1.1978, p. 18.](#)
- (4) [OJ L 226, 22.9.1995, p. 1.](#)
- (5) [OJ C 24, 28.1.2004, p. 6.](#)
- (6) [OJ L 224, 2.4.1990, p. 1.](#)

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