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Contents

[1] Text with EEA relevance.

EN

Acts whose titles are printed in light type are those relating to day-to-day management of agricultural matters, and are generally valid for a limited period.

The titles of all other acts are printed in bold type and preceded by an asterisk.

([1]) Text with EEA relevance.

II

(Non-legislative acts)

REGULATIONS

COUNCIL IMPLEMENTING REGULATION (EU) 2021/804

of 20 May 2021

implementing Article 15(3) of Regulation (EU) No 747/2014 concerning restrictive measures in view of the situation in Sudan

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Council Regulation (EU) No 747/2014 of 10 July 2014 concerning restrictive measures in view of the situation in Sudan and repealing Regulations (EC) No 131/2004 and (EC) No 1184/2005 [1], and in particular Article 15(3) thereof,

Having regard to the proposal from the High Representative of the Union for Foreign Affairs and Security Policy,

Whereas:

(1) On 10 July 2014 the Council adopted Regulation (EU) No 747/2014.

(2) On 5 March 2021 the United Nations Security Council (UNSC) Committee established pursuant to UNSC Resolution 1591(2005) approved the removal of one person from the list of persons and entities subject to restrictive measures.

(3) Annex I to Regulation (EU) No 747/2014 should therefore be amended accordingly,

HAS ADOPTED THIS REGULATION:

Article 1

Annex I to Regulation (EU) No 747/2014 is amended as set out in the Annex to this Regulation.

Article 2

This Regulation shall enter into force on the date of its publication in the *Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 20 May 2021.

For the Council
The President
A. SANTOS SILVA

[1] OJ L 203, 11.7.2014, p. 1.

ANNEX

In the list set out in Annex I to Regulation (EU) No 747/2014, the entry for the following person is deleted:

3. **SHAREIF, Adam**.

COMMISSION DELEGATED REGULATION (EU) 2021/805

of 8 March 2021

amending Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC ([1]), and in particular Article 146(2) thereof,

Whereas:

(1) It is appropriate to substantially update the requirements set out in Annex II to Regulation (EU) 2019/6, which took over the dossier requirements set out in Annex I to Directive 2001/82/EC of the European Parliament and of the Council ([2]), as that Regulation did not update those dossier requirements at the time of repealing that Directive. The dossier requirements set out in Annex I to Directive 2001/82/EC had last been updated in 2009. Therefore, Annex II should be amended to take account of scientific progress and developments since 2009, including international guidance from the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), World Health Organisation (WHO) and the organisation of Economic cooperation and development (OECD) standards.

(2) It is also appropriate to set out requirements for biological veterinary medicinal products and novel therapy veterinary medicinal products introduced as new categories of veterinary medicinal products by Regulation (EU) 2019/6. For those products, specific technical requirements to be presented when applying for a marketing authorisation should be defined.

(3) Recognising that antimicrobial resistance to medicinal products is a growing health problem in the Union and worldwide, Regulation (EU) 2019/6 introduced specific legal provisions aimed at limiting the risk of development of antimicrobial resistance to medicinal products. It is therefore appropriate to introduce specific technical requirements for antimicrobial veterinary medicinal products.

(4) This Regulation should apply from 28 January 2022 in accordance with Article 153(3) of Regulation (EU) 2019/6.

(5) Regulation (EU) 2019/6 should therefore be amended accordingly,

HAS ADOPTED THIS REGULATION:

Article 1

Annex II to Regulation (EU) 2019/6 is replaced by the text in the Annex to this Regulation.

Article 2

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

It shall apply from 28 January 2022.

([1]) OJ L 4, 7.1.2019, p. 43.

([2]) Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (OJ L 311, 28.11.2001, p. 1).

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 8 March 2021.

For the Commission
The President
Ursula VON DER LEYEN

ANNEX

'ANNEX II

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

Table of Contents

SECTION I

GENERAL PRINCIPLES AND REQUIREMENTS

I.1. General principles

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

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

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

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

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

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

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

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

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

I.2. Dossier composition requirements

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

I.2.1. *Part 1: Summary of the dossier*

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

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

(b) Part 1B: point 5;

(c) Part 1C: point 6.5.

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

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

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

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

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

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

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

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

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

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

(2) All monographs, including specific monographs, general monographs and general chapters of the European Pharmacopoeia are applicable. For immunological veterinary medicinal products, all monographs, including specific monographs, general monographs and general chapters of the European Pharmacopoeia are applicable, unless otherwise justified. In the absence of a European Pharmacopoeia monograph, the monograph of a Member State pharmacopoeia may be applied. In cases where a substance is described neither in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia may be accepted if its suitability is demonstrated; in such cases, the applicant shall submit a copy of the monograph accompanied by a translation where appropriate. Data to demonstrate the ability of the monograph to adequately control the quality of the substance shall be presented.

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

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

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

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

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

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

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

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

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

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

(2) The dossier shall include the following:

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

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

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

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

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

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

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

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

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

(3) The dossier shall include the following:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SECTION II

REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS OTHER THAN BIOLOGICAL VETERINARY MEDICINAL PRODUCTS

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

II.1. ***Part 1: Summary of the dossier***

Please refer to Section I.

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

II.2A. **Product description**

II.2A1. **Qualitative and quantitative composition**

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

(a) active substance(s);

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

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

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

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

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

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

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

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

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

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

(5) Quantitative composition shall be supplemented:

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

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

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

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

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

II.2A2. **Product development**

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

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

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

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

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

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

II.2B. **Description of the manufacturing method**

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

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

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

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

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

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

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

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

II.2C. **Production and control of starting material**

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

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

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

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

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

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

II.2C1. **Active substance(s)**

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

(2) The following details shall be submitted:

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

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

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

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

(3) Active Substance Master File

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

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

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

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

(1) Active substances fulfilling the requirements of the European Pharmacopoeia or, in the absence of a European Pharmacopoeia monograph, the pharmacopoeia of one of the Member States shall be deemed to comply sufficiently with Article 8. In this case the description of the analytical methods and procedures shall be replaced in each relevant section by an appropriate reference to the pharmacopoeia in question.

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

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

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

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

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

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

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

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

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

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

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

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

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

(a) crystalline form and solubility;

(b) particle size;

(c) state of hydration;

(d) oil/water coefficient of partition;

(e) pK/pH values.

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

II.2C2. **Excipients**

(1) Excipients fulfilling the requirements of the European Pharmacopoeia or, in the absence of a European Pharmacopoeia monograph, the pharmacopoeia of one of the Member States shall be deemed to comply sufficiently with Article 8. In that case, the description of the analytical methods and procedures shall be replaced in each relevant section by an appropriate reference to the pharmacopoeia in question. Where appropriate, additional tests to control parameters such as particle size, sterility, and/or residual solvents, shall supplement the requirements of the monograph.

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

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

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

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

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

II. 2C3.1. **Active substance**

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

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

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

II. 2C3.2. **Finished product**

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

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

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

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

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

II.2C4. **Substances of biological origin**

(1) Information on the source, processing, characterisation and control of all materials of biological origin (human, animal, herbal or from microorganisms) used in the manufacture of the veterinary medicinal products shall be provided, including viral safety data, in accordance with relevant guidelines.

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

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

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

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

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

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

II.2E. **Control tests on the finished product**

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

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

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

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

II.2E1. **General characteristics of the finished product**

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

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

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

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

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

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

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

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

II.2E3. **Identification and assay of excipient components**

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

II.2E4. **Microbiological controls**

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

II.2E5. **Batch-to-batch consistency**

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

II.2E6. **Other controls**

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

II.2F. **Stability test**

II.2F1. **Active substance(s)**

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

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

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

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

II.2F2. **Finished product**

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

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

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

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

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

(6) Where the stability data show that the assay of the active substance declines on storage, the description of the control tests on the finished product shall include, where appropriate, the chemical and, if necessary, the toxico-pharmacological investigation of the changes that this substance has undergone, and possibly the characterisation and/or assay of the degradation products.

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

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

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

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

II.2G. **Other information**

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

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

(1) Each study report shall include:

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

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

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

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

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

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

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

(h) the name of the laboratory;

(i) the name of the study director;

(j) signature and date;

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

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

(m) description of mathematical and statistical procedures.

(2) Published studies may be accepted if they contain a sufficient amount of data and sufficient details to allow an independent assessment. The experimental techniques shall be described in such detail as to allow them to be reproduced, and the investigator shall establish their validity. Summaries of studies for which detailed reports are not available shall not be accepted as valid documentation. When the substance has been previously evaluated for the establishment of maximum residues limit ("MRL") to address certain safety requirements reference may be made to the European public MRL assessment reports ("EPMARs"). Where reference to EPMAR is made there is no need to submit studies already evaluated as part of the MRL evaluation; only new studies not available for the MRL assessment shall be provided. If the route of exposure (for example, for the user) is not identical to the route used in accordance with Commission Regulation (EU) 2018/782 ([5]), new studies might be necessary.

II.3A. **Safety tests**

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

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

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

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

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

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

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

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

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

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

(c) Chemical Abstract Service (CAS) number;

(d) therapeutic, pharmacological and chemical classification;

(e) synonyms and abbreviations;

(f) structural formula;

(g) molecular formula,

(h) molecular weight;

(i) degree of purity;

(j) qualitative and quantitative composition of impurities;

(k) description of physical properties:

(i) melting point,

(ii) boiling point,

(iii) vapour pressure,

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

(v) density,

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

(l) formulation of the product.

II.3A2. **Pharmacology**

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

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

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

II.3A2.1. **Pharmacodynamics**

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

II.3A2.2. **Pharmacokinetics**

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

II.3A3. **Toxicology**

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

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

(3) Single-dose toxicity

Single-dose toxicity studies may be used to predict:

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

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

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

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

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

(4) Repeat-dose toxicity

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

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

(5) Tolerance in the target species

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

(6) Reproductive toxicity including developmental toxicity

Study of the effects on reproduction

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

(7) Study of developmental toxicity

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

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

(8) Genotoxicity

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

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

(9) Carcinogenicity

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

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

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

(10) Exceptions

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

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

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

II.3A4. **Other requirements**

II.3A.4.1. **Special studies**

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

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

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

II.3A.4.2. **Observations in humans**

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

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

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

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

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

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

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

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

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

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

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

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

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

(3) Resistance in the environment shall be addressed.

II.3A5. **User safety**

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

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

II.3A6. **Environmental risk assessment**

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

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

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

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

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

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

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

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

II.3B. **Residue tests**

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

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

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

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

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

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

II.3B1. **Identification of the product**

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

(a) composition;

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

(c) batch identification.

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

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

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

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

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

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

II.3B3. **Residue analytical method**

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

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

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

II.4A. **Pre-clinical studies**

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

II.4A1. **Pharmacology**

II.4A.1.1. **Pharmacodynamics**

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

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

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

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

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

II.4A.1.2. **Pharmacokinetics**

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

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

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

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

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

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

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

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

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

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

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

II.4A3. **Dose determination and confirmation**

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

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

II.4A4. **Tolerance in the target animal species**

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

II.4B. **Clinical trial(s)**

II.4B1. **General principles**

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

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

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

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

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

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

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

II.4B2. **Documentation**

II.4B2.1. **Results of pre-clinical studies**

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

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

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

(c) tests demonstrating target animal safety;

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

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

(a) a summary;

(b) a study protocol;

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

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

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

II.4B2.2. **Results of clinical trials**

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

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

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

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

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

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

(i) received no treatment,

(ii) received a placebo, or

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

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

(d) the frequency of observed adverse reactions;

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

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

(g) a statistical evaluation of the results.

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

SECTION III

REQUIREMENTS FOR BIOLOGICAL VETERINARY MEDICINAL PRODUCTS

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

SECTION IIIa

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

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

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

IIIa.1. ***Part 1: Summary of the dossier***

Please refer to Section I.

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

IIIa.2A. **Product description**

IIIa.2A1. **Qualitative and quantitative composition**

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

(a) the active substance(s);

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

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

(d) accompanying reconstitution solvent(s);

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

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

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

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

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

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

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

IIIa.2A2. **Product development**

An explanation shall be provided including but not limited to:

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

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

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

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

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

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

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

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

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

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

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

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

IIIa.2A3. **Characterisation**

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

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

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

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

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

IIIa.2A3.2. **Impurities**

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

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

IIIa.2B. **Description of the manufacturing method**

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

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

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

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

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

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

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

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

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

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

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

IIIa.2C. **Production and control of starting materials**

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

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

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

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

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

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

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

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

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

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

IIIa.2C1. **Starting materials listed in pharmacopoeias**

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

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

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

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

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

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

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

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

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

(3) Information shall be provided on all substances of biological origin used at any stage in the manufacturing procedure. The information shall include the manufacturing strategy, purification and inactivation procedures with their validation and all in-process control procedures designed to ensure the quality, safety and batch to batch consistency of the finished product as well as details of any tests for contamination carried out on each batch of the substance. Any special precautions which may be necessary during storage of the starting material and, if necessary, its storage life shall be given.

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

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

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

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

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

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

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

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

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

(c) the function of the starting material;

(d) methods of identification;

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

IIIa.2D. **Control tests during the manufacturing process**

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

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

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

IIIa.2E. **Control tests on the finished product**

IIIa.2E1 **Finish product specification**

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

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

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

IIIa.2E2 **Method descriptions and validation of release tests**

(1) General characteristics

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

(2) Identification and potency test

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

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

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

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

(3) Identification and assay of excipient components

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

(4) Sterility and purity tests

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

(5) Residual humidity

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

(6) Filling volume

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

IIIa.2E3. **Reference standards or materials**

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

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

IIIa.2F. **Batch-to-batch consistency**

IIIa.2F1. **Active substance**

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

IIIa.2F2. **Finished product**

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

IIIa.2G. **Stability tests**

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

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

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

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

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

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

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

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

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

IIIa.2H. **Other information**

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

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

(1) Each study report shall include:

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

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

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

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

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

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

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

(h) the name of the laboratory;

(i) the name of the study director;

(j) signature and date;

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

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

(m) description of mathematical and statistical procedures.

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

IIIa.3A. **Safety tests**

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

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

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

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

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

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

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

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

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

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

(c) Chemical Abstract Service (CAS) number;

(d) therapeutic, pharmacological and chemical classification;

(e) synonyms and abbreviations;

(f) structural formula;

(g) molecular formula;

(h) molecular weight;

(i) degree of impurity;

(j) qualitative and quantitative composition of impurities;

(k) description of physical properties;

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

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

(n) formulation of the product.

IIIa.3A2. **Pharmacology**

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

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

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

IIIa.3A2.1. **Pharmacodynamics**

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

IIIa.3A2.2. **Pharmacokinetics**

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

IIIa.3A3. **Toxicology**

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

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

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

IIIa.3A3.1. **Single-dose toxicity**

Single-dose toxicity studies may be used to predict:

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

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

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

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

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

IIIa.3A3.2. **Repeat-dose toxicity**

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

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

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

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

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

(1) Study of the effects on reproduction

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

(2) Study of developmental toxicity

For the evaluation of effects in the target animal species, developmental toxicity studies are not required for products intended only for use in non-breeding animals. For other products a study of developmental toxicity shall be performed in at least one species, which may be the target species.

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

IIIa.3A3.5. **Genotoxicity**

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

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

IIIa.3A3.6. **Carcinogenicity**

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

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

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

IIIa.3A3.7. **Exceptions**

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

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

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

IIIa.3A4. **Other requirements**

IIIa.3A4.1. **Special studies**

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

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

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

IIIa.3A4.2. **Observations in humans**

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

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

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

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

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

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

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

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

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

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

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

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

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

(3) Resistance in the environment shall be addressed.

IIIa.3A5. **User safety**

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

User safety shall be addressed in accordance with CVMP guidelines.

IIIa.3A6. **Environmental risk assessment**

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

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

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

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

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

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

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

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

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

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

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

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

IIIa.3B. **Residue tests**

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

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

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

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

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

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

IIIa.3B1. **Identification of the product**

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

(a) composition;

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

(c) batch identification.

IIIa.3B2. **Depletion of residues**

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

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

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

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

IIIa.3B3. **Residue analytical method**

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

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

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

IIIa.4A. **Pre-clinical studies**

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

IIIa.4A1. **Pharmacology**

IIIa.4A1.1. **Pharmacodynamics**

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

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

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

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

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

IIIa.4A1.2. **Pharmacokinetics**

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

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

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

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

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

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

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

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

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

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

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

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

IIIa.4A3. **Dose determination and confirmation**

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

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

IIIa.4A4. **Tolerance in the target animal species**

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

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

IIIa.4B. **Clinical trials**

IIIa.4B1. **General principles**

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

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

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

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

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

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

IIIa.4B2. **Documentation**

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

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

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

(a) tests demonstrating pharmacological activity;

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

(c) tests demonstrating the main pharmacokinetic profile;

(d) tests demonstrating target animal safety;

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

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

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

(a) a summary;

(b) a study protocol;

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

(d) a statistical analysis of the results;

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

Omission of any of those data shall be justified.

IIIa.4B2.2. **Results of clinical trials**

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

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

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

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

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

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

(i) received no treatment;

(ii) received a placebo;

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

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

(d) the frequency of observed adverse reactions;

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

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

(g) a statistical evaluation of the results.

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

SECTION IIIb

REQUIREMENTS FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

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

IIIb.1. ***Part 1: Summary of the dossier***

Please refer to Section I.

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

IIIb.2.A. **Product description**

IIIb.2A1. **Qualitative and quantitative composition**

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

(a) the active substance(s);

(b) the constituents of the adjuvants;

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

(d) accompanying reconstitution solvents.

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

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

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

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

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

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

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

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

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

IIIb.2A2. **Product development**

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

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

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

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

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

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

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

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

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

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

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

IIIb.2B. **Description of the manufacturing method**

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

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

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

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

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

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

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

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

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

IIIb.2C. **Production and control of starting materials**

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

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

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

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

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

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

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

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

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

IIIb.2C1. **Starting materials listed in pharmacopoeias**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(a) details of the source of the materials;

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

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

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

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

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

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

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

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

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

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

(c) the function of the starting material;

(d) methods of identification;

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

IIIb.2D. **Control tests during the manufacturing process**

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

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

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

IIIb.2E. **Control tests on the finished product**

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

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

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

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

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

(6) General characteristics of the finished product

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

(7) Identification of active substance(s)

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

(8) Batch titre or potency

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

(9) Identification and assay of adjuvants

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

(10) Identification and assay of excipient components

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

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

(11) Sterility and purity test

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

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

(12) Residual humidity

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

(13) Filling volume

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

IIIb.2F. **Batch-to-batch consistency**

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

IIIb.2G. **Stability tests**

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

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

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

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

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

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

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

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

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

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

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

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

IIIb.2H. **Other information**

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

IIIb.3. ***Part 3: Safety documentation (safety and residuestests)***

IIIb.3A. **General requirements**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

IIIb.3B. **Pre-clinical studies**

(1) Safety of the administration of one dose

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

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

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

(2) Safety of one administration of an overdose

Only live immunological veterinary medicinal products require overdose testing.

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

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

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

(3) Safety of the repeated administration of one dose

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

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

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

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

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

(4) Examination of reproductive performance

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

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

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

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

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

(5) Examination of immunological functions

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

(6) Special requirements for live vaccines

(1) Spread of the vaccine strain

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

(2) Dissemination in the vaccinated animal

Faeces, urine, milk, eggs, oral, nasal and other secretions shall be tested for the presence of the organism as appropriate. Moreover, studies may be required of the dissemination of the vaccine strain in the body, with particular attention being paid to the predilection sites for replication of the organism. In the case of live vaccines for zoonoses within the meaning of Directive 2003/99/EC of the European Parliament and of the Council to be used for food producing animals, those studies shall take particularly into account the persistence of the organism at the injection site.

(3) Increase in virulence

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

(4) Biological properties of the vaccine strain

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

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

(5) Recombination or genomic reassortment of strains

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

(7) User safety

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

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

(8) Interactions

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

IIIb.3C. **Clinical trials**

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

IIIb.3D. **Environmental risk assessment**

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

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

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

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

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

(d) the disposal of unused or waste product.

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

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

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

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

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

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

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

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

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

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

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

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

IIIb.4A. **General requirements**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

IIIb.4B. **Pre-clinical studies**

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

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

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

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

(a) a summary;

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

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

(d) a detailed experimental protocol giving a description of the methods, apparatus and materials used, details such as species or breed of animals, categories of animals, where they were obtained, their identification and number, the conditions under which they were housed and fed (stating, inter alia, whether they were free from any specified pathogens and/or specified antibodies, the nature and quantity of any additives contained in the feed), dose, route, schedule and dates of administration, a description and a justification of the statistical methods used;

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

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

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

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

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

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

(k) occurrence and course of any intercurrent disease;

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

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

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

IIIb.4C. **Clinical trials**

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

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

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

(a) a summary;

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

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

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

(e) details of the trial protocol, giving a description of the methods, apparatus and materials used, details such as the route and method of administration, the schedule of administration, the dose, the categories of animals, the duration of observation, the serological response and other investigations carried out on the animals after administration;

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

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

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

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

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

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

(l) effects on the animals' performance;

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

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

(o) occurrence and course of any intercurrent disease;

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

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

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

SECTION IV

REQUIREMENTS FOR SPECIFIC MARKETING AUTHORISATION APPLICATIONS

IV.1. Applications for generic veterinary medicinal products

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

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

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

(a) the grounds for claiming bioequivalence;

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

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

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

(e) a review of the user safety risk assessment focusing on differences between the generic and reference veterinary medicinal products (for example, composition in excipients);

(f) a review of environmental risk assessment, where relevant.

IV.1.3. For a generic veterinary medicinal product application containing an antimicrobial substance, information about the level of resistance, as known from bibliographic data, shall be provided.

IV.1.4. For a generic veterinary medicinal product containing an antiparasitic substance, information about the level of resistance, as known from bibliographic data, shall be provided.

IV.1.5. For generic veterinary medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes, the following additional data shall be provided:

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

(b) evidence to demonstrate target animal tolerance at the administration site, which may be substantiated by appropriate target animal tolerance studies.

IV.2. **Applications for hybrid veterinary medicinal products**

IV.2.1. Applications based on Article 19 (hybrid veterinary medicinal products) concern veterinary medicinal products, which are similar to a reference veterinary medicinal product, but which do not meet the conditions in the definition of generic veterinary medicinal product.

IV.2.2. For such applications, the following information shall be supplied:

(a) all the data referred to in Parts 1 and 2 of Sections II or III, as appropriate, of this Annex;

(b) for Parts 3 and 4 of the dossier, hybrid applications may rely in part on the results of the appropriate safety, residue, pre-clinical studies and clinical trials for an already authorised reference veterinary medicinal product, and in part on new data. New data shall include a user safety risk assessment and an environmental risk assessment in accordance with Article 18(7), if applicable. In addition, for relevant products (for example, antimicrobials, antiparasitics) the risk of development of resistance shall be addressed, if applicable.

IV.2.3. In the case of biological (including immunological) veterinary medicinal products, a comprehensive comparability review, addressing the quality, safety and efficacy part shall be provided.

IV.2.4. Where reference is made to data originating from another authorised veterinary medicinal product, a justification for the use and relevance of those data for the new product shall be provided.

IV.2.5. The extent of new data required to support safety and efficacy will depend on the specific characteristics of the individual new product, and its differences to the reference veterinary medicinal product, and shall be determined on a case-by-case basis. New pre-clinical and clinical data for the new product shall be presented for all aspects where the reference veterinary medicinal product does not provide relevant support.

IV.2.6. If new studies are conducted with batches of a reference veterinary medicinal product authorised in a third country, the applicant shall demonstrate that the reference veterinary medicinal product has been authorised in accordance with requirements equivalent to those established in the Union, and are so highly similar that they may substitute each other in the pre-clinical studies or clinical trials.

IV.3. **Applications for combination veterinary medicinal products**

IV.3.1. An application for a fixed combination product with individual active substances, which have already been the object of a marketing authorisation for a veterinary medicinal product in the EEA, shall be submitted under Article 20.

A fixed combination product containing at least one new active substance which has not yet been authorised for a veterinary medicinal product in the EEA, shall be submitted under Article 8.

IV.3.2. For applications submitted under Article 20, a full dossier containing Parts 1, 2, 3 and 4 shall be provided.

IV.3.3. A sound scientific justification based on valid therapeutic principles for the combination of active substances, including clinical data, shall be provided, which demonstrates the need for and contribution of all active substances at the moment of treatment.

IV.3.4. In general, all the data on the safety and efficacy shall be provided for the fixed combination product, and safety and efficacy data for the individual active substances alone are not required, except to clarify their individual pharmacological properties.

IV.3.5. If data on the safety and efficacy of an individual known active substance are available to the applicant with sufficient amount of detail, those data could be provided to obviate the need for some studies with the fixed combination, or contributing relevant information. In that case, possible interaction between active substances shall also be investigated.

IV.3.6. User safety assessment, environmental risk assessment, residues depletion studies, and clinical studies shall be conducted with the fixed combination product.

IV.3.7. Unless the omission is justified, a target animal safety study with the final formulation shall be provided.

IV.4. **Applications based on informed consent**

IV.4.1. Applications based on Article 21 concern products with identical composition, pharmaceutical form and manufacturing process (including raw and starting materials, process parameters and manufacturing sites) as the already authorised veterinary medicinal products.

IV.4.2. The dossier for such applications shall only include data for Part 1A and 1B, as described in Annex I (points 1 to 6.4), provided that the marketing authorisation holder for the already authorised veterinary medicinal product has given the applicant his written consent to refer to the content of Parts 1C, 2, 3 and 4 of the dossier of that product. In that case, there is also no need to submit quality, safety and efficacy critical expert reports. The applicant shall provide proof of the written consent with their application.

IV.5. **Applications based on bibliographic data**

IV.5.1. For veterinary medicinal products for which the active substance(s) has or have been in well-established veterinary use as referred to in Article 22, with recognised efficacy and an acceptable level of safety, the following specific rules shall apply.

IV.5.2. A full dossier (containing Parts 1, 2, 3 and 4) shall be provided. The applicant shall submit Parts 1 and 2 as described in this Annex. For Parts 3 and 4, a detailed scientific bibliography together with information demonstrating the appropriate bridging between bibliographic references and the veterinary medicinal product shall be submitted to address safety and efficacy. The bibliographic data may need to be complemented by some documentation specific to the product, for example, user safety and environmental risk assessments, or residue study data to justify any proposed withdrawal period(s).

IV.5.3. The specific rules set out in Part IV.5.3.1 to IV.5.3.12 shall apply in order to demonstrate well-established veterinary use.

IV.5.3.1. In order to establish a well-established veterinary medicinal use of constituents of veterinary medicinal products, the following factors shall be taken into account:

(a) the time over which an active substance has been regularly used in the target species using the proposed route of administration and dosage regimen;

(b) quantitative aspects of the use of the active substance(s), taking into account the extent to which the substance(s) has or have been used in practice, and the extent of use on a geographical basis;

(c) the degree of scientific interest in the use of the active substance(s) (reflected in the published scientific literature);

(d) the coherence of scientific assessments.

IV.5.3.2. Different periods of time may be necessary for establishing well-established use of different active substances. In any case, the period of time required for establishing a well-established veterinary use of a constituent of a medicinal product shall not be less than 10 years from the first systematic and documented use of that substance as a veterinary medicinal product in the Union.

IV.5.3.3. Veterinary use does not exclusively mean use as an authorised veterinary medicinal product. Well-established veterinary use refers to the use for a specific therapeutic purpose in the target species.

IV.5.3.4. If a substance in well-established use is proposed for entirely new therapeutic indications, it is not possible to solely refer to a well-established veterinary use. Additional data on the new therapeutic indication, together with appropriate safety and residue tests and preclinical and clinical data shall be provided and, in such a case, applications based on Article 21 is not possible.

IV.5.3.5. The published documentation submitted by the applicant shall be freely available to the public and published by a reputable source, preferably peer-reviewed.

IV.5.3.6. The documentation shall contain sufficient details to allow an independent assessment.

IV.5.3.7. The documentation shall cover all aspects of the safety and/or efficacy assessment of the product for the proposed indication in the target species using the proposed route of administration and dosage regimen. It shall include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and, in particular, of comparative epidemiological studies.

IV.5.3.8. All documentation, both favourable and unfavourable, shall be communicated. With respect to the provisions on well-established veterinary use, it is in particular necessary to clarify that bibliographic reference to other sources of evidence (post-marketing studies, epidemiological studies etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if the applicant explains and justifies the use of those sources of evidence satisfactorily.

IV.5.3.9. Public assessment reports or freedom of information summaries cannot be considered to supply sufficient information, apart from the assessment report published by the Agency following the evaluation of an application for the establishment of maximum residue limits, which may be used in an appropriate manner as literature, particularly for the safety tests.

IV.5.3.10. Particular attention shall be paid to any missing information, and justification shall be given as to why demonstration of an acceptable level of safety and/or efficacy may be supported although some information is lacking.

IV.5.3.11. The critical expert reports regarding safety and efficacy shall explain the relevance of any data submitted, which concern a product different from the product intended for marketing. A judgement shall be made whether or not the product studied in the bibliography may be satisfactorily or scientifically bridged to the product, for which the application for a marketing authorisation has been made in spite of the existing differences.

IV.5.3.12. Post-marketing experience with other products containing the same constituents is of particular importance and applicants shall put a special emphasis on this issue.

IV.6. **Applications for limited markets**

IV.6.1. A marketing authorisation may be granted for a limited market in the absence of comprehensive safety and/or efficacy data when, as provided for in Article 23, the applicant demonstrates that the product is intended for use in a limited market and that the benefit of availability of the new product outweighs the risk associated with the omission of some of the safety or efficacy data required by this Annex.

IV.6.2. For such applications, the applicant shall submit Parts 1 and 2 as described in this Annex.

IV.6.3. For Parts 3 and 4, some of the safety or efficacy data required by this Annex may be omitted. As regards the extent of safety and efficacy data that may be omitted, the relevant guidance published by the Agency shall be taken into account.

IV.7. **Applications in exceptional circumstances**

IV.7.1. In exceptional circumstances related to animal or public health, a marketing authorisation may be granted under Article 25 for a veterinary medicinal product, subject to certain specific obligations, conditions and/or restrictions.

IV.7.2. For such applications, the applicant shall submit Part 1 as described in this Annex, together with a justification as to why the benefit of the immediate availability on the market of the veterinary medicinal product concerned outweighs the risk inherent in the fact that certain quality, safety or efficacy documentation has not been provided.

IV.7.3. For Parts 2, 3 and 4, certain quality, safety or efficacy data required by this Annex may be omitted, if the applicant justifies that those data cannot be provided at the time of submission. For the identification of the essential requirements for all such applications, the relevant guidance published by the Agency shall be taken into account.

IV.7.4. Post-authorisation studies may be requested as part of the conditions for marketing authorisation, and shall be designed, conducted, analysed and presented according to the general principles for quality, safety and efficacy tests set out in this Annex, and relevant guidance documents, as applicable depending on the issue to be addressed in the study.

SECTION V

REQUIREMENTS FOR MARKETING AUTHORISATION APPLICATIONS FOR PARTICULAR VETERINARY MEDICINAL PRODUCTS

This Section lays down specific requirements for identified veterinary medicinal products related to the nature of the active substances contained therein.

V.1. **Novel therapies veterinary medicinal products**

V.1.1 **General requirements**

V.1.1.1. Depending on the active substance and the mode of action, a novel therapy veterinary medicinal product could fall under any of the three product categories:

(a) veterinary medicinal products other than biological veterinary medicinal products;

(b) biological veterinary medicinal products other than immunological veterinary medicinal products;

(c) immunological veterinary medicinal products.

V.1.1.2. In general, marketing authorisation applications for novel therapy veterinary medicinal products, as defined in Article 4(43), shall follow the format and data requirements described in Section II or III of this Annex depending on how the novel therapy is categorised. A full dossier containing Parts 1, 2, 3 and 4 shall normally be provided in accordance with the requirements described in Section II or III and any relevant guidance published by the Agency. Deviations from the requirements of this Annex may be possible when justified. Where appropriate and taking into account the specificities of novel therapy products, additional requirements may be relevant for particular types of products.

V.1.1.3. The manufacturing processes for novel therapy veterinary medicinal products shall comply with the principles of Good Manufacturing Practice (GMP) adapted where necessary, to reflect the specific nature of those products. Guidelines specific to novel therapy veterinary products shall be drawn up, to properly reflect the particular nature of their manufacturing process.

V.1.1.4. According to the specific nature of a novel therapy product the use of the product may potentially be associated with specific risks. Those risks shall be identified applying a risk profiling methodology to identify the risks inherent to the specific product and the risk factors contributing to those risks. In this context, risks would be any potential unfavourable effects that may be attributed to the use of the novel therapy product which are of concern to the target population and/or the user, the consumer, and/or the environment. The risk analysis may cover the entire development. Risk factors that may be considered include the origin of the starting material (cells etc.), the mode of action in the animal (proliferation, initiation of an immune response, permanence in the body, etc.), the level of cell manipulation (for example, the manufacturing process), the combination of the active substance with bioactive molecules or structural materials, the extent of replication competence of viruses or micro-organisms used *in vivo*, the level of integration of nucleic acids sequences or genes into the genome, the long-time functionality, the risk of oncogenicity, the off-target effects and the mode of administration or use.

V.1.1.5. Based on the evaluation of the information on the identified risks and risk factors a specific profile of each individual risk associated with a specific product shall be established and may be used to determine and justify how the data set provided gives the necessary assurances for quality, safety and efficacy and is adequate to support a marketing authorisation application, especially for those aspects of novel therapy products that are beyond current knowledge.

V.1.1.6. To address data gaps or uncertainties at the time of product authorisation, implementation of post-authorisation measures or studies may be considered on a case-by-case basis. In order to detect early or delayed signals of adverse reactions, to prevent clinical consequences of such reactions and to ensure timely treatment and to gain information on the long-term safety and efficacy of novel therapy veterinary medicinal products a risk management plan shall detail the measures envisaged to ensure such follow up.

V.1.1.7. For any novel therapy product, in particular those considered as a nascent field in veterinary medicine, it is recommended to seek the advice of the Agency in a timely manner before submission of the marketing authorisation dossier in order to classify the product, determine the applicable dossier structure and to receive relevant information about the additional data set which may be necessary to support quality, safety and efficacy.

V.1.2. **Quality requirements**

V.1.2.1. In general, description of the composition, the manufacturing method, consistency of production, controls of starting materials, controls implemented during the manufacturing process, finished product testing including implementation of an activity test or a quantification of the active substance and stability data shall be submitted.

V.1.2.2. The data requirements for manufacturing and testing for novel therapy veterinary medicinal products of biological origin and classified as a biological product or as an immunological product shall in general be in accordance with those for biological or immunological medicinal products (as described in Section III of this Annex) including the need for a relevant potency test. There may be cases where additional requirements are applicable, for example, cells and vector gene constructs.

V.1.2.3. For novel therapy veterinary medicinal products constructed by chemical synthesis, data requirements as for veterinary medicinal products other than biological products (as described in Section II of this Annex) are generally applicable. There may be cases where additional requirements are applicable, for example, a relevant potency test.

V.1.3. **Safety requirements**

V.1.3.1. Depending on the nature of the product and its intended use, further data to evaluate safety for the target animal, the user, the consumer or the environment could be relevant as determined by a risk analysis in each case.

V.1.3.2. The requirements of Directive 2001/18/EC shall be taken into consideration when the treated animal itself could become a genetically modified organism. While Directive 2001/18/EC applies to finished products containing genetic modified organisms, it remains the best technical guide currently available for listing the necessary data. In particular, a main issue is the integration rate of DNA into germ cells (thus transmissible to offspring) or the potential transmission of the genetically modified cells to offspring. It shall also be noted that this problem is not completely the same when considering companion animals and food-producing animals (human consumption of products containing genetic modified organisms).

V.1.3.3. For substances intended for integration into or editing of the genome, appropriate tests shall be performed to evaluate the risk of off-target modifications and/or insertional mutagenesis.

V.1.4. **Efficacy requirements**

V.1.4.1. Efficacy data requirements differ primarily depending on the intended indications for use in the target species. Depending on the novel therapy product categorisation and the intended use in the target species, the efficacy requirements set out in Sections II or III may be applicable for a novel therapy veterinary medicinal product.

V.1.4.2. The indications claimed shall be supported by appropriate data in the target species.

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

V.1.5.1. **Principles**

V.1.5.1.1. Taking into account the specificities of novel therapy products, specific requirements additional to the standard requirements for evaluation of quality, safety and efficacy may be appropriate.

V.1.5.1.2. The following sections highlight specific requirements to be considered for particular type of novel therapy products. Those specific requirements established for a particular type of novel therapy product represent a non-exhaustive list of requirements that may need to be adapted to the specific product concerned on a case-by-case basis and based on a risk analysis.

V.1.5.1.3. In all cases and especially for novel therapies that are considered nascent in the field of veterinary medicine, applicants will need to take into account the current state of veterinary medicinal knowledge and the scientific guidance published by the Agency and the Commission, consistent with Section I of this Annex.

V.1.5.2. **Gene therapy veterinary medicinal products**

V.1.5.2.1. Gene therapy products are biological veterinary medicinal products that contain an active substance which contains or consists of a recombinant nucleic acid used in or administered to animals with a view to regulating, repairing, replacing, adding or deleting a genetic sequence. Their therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence they contain, or to the product of genetic expression of this sequence.

V.1.5.2.2. In addition to the data requirements set out in Sections II or III the following requirements shall apply:

(a) information shall be provided on all the starting materials used for the manufacture of the active substance, including the products necessary for the genetic modification of cells, as applicable, subsequent culture and preservation of the genetically modified cells, taking into consideration the possible absence of purification steps;

(b) for products containing a microorganism or a virus, data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the microorganism or virus, pathogenicity and characteristics of the parental strain shall be provided;

(c) process-related impurities and product-related impurities shall be described in the relevant sections of the dossier and in particular replication competent virus contaminants if the vector is designed to be replication incompetent;

(d) for plasmids, quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product;

(e) for genetically modified cells, the characteristics of the cells before and after the genetic modification, as well as before and after any subsequent freezing/storage procedures, shall be tested. For genetically modified cells, in addition to the specific requirements for gene therapy medicinal products, the quality requirements for cell therapy medicinal products and tissue engineered products shall apply;

(f) off-target insertions (leading, for example, to tumours/cancer, metabolic dysfunctions) and insertional mutagenesis and genotoxicity (insertion of genetic elements and the expression of DNA-modifying proteins as mediators of genotoxic side effects) in target species need to be considered;

(g) germline transmission studies shall be provided, unless otherwise justified.

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

V.1.5.3.1. Regenerative medicines are considered to encompass a wide area of products and therapies with a general purpose of restoring functions. Those medicines include cell-based therapies in which tissue engineered products are included.

V.1.5.3.2. Cell therapy veterinary medicinal products are biological veterinary medicinal products that contain or consist of cells or tissues that have been subject to substantial manipulation in either nature or function so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor. They are presented as having properties for, or are used in or administered to animals with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues or to regenerating, repairing or replacing a tissue.

V.1.5.3.3. In addition to the data requirements set out in Sections II or III the following requirements shall apply:

(a) summary information shall be provided on procurement and testing of the animal tissue and cells used as starting materials. If non-healthy cells or tissues are used as starting materials, their use shall be justified;

(b) the potential variability introduced through the animal tissues and cells shall be addressed as part of the validation of the manufacturing process, characterisation of the active substance and the finished product, development of assays, setting of specifications and stability;

(c) for the genetic modification of the cells, the technical requirements specified for gene therapy products shall apply;

(d) relevant information shall be provided on the characterisation of the cell population or cell mixture in terms of identity, purity (for example, extraneous agents and cellular contaminants), viability, potency, karyology, tumourigenicity and suitability for the intended medicinal use. The genetic stability of the cells shall be demonstrated;

(e) the impact and interactions of any components likely to interact (directly or as a result of degradation or metabolism) with the active substance shall be investigated;

(f) where a three-dimensional structure is part of the intended function, the differentiation state, structural and functional organisation of the cells and, where applicable, the extracellular matrix generated shall be part of the characterisation for those cell-based products.

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

V.1.5.4.1. Bacteriophages are viruses that depend on bacterial hosts for proliferation and act very specifically on certain bacterial strains. Phage therapy may be used, for example, as an alternative to antibiotics. Generally, bacteriophages consist of a genome, comprised of single or double stranded DNA or RNA, encapsulated by a protein capsid. Due to the diversity of the intended targets for treatment and the specificity of the bacteriophages, it will be necessary to choose the suitable bacteriophage strain against the disease-causing bacterial strain on a case-by-case basis for the individual outbreak of the disease.

V.1.5.4.2. The quality and quantity of the bacteriophages to be used in the finished product are normally variable. Therefore, a fixed qualitative and quantitative composition of bacteriophages will not be the usual situation as the phages need to be adapted on an ongoing basis. Based on this a seed stock of bacteriophages strains need to be established and maintained (comparable with a multi-strain approach).

V.1.5.4.3. Bacteriophages as well as host bacteria/master cell banks for manufacturing shall preferably be produced based on a master seed system. Confirmation shall be provided that the bacteriophage used is lytic.

V.1.5.4.4. The absence of resistance gene(s) and the absence of genes coding for virulence factors shall be shown on all master seeds.

V.1.5.4.5. The indication shall be for prophylactic, metaphylactic and/or therapeutic treatment of one or several specific infection(s) or infectious disease(s). Efficacy of treatment is linked to the lytic activity of phages that confers bactericidal activity on those bacteriophages with specificity for the bacterial strain concerned.

V.1.5.4.6. For genetically modified phages, the genetic modification shall be described.

V.1.5.5. **Veterinary medicinal product issued from nanotechnologies**

V.1.5.5.1. Nanotechnologies are seen primarily as a technology to generate carriers for chemically synthesised substances but may also be carriers for biological substances. The use of nanoparticles may be a way of controlling delivery of substances with low solubility or toxic compounds.

V.1.5.5.2. "Nanotechnology" corresponds to the design, characterisation, and production of nanomaterials by controlling shape and size at the nanoscale (up to around 100 nm).

V.1.5.5.3. "Nanoparticles" are considered to have two or more dimensions at the nanoscale.

V.1.5.5.4. Within the veterinary field, nanoparticles for drug delivery system are relevant as "products issued from nanotechnologies": nanoparticles are conjugated with substances in order to change the pharmacokinetic and/or pharmacodynamic properties. mRNA drugs are rather encapsulated in nanoparticle delivery systems.

V.1.5.5.5. In addition to the quality data requirements set out in Sections II or III the following requirements shall apply:

(a) size distribution of particles shall be determined;

(b) a suitable *in vitro* test for their function and possible delivery capacity (if used as drug delivery system) shall be used.

V.1.5.5.6. With regard to safety, the kind of hazards that are introduced by using nanoparticles for drug delivery may be beyond conventional hazards imposed by chemicals in classical delivery matrices. Therefore, the following aspects shall be considered with regard to safety:

(a) The nanoparticles for drug delivery could influence the toxicity of the medicinal product. The toxicity of the active substance is pivotal to the product but the toxicity of the nanoparticle for drug delivery shall also be considered, as they may introduce specific risks (agglomerates, cytotoxicity), may convey impurities by adsorption, may generate toxic materials by degradation or solubilisation, or may be transferred through physiological barrier (haemato-encephalic, foeto-placental, cell and nuclear membranes, etc.). In this context:

(i) when physiological barriers are crossed, the impact of nanoparticles for drug delivery shall be investigated on the corresponding organ(s);

(ii) the impact of agglomerates shall be investigated in the different targeted organs, focusing in particular on the risk of embolism in the smaller blood vessels;

(iii) safety issues of the nanoparticles for drug delivery may be linked to a cumulative effect, a degradation profile or persistence in the body with negative effects on the functions of the targeted organs;

(iv) safety issues might also be perceived at the cell level. Cells might not always be able to eliminate the nanoparticles conveyed through the cell membrane, leading to cytotoxicity especially via the induction of an oxidative stress. The toxicological assays to be implemented shall be able to assess this cytotoxicity and the related aspects, such as the generation of toxic free radicals and biopersistence.

(b) The toxicology profile of the active substances contained in nanoparticles for drug delivery may differ as they may be distributed differently into various internal organs (different solubility in biological matrices), or as they may unexpectedly cross various biological barriers within the body, such as the brain barrier.

(c) The side effects linked to the active substances may be exacerbated when they are delivered by nanoparticles.

(d) Immunosafety issues such as immunotoxicity (direct damage to immune cells), immunostimulation, immunosuppression and immunomodulation (such as complement activation, inflammation, activation of the innate or adaptive immunity), were already identified for nanomedicines.

(e) The capacity of nanoparticles to create inflammatory or allergic reactions shall be considered. The capacity to penetrate into the blood stream and to induce inflammatory reactions may lead to disseminated intravascular coagulation or fibrinolysis with further consequences such as thrombosis. The haemocompatibility of the nanoparticles shall therefore be checked.

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

V.1.5.6.1. Antisense therapy and interference therapy products may be generated by synthesis or through recombinant techniques.

V.1.5.6.2. Antisense RNA is a single stranded RNA that is complementary to a protein coding messenger RNA with which it hybridises, and thereby blocks its translation into protein.

V.1.5.6.3. RNA interference is a biological process in which RNA molecules inhibit gene expression or translation, by neutralising targeted mRNA molecules.

V.1.5.6.4. In addition to the data requirements set out in Sections II or III the following requirements shall apply:

(a) the minimum amount of RNA segments per volume needs to be established as part of control tests of the finished product, as well as the confirmation that the RNA segments present the correct sequence;

(b) for certain antisense therapy products falling under Section II of this Annex a potency bioassay may be needed for their release testing;

(c) stability studies shall include a test to monitor the degradation rate of the RNA segments over time;

(d) for RNA antisense therapy products, the possible harmful effects due to on- or off-target binding shall be addressed as well as possible non-antisense harmful effects due to, for example, accumulation, pro-inflammatory responses and aptamer binding;

(e) for RNAi therapy products, the possible harmful effects of off-target interference (due to the positive RNAi strand) shall be addressed, as well as the possibility of crossing the blood-brain barrier and causing central nervous system disorders;

(f) for RNA antisense therapy and RNA interference therapy products intended for gene therapy the requirements for gene therapy veterinary medicinal product shall be considered.

V.2. **Vaccine Antigen Master File**

For particular immunological veterinary medicinal products and by derogation from Section IIIb, Part 2, the concept of a Vaccine Antigen Master File is introduced.

V.2.1. Principles

V.2.1.1. For the purpose of this Annex, a Vaccine Antigen Master File means a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information on quality concerning each of the active substances, which are part of the veterinary medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.

V.2.1.2. The use of Vaccine Antigen Master Files is optional. For combined vaccines, the vaccine antigen(s) to be included in Vaccine Antigen Master File(s) shall be specified and a separate Vaccine Antigen Master File shall be required for each of them.

V.2.1.3. The submission and approval of a Vaccine Antigen Master File shall comply with the relevant guidance published by the Agency.

V.2.2. Content

The Vaccine Antigen Master File dossier shall contain the information in Parts V.2.2.1 to V.2.3.3 extracted from the relevant sections of Part 1 (Summary of the dossier) and Part 2 (Quality documentation) as set out in Section IIIb of this Annex:

V.2.2.1. Summary of the dossier (Part 1)

The name and address of the manufacturer(s) and the site(s) involved in the different stages of manufacture and control of the active substance, accompanied by copies of the corresponding manufacturing authorisations, shall be given.

V.2.2.2. Qualitative and quantitative particulars of the constituents (Part 2.A)

The complete and exact name of the active substance (for example, virus or bacteria strain, antigen) shall be provided, in the same way as mentioned in any finished product. Information on product development relevant to the active substance shall be provided.

V.2.2.3. Description of the manufacturing method (Part 2.B)

The description of the manufacturing method for the active substance shall be provided including validation of the key stages of production and justification, if relevant, of any intermediate storage proposed. For inactivated vaccines, data relevant to the inactivation of the active substance, including the validation of the inactivation process shall be provided.

V.2.2.4. Production and control of starting materials (Part 2.C)

V.2.2.4.1. The standard requirements described in Section IIIb.2C and relevant to the active substance shall apply.

V.2.2.4.2. Information on the active substance (for example, virus/bacteria strain), the substrate/s (cells, culture medium) and all the raw materials (pharmacopoeia or non-pharmacopoeia, biological or non-biological) used in the production of the active substance shall be provided.

V.2.2.4.3. The dossier shall include the specifications, information on the processes implemented and on the tests to be conducted for the quality control of all batches of starting materials and results for a batch for all components used.

V.2.2.4.4. TSE and extraneous agents (EA) risk assessment shall be provided, where applicable. It is to be noted that the target species retained for the finished products making reference to the Vaccine Antigen Master File shall be considered for the TSE and EA risk assessment. Warnings or restrictions of use may be brought in at the Vaccine Antigen Master File level depending on the information presented, which may be mitigated during the risk analysis at the level of the finished product.

V.2.2.4.5. If the active substance is obtained by recombinant techniques, all corresponding relevant data on the genetically modified virus/bacteria shall be provided.

V.2.2.5. Control tests during the manufacturing process (Part 2.D)

The standard requirements described in Section IIIb.2D shall apply for the in-process control tests carried out during the manufacture of the active substance, including validations of key control tests and, if relevant, any intermediate storage proposed (prior to blending).

V.2.2.6. Batch-to-batch consistency (Part 2.F)

The standard requirements described in Section IIIb.2F shall apply for the demonstration of consistency in the manufacture of the antigen.

V.2.2.7. Stability (Part 2.G)

The standard requirements described in Section IIIb.2G to demonstrate the stability of the antigen and, where relevant any intermediate storage, shall apply.

V.2.3. Evaluation and certification

V.2.3.1. For vaccines containing new vaccine antigen(s) where no Vaccine Antigen Master File already exists, the applicant shall submit to the Agency a full marketing authorisation application dossier including all the Vaccine Antigen Master Files corresponding to each single vaccine antigen for which the use of a Vaccine Antigen Master File is intended. A scientific and technical evaluation of each Vaccine Antigen Master File shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance with Union legislation for each Vaccine Antigen Master File, which shall be accompanied by the evaluation report. The certificate shall apply throughout the Union.

V.2.3.2. Part V.2.3.1 shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of those vaccine antigens are part of vaccines already authorised in the Union.

V.2.3.3. Changes to the content of a Vaccine Antigen Master File for a vaccine authorised in the Union shall be subject to a scientific and technical evaluation carried out by the Agency. In the case of a positive evaluation, the Agency shall issue a certificate of compliance with Union legislation for the Vaccine Antigen Master File. The certificate issued shall apply throughout the Union.

V.3. **Multi-strain dossier**

V.3.1. For certain immunological veterinary medicinal products and by derogation from the provisions of Section IIIb, Part 2, the concept of the use of a multi-strain dossier is introduced.

V.3.2. A multi-strain dossier means a single dossier containing the relevant data for a unique and thorough scientific assessment of the different options of strains/combinations of strains permitting the authorisation of inactivated vaccines against antigenically variable viruses or bacteria for which rapid or frequent change in the composition of vaccine formulations is needed to ensure efficacy with regard to the epidemiological situation in the field. According to the epidemiological situation where the vaccine is intended to be used, a number of strains could be selected from those included in the dossier to formulate a final product.

V.3.3. Each multi-strain dossier is applicable only to one virus species, bacteria genus or vector for a given disease; mixtures of various viruses belonging to different families, genera, species or bacteria belonging to different families or genera cannot be approved in the context of a multi-strain dossier.

V.3.4. For new applications to multi-strain dossier marketing authorisations where no authorised multi-strain vaccine already exists for a particular virus/bacterium/disease, eligibility for the multi-strain dossier approach shall be confirmed by the Agency before submission of the application.

V.3.5. The submission of multi-strain dossiers shall comply with relevant guidance published by the Agency.

V.4. **Vaccine platform technology**

V.4.1. Principles

V.4.1.1. Vaccine platform technology is a collection of technologies that have in common the use of a "backbone" carrier or vector that is modified with a different antigen or set of antigens for each vaccine derived from the platform. This includes, but may not be limited to, protein-based platforms (virus-like particles), DNA vaccine platforms, mRNA based platforms, replicons (self-replicating RNA) and viral and bacterial vector vaccines.

V.4.1.2. Applications for marketing authorisations of immunological veterinary medicinal products manufactured based on vaccine platform technologies are considered to be eligible for reduced data requirements. A full dossier is required for the first product from a manufacturer based on a particular platform technology for a particular target species. At the time of submission of the first (full) dossier based on the platform technology, the applicant may submit in parallel a "Platform Technology Master File" comprising all data relative to the platform for which there is reasonable scientific certainty that will remain unchanged regardless of the antigen (s)/gene(s) of interest added to the platform. The nature of the data to be included in the Platform Technology Master File will depend on the type of platform.

V.4.1.3. Once a Platform Technology Master File is certified, the certificate may be used to fulfil the relevant data requirements in subsequent applications for marketing authorisations based on the same platform and intended for the same target species.

V.4.2. Evaluation and certification

V.4.2.1. The submission of Platform Technology Master Files shall comply with relevant guidance published by the Agency. A scientific and technical evaluation of a Platform Technology Master File shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance with Union legislation for the Platform Technology Master File, which shall be accompanied by the evaluation report. The certificate shall apply throughout the Union.

V.4.2.2. Changes to the content of a Platform Technology Master File for a vaccine authorised in the Union shall be subject to a scientific and technical evaluation carried out by the Agency.

V.4.2.3. In the case of a positive evaluation the Agency shall issue a certificate of compliance with Union legislation for the Platform Technology Master File.

V.5. **Authorised homeopathic veterinary medicinal products**

V.5.1. **Quality (Part 2)**

The provisions of Section II.2. Part 2 shall apply to the documents for authorisation of homeopathic veterinary medicinal products referred to in Article 85(2) with the following modifications.

V.5.2. **Terminology**

The Latin name of the homeopathic stock described in the marketing authorisation application dossier shall be in accordance with the Latin title of the European Pharmacopoeia or, in absence thereof, of an official pharmacopoeia of a Member State. Where relevant the traditional name(s) used in each Member State shall be provided.

V.5.3. **Control of starting materials**

The particulars and documents on the starting materials, that is to say, all of the materials used including raw materials and intermediates up to the final dilution to be incorporated into the finished authorised homeopathic veterinary medicinal product, accompanying the application, shall be supplemented by additional data on the homeopathic stock.

The general quality requirements shall apply to all of the starting and raw materials as well as intermediate steps of the manufacturing process up to the final dilution to be incorporated into the finished homeopathic product. Where a toxic component is present, this shall be controlled, if possible, in the final dilution. If this is not possible because of the high dilution, the toxic component shall normally be controlled at an earlier stage. Every step of the manufacturing process from the starting materials up to the final dilution to be incorporated into the finished product shall be fully described.

Where dilutions are involved, those dilution steps shall be done in accordance with the homeopathic manufacturing methods laid down in the relevant monograph of the European Pharmacopoeia or, in absence thereof, in an official pharmacopoeia of a Member State.

V.5.4. **Control tests on the finished medicinal product**

The general quality requirements shall apply to the homeopathic finished veterinary medicinal products. Any exception shall be duly justified by the applicant.

Identification and assay of all the toxicologically relevant constituents shall be carried out. If justified that identification and/or an assay on all the toxicologically relevant constituents is not possible, for example, due to their dilution in the finished medicinal product the quality shall be demonstrated by complete validation of the manufacturing and dilution process.

V.5.5. **Stability tests**

The stability of the finished product shall be demonstrated. Stability data from the homeopathic stocks are generally transferable to dilutions/potentisations obtained thereof. If no identification or assay of the active substance is possible due to the degree of dilution, stability data of the pharmaceutical form may be considered.

V.5.6. **Safety documentation (Part 3)**

Part 3 shall apply to homeopathic veterinary medicinal products referred to in Article 4(10) of this Regulation with the following specification, without prejudice to the provisions of Commission Regulation (EU) No 37/2010 ([7]) on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin.

Any missing information shall be justified, for example, justification shall be given as to why demonstration of an acceptable level of safety may be supported, even where some studies are lacking.'

([7]) Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin (OJ L 15, 20.1.2010, p. 1).

COMMISSION DELEGATED REGULATION (EU) 2021/806

of 10 March 2021

amending Regulation (EU) No 528/2012 of the European Parliament and of the Council to include carbon dioxide generated from propane, butane or a mixture of both by combustion as an active substance in Annex I thereto

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products ([1]), and in particular Article 28(1) thereof,

Whereas:

(1) Commission Delegated Regulation (EU) No 1062/2014 ([2]) establishes a list of existing active substances to be evaluated for their possible approval for use in biocidal products. That lists includes carbon dioxide generated from propane, butane or a mixture of both by combustion.

(2) Carbon dioxide generated from propane, butane or a mixture of both by combustion has been evaluated for use in biocidal products of product-type 19, repellents and attractants, as described in Annex V to Regulation (EU) No 528/2012.

(3) France was designated as the rapporteur Member State and its evaluating competent authority submitted the assessment report together with its conclusions to the European Chemicals Agency ('the Agency') on 18 September 2019.

(4) In accordance with Article 7(2) of Delegated Regulation (EU) No 1062/2014, the Biocidal Products Committee adopted the opinion of the Agency on 16 June 2020 ([3]), having regard to the conclusions of the evaluating competent authority.

(5) According to that opinion, biocidal products of product-type 19 using carbon dioxide generated from propane, butane or a mixture of both by combustion may be expected to satisfy the requirements of Article 19(1)(b) of Regulation (EU) No 528/2012. The opinion of the Agency also concluded that this active substance does not give rise to concern and is eligible for inclusion in Annex I to Regulation (EU) No 528/2012.

(6) Taking into account the opinion of the Agency, it is therefore appropriate to include carbon dioxide generated from propane, butane or a mixture of both by combustion in Annex I to Regulation (EU) No 528/2012. As carbon dioxide generated from propane, butane or a mixture of both by combustion has been assessed based on an active substance dossier complying with the requirements set out in Article 11(1) of Directive 98/8/EC of the European Parliament and of the Council ([4]), carbon dioxide generated from propane, butane or a mixture of both by combustion should be included in category 6 of Annex I to Regulation (EU) No 528/2012, 'Substances for which a Member State has validated an active substance dossier in accordance with Article 7(3) of this Regulation or accepted such a dossier in accordance with Article 11(1) of Directive 98/8/EC'.

(7) Article 89(3) of Regulation (EU) No 528/2012 contains transitional measures where an existing active substance included in the work programme for the systematic examination of existing active substances is approved in accordance with that Regulation. With respect to carbon dioxide generated from propane, butane or a mixture of

([1]) OJ L 167, 27.6.2012, p. 1.

([2]) Commission Delegated Regulation (EU) No 1062/2014 of 4 August 2014 on the work programme for the systematic examination of all existing active substances contained in biocidal products referred to in Regulation (EU) No 528/2012 of the European Parliament and of the Council (OJ L 294, 10.10.2014, p. 1).

([3]) Biocidal Products Committee Opinion on the application for approval of the active substance: Carbon dioxide generated from propane, butane or a mixture of both by combustion, Product type: 19, ECHA/BPC/249/2020, adopted on 16 June 2020.

([4]) Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market (OJ L 123, 24.4.1998, p. 1).

both by combustion for product-type 19, the date of approval for the purposes of Article 89(3) of that Regulation should be set at 1 July 2022, in order to allow sufficient time for applications for authorisation to be submitted in accordance with the second subparagraph of Article 89(3) of that Regulation,

HAS ADOPTED THIS REGULATION:

Article 1

Annex I to Regulation (EU) No 528/2012 is amended in accordance with the Annex to this Regulation.

Article 2

For the purposes of Article 89(3) of Regulation (EU) No 528/2012, the date of approval of carbon dioxide generated from propane, butane or a mixture of both by combustion for product-type 19 is 1 July 2022.

Article 3

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 10 March 2021.

For the Commission
The President
Ursula VON DER LEYEN

ANNEX

In Annex I to Regulation (EU) No 528/2012, in Category 6 of the list of active substances referred to in Article 25(a), the following entry is added:

EC number	Name/group	Restriction	Comment
'204-696-9	Carbon dioxide generated from propane, butane or a mixture of both by combustion (*)		CAS No 124-38-9

(*) The date of approval of carbon dioxide generated from propane, butane or a mixture of both by combustion for product-type 19 for the purposes of Article 89(3) is 1 July 2022.'.

COMMISSION DELEGATED REGULATION (EU) 2021/807

of 10 March 2021

amending Regulation (EU) No 528/2012 of the European Parliament and of the Council to include potassium sorbate as an active substance in Annex I thereto

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products ([1]), and in particular Article 28(1) thereof,

Whereas:

(1) Potassium (E,E)-hexa-2,4-dienoate (potassium sorbate) has been assessed as an existing active substance included in the work programme for the systematic examination of all existing active substances, referred to in Article 89(1) of Regulation (EU) No 528/2012 and carried out in accordance with Commission Delegated Regulation (EU) No 1062/2014 ([2]).

(2) In accordance with Article 7(2) of Delegated Regulation (EU) No 1062/2014, the opinion of the European Chemicals Agency ('the Agency') was adopted on 4 December 2014 by the Biocidal Products Committee ([3]), having regard to the conclusions of the evaluating competent authority. As the evaluation of the competent authority was completed on 20 October 2010, the application for approval of potassium sorbate was examined in accordance with Directive 98/8/EC of the European Parliament and of the Council ([4]), as provided for in Article 90(2) of Regulation (EU) No 528/2012, and the Agency concluded in its opinion that biocidal products of product-type 8 containing potassium sorbate may be expected to fulfil the requirements of Article 5 of Directive 98/8/EC.

(3) Potassium sorbate was therefore approved as an active substance for use in biocidal products of product-type 8 by Commission Implementing Regulation (EU) 2015/1729 ([5]).

(4) Potassium sorbate is still included in the work programme for the systematic examination of all existing active substances for its use in biocidal products of product-type 6.

(5) In the opinion of 4 December 2014, the Agency also concluded that potassium sorbate fulfils the criteria for inclusion in Annex I to Regulation (EU) No 528/2012.

(6) Taking into account the opinion of the Agency, it is appropriate to include potassium sorbate in Annex I to Regulation (EU) No 528/2012. As potassium sorbate has been assessed on the basis of an active substance dossier that has been accepted in accordance with Article 11(1) of Directive 98/8/EC, potassium sorbate should be included in category 6 of Annex I to Regulation (EU) No 528/2012.

(7) Article 89(3) of Regulation (EU) No 528/2012 contains transitional measures where an existing active substance included in the work programme for the systematic examination of existing active substances is approved in accordance with that Regulation. With respect to potassium sorbate for product-type 6, the date of approval for the purposes of Article 89(3) of that Regulation should be set at 1 February 2023, in order to allow sufficient time for applications for authorisation to be submitted in accordance with the second subparagraph of Article 89(3) of that Regulation,

([1]) OJ L 167, 27.6.2012, p. 1.

([2]) Commission Delegated Regulation (EU) No 1062/2014 of 4 August 2014 on the work programme for the systematic examination of all existing active substances contained in biocidal products referred to in Regulation (EU) No 528/2012 of the European Parliament and of the Council (OJ L 294, 10.10.2014, p. 1).

([3]) Biocidal Products Committee Opinion on the application for approval of the active substance: Potassium sorbate, Product type: 8, ECHA/BPC/37/2014, adopted on 4 December 2014.

([4]) Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market (OJ L 123, 24.4.1998, p. 1).

([5]) Commission Implementing Regulation (EU) 2015/1729 of 28 September 2015 approving potassium sorbate as an existing active substance for use in biocidal products of product-type 8 (OJ L 252, 29.9.2015, p. 24).

HAS ADOPTED THIS REGULATION:

Article 1

Annex I to Regulation (EU) No 528/2012 is amended in accordance with the Annex to this Regulation.

Article 2

For the purposes of Article 89(3) of Regulation (EU) No 528/2012, the date of approval of potassium sorbate for product-type 6 is 1 February 2023.

Article 3

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 10 March 2021.

For the Commission
The President
Ursula VON DER LEYEN

ANNEX

In Annex I to Regulation (EU) No 528/2012, in Category 6 of the List of active substances referred to in Article 25(a), the following entry is added:

EC number	Name/group	Restriction	Comment
'246-376-1	Potassium (E,E)-hexa-2,4-dienoate (potassium sorbate) (*)	Minimum degree of purity of the active substance (**): 990 g/kg	CAS No 24634-61-5

(*) The date of approval of potassium sorbate for product-type 6 for the purposes of Article 89(3) is 1 February 2023.

(**) The purity indicated in this column was the minimum degree of purity of the active substance evaluated. The active substance in the product placed on the market can be of equal or different purity if it has been proven to be technically equivalent to the evaluated active substance.'.

COMMISSION IMPLEMENTING REGULATION (EU) 2021/808

of 22 March 2021

on the performance of analytical methods for residues of pharmacologically active substances used in food-producing animals and on the interpretation of results as well as on the methods to be used for sampling and repealing Decisions 2002/657/EC and 98/179/EC

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EU) 2017/625 of the European Parliament and of the Council of 15 March 2017 on official controls and other official activities performed to ensure the application of food and feed law, rules on animal health and welfare, plant health and plant protection products, amending Regulations (EC) No 999/2001, (EC) No 396/2005, (EC) No 1069/2009, (EC) No 1107/2009, (EU) No 1151/2012, (EU) No 652/2014, (EU) 2016/429 and (EU) 2016/2031 of the European Parliament and of the Council, Council Regulations (EC) No 1/2005 and (EC) No 1099/2009 and Council Directives 98/58/EC, 1999/74/EC, 2007/43/EC, 2008/119/EC and 2008/120/EC, and repealing Regulations (EC) No 854/2004 and (EC) No 882/2004 of the European Parliament and of the Council, Council Directives 89/608/EEC, 89/662/EEC, 90/425/EEC, 91/496/EEC, 96/23/EC, 96/93/EC and 97/78/EC and Council Decision 92/438/EEC (Official Controls Regulation) ([1]), and in particular Article 34(6) thereof,

Whereas:

(1) Regulation (EU) 2017/625 lays down rules for the performance of official controls and other official activities by the competent authorities of the Member States to verify compliance with Union legislation, inter alia, in the area of food safety at all stages of production, processing and distribution. It provides for specific rules on official controls in relation to substances whose use may result in residues in food and feed and sets general requirements for the methods to be used for sampling, laboratory analyses and tests during official controls and other official activities.

(2) Commission Decision 2002/657/EC ([2]) sets requirements for the performance of analytical methods and the interpretation of results of analyses of certain substances and residues thereof in live animals and animal products and Commission Decision 98/179/EC ([3]) lays down detailed rules on official sampling for the monitoring of certain substances and residues thereof in live animals and animal products. Both Decisions were adopted on the basis of Council Directive 96/23/EC ([4]), which was repealed by Regulation (EU) 2017/625. In view of new scientific developments, those rules should be updated and they should be integrated into the framework for official controls defined by Regulation (EU) 2017/625.

(3) In accordance with Article 1(2) of Decision 2002/657/EC, that Decision is not to apply to substances for which more specific rules have been laid down in other Union legislation. Those substances are mycotoxins in foodstuffs, dioxins and dioxins-like polychlorinated biphenyls (PCBs) in foodstuffs and lead, cadmium, mercury and benzo(a)p yrene in foodstuffs. Mycotoxins in foodstuffs are to fulfil the requirements set by Commission Regulation (EC) No 401/2006 ([5]) laying down the methods of sampling and analysis for the official control of the levels of mycotoxins in foodstuffs. Commission Regulation (EU) 2017/644 ([6]) laying down methods of sampling and

([1]) OJ L 95, 7.4.2017, p. 1.

([2]) Commission Decision 2002/657/EC of 14 August 2002 implementing Council Directive 96/23/EC concerning the performance of analytical methods and the interpretation of results (OJ L 221, 17.8.2002, p. 8).

([3]) Commission Decision 98/179/EC of 23 February 1998 laying down detailed rules on official sampling for the monitoring of certain substances and residues thereof in live animals and animal products (OJ L 65, 5.3.1998, p. 31).

([4]) Council Directive 96/23/EC of 29 April 1996 on measures to monitor certain substances and residues thereof in live animals and animal products and repealing Directives 85/358/EEC and 86/469/EEC and Decisions 89/187/EEC and 91/664/EEC (OJ L 125, 23.5.1996, p. 10).

([5]) Commission Regulation (EC) No 401/2006 of 23 February 2006 laying down the methods of sampling and analysis for the official control of the levels of mycotoxins in foodstuffs (OJ L 70, 9.3.2006, p. 12).

([6]) Commission Regulation (EU) 2017/644 of 5 April 2017 laying down methods of sampling and analysis for the control of levels of dioxins, dioxin-like PCBs and non-dioxin-like PCBs in certain foodstuffs and repealing Regulation (EU) No 589/2014 (OJ L 92, 6.4.2017, p. 9).

analysis for the control of levels of dioxins, dioxin-like PCBs and non-dioxin-like PCBs in certain foodstuffs apply in the case of dioxins and dioxins-like PCBs. Provisions for the sampling and analysis for the official controls for lead, cadmium, mercury and benzo(a)pyrene in foodstuffs are laid down in Commission Regulation (EC) No 333/2007 ([7]).

(4) For reasons of clarity and legal certainty, it is appropriate to merge the provisions applicable to sampling and analysis for pharmacologically active substances into one legal act as in case of mycotoxins, dioxins, dioxin-like PCBs, lead, cadmium, mercury and benzo(a)pyrene in foodstuffs.

(5) Decisions 98/179/EC and 2002/657/EC should therefore be repealed and replaced by this Regulation.

(6) In accordance with Regulation (EC) No 1831/2003 of the European Parliament and of the Council ([8]) coccidiostats and histomonostats can be used as feed additives, therefore Commission Regulation (EC) No 152/2009 ([9]) laying down the methods of sampling and analysis for the official control of feed applies to analyses of their content in feed. However, this Regulation should apply where feed are analysed as part of follow-up actions during investigations of the source of non-compliant samples in cases of suspected or established non-compliance with Union rules applicable to the use or residues of pharmacologically active substances authorised in veterinary medicinal products or as feed additives or with Union rules applicable to the use or residues of prohibited or unauthorised pharmacologically active substances.

(7) In order to ensure continuity in the performance of official controls and other official activities on residues of pharmacologically active substances and in order to avoid that all methods need to be re-validated at once, methods which have been validated before the date of entry into force of this Regulation may remain in use for a limited period, subject to the requirements of points 2 and 3 of Annex I to Decision 2002/657/EC. It is therefore appropriate to provide the Member States with sufficient time to apply the requirements laid down in this Regulation to all analytical methods.

(8) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Plants, Animals, Food and Feed,

HAS ADOPTED THIS REGULATION:

Article 1

Subject matter and scope

This Regulation lays down rules concerning the methods of analysis used for sampling and for laboratory analyses in relation to residues of pharmacologically active substances in live food-producing animals, their body parts and fluids, excrements, tissues, products of animal origin, animal by-products, feed and water. It also lays down rules for the interpretation of analytical results of these laboratory analyses.

This Regulation applies to official controls aimed at verifying compliance with the requirements on the presence of residues of pharmacologically active substances.

([7]) Commission Regulation (EC) No 333/2007 of 28 March 2007 laying down the methods of sampling and analysis for the control of the levels of trace elements and processing contaminants in foodstuffs (OJ L 88, 29.3.2007, p. 29).

([8]) Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition (OJ L 268, 18.10.2003, p. 29).

([9]) Commission Regulation (EC) No 152/2009 of 27 January 2009 laying down the methods of sampling and analysis for the official control of feed (OJ L 54, 26.2.2009, p. 1).

Article 2

Definitions

For the purposes of this Regulation, the definitions in Article 2 of Commission Delegated Regulation (EU) 2019/2090 ([10]), in Commission Regulation (EU) 2019/1871 ([11]), in Article 2 of Regulation (EC) No 470/2009 of the European Parliament and of the Council ([12]) and in Council Regulation (EEC) No 315/93 ([13]) shall apply.

The following definitions shall also apply:

(1) 'absolute recovery' means the yield of the final stage of an analytical process for an analyte divided by the amount of the analyte in the original sample, expressed as a percentage;

(2) 'accuracy' means the closeness of agreement between a test result and the accepted true reference value, determined by estimating trueness and precision ([14]);

(3) 'alpha (α) error' means the probability that the tested sample is compliant, even though a non-compliant measurement result has been obtained;

(4) 'analyte' means the component of a system to be analysed;

(5) 'authorised substance' means a pharmacologically active substance authorised for use in food-producing animals in accordance with Directive 2001/82/EC of the European Parliament and of the Council ([15]);

(6) 'beta (β) error' means the probability that the tested sample is truly non-compliant, even though a compliant measurement result has been obtained;

(7) 'bias' means the difference between the estimated value of the test result and an accepted reference value;

(8) 'calibration standard' means a traceable reference for measurements that represents the quantity of substance of interest in a way that ties its value to a reference base;

(9) 'certified reference material' (CRM) means a reference material, accompanied by documentation issued by a delegated body and providing one or more specified property values with associated uncertainties and traceabilities, using valid procedures ([16]);

(10) 'co-chromatography' means a technique in which an unknown substance is applied to a chromatographic support together with one or more known compounds, in the expectation that the relative behaviour of the unknown and known substances will assist in the identification of the unknown one;

(11) 'collaborative study' means analysing the same sample(s) by using the same method to determine performance characteristics of the method in different laboratories, where the study allows to calculate the random measurement error and laboratory bias for the method used;

([10]) Commission Delegated Regulation (EU) 2019/2090 of 19 June 2019 supplementing Regulation (EU) 2017/625 of the European Parliament and Council regarding cases of suspected or established non-compliance with Union rules applicable to the use or residues of pharmacologically active substances authorised in veterinary medicinal products or as feed additives or with Union rules applicable to the use or residues of prohibited or unauthorised pharmacologically active substances (OJ L 317, 9.12.2019, p. 28).

([11]) Commission Regulation (EU) 2019/1871 of 7 November 2019 on reference points for action for non-allowed pharmacologically active substances present in food of animal origin and repealing Decision 2005/34/EC (OJ L 289, 8.11.2019, p. 41).

([12]) Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council (OJ L 152, 16.6.2009, p. 11).

([13]) Council Regulation (EEC) No 315/93 of 8 February 1993 laying down Community procedures for contaminants in food (OJ L 37, 13.2.1993, p. 1).

([14]) ISO 3534-1: 2006 Statistics – Vocabulary and symbols – Part 1: General statistical terms and terms used in probability (Chapter 1).

([15]) Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (OJ L 311, 28.11.2001, p. 1).

([16]) JCGM 200:2008, International vocabulary of metrology – Basic and general concepts and associated terms (VIM), Third Edition 2008: https://www.iso.org/sites/JCGM/VIM-JCGM200.htm (Chapter 5 Measurement standards (Etalons)).

(12) 'confirmatory method' means a method that provides full or complementary information enabling the substance to be unequivocally identified and if necessary quantified in one of the following manners:

(a) at the maximum residue level or maximum level for authorised substances;

(b) at the reference points for action (RPA) for prohibited or unauthorised substances, for which a reference point for action is established;

(c) at a concentration as low as reasonably achievable for prohibited or unauthorised substance, for which no reference point for action is established;

(13) 'coverage factor (k)' means a number which expresses the desired level of confidence and which is associated with the expanded measurement uncertainty;

(14) 'decision limit for confirmation (CCα)' means the limit at and above which it can be concluded with an error probability of α that a sample is non-compliant and the value 1 − α means statistical certainty in percentage that the permitted limit has been exceeded;

(15) 'detection capability for screening (CCβ)' means the smallest content of the analyte that may be detected or quantified in a sample with an error probability of β:

(a) in the case of prohibited or unauthorised pharmacologically active substances, the CCβ is the lowest concentration at which a method is able to detect or quantify, with a statistical certainty of 1 − β, samples containing residues of prohibited or unauthorised substances;

(b) in the case of authorised substances, the CCβ is the concentration at which the method is able to detect concentrations below the permitted limit with a statistical certainty of 1 − β;

(16) 'fortified sample material' means a sample enriched with a known amount of the analyte to be detected or quantified;

(17) 'inter-laboratory study' means the organisation, performance and evaluation of tests on the same sample(s) by two or more laboratories in accordance with predetermined conditions to evaluate testing performance, either as a collaborative study or a proficiency test;

(18) 'internal standard (IS)' means a substance not contained in the sample and having physico-chemical properties as similar as possible to those of the analyte to be identified or quantified;

(19) 'level of interest' means the concentration of a substance or analyte in a sample that is significant to determine its compliance with the legislation as regards:

(a) the maximum residue level or maximum level for authorised substances in accordance with Commission Regulation (EC) No 124/2009 ([17]) and Commission Regulation (EU) No 37/2010 ([18]);

(b) reference points for action for prohibited or unauthorised substances, for which a reference point for action is established in accordance with Regulation (EU) 2019/1871;

(c) a concentration as low as analytically achievable for prohibited or unauthorised substance, for which no reference point for action is established;

(20) 'lowest calibrated level' (LCL) means the lowest concentration on which the measuring system has been calibrated;

(21) 'matrix' means the material from which a sample is taken;

(22) 'matrix effect' means the difference in analytical response between a standard dissolved in the solvent and a matrix-matched standard either without a correction using an internal standard or with correction using an internal standard;

([17]) Commission Regulation (EC) No 124/2009 of 10 February 2009 setting maximum levels for the presence of coccidiostats or histomonostats in food resulting from the unavoidable carry-over of these substances in non-target feed (OJ L 40, 11.2.2009, p. 7).

([18]) Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin (OJ L 15, 20.1.2010, p. 1).

(23) 'matrix-matched standard' means a blank (i.e. analyte-free) matrix to which the analyte is added at a range of concentrations after sample processing;

(24) 'matrix-fortified standard' means a blank (i.e. analyte-free) matrix, which prior to solvent extraction and sample processing, is spiked with the analyte at a range of concentrations;

(25) 'measurand' means the particular quantity subject to measurement;

(26) 'measurement uncertainty' means a non-negative parameter associated with the result of measurement, which characterises the dispersion of values that could reasonably be attributed to the measurand, based on the information used;

(27) 'performance criteria' means requirements for a performance characteristic according to which it can be judged that the analytical method is fit for the intended use and generates reliable results;

(28) 'precision' means the closeness of agreement between independent test results obtained under stipulated conditions and is expressed as the standard deviation or coefficient of variation of the test results;

(29) 'qualitative method' means an analytical method, which detects or identifies a substance or a group of substances on the basis of its chemical, biological or physical properties;

(30) 'quantitative method' means an analytical method, which determines the amount or mass fraction of a substance so that it may be expressed as a numerical value of appropriate units;

(31) 'recovery' means the recovery corrected amount of an analyte divided by the fortified amount of the analyte in the matrix sample, expressed as a percentage;

(32) 'recovery correction' means the use of internal standards, the use of a matrix calibration curve as well as the use of a recovery correction factor and also a combination of these approaches;

(33) 'reference material' means a material sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process or in examination of nominal properties ([19]);

(34) 'relative matrix effect' means the difference in analytical response between a standard dissolved in the solvent and a matrix-matched standard with a correction using an internal standard;

(35) 'repeatability' means precision under conditions, where independent test results are obtained with the same method on identical test items in the same laboratory by the same operator using the same equipment within short intervals of time;

(36) 'reproducibility' means precision under conditions, where test results are obtained with the same method on identical test items in different laboratories with different operators using different equipment ([20]);

(37) 'ruggedness' means the susceptibility of an analytical method to changes in experimental conditions under which the method can be applied as presented or with specified minor modifications;

(38) 'screening method' means a method that is used for screening of a substance or class of substances at the level of interest;

(39) 'screening target concentration' (STC) means the concentration lower than or equal to the CCβ at which a screening measurement categorises the sample as potentially non-compliant 'Screen Positive' and triggers a confirmatory testing;

(40) 'selectivity' means the ability of a method to distinguish between the analyte being measured and other substances;

(41) 'single laboratory study' or 'in-house validation' means an analytical study involving a single laboratory using one method to analyse the same or different test materials under different conditions over justified long time intervals;

([19]) Codex Alimentarius Commission, Food and Agriculture Organization of the United Nations/World Health Organization, Guidelines on analytical terminology (CAC/GL 72-2009).

([20]) ISO 5725-1:1994 Accuracy (trueness and precision) of measurement methods and results – Part 1: General principles and definitions (Chapter 3).

(42) 'standard addition' means a procedure in which one part of the sample is analysed as such and known amounts of the standard analyte are added to the other test portions before analysis;

(43) 'standard analyte' means an analyte of known and certified content and purity to be used as a reference in the analysis;

(44) 'substance' means matter of constant composition characterised by the entities which compose it and by certain physical properties;

(45) 'test portion' means the quantity of material drawn from the sample on which the test or observation is carried out;

(46) 'trueness' means the closeness of agreement between the average value obtained from a large series of test results and an accepted reference value;

(47) 'units' means those units described in ISO 80000 ([21]) and Council Directive 80/181/EEC ([22]);

(48) 'validation' means the demonstration by examination and the provision of effective evidence that the particular requirements of a specific intended use are fulfilled ([23]), through a single laboratory study or a collaborative study;

(49) 'within-laboratory reproducibility' or 'intermediate precision/in-house reproducibility' means measurement precision under a set of within-laboratory conditions in a specific laboratory.

Article 3

Methods of analysis

Member States shall ensure that the samples taken in accordance with Article 34 of Regulation (EU) 2017/625 are analysed using methods that comply with the following requirements:

(1) they are documented in test instructions, preferably according to Annexes of ISO 78-2:1999 Chemistry-Layouts for standards – Part 2: Methods of chemical analysis ([24]);

(2) they comply with the performance criteria and other requirements for analytical methods laid down in Chapter 1 of Annex I to this Regulation;

(3) they have been validated in accordance with the requirements laid down in Chapters 2 and 4 of Annex I to this Regulation;

(4) they allow enforcement of the reference points for action laid down in Regulation (EU) 2019/1871, the identification of the presence of prohibited and unauthorised substances and the enforcement of maximum levels (MLs), which have been set on the basis of Regulation (EEC) No 315/93 and Regulation (EC) No 124/2009 and maximum residue limits (MRLs), which have been set on the basis of Regulations (EC) No 1831/2003 and (EC) No 470/2009.

Article 4

Quality control

Member States shall ensure the quality of the results of analyses performed pursuant to Regulation (EU) 2017/625, in particular by monitoring tests or calibration results in accordance with ISO/IEC 17025:2017 General requirements for the competence of testing and calibration laboratories and with the requirements for quality control during routine analysis as laid down in Chapter 3 of Annex I to this Regulation.

([21]) ISO 80000-1:2009 Quantities and units – Part 1: General (Introduction).
([22]) Council Directive 80/181/EEC of 20 December 1979 on the approximation of the laws of the Member States relating to units of measurement and on the repeal of Directive 71/354/EEC (OJ L 39, 15.2.1980, p. 40).
([23]) ISO/IEC 17025:2017 General requirements for the competence of testing and calibration laboratories (Chapter 3).
([24]) ISO 78-2: 1999 Chemistry – Layouts for standards – Part 2: Methods of chemical analysis (Annexes).

Article 5

Interpretation of results

(1) The result of an analysis shall be considered non-compliant where it is equal to or above the decision limit for confirmation (CCα).

(2) For authorised substances for which an MRL or ML has been established, the decision limit for confirmation (CCα) shall be the concentration at and above which it can be decided with a statistical certainty of numerical value 1 – α that the permitted limit has been exceeded.

(3) For unauthorised or prohibited substances or for authorised substances for which no MRL or ML has been established in a specific species or product, the decision limit for confirmation (CCα) shall be the lowest concentration level at which it can be decided with a statistical certainty of numerical value 1 – α that the particular analyte is present.

(4) For unauthorised or prohibited pharmacologically active substances the α error shall be 1 % or lower. For all other substances, the α error shall be 5 % or lower.

Article 6

Methods for sampling

Member States shall ensure that samples are taken, handled and labelled in accordance with the detailed methods for sampling laid down in Annex II to this Regulation.

Article 7

Repeals and transitional measures

Decisions 2002/657/EC and 98/179/EC are repealed from the date of entry into force of this Regulation.

However, until 10 June 2026, the requirements laid down in points 2 and 3 of Annex I to Decision 2002/657/EC shall continue to apply to methods, which have been validated before the date of entry into force of this Regulation.

Article 8

Entry into force

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 22 March 2021.

For the Commission
The President
Ursula VON DER LEYEN

ANNEX I

CHAPTER 1

PERFORMANCE CRITERIA AND OTHER REQUIREMENTS FOR ANALYTICAL METHODS

1.1. Requirements of screening methods

1.1.1. *Categories of suitable screening methods*

Qualitative, semi-quantitative or quantitative methods shall be used as suitable screening methods.

1.1.2. *Requirements for biological, biochemical or physico-chemical screening* methods

For prohibited or unauthorised substances, the CCβ shall be as low as reasonably achievable and in any case lower than the reference point of action (RPA) for substances for which RPAs are established under Regulation (EU) 2019/1871.

For authorised pharmacologically active substances, the CCβ shall be lower than the MRL or ML.

Only those analytical methods, for which it can be demonstrated in a documented traceable manner that they are validated and have a false compliant rate lower than or equal to 5 % (β error), shall be used for screening purposes. In the case of a suspected non-compliant result, that result shall be confirmed by a confirmatory method.

Quantitative screening methods, used for both screening and confirmation shall meet the same requirements for accuracy, range, and precision as described in 1.2.2.1 and 1.2.2.2.

1.2. Requirements of confirmatory methods

1.2.1. *General requirements for confirmatory methods*

For prohibited or unauthorised substances, the CCα shall be as low as reasonably achievable. For prohibited or unauthorised substances, for which an RPA is established under Regulation (EU) 2019/1871 the CCα shall be lower than or equal to the reference point for action.

For authorised substances, the CCα shall be higher than but as close as possible to the MRL or ML.

For confirmation purposes, only analytical methods for which it can be demonstrated in a documented traceable manner that they are validated and have a false non-compliant rate (α error) which is less or equal to 1 % for prohibited or unauthorised substances or which is less or equal to 5 % for authorised substances shall be used.

Confirmatory methods shall provide information on the structural chemical composition of the analyte. Consequently, confirmatory methods based only on chromatographic analysis without the use of mass spectrometric detection are not suitable on their own for use as confirmatory methods for prohibited or unauthorised pharmacologically active substances. In the case of mass spectrometry not being suitable for authorised substances, other methods such as HPLC-DAD and -FLD, or a combination of them, can be used.

When required according to the confirmatory method, a suitable internal standard shall be added to the test portion at the beginning of the extraction procedure. Depending on availability, either stable isotope-labelled forms of the analyte, which are particularly suited for mass spectrometric detection, or analogue compounds that are structurally closely related to the analyte, shall be used. When no suitable internal standard can be used, the identification of the analyte shall preferably be confirmed by co-chromatography ([1]). In this case only one peak shall be obtained, the enhanced peak height (or area) being equivalent to the amount of added analyte. If this is not practicable, matrix-matched or matrix-fortified standards shall be used.

([1]) Co-chromatography is a procedure in which the sample extract prior to the chromatographic step(s) is divided into two parts. Part one is chromatographed as such. Part two is mixed with the standard analyte that is to be measured. Then this mixture is also chromatographed. The amount of added standard analyte has to be similar to the estimated amount of the analyte in the extract. Co-chromatography is used to improve the identification of an analyte when chromatographic methods are used, especially when no suitable internal standard can be used.

1.2.2. *General performance criteria for confirmatory methods*

1.2.2.1. Trueness by recovery

For repeated analyses of a certified reference material, the deviation of the experimentally determined recovery corrected mean mass fraction from the certified value shall comply with the minimum trueness ranges listed in Table 1.

Table 1

Minimum trueness of quantitative methods

Mass Fraction	Range
≤ 1 µg/kg	−50 % to +20 %
> 1 µg/kg to 10 µg/kg	−30 % to +20 %
≥ 10 µg/kg	−20 % to +20 %

When no certified reference materials are available, it is acceptable that trueness of measurements is assessed in other ways, such as using materials with assigned values from inter-laboratory studies or through additions of known amounts of the analyte(s) to a blank matrix.

1.2.2.2. Precision

The coefficient of variation (CV) for the repeated analysis of a reference or fortified material, under within-laboratory reproducibility conditions, shall not exceed the level calculated by the Horwitz Equation. The equation is:

$CV = 2^{(1 - 0,5 \log C)}$

where C is the mass fraction expressed as a power (exponent) of 10 (e.g. 1 mg/g = 10^{-3}). For mass fractions below 120 µg/kg the application of the Horwitz equation yields unacceptably high values. Therefore, the allowed maximum coefficient of variation shall not be greater than the values presented in Table 2.

Table 2

Acceptable coefficient of variation

Mass fraction	**Reproducibility CV (%)**
> 1 000 µg/kg	16 (adapted from Horwitz equation)
> 120 µg/kg – 1 000 µg/kg	22 (adapted from Horwitz equation)
10 – 120 µg/kg	25 *
< 10 µg/kg	30 *

* The CV (%) presented is a guideline and should be as low as reasonably possible.

For analyses carried out under repeatability conditions, the coefficient of variation under repeatability conditions shall be equal or below two thirds of the values listed in Table 2.

1.2.3. *Requirements for chromatographic separation*

For liquid (LC) or gas chromatography (GC), the minimum acceptable retention time for the analyte(s) under examination shall be twice the retention time corresponding to the void volume of the column. The retention time of the analyte in the extract shall correspond to that of the calibration standard, a matrix-matched standard or a matrix-fortified standard with a tolerance of ± 0,1 minute. For fast chromatography, where the retention time is below 2 minutes, a deviation of less than 5 % of the retention time is acceptable. In case an internal standard is used, the ratio of the chromatographic retention time of the analyte to that of the internal standard,

that means the relative retention time of the analyte, shall correspond to that of the calibration standard, matrix-matched standard or matrix-fortified standard with a maximum deviation 0,5 % for gas chromatography and 1 % for liquid chromatography for methods validated from the date of entry into force of this Regulation.

1.2.4. *Specific performance criteria for mass spectrometry*

1.2.4.1. Mass spectrometric detection

Mass spectrometric detection shall be carried out by using some of the following options:

1. recording full scan (FS) mass spectra;

2. selected ion monitoring (SIM);

3. sequential mass spectrometry (MS^n) techniques such as Selected Reaction Monitoring (SRM);

4. a combination of mass spectrometry (MS) or sequential mass spectrometry (MS^n) techniques with appropriate ionisation modes.

Both low-resolution mass spectrometry (LRMS, at unit mass resolution) and high-resolution mass spectrometry (HRMS), including e.g. double focusing sectors, Time of Flight (TOF) and Orbitrap instruments are appropriate.

For confirmation of the identity of an analyte in high-resolution mass spectrometry (HRMS) the mass deviation of all diagnostic ions shall be below 5 ppm (or in case of m/z < 200 below 1 mDa). On basis of this the effective resolution should be selected fit for purpose and the resolution shall typically be greater than 10 000 for the entire mass range at 10 % valley or 20 000 at full width at half maximum (FWHM).

When mass spectrometric determination is performed by the recording of full scan spectra (both LRMS and HRMS), only diagnostic ions with a relative intensity of more than 10 % in the reference spectrum of the calibration standard, matrix-matched standard or matrix-fortified standards are suitable. Diagnostic ions shall include the molecular ion (if present at ≥ 10 % intensity of the base peak) and characteristic fragment or product ions.

Precursor ion selection: When mass spectrometric determination is performed by fragmentation after precursor ion selection, precursor ion selection is carried out at unit mass resolution or better. The selected precursor ion shall be the molecular ion, characteristic adducts of the molecular ion, characteristic product ions or one of their isotope ions. In case the precursor selection has a mass selection window of more than one Dalton (e.g. in case of Data Independent Acquisition) the technique is considered as full-scan confirmatory analysis.

Fragment and product ions: The selected fragment or product ions shall be diagnostic fragment for the analyte/product measured. Non-selective transitions (e.g. the tropylium cation or loss of water) shall be omitted whenever possible. The abundance of diagnostic ions shall be determined from the peak area or height of integrated extracted ion chromatograms. This is also applicable when full-scan measurements are used for identification. The signal-to-noise (S/N) ratio of all diagnostic ions shall be greater or equal than three to one (3:1).

Relative intensities: The relative intensities of the diagnostic ions (ion ratio) are expressed as a percentage of the intensity of the most abundant ion or transition. The ion ratio has to be determined by comparing spectra or by integrating the signals of the extracted ion mass traces. The ion ratio of the analyte to be confirmed shall correspond to those of the matrix-matched standards, matrix-fortified standards or standard solutions at comparable concentrations, measured under the same conditions, within ± 40 % relative deviation.

For all mass spectrometric analyses, at least one ion ratio shall be determined. These are preferably ions obtained within a single scan, but the ions can also originate from different scans in the same injection (i.e. full scan and fragmentation scan).

1.2.4.2. Identification

A system of identification points shall be used to select adequate acquisition modes and evaluation criteria. For confirmation of the identity of substances in a matrix for which an MRL is established (authorised use), a minimum of 4 identification points is required. For unauthorised or prohibited substances, 5 identification points are required. One point can originate from the chromatographic separation. Table 3 shows the number of identification points that each of the techniques yields. To qualify for the identification points required for confirmation, identification points obtained from different techniques can be added.

1. All mass spectrometric analyses shall be combined with a separation technique that shows sufficient separation power and selectivity for the specific application. Suitable separation techniques are amongst others liquid and gas chromatography, capillary electrophoresis (CE) and supercritical fluid chromatography (SFC). In the case of analyte which presents any isobar or isomer compound, the acceptability of the retention time (i.e. ± 0,5 % in GC and ± 1 % in LC and SFC) is mandatory to confirm its identity.

2. A maximum of three separate techniques can be combined to achieve the minimum number of identification points.

3. Different ionisation modes (e.g. electron ionisation and chemical ionisation) are considered as different techniques.

Table 3

Identification points per technique

Technique	Identification Points
Separation (mode GC, LC, SFC, CE)	1
LR-MS ion	1
Precursor ion selection at <±0,5 Da mass range	1 (indirect)
LR-MS^n product ion	1,5
HR-MS ion	1,5
HR-MS^n product ion	2,5

Table 4

Examples of the number of identification points specific techniques and combinations of techniques (n = an integer)

Technique(s)	Separation	Number of ions	Identification points
GC-MS (EI or CI)	GC	n	1 + n
GC-MS (EI and CI)	GC	2 (EI) + 2 (CI)	1 + 4 = 5
GC-MS (EI or CI) 2 derivates	GC	2 (Derivate A) + 2 (Derivate B)	1 + 4 = 5
LC-MS	LC	n (MS)	1 + n
GC- or LC-MS/MS	GC or LC	1 precursor + 2 products	1 + 1 + 2 × 1,5 = 5
GC- or LC-MS/MS	GC or LC	2 precursor + 2 products	1 + 2 + 2 × 1,5 = 6
GC- or LC-MS^3	GC or LC	1 precursor + 1 MS^2 product + 1 MS^3 product	1 + 1 + 1,5 + 1,5 = 5
GC- or LC-HRMS	GC or LC	n	1 + n × 1,5

GC- or LC-HRMS/MS	GC or LC	1 precursor (<±0,5 Da mass range) + 1 product	1 + 1 + 2,5 = 4,5
GC- or LC-HRMS and HRMS/MS	GC or LC	1 full scan ion + 1 HRMS product ion [a]	1 + 1,5 + 2,5 = 5
GC- and LC-MS	GC and LC	2 ions (GCMS) + 1 ion (LCMS)	1 + 1 + 2 + 1 + 1 = 6

[a] No additional identification point is obtained for the precursor ion selection, if this precursor ion is the same ion (or an adduct or isotope) as the HRMS ion monitored in full scan.

1.2.5. *Specific performance criteria for the determination of an analyte using liquid chromatography with detection techniques other than mass spectrometry*

For authorised substances only, the following techniques can be used as alternative for mass spectrometry based methods, provided that the relevant criteria for these techniques are fulfilled:

1. full-scan diode array detection spectrophotometry (DAD) in case used with HPLC;

2. fluorescence detection spectrophotometry (FLD) in case used with HPLC.

Liquid chromatography with UV/VIS detection (single wavelength) is not suitable on its own for use as a confirmatory method.

1.2.5.1. Performance criteria for full-scan diode array spectrophotometry

The performance criteria for chromatographic separation included in Chapter 1.2.3 shall be fulfilled.

The absorption maxima in the UV spectrum of the analyte shall be at the same wavelengths as those of the calibration standard in matrix within a maximum margin, which is determined by the resolution of the detection system. For diode array detection, this maximum margin is typically within ± 2 nm. The spectrum of the analyte above 220 nm shall, for those parts of the two spectra with a relative absorbance greater than or equal to 10 %, not be visibly different from the spectrum of the calibration standard. This criterion is met when firstly the same maxima are present and secondly when the difference between the two spectra is at no point greater than 10 % of the absorbance of the calibration standard. In the case computer-aided library, searching and matching are used, the comparison of the spectral data in the official samples to that of the calibration solution has to exceed a critical match factor. This factor shall be determined during the validation process for every analyte on the basis of spectra for which the criteria described above are fulfilled. Variability in the spectra caused by the sample matrix and the detector performance shall be checked.

1.2.5.2. Performance criteria for fluorescence detection spectrophotometry

The performance criteria for chromatographic separation included in Chapter 1.2.3 shall be fulfilled.

The selection of the excitation and emission wavelengths in combination with the chromatographic conditions shall be done in such a way to minimise the effects of interfering components in blank sample extracts. There should be a minimum of 50 nanometres between the excitation and emission wavelength.

The nearest peak maximum in the chromatogram shall be separated from the designated analyte peak by at least one full peak width at 10 % of the maximum height of the analyte peak.

This applies to molecules that exhibit native fluorescence and to molecules that exhibit fluorescence after either transformation or derivatisation.

CHAPTER 2

VALIDATION

2.1. Performance characteristics to be determined for analytical methods

By means of the validation of the method, it shall be demonstrated that the analytical method complies with the criteria applicable for the relevant performance characteristics. Different control purposes require different categories of methods. Table 5 determines which performance characteristic shall be verified for which type of method, further explanation of each parameter is given in this chapter.

Table 5

Classification of analytical methods by the performance characteristics that have to be determined

Method	Confirmation		Screening		
	Qualitative	Quantitative	Qualitative	Semi-quantitative	Quantitative
Substances	A	A, B	A, B	A, B	A, B
Identification in accordance with 1.2	x	x			
CCα	x	x			
CCβ	-		x	x	x
Trueness		x			x
Precision		x		(x)	x
Relative matrix effect/absolute recovery *		x			x
Selectivity/Specificity		x	x	x	x
Stability #		x	x	x	x
Ruggedness		x	x	x	x

x: It is required to prove by means of the validation that the requirements for the performance characteristic are met.
(x) The precision requirements of Chapter 1.2.2.2 do not need to be met for semi-quantitative screening methods. However, the precision shall be determined to prove the suitability of the method for avoiding false compliant analytical results.
A: prohibited or unauthorised substances
B: authorised substances
If stability data for analytes in a matrix are available from scientific literature or from another laboratory, these data do not need to be determined again by the concerned laboratory. However, a reference to available stability data of analytes in solution is only acceptable if identical conditions are applied.
* Relevant for MS methods to prove by means of the validation that the requirements for the performance characteristics are met. The relative matrix effect of the method shall be determined when this effect was not assessed during the validation procedure. The absolute recovery of the method shall be determined when no internal standard or no matrix-fortified calibration is used.

2.2. Trueness, repeatability and within-laboratory reproducibility

This chapter provides examples and references for validation procedures. Other approaches to demonstrate that the method complies with performance criteria may be used, provided that they achieve the same level and quality of information.

2.2.1. *Conventional validation*

The calculation of the parameters in accordance with conventional methods requires the performance of several individual experiments. Each performance characteristic has to be determined for each major change (see Section 2.4). For multi-analyte methods, several analytes can be analysed simultaneously, as long as possibly relevant interferences have been ruled out. Several performance characteristics can be determined in a similar way. Therefore, in order to minimise the workload, it is advised to combine experiments as much as possible (e.g., repeatability and within-laboratory reproducibility with specificity, analysis of blank samples to determine the decision limit for confirmation and testing for specificity).

2.2.1.1. Trueness on the basis of a certified reference material

It is preferred to determine the trueness of an analytical method by means of certified reference material (CRM). The procedure for this is described in ISO 5725-4:1994 ([2]).

An example is given below:

1. Analyse six replicates of the CRM in accordance with the test instructions for the method;
2. Determine the concentration of the analyte present in each sample of the replicates;
3. Calculate the mean, the standard deviation and the coefficient of variation (%) *for these six replicates*;
4. Calculate the trueness by dividing the detected mean concentration by the certified value (measured as concentration) and multiply by 100, to express the result as a percentage.

Trueness (%) = (mean recovery-corrected concentration detected) × 100/certified value

2.2.1.2. Trueness on basis of fortified samples

If no certified reference material is available, the trueness of the method shall be determined by experiments using a fortified blank matrix, as a minimum in accordance with the following scheme:

1. For methods validated from the date of entry into force of this Regulation, select blank material and fortify at a concentration of:
   (a) 0,5 ([3]), 1,0 and 1,5 times the RPA; or
   (b) 0,1 ([4]), 1,0 and 1,5 times the MRL or ML for authorised substances; or
   (c) 1,0, 2,0 and 3,0 times the LCL for unauthorised substances (for which no RPA has been established).
2. At each level, the analysis shall be performed with six replicates.
3. Analyse the samples.
4. Calculate the concentration detected in each sample.
5. Calculate the trueness for each sample using the equation below and subsequently calculate the mean trueness and coefficient of variation for the six results at each concentration level.

Trueness (%) = (mean recovery-corrected concentration detected) × 100/fortification level

For methods for authorised substances validated before the date of application of this Regulation, a determination of the trueness of the method using 6 fortified aliquots at 0,5, 1,0 and 1,5 times the MRL or ML is sufficient.

([2]) ISO 5725-4:2020 Accuracy (trueness and precision) of measurement methods and results – Part 4: Basic methods for the determination of the trueness of a standard measurement method (Clause 3).

([3]) Where, for a non-allowed pharmacologically active substance validation of a concentration of 0,5 times the RPA is not reasonably achievable, the concentration of 0,5 times the RPA can be replaced by the lowest concentration between 0,5 times and 1,0 times the RPA, which is reasonably achievable.

([4]) Where, for a specific pharmacologically active substance validation of a concentration of 0,1 times the MRL is not reasonably achievable, the concentration of 0,1 times the MRL can be replaced by the lowest concentration between 0,1 times and 0,5 times the MRL, which is reasonably achievable.

2.2.1.3. Repeatability

1. For methods validated from the date of entry into force of this Regulation a set of samples of identical blank matrices of the same species shall be prepared. They shall be fortified with the analyte to yield concentrations equivalent to:

   (a) 0,5 ([5]), 1,0 and 1,5 times the RPA, or

   (b) 0,1 ([6]), 1,0 and 1,5 times the MRL or ML for authorised substances, or

   (c) 1,0, 2,0 and 3,0 times the LCL for unauthorised or prohibited substances in case no RPA is applicable.

2. At each level, the analysis shall be performed with at least six replicates.

3. Analyse the samples.

4. Calculate the concentration detected in each sample.

5. Calculate the mean concentration, standard deviation and the coefficient of variation (%) of the fortified samples.

6. Repeat these steps on at least two other occasions.

7. Calculate the overall mean concentrations, standard deviations (by averaging the standard deviation squared of the individual occasions and taking the square root of that) and coefficients of variation for the fortified samples.

For methods for authorised substances validated before the date of entry into force of this Regulation, a determination of the repeatability with fortified matrices in concentrations at 0,5, 1,0 and 1,5 times the MRL or ML is sufficient.

Alternatively, the calculation for repeatability can be performed according to ISO 5725-2:2019 ([7]).

2.2.1.4. Within-laboratory reproducibility

1. For validations carried out after the date of entry into force of this Regulation, prepare a set of samples of specified test material (identical or different matrices), fortified with the analyte(s) to yield concentrations equivalent to:

   (a) 0,5([5]), 1,0 and 1,5 times the RPA, or

   (b) 0,1([6]), 1,0 and 1,5 times the MRL or ML for authorised substances, or

   (c) 1,0, 2,0 and 3,0 times the LCL for unauthorised or prohibited substances in case no RPA is applicable.

2. Perform the analysis at each concentration level with at least six replicates of blank material.

3. Analyse the samples.

4. Calculate the concentration detected in each sample.

([5]) Where, for a non-allowed pharmacologically active substance validation of a concentration of 0,5 times the RPA is not reasonably achievable, the concentration of 0,5 times the RPA can be replaced by the lowest concentration between 0,5 times and 1,0 times the RPA, which is reasonably achievable.

([6]) Where, for a specific pharmacologically active substance validation of a concentration of 0,1 times the MRL is not reasonably achievable, the concentration of 0,1 times the MRL can be replaced by the lowest concentration between 0,1 times and 0,5 times the MRL, which is reasonably achievable.

([7]) ISO 5725-2:2019 Accuracy (trueness and precision) of measurement methods and results – Part 2: Basic method for the determination of repeatability and reproducibility of a standard measurement method (Clause 3).

5. Repeat these steps on at least two other occasions with different batches of blank material, different operators and as many different environmental conditions as possible, e.g. different batches of reagents, solvents, different room temperatures, different instruments or a variation of other parameters.

6. Determine the mean concentration, standard deviation and the coefficient of variation (%) of the fortified samples.

For methods for authorised substances validated before the date of entry into force of this Regulation, a determination of the within-laboratory reproducibility with fortified matrices in concentrations at 0,5, 1,0 and 1,5 times the MRL or ML is sufficient.

Alternatively, the calculation for within-laboratory reproducibility/intermediate precision can also be performed according to ISO 5725-2:2019, ISO 11843-1:1997 ([8]), Codex CAC/GL 59-2006 ([9]).

2.2.2. *Validation according to alternative models*

The calculation of the parameters in accordance with alternative models requires the performance of an experimental plan. The experimental plan shall be designed depending on the number of different species and different factors under investigation. Hence, the first step of the entire validation procedure is to consider the sample populations that will be analysed in the laboratory in the future, in order to determine the most important species and the factors, which may influence the measurement results. The factorial approach allows the assessment of the measurement uncertainty of the test results, obtained under a variety of test conditions in a given laboratory, such as different analysts, different instruments, different lots of reagents, different matrices, different elapsed assay times and different assay temperatures. Subsequently, the concentration range has to be chosen in a purpose-adapted way according to the MRL or ML for authorised substances or the RPA or LCL for prohibited or unauthorised substances.

The factorial approach aims at establishing reliable precision data and measurement data by simultaneous controlled variation of the selected factors. It allows the evaluation of the combined impact of factorial effects and random effects. The experimental design allows also the investigation of the ruggedness ([10]) of the analytical method and the determination of the in-house reproducibility standard deviation across matrices.

In the following an example for an alternative approach using an orthogonal experimental design plan is given.

Up to seven factors (noise factors) can be examined. The study is designed in such a way that precision, trueness (based on fortified samples), sensitivity, measurement uncertainty and critical concentrations can be determined simultaneously by implementation of the experimental plan.

Table 6

Example of an orthogonal experimental design plan with 7 factors (I – VII) varied at two levels (A/B) in a validation study with eight runs (factor level combination)

Factor	I	II	III	IV	V	VI	VII
Run 01	A	A	A	A	A	A	A
Run 02	A	A	B	A	B	B	B
Run 03	A	B	A	B	A	B	B
Run 04	A	B	B	B	B	A	A

([8]) ISO 11843-1:1997 Capability of detection – Part 1: Terms and definitions.

([9]) Codex Alimentarius Commission, Food and Agriculture Organization of the United Nations, World Health Organization, Guidelines on estimation of uncertainty of results (CAC/GL 59-2006).

([10]) The changes in experimental conditions referred to therein can consist of the sample materials, analytes, storage conditions, environmental and/or sample preparation conditions. For all experimental conditions, which could in practice be subject to fluctuation (e.g. stability of reagents, composition of the sample, pH, temperature) any variations which could affect the analytical result shall be indicated.

Run 05	B	A	A	B	B	A	B
Run 06	B	A	B	B	A	B	A
Run 07	B	B	A	A	B	B	A
Run 08	B	B	B	A	A	A	B

The calculation of the method characteristics shall be performed as described by Jülicher et al. ([11]).

2.2.3. *Other validation approaches*

Other approaches to demonstrate that the method complies with performance criteria for the performance characteristics may be used, provided that they achieve the same level and quality of information. Validation can also be performed by conducting an inter-laboratory study such as established by Codex Alimentarius, ISO or the IUPAC ([12]), or according to alternative methods such as single laboratory studies or in-house validation ([13]). When alternative validation procedures are applied, the underlying model and strategy with the respective prerequisites, assumptions and formulae shall be laid down in the validation protocol or at least references shall be given to their availability.

2.3. **Selectivity/Specificity**

The power of discrimination between the analyte and closely related substances shall be determined to the best possible extent. Interference of homologues, isomers, degradation products, endogenous substances, analogues, metabolic products of the residue of interest, of matrix compounds or of any other possibly interfering substance shall be determined and if needed the method shall be amended to avoid the identified interferences. For determining the specificity of the method, the following approach shall be used:

1. Select a range of chemically related compounds or other substances likely to be encountered with the compound of interest that may be present in the samples and verify whether they could interfere with the analysis of the target analyte(s).

2. Analyse an appropriate number of representative blank samples e.g. different lots or lots of different animal species ($n \geq 20$) and check for any interferences of signals, peaks or ion traces in the region of interest where the target analyte is expected to elute.

3. Fortify representative blank samples at a relevant concentration with substances that could possibly interfere with the identification and/or quantification of the analyte and investigate whether the added substance:

   (a) may lead to a false identification;

   (b) hinders the identification of the target analyte;

   (c) influences the quantification notably.

2.4. **Ruggedness**

The analytical method shall be tested for its continued performance under different experimental conditions, which include for example different sampling conditions and minor changes that can occur in routine testing. For testing the ruggedness of the method, the changes introduced in the experimental conditions should be minor. The importance of these changes shall be evaluated. Each performance characteristic shall be determined for all minor changes that have been shown to have a significant effect on the performance of the assay.

([11]) Jülicher, B., Gowik, P. and Uhlig, S. (1998) Assessment of detection methods in trace analysis by means of a statistically based in-house validation concept. Analyst, 120, 173.

([12]) IUPAC (1995), Protocol for the design, conduct and interpretation of method-performance studies, Pure & Applied Chem, 67, 331.

([13]) Gowik, P., Jülicher, B. and Uhlig, S. (1998) Multi-residue method for non-steroidal anti-inflammatory drugs in plasma using high performance liquid chromatography-photodiode-array detection. Method description and comprehensive in-house validation. J. Chromatogr., 716, 221.

2.5. **Stability**

The stability of the calibration standard, matrix-matched standard and/or matrix-fortified standards and of analyte or matrix constituents in the sample during storage or analysis shall be determined, as instabilities might influence the test results.

Usually the analyte stability is well characterised under various storage conditions. The experiments carried out for monitoring the storage conditions of standards and samples, which are carried out as part of the normal laboratory accreditation and quality control system, can provide the required information. If stability data for analytes in the matrix are available (e.g. on the basis of information from the EURLs, published data, etc.), these data do not need to be determined by each laboratory. However, referring to available stability data of analytes in solution and in matrix is only acceptable if identical conditions are applied.

In case the required stability data are not available, the following approaches should be used.

2.5.1. *Determination of the stability of the analyte in solution*

1. Prepare fresh stock solutions of the analyte(s) and dilute as specified in the test instructions to yield sufficient aliquots (e.g. 40) of each selected concentration. Samples shall be prepared of:

   (a) Solutions of the analyte, which are used for fortification;

   (b) Analyte solutions, used for the final analysis;

   (c) Any other solution that is of interest (e.g. derivatised standards).

2. Measure the analyte content in the freshly prepared solution according to the test instructions.

3. Dispense appropriate volumes into suitable containers, label and store according to the light and temperature conditions of the scheme included in Table 7. The storage time shall be chosen taking into account the applied analytical practice, ideally until the first degradation phenomena are observable during identification and/or quantification. If no degradation is observed during the stability study, the storage duration of the stability study shall be equal to the duration of the maximum storage period of the solution.

4. Calculate the concentration of the analyte(s) in each aliquot compared to the concentration of the analyte in the freshly prepared solution, following the formula below:

$$\text{Analyte Remaining (\%)} = C_i \times 100/C_{fresh}$$

C_i = concentration at time point i

C_{fresh} = concentration of fresh solution

The mean value of five replicate solutions, which were stored, shall not differ by more than 15 % from the mean value of five freshly prepared replicate solutions. The mean value of the five freshly prepared solutions shall be used as the basis for calculating the percentage difference.

Table 7

Scheme for determination of analyte stability in solution

	−20 °C	+4 °C	+20 °C
Dark	10 aliquots	10 aliquots	10 aliquots
Light			10 aliquots

2.5.2. *Determination of the stability of analyte(s) in matrix*

1. Use where possible incurred samples. When no incurred matrix is available, a blank matrix fortified with the analyte shall be used.

2. When incurred matrix is available, determine the concentration in the matrix, while the matrix is still fresh. Store further aliquots of the homogenised incurred matrix at minus 20 °C or lower if required, and determine the concentrations of the analyte as long as the sample is retained in the laboratory.

3. If no incurred matrix is available, take some blank matrix and homogenise it. Divide the matrix into five aliquots. Fortify each aliquot with the analyte, which should preferably be prepared in a small quantity of aqueous solution. Analyse one aliquot immediately. Store the remaining aliquots at least minus 20 °C or lower if required and analyse them after short term, mid-long term and long term storage taken into account the applied analytical methods.

4. Record the maximum acceptable storage time and the optimum storage conditions.

The mean value of five replicate solutions, which were stored, shall not differ by more than the within-lab reproducibility of the method from the mean value of five freshly prepared replicate solutions. The mean value of the five freshly prepared solutions shall be used as the basis for calculating the percentage difference.

2.6. **Decision limit for confirmation (CCα)**

The CCα shall be determined for confirmatory methods. The CCα shall be established under conditions complying with the requirements for identification or identification plus quantification as defined under 'Performance criteria and other requirements for analytical methods' as laid down in Chapter 1.

For the control of the compliance of samples, the combined standard measurement uncertainty has already been taken into account in the CCα value (decision limit for confirmation).

1. For unauthorised or prohibited pharmacologically active substances, the CCα shall be calculated as follows:

   (a) Method 1: by the calibration curve procedure according to ISO 11843-1:1997 ([14]) (here referred to as critical value of the net state variable). In this case, blank material shall be used, which is fortified at and above the RPA or LCL in equidistant steps. Analyse the samples. After identification, plot the signal where possible, or the recalculated concentration against the added concentration. The corresponding concentration at the y-intercept plus 2,33 times the standard deviation of the within-laboratory reproducibility at the intercept equals the decision limit. This method is applicable to quantitative assays only. Decision limits obtained with this approach shall be verified by analysing blank matrix fortified at the calculated decision limit.

   (b) Method 2: by analysing at least 20 representative blank materials per matrix to be able to calculate the signal to noise ratio at the time window in which the analyte is expected. Three times the signal-to-noise ratio can be used as the decision limit. This is applicable to quantitative and qualitative assays. Decision limits obtained with this approach shall be verified by analysing blank matrix fortified at the calculated decision limit.

   (c) Method 3: CCα = LCL + k(one-sided, 99 %) × (combined) standard measurement uncertainty at LCL

   For unauthorised or prohibited pharmacologically active substances, depending on the validation experiment (and its respective degrees of freedom) the t-distribution might be reasonably applied, or – if the Gaussian distribution (one-sided, n=∞) is taken as a basis – a k-factor of 2,33 shall be used.

   The within-laboratory reproducibility and the trueness are suitable to define the (combined) standard measurement uncertainty, if determined by taking into account all relevant influencing factors.

Method 2 for the calculation of CCα can only be used until 1 January 2026 in case of methods validated before the date of entry into force of this Regulation. For the methods validated after the entry into force of this Regulation, only Methods 1 or 3 shall be used.

([14]) ISO 11843-1:1997 Capability of detection – Part 1: Terms and definitions.

2. For authorised substances, the CCα shall be calculated as follows:

(a) For authorised substances in matrix/species combinations for which an MRL or ML has been set:

(i) Method 1: by the calibration curve procedure according to ISO 11843-1:1997 (here referred to as critical value of the net state variable). In this case, blank material shall be used, which is fortified at and above the MRL or ML in equidistant steps. Analyse the samples. After identification, plot the signal, where possible, or the recalculated concentration, against the added concentration. The corresponding concentration at the MRL or ML plus 1,64 times the standard deviation of the within-laboratory reproducibility at the permitted limit equals the decision limit (α = 5 %).

(ii) Method 2: CCα = MRL (or ML) + k(one-sided, 95 %) × (combined) standard measurement uncertainty at the MRL or ML.

For authorised substances, depending on the validation experiment (and its respective degrees of freedom) the t-distribution might be reasonably applied, or – if the Gaussian distribution (one-sided, n=∞) is taken as a basis, a k-factor of 1,64 shall be used.

The within-laboratory reproducibility and the trueness are suitable to define the (combined) standard measurement uncertainty, if determined by taking into account all relevant influencing factors.

For pharmacologically active substances for which the MRL is established for the sum of different substances, the CCα of the substance with the highest concentration in the sample shall be used as the CCα to assess the sum of substances in the measured sample.

(b) For authorised substances in matrix/species combinations for which no MRL has been set, no residues shall be present unless an authorised treatment in accordance with Article 11 of Directive 2001/82/EC took place. For authorised substances, for which no MRL has been set, the cascade MRL, established under Commission Implementing Regulation (EU) 2018/470 ([15]), shall be used for the calculation of the CCα. Method 1 or 2 of the paragraph above shall be applied but 'MRL' refers to the '0,5 times cascade MRL, with the target 0,1 times cascade MRL, where reasonably feasible'.

2.7. **Detection capability for screening (CCβ)**

The CCβ shall be determined for screening methods. The CCβ shall be established as defined under 'Performance criteria and other requirements for analytical methods' as laid down in Chapter 1 of this Annex and according to the requirements laid down in Table 5. However, the full requirements for identification (cf. 1.2.3, 1.2.4, 1.2.5) do not need to be applied for screening methods.

1. For unauthorised or prohibited pharmacologically active substances, a maximum β error of 5 % shall be ensured. The CCβ shall be calculated as follows:

(a) Method 1: The calibration curve procedure according to ISO 11843-1:1997 (here referred to as minimum detectable value of the net state variable). In this case, representative blank material shall be used, which is fortified at and below the RPA, or if no RPA has been established, around the STC in equidistant steps. Analyse the samples. Plot the signal against the added concentration. The corresponding concentration at the STC plus 1,64 times the standard deviation of the within-laboratory reproducibility of the mean measured content at the STC equals the detection capability. Extrapolation far below the lowest fortification level (< 50 % of lowest fortification level) shall be confirmed by experimental data at the validation step.

(b) Method 2: Investigation of fortified blank material at concentration levels at and above the STC. For each concentration level 20 fortified blanks shall be analysed in order to ensure a reliable basis for this determination. The concentration level, where only ≤ 5 % false compliant results remain, equals the detection capability of the method.

(c) Method 3: CCβ = STC + k(one-sided, 95 %) × (combined) standard measurement uncertainty at or above the STC.

([15]) Commission Implementing Regulation (EU) 2018/470 of 21 March 2018 on detailed rules on the maximum residue limit to be considered for control purposes for foodstuffs derived from animals which have been treated in the EU under Article 11 of Directive 2001/82/EC (OJ L 79, 22.3.2018, p. 16).

For unauthorised or prohibited pharmacologically active substances, depending on the validation experiment (and its respective degrees of freedom) the t-distribution might be reasonably applied, or if the Gaussian distribution (one-sided, n=∞) is taken as a basis, a k-factor of 1,64 shall be used.

The within-laboratory reproducibility and the trueness are suitable to define the (combined) standard measurement uncertainty, if determined by taking into account all relevant influencing factors.

2. For authorised substances, a maximum β error of 5 % shall be ensured. The CCβ shall be calculated as follows:

(a) Method 1: by the calibration curve procedure according to ISO 11843-1:1997 (here referred to as a minimum detectable value of the net state variable). In this case, representative blank material shall be used, which is fortified at and below the permitted limit, starting from the STC in equidistant steps. Analyse the samples and identify the analyte(s). Calculate the standard deviation of the mean measured content at the STC.

The corresponding concentration at the STC plus 1,64 times the standard deviation of the within-laboratory reproducibility of the mean measured content at the STC equals the detection capability,

(b) Method 2: by investigation of fortified blank material at concentration levels below the permitted limit. For each concentration level 20 fortified blanks shall be analysed in order to ensure a reliable basis for this determination. The concentration level, where only ≤ 5 % false compliant results remain, equals the detection capability of the method.

(c) Method 3: CCβ = STC + k(one-sided, 95 %) × (combined) standard measurement uncertainty at or above STC.

For authorised substances, depending on the validation experiment (and its respective degrees of freedom) the t-distribution might be reasonably applied, or if the Gaussian distribution (one-sided, n=∞) is taken as a basis, a k-factor of 1,64 shall be used (whatever under cascade use or under regular MRL use).

The within-laboratory reproducibility and the trueness are suitable to define the (combined) standard measurement uncertainty, if determined by taking into account all relevant influencing factors.

For pharmacologically active substances for which the MRL is established for the sum of different substances, the CCβ of the substance with the highest concentration in the sample shall be used as the CCβ to assess the sum of substances in the measured sample.

2.8. **Calibration curves**

When calibration curves are used for quantification:

(1) at least five preferably equidistant levels (including zero level) should be used in the construction of the curve;

(2) the working range of the curve shall be described;

(3) the mathematical formula of the curve and the goodness-of-fit of the data (coefficient of determination R^2) to the curve shall be described;

(4) acceptability ranges for the parameters of the curve shall be described.

For calibration curves based on a standard solution, matrix-matched standards or matrix-fortified standards acceptable ranges shall be indicated for the parameters of the calibration curve, which may vary from series to series.

2.9. **Absolute recovery**

The absolute recovery of the method shall be determined when no internal standard or no matrix-fortified calibration is used.

When requirements for trueness, as set out in Table 1, are fulfilled, a fixed correction factor may be used. Otherwise, the recovery factor obtained for that specific batch shall be used. Alternatively, the standard addition ([16]) procedure or an internal standard shall be used instead of using a recovery correction factor.

The absolute recovery shall be calculated for at least six representative lots of matrix.

An aliquot of blank matrix shall be fortified with the analyte before extraction, and a second aliquot of blank matrix shall be fortified after sample preparation at a relevant concentration level and the concentration of the analyte shall be determined.

The recovery shall be calculated as:

Rec (analyte) = (*area* matrix-fortified standard)/(*area* matrix-matched standard) × 100

2.10. **Relative matrix effects**

The relative matrix effect shall be determined in all cases. This can be done either as part of the validation or in separate experiments. The calculation of the relative matrix effect shall be done for at least 20 different blanks lots (matrix/species), according to the scope of the method e.g. different species to be covered.

The blank matrix should be fortified after extraction with the analyte at the RPA, MRL or ML and should be analysed together with a pure solution of the analyte.

The relative matrix effect or matrix factor (MF) is calculated as:

$$\text{MF (standard)} = \frac{\text{peak area of MMS standard}}{\text{peak area of solution standard}}$$

$$\text{MF (IS)} = \frac{\text{peak area of MMS IS}}{\text{peak area of solution IS}}$$

$$\text{MF (standard normalised for IS)} = \frac{\text{MF (standard)}}{\text{MF (IS)}}$$

IS: internal standard

MMS: matrix-matched standard

The coefficient of variation shall not be greater than 20 % for the MF (standard normalised for IS).

CHAPTER 3

QUALITY CONTROL DURING ROUTINE ANALYSIS – ONGOING METHOD PERFORMANCE VERIFICATION

The requirements for assuring the quality of analytical results of Chapter 7.7 of ISO/IEC 17025:2017 ([17]) shall be complied with.

During routine analysis, the analysis of certified reference materials (CRMs) is the preferable option to provide evidence of method performance. Since CRMs that contain the relevant analytes at the required concentration levels are seldom available, also reference materials provided and characterised by the EURLs or laboratories that hold an ISO/IEC 17043:2010 ([18]) accreditation may be used as an alternative. As another alternative in-house reference materials, which are controlled regularly, may be used.

The ongoing method performance verification during routine analysis should be carried out at the screening step and the confirmatory step.

([16]) The amount of the standard analyte added, can be, for example, between two and five times the estimated amount of the analyte in the sample. This procedure is designed to determine the content of an analyte in a sample, taking account of the recovery of the analytical procedure.

([17]) ISO/IEC 17025: 2017 General requirements for the competence of testing and calibration laboratories (Chapter 7.7).

([18]) ISO/IEC 17043:2010 Conformity assessment – General requirements for proficiency testing.

1. For the screening step:

   For each series (batch) of analyses performed, a set of the following quality control samples shall be simultaneously analysed:

   (a) control sample for system suitability of the instrument, ideally method specific;

   (b) quality control samples which are fortified at a concentration close to the STC and ideally at the CCβ of screening for authorised pharmacologically active substances as well as for the prohibited or unauthorised substances);

   (c) compliant control sample (blank samples), and when relevant, reagent blanks.

2. For the confirmatory step:

   For each series (batch) of analyses performed, a set of the following quality control samples shall be simultaneously analysed:

   (a) control sample for system suitability of the instrument, ideally method specific;

   (b) quality control samples which are fortified at a concentration close to the MRL or ML for authorised pharmacologically active substances or close to the RPA or LCL for prohibited or unauthorised substances (non-compliant control samples);

   (c) compliant control sample (blank samples), and when relevant, reagent blanks.

The following order is recommended for the quality control samples: control sample for system suitability of the instrument, compliant control sample, sample(s) to be confirmed, compliant control sample again and fortified quality control sample (non-compliant control samples).

For quantitative methods with each batch of official samples, a calibration curve shall be analysed and measured before or after the above listed samples.

Where practicable, trueness (on basis of fortified samples) of all target analytes in the non-compliant control samples shall be evaluated, by means of quality control charts in accordance with Chapter 7.7 of ISO/IEC 17025:2017. If this requires a disproportionately large number of trueness determinations, the number of analytes may be reduced to a number of representative analytes.

CHAPTER 4

EXTENSION OF THE VALIDATED SCOPE OF A PREVIOUSLY VALIDATED METHOD

Sometimes it is necessary to extend the scope of a previously comprehensively validated method. In these cases an extension of the scope should be accomplished in an efficient and analytically sound way. This can be achieved by carrying out a validation on a reduced number of samples (e.g. the half number of samples) compared to a full validation.

Nevertheless, the type and number of modifications to be validated in a single reduced validation scheme shall always be based on expert knowledge and previous experiences, e.g. a change in detection technique would require a complete validation in any case.

In general, to assure the ongoing validity of the method, its performance shall be monitored continuously and compared to the initially obtained validation parameters. Ideally, this ongoing method performance control is designed in a way that the missing data for a complete validation can be collected over time (e.g. with a few data points from QC samples in each analytical series).

4.1. Extensions of methods as regards to the range of concentrations

Due to changes of MRLs, MLs, and RPAs it may become necessary to adjust the concentration range for which a method is validated. For such a case, the application of a reduced validation scheme is acceptable.

Calibration curves for the modified range should be prepared according to the validated procedure. Different batches fortified at different concentration levels (cf. 2.2.1, 2.2.2) should be analysed. Trueness, repeatability and within-laboratory reproducibility/intermediate precision should be within an acceptable range compared to those of the originally validated method. A recalculation of CCβ (screening methods) and CCα (confirmation methods) should be performed, where relevant.

4.2. **Extensions of methods as regards to additional substances**

Generally, the method extension to additional compounds is only possible for analytes, which are similar structure and characteristic-wise compared to those already included in the analytical method. For such a case, the application of a reduced validation scheme is acceptable. Likewise, no divergence from the method description is allowed.

Calibration curves for the additional substances should be prepared according to the validated procedure. Different batches of matrix materials fortified at different concentration levels (cf. 2.2.1, 2.2.2) should be analysed. Trueness, repeatability and within-laboratory reproducibility/intermediate precision should be within a comparable range to those of the other analytes of the originally validated method and in line with the requirements set in 1.2.2. A calculation of CCβ (screening methods) and CCα (confirmation methods) for the new analytes has to be done.

4.3. **Extensions of methods as regards to matrices/species**

The inclusion of new matrices or species in an already validated analytical method shall always be a case-by-case decision based on the knowledge and experiences gained so far with the method and preliminary experiments assessing potential matrix effects and interferences. Generally, this will only be possible for matrices that exhibit similar properties and for non-critical analytes (stability, detectability).

Calibration curves (standard or matrix) should be prepared according to the validated procedure. Different batches of matrix material fortified at different concentration levels (cf. 2.2.1, 2.2.2) should be analysed. Trueness, repeatability and within-laboratory reproducibility/intermediate precision should be within an acceptable range to those of the originally validated method and in line with the requirements set in 1.2.2. Depending on the validation approach, a recalculation of CCβ (screening methods) or CCα (confirmation methods) might be necessary.

If the results are not within an acceptable range compared to the values for the original matrix, an additional full validation will be necessary, in order to determine the matrix/species specific performance parameters.

In cases where MRLs for a specific substance differ for certain matrices, it will most likely be difficult to adapt the method scope to the additional matrix/species and concentration, since in this case two modifications have to be considered. In such cases a full validation is recommended.

ANNEX II

SAMPLING PROCEDURES AND OFFICIAL SAMPLE TREATMENT

1. **Sample quantity**

The minimum sample quantities shall be defined in the national residue control programme. The minimum sample quantities shall be sufficient to enable the approved laboratories to carry out the analytical procedures necessary to complete the screening and the confirmatory analyses. Specifically for poultry, aquaculture, rabbits, farmed game, reptiles and insects a sample consists out of one or more animals, depending the requirements of the analytical methods. For eggs, the sample size is at least 12 eggs or more, according to the analytical methods used. In case several substance categories need to be analysed in one sample with different analytical methods, the sample size shall be increased accordingly.

2. **Division into sub-samples**

Unless technically impossible or not required by national legislation, each sample shall be divided into at least two equivalent sub-samples each allowing the complete analytical procedure. The subdivision can take place at the sampling location or in the laboratory.

3. **Traceability**

Each sample shall be taken in such way that it is always possible to trace it back to the farm of origin and the batch of animals or the individual animal, where relevant. In particular, for milk, according to the choice of the Member State, the samples can be taken, in either of the following places:

1. at the farm from the collection tank;
2. at the level of the dairy industry, before the milk has been discharged.

4. **Sample containers**

Samples shall be collected in suitable containers to maintain sample integrity and traceability. In particular, containers shall prevent substitution, cross-contamination and degradation. The containers shall be officially sealed.

5. **Sampling report**

A report shall be produced after each sampling procedure.

The inspector collects at least the following data in the sampling report:

1. address of the competent authorities;
2. name of the inspector or identification code;
3. official code number of the sample;
4. sampling date;
5. name and address of the owner or the person having charge of the animals or the animal products;
6. name and address of the animal's farm of origin (when sampling on farm);
7. registration number of the establishment-slaughterhouse number;
8. animal or product identification;
9. animal species;
10. sample matrix;
11. where relevant, medication within the last four weeks before sampling (when sampling on farm);
12. substance or substance groups for examination;
13. particular remarks.

Paper or electronic copies of the report are to be provided depending on the sampling procedure. The sampling report and its copies shall be completed in a way that ensures their authenticity and legal validity, which may require that these documents are signed by the inspector. In case of on-farm sampling, the farmer or his deputy may be invited to sign the original sampling report.

The original of the sampling report remains at the competent authority, which has to guarantee that unauthorised persons cannot access this original report.

If necessary, the farmer or the owner of the establishment may be informed of the sampling undertaken.

6. **Sampling report for the laboratory**

The sampling report for the laboratory established by the competent authorities shall be in accordance with the requirements set in Chapter 7 of ISO/IEC 17025:2017 ([1]) and shall contain at least the following information:

1. address of the competent authorities or designated bodies;
2. name of inspector or identification code;
3. official code number of the sample;
4. sampling date;
5. animal species;
6. sample matrix;
7. substances or substance groups for examination;
8. particular remarks.

The sampling report for the laboratory shall accompany the sample when sent to the laboratory.

7. **Transport and storage**

Residue control programmes shall specify the suitable storage and transport conditions for each analyte/matrix combination to ensure analyte stability and sample integrity. The transport time shall be as short as possible and the temperature during transport shall be adequate to ensure analyte stability.

Specific attention shall be paid to transport boxes, temperature and delivery times to the responsible laboratory.

In case of any non-compliance with the requirements of the control programme, the laboratory shall inform the competent authority without delay.

([1]) ISO/IEC 17025: 2017 General requirements for the competence of testing and calibration laboratories (Chapter 7.7).

COMMISSION IMPLEMENTING REGULATION (EU) 2021/809

of 20 May 2021

concerning the non-approval of fermented extract from leaves of *Symphytum officinale* L. (comfrey) as a basic substance in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC ([1]), and in particular Article 13(2) in conjunction with Article 23(5) thereof,

Whereas:

(1) On 22 January 2015, the Commission received an application from the company Greenprotech for the approval of 'comfrey steeping' as a basic substance to be used as an insect repellent and plant elicitor in fruit trees, grass and vegetables. That application was accompanied by the information required under the second subparagraph of Article 23(3) of Regulation (EC) No 1107/2009.

(2) The Commission asked the European Food Safety Authority ('the Authority') for scientific assistance. The Authority provided the Commission with a technical report on 'comfrey steeping' on 28 November 2019 ([2]). Based on that technical report and the documentation provided by the applicant, it is appropriate to define the scope of the application as covering the active substance 'fermented extract from leaves of *Symphytum officinale* L. (comfrey)'.

(3) The information provided by the applicant on the fermented extract from leaves of *Symphytum officinale* L. (comfrey) was insufficient to demonstrate that it fulfils the criteria of a foodstuff as defined in Article 2 of Regulation (EC) No 178/2002 of the European Parliament and of the Council ([3]).

(4) The Authority concluded that the specification of the fermented extract from leaves of *Symphytum officinale* L. (comfrey) is not well defined. The Authority also indicated that comfrey is known to contain genotoxic and carcinogenic components, and information on the concentration of genotoxic and carcinogenic compounds in the fermented extract from leaves of *Symphytum officinale* L. was not available. Consequently, it was not possible to conclude that the fermented extract from leaves of *Symphytum officinale* L. is not to be considered as a substance of concern as provided for by Article 23(1)(a) of Regulation (EC) No 1107/2009.

(5) Moreover, the available information on the fermented extract from leaves of *Symphytum officinale* L. did not allow the Authority to finalise a non-dietary exposure risk assessment and the assessment of the risk to consumers. Furthermore, there was not sufficient information available regarding environmental exposure and the risks to non-target organisms.

(6) No relevant evaluation, carried out in accordance with other Union legislation as referred to in Article 23(2) of Regulation (EC) No 1107/2009, was available.

([1]) OJ L 309, 24.11.2009, p. 1.

([2]) EFSA (European Food Safety Authority), 2019. Technical report on the outcome of the consultation with Member States and EFSA on the basic substance application for approval of Comfrey steeping to be used in plant protection as an insect repellent and plant elicitor in fruit trees, grass and vegetables. EFSA supporting publication 2019:EN-1753. 64 pp. doi:10.2903/sp.efsa.2019.EN-1753.

([3]) Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety (OJ L 31, 1.2.2002, p. 1).

(7) The Commission presented the review report ([4]) and a draft Regulation to the Standing Committee on Plants, Animals, Food and Feed on 19 May 2020 and 26 January 2021, respectively, and finalised them for the meeting of that Committee on 24 March 2021.

(8) The Commission invited the applicant to submit its comments on the technical report of the Authority and on the Commission's draft review report. The applicant submitted its comments, which have been carefully examined.

(9) However, despite the arguments put forward by the applicant, the concerns related to the substance cannot be eliminated.

(10) Consequently, it has not been established that the conditions laid down in Article 23 of Regulation (EC) No 1107/2009 are fulfilled. It is therefore appropriate not to approve fermented extract from leaves of *Symphytum officinale* L. (comfrey) as a basic substance.

(11) This Regulation does not prevent the submission of a further application for the approval of fermented extract from leaves of *Symphytum officinale* L. (comfrey) as a basic substance in accordance with Article 23(3) of Regulation (EC) No 1107/2009 or an application for approval as active substance in accordance with Article 7 of that Regulation.

(12) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Plants, Animals, Food and Feed,

HAS ADOPTED THIS REGULATION:

Article 1

The substance fermented extract from leaves of *Symphytum officinale* L. (comfrey) is not approved as a basic substance.

Article 2

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 20 May 2021.

For the Commission
The President
Ursula VON DER LEYEN

([4]) https://ec.europa.eu/food/plant/pesticides/eu-pesticides-db_en

COMMISSION IMPLEMENTING REGULATION (EU) 2021/810

of 20 May 2021

amending Implementing Regulation (EU) 2021/2021/808 as regards transitional provisions for certain substances listed in Annex II to Decision 2002/657/EC

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EU) 2017/625 of the European Parliament and of the Council of 15 March 2017 on official controls and other official activities performed to ensure the application of food and feed law, rules on animal health and welfare, plant health and plant protection products, amending Regulations (EC) No 999/2001, (EC) No 396/2005, (EC) No 1069/2009, (EC) No 1107/2009, (EU) No 1151/2012, (EU) No 652/2014, (EU) 2016/429 and (EU) 2016/2031 of the European Parliament and of the Council, Council Regulations (EC) No 1/2005 and (EC) No 1099/2009 and Council Directives 98/58/EC, 1999/74/EC, 2007/43/EC, 2008/119/EC and 2008/120/EC, and repealing Regulations (EC) No 854/2004 and (EC) No 882/2004 of the European Parliament and of the Council, Council Directives 89/608/EEC, 89/662/EEC, 90/425/EEC, 91/496/EEC, 96/23/EC, 96/93/EC and 97/78/EC and Council Decision 92/438/EEC (Official Controls Regulation) ([1]), and in particular Article 34(6) thereof,

Whereas:

(1) Commission Implementing Regulation (EU) 2021/2021/808 ([2]) repeals, inter alia, Commission Decision 2002/657/EC ([3]). Article 4 of that Decision in conjunction with Annex II thereto set out the minimum required performance limits for the pharmacologically active substances chloramphenicol, nitrofuran metabolites, medroxyprogesterone acetate and malachite green in certain matrixes.

(2) Article 8 of Commission Regulation (EU) 2019/1871 ([4]) lays down the transitional provisions for reference points for action (RPA) for prohibited pharmacologically active substances. The minimum required performance limits for chloramphenicol, nitrofuran metabolites and the sum of malachite green and leucomalachite green, included in Annex II to Decision 2002/657/EC, should be applied as RPA for food of animal origin imported from third countries and for food of animal origin produced in the Union until 27 November 2022.

(3) For the purposes referred to in Article 8 of Regulation (EU) 2019/1871, Annex II to Decision 2002/657/EC should therefore remain applicable until 27 November 2022.

(4) To maintain continuity, this Regulation should apply from the same date as Implementing Regulation (EU) 2021/2021/808.

(5) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Plants, Animals, Food and Feed,

HAS ADOPTED THIS REGULATION:

Article 1

Article 7 of Implementing Regulation (EU) 2021/2021/808 is replaced by the following:

'*Article 7*

Repeals and transitional measures

Decisions 2002/657/EC and 98/179/EC are repealed from the date of entry into force of this Regulation.

([1]) OJ L 95, 7.4.2017, p. 1.

([2]) Commission Implementing Regulation (EU) 2021/2021/808 of 22 March 2021 on the performance of analytical methods for residues of pharmacologically active substances used in food-producing animals and on the interpretation of results as well as on the methods to be used for sampling and repealing Decisions 2002/657/EC and 98/179/EC (see page 84 of this Official Journal).

([3]) Commission Decision 2002/657/EC of 14 August 2002 implementing Council Directive 96/23/EC concerning the performance of analytical methods and the interpretation of results (OJ L 221, 17.8.2002, p. 8).

([4]) Commission Regulation (EU) 2019/1871 of 7 November 2019 on reference points for action for non-allowed pharmacologically active substances present in food of animal origin and repealing Decision 2005/34/EC (OJ L 289, 8.11.2019, p. 41).

However, until 10 June 2026, the requirements laid down in points 2 and 3 of Annex I to Decision 2002/657/EC shall continue to apply to methods, which have been validated before the date of entry into force of this Regulation.

For the purposes referred to in the second paragraph of Article 8 of Regulation (EU) 2019/1871, Annex II to Decision 2002/657/EC shall continue to apply until 27 November 2022.'

Article 2

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 20 May 2021.

For the Commission
The President
Ursula VON DER LEYEN

COMMISSION IMPLEMENTING REGULATION (EU) 2021/811

of 20 May 2021

amending Annex I to Implementing Regulation (EU) 2021/605 laying down special control measures for African swine fever

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EU) 2016/429 of the European Parliament and of the Council of 9 March 2016 on transmissible animal diseases and amending and repealing certain acts in the area of animal health ('Animal Health Law') ([1]), and in particular Article 71(3) thereof,

Whereas:

(1) African swine fever is an infectious viral disease affecting kept and wild porcine animals and can have a severe impact on the concerned animal population and the profitability of farming causing disturbance to movements of consignments of those animals and products thereof within the Union and exports to third countries.

(2) Commission Implementing Regulation (EU) 2021/605 ([2]) was adopted within the framework of Regulation (EU) 2016/429, and it lays down special disease control measures regarding African swine fever to be applied for a limited period of time by the Member States listed in Annex I thereto, in the restricted zones listed in that Annex. The areas listed as restricted zones I, II and III in Annex I to Implementing Regulation (EU) 2021/605 are based on the epidemiological situation of African swine fever in the Union. Annex I to Implementing Regulation (EU) 2021/605 was amended by Commission Implementing Regulation (EU) 2021/687 ([3]), to ensure the continuity and consistency of special disease control measures regarding African swine fever in the Union following the expiry of Commission Implementing Decision 2014/709/EU ([4]), and the commencement of application of Implementing Regulation (EU) 2021/605 on 21 April 2021.

(3) Any amendments to restricted zones I, II and III in Annex I to Implementing Regulation (EU) 2021/605 should be based on the epidemiological disease situation as regards African swine fever in the areas affected by that disease and the overall epidemiological situation of African swine fever in the Member State concerned, the level of risk for the further spread of that disease, scientifically based principles and criteria for geographically defining zoning due to African swine fever and the Union's guidelines agreed with the Member States at the Standing Committee on Plants, Animals, Food and Feed and publicly available on Commission's website ([5]). Such amendments should also take account of international standards, such as the Terrestrial Animal Health Code ([6]) of the World Organisation for Animal Health (the OIE Code) and justifications for zoning provided by the competent authorities of the Member States concerned.

(4) Since the date of adoption of Implementing Regulation (EU) 2021/687, there have been new outbreaks of African swine fever in wild porcine animals in Slovakia and Poland.

(5) In April 2021, one case of African swine fever in a wild porcine animal was observed in the Rimavska Sobota district in Slovakia in an area currently listed as a restricted zone I in Annex I to Implementing Regulation (EU) 2021/605. This new outbreak of African swine fever in a wild porcine animal constitutes an increased level of risk, which should be reflected in that Annex. Accordingly, that area of Slovakia currently listed as a restricted zone I in that Annex affected by this recent outbreak of African swine fever, should now be listed as a restricted zone II in that Annex instead of as a restricted zone I.

([1]) OJ L 84, 31.3.2016, p. 1.

([2]) Commission Implementing Regulation (EU) 2021/605 of 7 April 2021 laying down special control measures for African swine fever (OJ L 129, 15.4.2021, p. 1).

([3]) Commission Implementing Regulation (EU) 2021/687 of 26 April 2021 amending Annex I to Implementing Regulation (EU) 2021/605 laying down special control measures for African swine fever (OJ L 143, 27.4.2021, p. 11).

([4]) Commission Implementing Decision 2014/709/EU of 9 October 2014 concerning animal health control measures relating to African swine fever in certain Member States and repealing Implementing Decision 2014/178/EU (OJ L 295, 11.10.2014, p. 63).

([5]) Working Document SANTE/7112/2015/Rev. 3 'Principles and criteria for geographically defining ASF regionalisation'. https://ec.europa.eu/food/animals/animal-diseases/control-measures/asf_en

([6]) OIE Terrestrial Animal Health Code, 28th Edition, 2019. ISBN of volume I: 978-92-95108-85-1; ISBN of volume II: 978-92-95108-86-8. https://www.oie.int/standard-setting/terrestrial-code/access-online/

(6) In May 2021, one case of African swine fever in a wild porcine animal was observed in the szamotulski district in Poland in an area currently listed as a restricted zone I in Annex I to Implementing Regulation (EU) 2021/605. This new outbreak of African swine fever in a wild porcine animal constitutes an increased level of risk, which should be reflected in that Annex. Accordingly, that area of Poland currently listed as a restricted zone I in that Annex affected by this recent outbreak of African swine fever, should now be listed as a restricted zone II in that Annex instead of as a restricted zone I.

(7) Following these recent outbreaks of African swine fever in wild porcine animals in Slovakia and Poland and taking into account the current epidemiological situation as regards African swine fever in the Union, zoning in those Member States has been reassessed and updated. In addition, the risk management measures in place have also been reassessed and updated. These changes should be reflected in Annex I to Implementing Regulation (EU) 2021/605.

(8) In order to take account of recent developments in the epidemiological situation of African swine fever in the Union, and in order to combat the risks associated with the spread of that disease in a proactive manner, new restricted zones of a sufficient size should be demarcated for Slovakia and Poland and duly listed as restricted zone II in Annex I to Implementing Regulation (EU) 2021/605. As the situation as regards African swine fever is very dynamic in the Union, when demarcating those new restricted zones, account has been taken of the situation in the surrounding areas.

(9) Given the urgency of the epidemiological situation in the Union as regards the spread of African swine fever, it is important that the amendments to be made to Annex I to Implementing Regulation (EU) 2021/605 by this Implementing Regulation take effect as soon as possible.

(10) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Plants, Animals, Food and Feed,

HAS ADOPTED THIS REGULATION:

Article 1

Annex I to Implementing Regulation (EU) 2021/605 is replaced by the text set out in the Annex to this Regulation.

Article 2

This Regulation shall enter into force on the day following that of its publication in the *Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 20 May 2021.

For the Commission
The President
Ursula VON DER LEYEN

ANNEX

Annex I to Implementing Regulation (EU) 2021/605 is replaced by the following:

'*ANNEX I*

RESTRICTED ZONES

PART I

1. **Germany**

The following restricted zones I in Germany:

Bundesland Brandenburg:

— Landkreis Dahme-Spreewald:

  — Gemeinde Alt Zauche-Wußwerk,

  — Gemeinde Byhleguhre-Byhlen,

  — Gemeinde Märkische Heide, mit den Gemarkungen Alt Schadow, Neu Schadow, Pretschen, Plattkow, Wittmannsdorf, Schuhlen-Wiese, Bückchen, Kuschkow, Gröditsch, Groß Leuthen, Leibchel, Glietz, Groß Leine, Dollgen, Krugau, Dürrenhofe, Biebersdorf und Klein Leine,

  — Gemeinde Neu Zauche,

  — Gemeinde Schwielochsee mit den Gemarkungen Groß Liebitz, Guhlen, Mochow und Siegadel,

  — Gemeinde Spreewaldheide,

  — Gemeinde Straupitz,

— Landkreis Märkisch-Oderland:

  — Gemeinde Lietzen,

  — Gemeinde Falkenhagen (Mark),

  — Gemeinde Zeschdorf,

  — Gemeinde Treplin,

  — Gemeinde Fichtenhöhe mit den Gemarkungen Niederjesar, Alt Mahlisch und Carzig – westlich der B 167,

  — Gemeinde Lindendorf mit den Gemarkungen Neu Mahlisch, Libbenichen und Dolgelin – westlich der B 167,

  — Gemeinde Müncheberg mit den Gemarkungen Müncheberg, Eggersdorf bei Müncheberg und Hoppegarten bei Müncheberg,

  — Gemeinde Neulewin,

  — Gemeinde Bliesdorf mit den Gemarkungen Kunersdorf und Bliesdorf,

  — Gemeinde Neutrebbin mit den Gemarkungen Neutrebbin und Alttrebbin westlich der L 34 und Altelewin westlich und nordöstlich der L 33,

  —

  — Gemeinde Märkische Höhe mit den Gemarkungen Reichenberg und Batzlow,

  — Gemeinde Wriezen mit den Gemarkungen Haselberg, Frankenfelde, Schulzendorf, Lüdersdorf, Biesdorf, Rathsdorf, Wriezen, Altwriezen, Beauregard, Eichwerder und Jäckelsbruch,

  — Gemeinde Oderaue mit den Gemarkungen Neuranft, Neuküstrinchen, Neurüdnitz, Altwustrow, Neuwustrow und Zäckericker Loose, Altreetz, Altmädewitz und Neumädewitz,

  — Gemeinde Buckow (Märkische Schweiz),

  — Gemeinde Strausberg mit den Gemarkungen Hohenstein und Ruhlsdorf,

  — Gemeine Garzau-Garzin,

- Gemeinde Waldsieversdorf,
- Gemeinde Rehfelde mit der Gemarkung Werder,
- Gemeinde Reichenow-Mögelin,
- Gemeinde Prötzel mit den Gemarkungen Harnekop, Sternebeck und Prötzel östlich der B 168 und der L35,
- Gemeinde Oberbarnim.

— Landkreis Oder-Spree:

- Gemeinde Storkow (Mark),
- Gemeinde Wendisch Rietz,
- Gemeinde Reichenwalde,
- Gemeinde Diensdorf-Radlow,
- Gemeinde Bad Saarow,
- Gemeinde Rietz-Neuendorf mit den Gemarkungen Buckow, Glienicke, Behrensdorf, Ahrensdorf, Herzberg, Görzig, Pfaffendorf, Sauen, Wilmersdorf (G), Neubrück, Drahendorf, Alt Golm,
- Gemeinde Tauche mit den Gemarkungen Briescht, Kossenblatt, Werder, Görsdorf (B), Giesendorf, Wulfersdorf, Falkenberg (T), Lindenberg,
- Gemeinde Steinhöfel mit den Gemarkungen Demnitz, Steinhöfel, Hasenfelde, Ahrensdorf, Heinersdorf, Tempelberg,
- Gemeinde Langewahl,
- Gemeinde Berkenbrück,
- Gemeinde Briesen (Mark),
- Gemeinde Jacobsdorf,

— Landkreis Spree-Neiße:

- Gemeinde Jänschwalde,
- Gemeinde Peitz,
- Gemeinde Tauer,
- Gemeinde Turnow-Preilack,
- Gemeinde Drachhausen,
- Gemeinde Schmogrow-Fehrow,
- Gemeinde Drehnow,
- Gemeinde Guben mit der Gemarkung Schlagsdorf,
- Gemeinde Schenkendöbern mit den Gemarkungen Grabko, Kerkwitz, Groß Gastrose,
- Gemeinde Teichland,
- Gemeinde Dissen-Striesow,
- Gemeinde Heinersbrück,
- Gemeinde Briesen,
- Gemeinde Forst mit den Gemarkungen Briesníg, Weißagk, Bohrau, Naundorf, Mulknitz, Klein Jamno, Forst (Lausitz) und Groß Jamno,
- Gemeinde Wiesengrund,
- Gemeinde Groß Schacksdorf-Simmersdorf mit der Gemarkung Simmersdorf,
- Gemeinde Neiße-Malxetal mit den Gemarkungen Jocksdorf, Klein Kölzig und Groß Kölzig,
- Gemeinde Tschernitz mit der Gemarkung Wolfshain,
- Gemeinde Felixsee,

— Gemeinde Spremberg mit den Gemarkungen Lieskau, Schönheide, Graustein, Türkendorf, Groß Luja, Wadelsdorf, Hornow, Sellessen, Spremberg, Bühlow,

— Gemeinde Neuhausen/Spree mit den Gemarkungen Kathlow, Haasow, Sergen, Roggosen, Gablenz, Komptendorf, Laubsdorf, Koppatz, Neuhausen, Drieschnitz, Kahsel, Bagenz,

— Stadt Cottbus mit den Gemarkungen Dissenchen, Döbbrick, Merzdorf, Saspow, Schmellwitz, Sielow, Willmersdorf.

Bundesland Sachsen:

— Landkreis Bautzen

— Gemeinde Großdubrau: Ortsteile Commerau, Göbeln, Jetscheba, Kauppa, Särchen, Spreewiese,

— Gemeinde Hochkirch: Ortsteile Kohlwesa, Niethen, Rodewitz, Wawitz, Zschorna,

— Gemeinde Königswartha: Ortsteil Oppitz,

— Gemeinde Lohsa: Ortsteile Dreiweibern, Driewitz, Friedersdorf, Hermsdorf/Spree, Lippen, Litschen, Lohsa, Riegel, Tiegling, Weißkollm,

— Gemeinde Malschwitz: Ortsteile Baruth, Brießnitz, Brösa, Buchwalde, Cannewitz, Dubrauke, Gleina, Guttau, Halbendorf/Spree, Kleinsaubernitz, Lieske, Lömischau, Neudorf/Spree, Preititz, Rackel, Ruhethal, Wartha,

— Gemeinde Radibor: Ortsteile Droben, Lippitsch, Milkel, Teicha, Wessel,

— Gemeinde Spreetal,

— Gemeinde Weißenberg.

— Landkreis Görlitz:

— Gemeinde Boxberg/O.L., sofern nicht bereits Teil des gefährdeten Gebietes,

— Gemeinde Görlitz südlich der Bundesautobahn A4 mit den Ortsteilen Biesnitz, Deutsch Ossig, Historische Altstadt, Innenstadt, Klein Neundorf, Klingewalde, Königshufen, Kunnerwitz, Ludwigsdorf, Nikolaivorstadt, Rauschwalde, Schlauroth, Südstadt, Weinhübel,

— Gemeinde Groß Düben, sofern nicht bereits Teil des gefährdeten Gebietes,

— Gemeinde Hohendubrau, sofern nicht bereits Teil des gefährdeten Gebietes,

— Gemeinde Kodersdorf, sofern nicht bereits Teil des gefährdeten Gebietes,

— Gemeinde Königshain,

— Gemeinde Löbau: Ortsteile Altcunnewitz, Bellwitz, Dolgowitz, Glossen, Kittlitz, Kleinradmeritz, Krappe, Lautitz, Mauschwitz, Neucunnewitz, Neukittlitz, Oppeln, Rosenhain,

— Gemeinde Markersdorf: Ortsteile Holtendorf, Markersdorf, Pfaffendorf,

— Gemeinde Mücka, sofern nicht bereits Teil des gefährdeten Gebietes,

— Gemeinde Reichenbach/O.L.: Ortsteile Biesig, Borda, Dittmannsdorf, Feldhäuser, Goßwitz, Krobnitz, Lehnhäuser, Löbensmüh, Mengelsdorf, Meuselwitz, Oehlisch, Stadt Reichenbach/O.L., Reißaus, Schöps, Zoblitz,

— Gemeinde Schleife, sofern nicht bereits Teil des gefährdeten Gebietes,

— Gemeinde Schöpstal, sofern nicht bereits Teil des gefährdeten Gebietes,

— Gemeinde Trebendorf, sofern nicht bereits Teil des gefährdeten Gebietes,

— Gemeinde Vierkirchen, sofern nicht bereits Teil des gefährdeten Gebietes,

— Gemeinde Waldhufen, sofern nicht bereits Teil des gefährdeten Gebietes,

— Gemeinde Weißwasser/O.L., sofern nicht bereits Teil des gefährdeten Gebietes.

2. **Estonia**

The following restricted zones I in Estonia:

— Hiiu maakond.

3. **Greece**

The following restricted zones I in Greece:

— in the regional unit of Drama:

  — the community departments of Sidironero and Skaloti and the municipal departments of Livadero and Ksiropotamo (in Drama municipality),

  — the municipal department of Paranesti (in Paranesti municipality),

  — the municipal departments of Kokkinogeia, Mikropoli, Panorama, Pyrgoi (in Prosotsani municipality),

  — the municipal departments of Kato Nevrokopi, Chrysokefalo, Achladea, Vathytopos, Volakas, Granitis, Dasotos, Eksohi, Katafyto, Lefkogeia, Mikrokleisoura, Mikromilea, Ochyro, Pagoneri, Perithorio, Kato Vrontou and Potamoi (in Kato Nevrokopi municipality),

— in the regional unit of Xanthi:

  — the municipal departments of Kimmerion, Stavroupoli, Gerakas, Dafnonas, Komnina, Kariofyto and Neochori (in Xanthi municipality),

  — the community departments of Satres, Thermes, Kotyli, and the municipal departments of Myki, Echinos and Oraio and (in Myki municipality),

  — the community department of Selero and the municipal department of Sounio (in Avdira municipality),

— in the regional unit of Rodopi:

  — the municipal departments of Komotini, Anthochorio, Gratini, Thrylorio, Kalhas, Karydia, Kikidio, Kosmio, Pandrosos, Aigeiros, Kallisti, Meleti, Neo Sidirochori and Mega Doukato (in Komotini municipality),

  — the municipal departments of Ipio, Arriana, Darmeni, Archontika, Fillyra, Ano Drosini, Aratos and the Community Departments Kehros and Organi (in Arriana municipality),

  — the municipal departments of Iasmos, Sostis, Asomatoi, Polyanthos and Amvrosia and the community department of Amaxades (in Iasmos municipality),

  — the municipal department of Amaranta (in Maroneia Sapon municipality),

— in the regional unit of Evros:

  — the municipal departments of Kyriaki, Mandra, Mavrokklisi, Mikro Dereio, Protokklisi, Roussa, Goniko, Geriko, Sidirochori, Megalo Derio, Sidiro, Giannouli, Agriani and Petrolofos (in Soufli municipality),

  — the municipal departments of Dikaia, Arzos, Elaia, Therapio, Komara, Marasia, Ormenio, Pentalofos, Petrota, Plati, Ptelea, Kyprinos, Zoni, Fulakio, Spilaio, Nea Vyssa, Kavili, Kastanies, Rizia, Sterna, Ampelakia, Valtos, Megali Doxipara, Neochori and Chandras (in Orestiada municipality),

  — the municipal departments of Asvestades, Ellinochori, Karoti, Koufovouno, Kiani, Mani, Sitochori, Alepochori, Asproneri, Metaxades, Vrysika, Doksa, Elafoxori, Ladi, Paliouri and Poimeniko (in Didymoteixo municipality),

— in the regional unit of Serres:

  — the municipal departments of Kerkini, Livadia, Makrynitsa, Neochori, Platanakia, Petritsi, Akritochori, Vyroneia, Gonimo, Mandraki, Megalochori, Rodopoli, Ano Poroia, Katw Poroia, Sidirokastro, Vamvakophyto, Promahonas, Kamaroto, Strymonochori, Charopo, Kastanousi and Chortero and the community departments of Achladochori, Agkistro and Kapnophyto (in Sintiki municipality),

  — the municipal departments of Serres, Elaionas and Oinoussa and the community departments of Orini and Ano Vrontou (in Serres municipality),

  — the municipal departments of Dasochoriou, Irakleia, Valtero, Karperi, Koimisi, Lithotopos, Limnochori, Podismeno and Chrysochorafa (in Irakleia municipality).

4. **Latvia**

The following restricted zones I in Latvia:

— Pāvilostas novada Vērgales pagasts,

— Stopiņu novada daļa, kas atrodas uz rietumiem no autoceļa V36, P4 un P5, Acones ielas, Dauguļupes ielas un Dauguļupītes,

— Grobiņas novada Medzes, Grobiņas un Gaviezes pagasts. Grobiņas pilsēta,

— Rucavas novada Rucavas pagasts,

— Nīcas novads.

5. **Lithuania**

The following restricted zones I in Lithuania:

— Klaipėdos rajono savivaldybė: Agluonėnų, Dovilų, Gargždų, Priekulės, Vėžaičių, Kretingalės ir Dauparų-Kvietinių seniūnijos,

— Palangos miesto savivaldybė.

6. **Hungary**

The following restricted zones I in Hungary:

— Békés megye 950950, 950960, 950970, 951950, 952050, 952750, 952850, 952950, 953050, 953150, 953650, 953660, 953750, 953850, 953960, 954250, 954260, 954350, 954450, 954550, 954650, 954750, 954850, 954860, 954950, 955050, 955150, 955250, 955260, 955270, 955350, 955450, 955510, 955650, 955750, 955760, 955850, 955950, 956050, 956060, 956150 és 956160 kódszámú vadgazdálkodási egységeinek teljes területe,

— Bács-Kiskun megye 600150, 600850, 601550, 601650, 601660, 601750, 601850, 601950, 602050, 603250, 603750 és 603850 kódszámú vadgazdálkodási egységeinek teljes területe,

— Budapest 1 kódszámú, vadgazdálkodási tevékenységre nem alkalmas területe,

— Csongrád-Csanád megye 800150, 800160, 800250, 802220, 802260, 802310 és 802450 kódszámú vadgazdálkodási egységeinek teljes területe,

— Fejér megye 400150, 400250, 400351, 400352, 400450, 400550, 401150, 401250, 401350, 402050, 402350, 402360, 402850, 402950, 403050, 403250, 403350, 403450, 403550, 403650, 403750, 403950, 403960, 403970, 404570, 404650, 404750, 404850, 404950, 404960, 405050, 405750, 405850, 405950,

— 406050, 406150, 406550, 406650 és 406750 kódszámú vadgazdálkodási egységeinek teljes területe,

— Jász-Nagykun-Szolnok megye 750150, 750160, 750260, 750350, 750450, 750460, 754450, 754550, 754560, 754570, 754650, 754750, 754950, 755050, 755150, 755250, 755350 és 755450 kódszámú vadgazdálkodási egységeinek teljes területe,

— Komárom-Esztergom megye 250150, 250250, 250350, 250450, 250460, 250550, 250650, 250750, 250850, 250950, 251050, 251150, 251250, 251350, 251360, 251450, 251550, 251650, 251750, 251850, 252150 és 252250, kódszámú vadgazdálkodási egységeinek teljes területe,

— Pest megye 571550, 572150, 572250, 572350, 572550, 572650, 572750, 572850, 572950, 573150, 573250, 573260, 573350, 573360, 573450, 573850, 573950, 573960, 574050, 574150, 574350, 574360, 574550, 574650, 574750, 574850, 574860, 574950, 575050, 575150, 575250, 575350, 575550, 575650, 575750, 575850, 575950, 576050, 576150, 576250, 576350, 576450, 576650, 576750, 576850, 576950, 577050, 577150, 577350, 577450, 577650, 577850, 577950, 578050, 578150, 578250, 578350, 578360, 578450, 578550, 578560, 578650, 578850, 578950, 579050, 579150, 579250, 579350, 579450, 579460, 579550, 579650, 579750, 580250 és 580450 kódszámú vadgazdálkodási egységeinek teljes területe.

7. **Poland**

The following restricted zones I in Poland:

w województwie warmińsko-mazurskim:

— gminy Wielbark i Rozogi w powiecie szczycieńskim,

— gminy Janowiec Kościelny, Janowo i część gminy Kozłowo położona na południe od linii wyznaczonej przez linię kolejową w powiecie nidzickim,

— gminy Iłowo – Osada, Lidzbark, Płośnica, miasto Działdowo, część gminy Rybno położona na południe od linii wyznaczonej przez drogę kolejową, część gminy wiejskiej Działdowo położona na południe od linii wyznaczonej przez linie kolejowe biegnące od wschodniej do zachodniej granicy gminy w powiecie działdowskim,

— gminy Kisielice, Susz i część gminy wiejskiej Iława położona na zachód od linii wyznaczonej przez drogę nr 521 biegnącą od zachodniej granicy gminy do skrzyżowania z drogą łączącą miejscowości Szymbark - Ząbrowo - Segnowy – Laseczno – Gulb, a następnie na zachód od linii wyznaczonej przez drogę łączącą miejscowości Szymbark - Ząbrowo - Segnowy – Laseczno - Gulb biegnącą do południowej granicy gminy w powiecie iławskim,

— gminy Biskupiec, Kurzętnik, część gminy wiejskiej Nowe Miasto Lubawskie położona na południe od linii wyznaczonej przez drogę biegnącą od zachodniej granicy gminy do miejscowości Lekarty, a następnie na południowy - zachód od linii wyznaczonej przez drogę łączącą miejscowości Lekarty – Nowy Dwór Bratiański biegnącą do północnej granicy gminy miejskiej Nowe Miasto Lubawskie oraz na południe od linii wyznaczonej przez drogę nr 538, część gminy Grodziczno położona na południe od linii wyznaczonej przez drogę nr 538 w powiecie nowomiejskim.

w województwie podlaskim:

— gminy Wysokie Mazowieckie z miastem Wysokie Mazowieckie, Czyżew i część gminy Kulesze Kościelne położona na południe od linii wyznaczonej przez linię koleją w powiecie wysokomazowieckim,

— gminy Miastkowo, Nowogród, Śniadowo i Zbójna w powiecie łomżyńskim,

— gminy Szumowo, Zambrów z miastem Zambrów i część gminy Kołaki Kościelne położona na południe od linii wyznaczonej przez linię kolejową w powiecie zambrowskim,

— gminy Grabowo, Kolno i miasto Kolno, Turośl w powiecie kolneńskim,

w województwie mazowieckim:

— powiat ostrołęcki,

— powiat miejski Ostrołęka,

— gminy Bielsk, Brudzeń Duży, Bulkowo, Drobin, Gąbin, Łąck, Nowy Duninów, Radzanowo, Słupno, Staroźreby i Stara Biała w powiecie płockim,

— powiat miejski Płock,

— powiat ciechanowski,

— gminy Baboszewo, Dzierzążnia, Joniec, Nowe Miasto, Płońsk i miasto Płońsk, Raciąż i miasto Raciąż, Sochocin w powiecie płońskim,

— powiat sierpecki,

— powiat żuromiński,

— gminy Andrzejewo, Brok, Stary Lubotyń, Szulborze Wielkie, Wąsewo, Ostrów Mazowiecka z miastem Ostrów Mazowiecka, część gminy Małkinia Górna położona na północ od rzeki Brok w powiecie ostrowskim,

— powiat mławski,

— powiat przasnyski,

— powiat makowski,

— powiat pułtuski,

— powiat wyszkowski,

— powiat węgrowski,

— gminy Dąbrówka, Jadów, Klembów, Poświętne, Radzymin, Strachówka Wołomin i Tłuszcz w powiecie wołomińskim,

— gminy Mokobody i Suchożebry w powiecie siedleckim,

— gminy Dobre, Jakubów, Kałuszyn, Stanisławów w powiecie mińskim,

— gminy Bielany i gmina wiejska Sokołów Podlaski w powiecie sokołowskim,

— gminy Kowala, Wierzbica, część gminy Wolanów położona na południe od linii wyznaczonej przez drogę nr 12 w powiecie radomskim,

— powiat miejski Radom,

— gminy Jastrząb, Mirów, Orońsko w powiecie szydłowieckim,

— powiat gostyniński,

w województwie podkarpackim:

— gminy Pruchnik, Rokietnica, Roźwienica, w powiecie jarosławskim,

— gminy Fredropol, Krasiczyn, Krzywcza, Medyka, Orły, Żurawica, Przemyśl w powiecie przemyskim,

— powiat miejski Przemyśl,

— gminy Gać, Jawornik Polski, Kańczuga, część gminy Zarzecze położona na południe od linii wyznaczonej przez rzekę Mleczka w powiecie przeworskim,

— powiat łańcucki,

— gminy Trzebownisko, Głogów Małopolski i część gminy Sokołów Małopolski położona na południe od linii wyznaczonej przez drogę nr 875 w powiecie rzeszowskim,

— gminy Dzikowiec, Kolbuszowa, Niwiska i Raniżów w powiecie kolbuszowskim,

— gminy Borowa, Czermin, Gawłuszowice, Mielec z miastem Mielec, Padew Narodowa, Przecław, Tuszów Narodowy w powiecie mieleckim,

w województwie świętokrzyskim:

— powiat opatowski,

— powiat sandomierski,

— gminy Bogoria, Łubnice, Oleśnica, Osiek, Połaniec, Rytwiany i Staszów w powiecie staszowskim,

— gminy Bliżyn, Skarżysko – Kamienna, Suchedniów i Skarżysko Kościelne w powiecie skarżyskim,

— gmina Wąchock, część gminy Brody położona na zachód od linii wyznaczonej przez drogę nr 9 oraz na południowy - zachód od linii wyznaczonej przez drogi: nr 0618T biegnącą od północnej granicy gminy do skrzyżowania w miejscowości Lipie, drogę biegnącą od miejscowości Lipie do wschodniej granicy gminy oraz na północ od drogi nr 42 i część gminy Mirzec położona na zachód od linii wyznaczonej przez drogę nr 744 biegnącą od południowej granicy gminy do miejscowości Tychów Stary a następnie przez drogę nr 0566T biegnącą od miejscowości Tychów Stary w kierunku północno - wschodnim do granicy gminy w powiecie starachowickim,

— powiat ostrowiecki,

— gminy Fałków, Ruda Maleniecka, Radoszyce, Smyków, część gminy Końskie położona na zachód od linii kolejowej, część gminy Stąporków położona na południe od linii kolejowej w powiecie koneckim,

— gminy Mniów i Zagnańsk w powiecie kieleckim,

w województwie łódzkim:

— gminy Łyszkowice, Kocierzew Południowy, Kiernozia, Chąśno, Nieborów, część gminy wiejskiej Łowicz położona na północ od linii wyznaczonej przez drogę nr 92 biegnącej od granicy miasta Łowicz do zachodniej granicy gminy oraz część gminy wiejskiej Łowicz położona na wschód od granicy miasta Łowicz i na północ od granicy gminy Nieborów w powiecie łowickim,

— gminy Cielądz, Rawa Mazowiecka z miastem Rawa Mazowiecka w powiecie rawskim,

— gminy Bolimów, Głuchów, Godzianów, Lipce Reymontowskie, Maków, Nowy Kawęczyn, Skierniewice, Słupia w powiecie skierniewickim,

— powiat miejski Skierniewice,

— gminy Mniszków, Paradyż, Sławno i Żarnów w powiecie opoczyńskim,

— gminy Czerniewice, Inowłódz, Lubochnia, Rzeczyca, Tomaszów Mazowiecki z miastem Tomaszów Mazowiecki i Żelechlinek w powiecie tomaszowskim,

— gmina Aleksandrów w powiecie piotrkowskim,

w województwie pomorskim:

— gminy Ostaszewo, miasto Krynica Morska oraz część gminy Nowy Dwór Gdański położona na południowy - zachód od linii wyznaczonej przez drogę nr 55 biegnącą od południowej granicy gminy do skrzyżowania z drogą nr 7, następnie przez drogę nr 7 i S7 biegnącą do zachodniej granicy gminy w powiecie nowodworskim,

— gminy Lichnowy, Miłoradz, Nowy Staw, Malbork z miastem Malbork w powiecie malborskim,

— gminy Mikołajki Pomorskie, Stary Targ i Sztum w powiecie sztumskim,

— powiat gdański,

— Miasto Gdańsk,

— powiat tczewski,

— powiat kwidzyński,

w województwie lubuskim:

— gminy Przytoczna, Pszczew, Skwierzyna i część gminy Trzciel położona na północ od linii wyznaczonej przez drogę nr 92 w powiecie międzyrzeckim,

— gminy Lubniewice i Krzeszyce w powiecie sulęcińskim,

— gminy Bogdaniec, Deszczno, Lubiszyn i część gminy Witnica położona na północny - wschód od drogi biegnącej od zachodniej granicy gminy od miejscowości Krześnica, przez miejscowości Kamień Wielki - Mościce -Witnica - Kłopotowo do południowej granicy gminy w powiecie gorzowskim,

w województwie dolnośląskim:

— gminy Bolesławiec z miastem Bolesławiec, Gromadka i Osiecznica w powiecie bolesławieckim,

— gmina Węgliniec w powiecie zgorzeleckim,

— gmina Chocianów i część gminy Przemków położona na południe od linii wyznaczonej przez drogę nr 12 w powiecie polkowickim,

— gmina Góra , Wąsosz, część gminy Niechlów położona na północny – wschód od linii wyznaczonej przez rzekę Barycz i część gminy Jemielno położona na wschód od linii wyznaczonej przez drogę nr 323 w powiecie górowskim,

— gmina Wińsko w powiecie wołowskim,

— gminy Ścinawa i Lubin z miastem Lubin w powiecie lubińskim,

w województwie wielkopolskim:

— gminy Krzemieniewo, Osieczna, Rydzyna, część gminy Lipno położona na wschód od linii wyznaczonej przez drogę nr S5, część gminy Święciechowa położona na południe od linii wyznaczonej przez drogę nr 12 oraz na wschód od linii wyznaczonej przez drogę nr S5 w powiecie leszczyńskim,

— powiat miejski Leszno,

— gminy Chrzypsko Wielkie, Międzychód, część gminy Sieraków położona na zachód od linii wyznaczonej przez drogę nr 186 biegnącą od południowej granicy gminy do miejscowości Lutomek, a następnie na zachód od linii wyznaczonej przez drogę biegnącą od skrzyżowania z drogą nr 186 w miejscowości Lutomek biegnącą do skrzyżowania z ul. Leśną w miejscowości Lutom i dalej na zachód od ul. Leśnej biegnącej do wschodniej granicy gminy, część gminy Kwilcz położona na zachód linii wyznaczonej przez drogę nr 186 biegnącą od północnej granicy gminy do skrzyżowania z drogą nr 24, następnie na południe od linii wyznaczonej przez drogę nr 24 biegnącą od skrzyżowania z drogą nr 186 do skrzyżowania z drogą w miejscowości Pólko, i dalej na zachód od linii wyznaczonej przez drogę biegnącą od miejscowości Pólko przez miejscowość Wituchowo do południowej granicy gminy, w powiecie międzychodzkim,

— gminy Lwówek, Kuślin, Opalenica, część gminy Miedzichowo położona na północ od linii wyznaczonej przez drogę nr 92, część gminy Nowy Tomyśl położona na wschód od linii wyznaczonej przez drogę nr 305 w powiecie nowotomyskim,

— gminy Granowo, Grodzisk Wielkopolski i część gminy Kamieniec położona na wschód od linii wyznaczonej przez drogę nr 308 w powiecie grodziskim,

— gminy Czempiń, Kościan i miasto Kościan, Krzywiń, część gminy Śmigiel położona na wschód od linii wyznaczonej przez drogę nr S5 w powiecie kościańskim,

— powiat miejski Poznań,

— gminy Buk, Dopiewo, Komorniki, Tarnowo Podgórne, Stęszew, Swarzędz, Pobiedziska, Czerwonak, Mosina, miasto Luboń, miasto Puszczykowo i część gminy Kórnik położona na zachód od linii wyznaczonych przez drogi: nr S11 biegnącą od północnej granicy gminy do skrzyżowania z drogą nr 434 i drogę nr 434 biegnącą od tego skrzyżowania do południowej granicy gminy, część gminy Rokietnica położona na południowy zachód od linii kolejowej biegnącej od północnej granicy gminy w miejscowości Krzyszkowo do południowej granicy gminy w miejscowości Kiekrz oraz część gminy wiejskiej Murowana Goślina położona na południe od linii kolejowej biegnącej od północnej granicy miasta Murowana Goślina do północno-wschodniej granicy gminy w powiecie poznańskim,

— gmina Kiszkowo i część gminy Kłecko położona na zachód od rzeki Mała Wełna w powiecie gnieźnieńskim,

— gminy Lubasz, Czarnków z miastem Czarnków, część gminy Połajewo na położona na północ od drogi łączącej miejscowości Chraplewo, Tarnówko-Boruszyn, Krosin, Jakubowo, Połajewo - ul. Ryczywolska do północno-wschodniej granicy gminy oraz część gminy Wieleń położona na południe od linii kolejowej biegnącej od wschodniej granicy gminy przez miasto Wieleń i miejscowość Herburtowo do zachodniej granicy gminy w powiecie czarnkowsko-trzcianeckim,

— gmina Kaźmierz część gminy Duszniki położona na południowy – wschód od linii wyznaczonej przez drogę nr 306 biegnącą od północnej granicy gminy do miejscowości Duszniki, a następnie na południe od linii wyznaczonej przez ul. Niewierską oraz drogę biegnącą przez miejscowość Niewierz do zachodniej granicy gminy, część gminy Ostroróg, położona na wschód od linii wyznaczonej przez drogę nr 186 i 184 biegnące od granicy gminy do miejscowości Ostroróg, a następnie od miejscowości Ostroróg przez miejscowości Piaskowo – Rudki do południowej granicy gminy, część gminy Wronki położona na północ od linii wyznaczonej przez drogi nr 182 i 186, miasto Szamotuły i część gminy Szamotuły położona na wschód od linii wyznaczonej przez drogę nr 306 do linii wyznaczonej przez wschodnią granicę miasta Szamotuły i na południe od linii kolejowej biegnącej od południowej granicy miasta Szamotuły, do południowo-wschodniej granicy gminy oraz część gminy Obrzycko położona na zachód od drogi nr 185 łączącej miejscowości Gaj Mały, Słopanowo i Obrzycko do północnej granicy miasta Obrzycko, a następnie na zachód od drogi przebiegającej przez miejscowość Chraplewo w powiecie szamotulskim,

— gmina Budzyń w powiecie chodzieskim,

— gminy Mieścisko, Skoki i Wągrowiec z miastem Wągrowiec w powiecie wągrowieckim,

— powiat pleszewski,

— gmina Zagórów w powiecie słupeckim,

— gmina Pyzdry w powiecie wrzesińskim,

— gminy Kotlin, Żerków i część gminy Jarocin położona na wschód od linii wyznaczonej przez drogi nr S11 i 15 w powiecie jarocińskim,

— gmina Rozdrażew, część gminy Koźmin Wielkopolski położona na wschód od linii wyznaczonej przez drogę nr 15, część gminy Krotoszyn położona na wschód od linii wyznaczonej przez drogę nr 15 oraz na wschód od granic miasta Krotoszyn w powiecie krotoszyńskim,

— gminy Nowe Skalmierzyce, Raszków, Ostrów Wielkopolski z miastem Ostrów Wielkopolski w powiecie ostrowskim,

— powiat miejski Kalisz,

— gminy Blizanów, Stawiszyn, Żelazków, Ceków – Kolonia, Godziesze Wielkie, Koźminek, Lisków, Mycielin, Opatówek, Szczytniki w powiecie kaliskim,

— gmina Malanów i część gminy Tuliszków położona na zachód od linii wyznaczonej przez drogę nr 72 w powiecie tureckim,

— gminy Rychwał, Rzgów, Grodziec, część gminy Stare Miasto położona na południe od linii wyznaczonej przez autostradę nr A2 w powiecie konińskim,

w województwie zachodniopomorskim:

— część gminy Dębno położona na wschód od linii wyznaczonej przez drogę nr 126 biegnącą od zachodniej granicy gminy do skrzyżowania z drogą nr 23 w miejscowości Dębno, następnie na wschód od linii wyznaczonej przez drogę nr 23 do skrzyżowania z ul. Jana Pawła II w miejscowości Cychry, następnie na północ od ul. Jana Pawła II do skrzyżowania z ul. Ogrodową i dalej na północ od linii wyznaczonej przez ul. Ogrodową, której przedłużenie biegnie do wschodniej granicy gminy w powiecie myśliborskim,

— gminy Chojna, Trzcińsko - Zdrój oraz część gminy Cedynia położona na północ od linii wyznaczonej przez drogę nr 124 biegnącą od zachodniej granicy gminy do miasta Cedynia, a następnie na północ od linii wyznaczonej przez drogę nr 125 biegnącą od miasta Cedynia do wschodniej granicy gminy w powiecie gryfińskim.

8. **Slovakia**

The following restricted zones I in Slovakia:

— the whole district of Vranov nad Topľou, except municipalities included in part II,

— the whole district of Humenné, except municipalities included in part II,

— the whole district of Snina,

— the whole district of Medzilaborce

— the whole district of Stropkov

— the whole district of Svidník, except municipalities included in part II,

— the whole district of Stará Ľubovňa, except municipalities included in part II,

— the whole district of whole Kežmarok,

— the whole district of Poprad,

— the whole district of Veľký Krtíš, except municipalities included in part II,

— in the whole district of Zvolen, except municipalities included in part II,

— the whole district of Detva, except municipalities included in part II,

— the whole district of Krupina, except municipalities included in part II,

— the whole district of Brezno.

PART II

1. **Bulgaria**

The following restricted zones II in Bulgaria:

— the whole region of Haskovo,

— the whole region of Yambol,

— the whole region of Stara Zagora,

— the whole region of Pernik,

— the whole region of Kyustendil,

— the whole region of Plovdiv,

— the whole region of Pazardzhik,

— the whole region of Smolyan,

— the whole region of Dobrich,

— the whole region of Sofia city,
— the whole region of Sofia Province,
— the whole region of Blagoevgrad,
— the whole region of Razgrad,
— the whole region of Kardzhali,
— the whole region of Burgas excluding the areas in Part III,
— the whole region of Varna excluding the areas in Part III,
— the whole region of Silistra, excluding the areas in Part III,
— the whole region of Ruse, excluding the areas in Part III,
— the whole region of Veliko Tarnovo, excluding the areas in Part III,
— the whole region of Pleven, excluding the areas in Part III,
— the whole region of Targovishte, excluding the areas in Part III,
— the whole region of Shumen, excluding the areas in Part III,
— the whole region of Sliven, excluding the areas in Part III,
— the whole region of Vidin, excluding the areas in Part III.

2. **Germany**

The following restricted zones II in Germany:

Bundesland Brandenburg:

— Landkreis Oder-Spree:
  — Gemeinde Grunow-Dammendorf,
  — Gemeinde Mixdorf
  — Gemeinde Schlaubetal,
  — Gemeinde Neuzelle,
  — Gemeinde Neißemünde,
  — Gemeinde Lawitz,
  — Gemeinde Eisenhüttenstadt,
  — Gemeinde Vogelsang,
  — Gemeinde Ziltendorf,
  — Gemeinde Wiesenau,
  — Gemeinde Friedland,
  — Gemeinde Siehdichum
  — Gemeinde Müllrose,
  — Gemeinde Groß Lindow,
  — Gemeinde Brieskow-Finkenheerd,
  — Gemeinde Ragow-Merz,
  — Gemeinde Beeskow,
  — Gemeinde Rietz-Neuendorf mit den Gemarkungen Groß Rietz und Birkholz,
  — Gemeinde Tauche mit den Gemarkungen Stremmen, Ranzig, Trebatsch, Sabrodt, Sawall, Mitweide und Tauche,
— Landkreis Dahme-Spreewald:
  — Gemeinde Jamlitz,
  — Gemeinde Lieberose,
  — Gemeinde Schwielochsee mit den Gemarkungen Goyatz, Jessern, Lamsfeld, Ressen, Speichrow und Zaue,

— Landkreis Spree-Neiße:

  — Gemeinde Schenkendöbern mit den Gemarkungen Stakow, Reicherskreuz, Groß Drewitz, Sembten, Lauschütz, Krayne, Lübbinchen, Grano, Pinnow, Bärenklau, Schenkendöbern und Atterwasch,

  — Gemeinde Guben mit den Gemarkungen Bresinchen, Guben und Deulowitz,

  — Gemeinde Forst (Lausitz) mit den Gemarkungen Groß Bademeusel und Klein Bademeusel,

  — Gemeinde Groß Schacksdorf-Simmersdorf mit der Gemarkung Groß Schacksdorf,

  — Gemeinde Neiße-Malxetal mit den Gemarkungen Preschen und Jerischke,

  — Gemeinde Döbern,

  — Gemeinde Jämlitz-Klein Düben,

  — Gemeinde Tschernitz mit der Gemarkung Tschernitz,

— Landkreis Märkisch-Oderland:

  — Gemeinde Zechin,

  — Gemeinde Bleyen-Genschmar,

  — Gemeinde Neuhardenberg,

  — Gemeinde Golzow,

  — Gemeinde Küstriner Vorland,

  — Gemeinde Alt Tucheband,

  — Gemeinde Reitwein,

  — Gemeinde Podelzig,

  — Gemeinde Letschin,

  — Gemeinde Gusow-Platkow,

  — Gemeinde Seelow,

  — Gemeinde Vierlinden,

  — Gemeinde Lindendorf mit den Gemarkungen Sachsendorf, Libbenichen und Dolgelin – östlich der B 167,

  — Gemeinde Fichtenhöhe mit der Gemarkung Carzig – östlich der B 167,

  — Gemeinde Lebus,

  — Gemeinde Müncheberg mit den Gemarkungen Jahnsfelde, Trebnitz, Obersdorf, Münchehofe und Hermersdorf,

  — Gemeinde Märkische Höhe mit der Gemarkung Rindenwalde,

  — Gemeinde Bliesdorf mit der Gemarkung Metzdorf,

  — Gemarkung Neutrebbin mit den Gemarkungen Wuschewier, Altbarnim, Neutrebbin, Alttrebbin östlich der L 34 und Altlewin östlich der L 34 und südwestlich der L 33,

— kreisfreie Stadt Frankfurt (Oder),

Bundesland Sachsen:

— Landkreis Görlitz:

  — Gemeinde Bad Muskau,

  — Gemeinde Boxberg/O.L. östlich des Straßenverlaufes K8472 bis Kaschel – S121 – Jahmen –Dürrbacher Straße – K8472 – Eselsberg – S131 – Boxberg – K8481,

  — Gemeinde Gablenz,

  — Gemeinde Görlitz nördlich der Bundesautobahn A4,

  — Gemeinde Groß Düben südlich des Straßenverlaufes S126 – Halbendorf – K8478,

  — Gemeinde Hähnichen,

— Gemeinde Hohendubrau östlich des Straßenverlaufes der Verbindungsstraße Buchholz-Gebelzig – S55,

— Gemeinde Horka

— Gemeinde Kodersdorf nördlich der Bundesautobahn A4,

— Gemeinde Krauschwitz i.d. O.L.,

— Gemeinde Kreba-Neudorf,

— Gemeinde Mücka östlich des Straßenverlaufes S55 - K8471 - Förstgen - K8472,

— Gemeinde Neißeaue,

— Gemeinde Niesky,

— Gemeinde Quitzdorf am See,

— Gemeinde Rietschen,

— Gemeinde Rothenburg/ O.L.,

— Gemeinde Schleife östlich des Straßenverlaufes S130 – S126,

— Gemeinde Schöpstal nördlich der Bundesautobahn A4,

— Gemeinde Trebendorf östlich der K8481,

— Gemeinde Vierkirchen nördlich der Bundesautobahn A4 und östlich der Verbindungsstraße Buchholz-Gebelzig,

— Gemeinde Waldhufen nördlich der Bundesautobahn A4,

— Gemeinde Weißkeißel,

— Gemeinde Weißwasser/O.L. östlich der K8481.

3. **Estonia**

The following restricted zones II in Estonia:

— Eesti Vabariik (välja arvatud Hiiu maakond).

4. **Latvia**

The following restricted zones II in Latvia:

— Ādažu novads,

— Aizputes novada Aizputes, Cīravas un Lažas pagasts, Kalvenes pagasta daļa uz rietumiem no ceļa pie Vārtājas upes līdz autoceļam A9, uz dienvidiem no autoceļa A9, uz rietumiem no autoceļa V1200, Kazdangas pagasta daļa uz rietumiem no ceļa V1200, P115, P117, V1296, Aizputes pilsēta,

— Aglonas novads,

— Aizkraukles novads,

— Aknīstes novads,

— Alojas novads,

— Alsungas novads,

— Alūksnes novads,

— Amatas novads,

— Apes novads,

— Auces novads,

— Babītes novads,

— Baldones novads,

— Baltinavas novads,

— Balvu novads,

— Bauskas novads,

— Beverīnas novads,

— Brocēnu novads,

— Burtnieku novads,

— Carnikavas novads,

— Cēsu novads

— Cesvaines novads,

— Ciblas novads,

— Dagdas novads,

— Daugavpils novads,

— Dobeles novads,

— Dundagas novads,

— Durbes novads,

— Engures novads,

— Ērgļu novads,

— Garkalnes novads,

— Grobiņas novada Bārtas pagasts,

— Gulbenes novads,

— Iecavas novads,

— Ikšķiles novads,

— Ilūkstes novads,

— Inčukalna novads,

— Jaunjelgavas novads,

— Jaunpiebalgas novads,

— Jaunpils novads,

— Jēkabpils novads,

— Jelgavas novads,

— Kandavas novads,

— Kārsavas novads,

— Ķeguma novads,

— Ķekavas novads,

— Kocēnu novads,

— Kokneses novads,

— Krāslavas novads,

— Krimuldas novads,

— Krustpils novads,

— Kuldīgas novada, Laidu pagasta daļa uz ziemeļiem no autoceļa V1296, Padures, Rumbas, Rendas, Kabiles, Vārmes, Pelču, Ēdoles, Īvandes, Kurmāles, Turlavas, Gudenieku un Snēpeles pagasts, Kuldīgas pilsēta,

— Lielvārdes novads,

— Līgatnes novads,

— Limbažu novads,

— Līvānu novads,

— Lubānas novads,

— Ludzas novads,

— Madonas novads,

— Mālpils novads,

— Mārupes novads,

— Mazsalacas novads,

— Mērsraga novads,

— Naukšēnu novads,

— Neretas novads,

— Ogres novads,

— Olaines novads,

— Ozolnieku novads,

— Pārgaujas novads,

— Pāvilostas novada Sakas pagasts, Pāvilostas pilsēta,

— Pļaviņu novads,

— Preiļu novads,

— Priekules novads,

— Priekuļu novads,

— Raunas novads,

— republikas pilsēta Daugavpils,

— republikas pilsēta Jelgava,

— republikas pilsēta Jēkabpils,

— republikas pilsēta Jūrmala,

— republikas pilsēta Rēzekne,

— republikas pilsēta Valmiera,

— Rēzeknes novads,

— Riebiņu novads,

— Rojas novads,

— Ropažu novads,

— Rucavas novada Dunikas pagasts,

— Rugāju novads,

— Rundāles novads,

— Rūjienas novads,

— Salacgrīvas novads,

— Salas novads,

— Salaspils novads,

— Saldus novads,

— Saulkrastu novads,

— Sējas novads,

— Siguldas novads,

— Skrīveru novads,

— Skrundas novada Raņķu pagasta daļa uz ziemeļiem no autoceļa V1272 līdz robežai ar Ventas upi, Skrundas pagasta daļa no Skrundas uz ziemeļiem no autoceļa A9 un austrumiem no Ventas upes,

— Smiltenes novads,

— Stopiņu novada daļa, kas atrodas uz austrumiem no autoceļa V36, P4 un P5, Acones ielas, Dauguļupes ielas un Dauguļupītes,

— Strenču novads,

— Talsu novads,

— Tērvetes novads,

— Tukuma novads,

— Vaiņodes novada Vaiņodes pagasts un Embūtes pagasta daļa uz dienvidiem autoceļa P116, P106,

— Valkas novads,

— Varakļānu novads,

— Vārkavas novads,

— Vecpiebalgas novads,

— Vecumnieku novads,

— Ventspils novads,

— Viesītes novads,

— Viļakas novads,

— Viļānu novads,

— Zilupes novads.

5. **Lithuania**

The following restricted zones II in Lithuania:

— Alytaus miesto savivaldybė,

— Alytaus rajono savivaldybė,

— Anykščių rajono savivaldybė,

— Akmenės rajono savivaldybė,

— Birštono savivaldybė,

— Biržų miesto savivaldybė,

— Biržų rajono savivaldybė,

— Druskininkų savivaldybė,

— Elektrėnų savivaldybė,

— Ignalinos rajono savivaldybė,

— Jonavos rajono savivaldybė,

— Joniškio rajono savivaldybė,

— Jurbarko rajono savivaldybė: Eržvilko, Girdžių, Jurbarko miesto, Jurbarkų, Raudonės, Šimkaičių, Skirsnemunės, Smalininkų, Veliuonos ir Viešvilės seniūnijos,

— Kaišiadorių rajono savivaldybė,

— Kalvarijos savivaldybė,

— Kauno miesto savivaldybė,

— Kauno rajono savivaldybė: Akademijos, Alšėnų, Batniavos, Ežerėlio, Domeikavos, Garliavos, Garliavos apylinkių, Karmėlavos, Kulautuvos, Lapių, Linksmakalnio, Neveronių, Raudondvario, Ringaudų, Rokų, Samylų, Taurakiemio, Vandžiogalos, Užliedžių, Vilkijos, ir Zapyškio seniūnijos, Babtų seniūnijos dalis į rytus nuo kelio A1, ir Vilkijos apylinkių seniūnijos dalis į vakarus nuo kelio Nr. 1907,

— Kazlų rūdos savivaldybė,

— Kelmės rajono savivaldybė,

— Kėdainių rajono savivaldybė: Dotnuvos, Gudžiūnų, Kėdainių miesto, Krakių, Pelėdnagių, Surviliškio, Šėtos, Truskavos, Vilainių ir Josvainių seniūnijos dalis į šiaurę ir rytus nuo kelio Nr. 229 ir Nr. 2032,

— Klaipėdos rajono savivaldybė: Judrėnų, Endriejavo ir Veiviržėnų seniūnijos,

— Kupiškio rajono savivaldybė,

— Kretingos rajono savivaldybė,

— Lazdijų rajono savivaldybė,

— Marijampolės savivaldybė,

— Mažeikių rajono savivaldybė,

— Molėtų rajono savivaldybė,

— Pagėgių savivaldybė,

— Pakruojo rajono savivaldybė,

— Panevėžio rajono savivaldybė,

— Panevėžio miesto savivaldybė,

— Pasvalio rajono savivaldybė,

— Radviliškio rajono savivaldybė,

— Rietavo savivaldybė,

— Prienų rajono savivaldybė,

— Plungės rajono savivaldybė: Žlibinų, Stalgėnų, Nausodžio, Plungės miesto, Šateikių ir Kulių seniūnijos,

— Raseinių rajono savivaldybė: Betygalos, Girkalnio, Kalnujų, Nemakščių, Pagojukų, Paliepių, Raseinių miesto, Raseinių, Šiluvos, Viduklės seniūnijos,

— Rokiškio rajono savivaldybė,

— Skuodo rajono savivaldybės: Aleksandrijos, Ylakių, Lenkimų, Mosėdžio, Skuodo ir Skuodo miesto seniūnijos,

— Šakių rajono savivaldybė,

— Šalčininkų rajono savivaldybė,

— Šiaulių miesto savivaldybė,

— Šiaulių rajono savivaldybė,

— Šilutės rajono savivaldybė,

— Širvintų rajono savivaldybė,

— Šilalės rajono savivaldybė,

— Švenčionių rajono savivaldybė,

— Tauragės rajono savivaldybė,

— Telšių rajono savivaldybė,

— Trakų rajono savivaldybė,

— Ukmergės rajono savivaldybė,

— Utenos rajono savivaldybė,

— Varėnos rajono savivaldybė,

— Vilniaus miesto savivaldybė,

— Vilniaus rajono savivaldybė,

— Vilkaviškio rajono savivaldybė,

— Visagino savivaldybė,

— Zarasų rajono savivaldybė.

6. **Hungary**

The following restricted zones II in Hungary:

— Békés megye 950150, 950250, 950350, 950450, 950550, 950650, 950660, 950750, 950850, 950860, 951050, 951150, 951250, 951260, 951350, 951450, 951460, 951550, 951650, 951750, 952150, 952250, 952350, 952450, 952550, 952650, 953250, 953260, 953270, 953350, 953450, 953550, 953560, 953950, 954050, 954060, 954150, 956250, 956350, 956450, 956550, 956650 és 956750 kódszámú vadgazdálkodási egységeinek teljes területe,

— Borsod-Abaúj-Zemplén megye valamennyi vadgazdálkodási egységének teljes területe,

— Fejér megye 403150, 403160, 403260, 404250, 404550, 404560, 405450, 405550, 405650, 406450 és 407050 kódszámú vadgazdálkodási egységeinek teljes területe,

— Hajdú-Bihar megye valamennyi vadgazdálkodási egységének teljes területe,

— Heves megye valamennyi vadgazdálkodási egységének teljes területe,

— Jász-Nagykun-Szolnok megye 750250, 750550, 750650, 750750, 750850, 750970, 750980, 751050, 751150, 751160, 751250, 751260, 751350, 751360, 751450, 751460, 751470, 751550, 751650, 751750, 751850, 751950, 752150, 752250, 752350, 752450, 752460, 752550, 752560, 752650, 752750, 752850, 752950, 753060, 753070, 753150, 753250, 753310, 753450, 753550, 753650, 753660, 753750, 753850, 753950, 753960, 754050, 754150, 754250, 754360, 754370, 754850, 755550, 755650 és 755750 kódszámú vadgazdálkodási egységeinek teljes területe,

— Komárom-Esztergom megye: 251950, 252050, 252350, 252450, 252460, 252550, 252650, 252750, 252850, 252860, 252950, 252960, 253050, 253150, 253250, 253350, 253450 és 253550 kódszámú vadgazdálkodási egységeinek teljes területe,

— Nógrád megye valamennyi vadgazdálkodási egységeinek teljes területe,

— Pest megye 570150, 570250, 570350, 570450, 570550, 570650, 570750, 570850, 570950, 571050, 571150, 571250, 571350, 571650, 571750, 571760, 571850, 571950, 572050, 573550, 573650, 574250, 577250, 580050 és 580150 kódszámú vadgazdálkodási egységeinek teljes területe,

— Szabolcs-Szatmár-Bereg megye valamennyi vadgazdálkodási egységének teljes területe.

7. **Poland**

The following restricted zones II in Poland:

w województwie warmińsko-mazurskim:

— gminy Kalinowo, Stare Juchy, Prostki oraz gmina wiejska Ełk w powiecie ełckim,

— powiat elbląski,

— powiat miejski Elbląg,

— powiat gołdapski,

— powiat piski,

— powiat bartoszycki,

— gminy Biskupiec, Jeziorany, Kolno, część gminy Olsztynek położona na południe od linii wyznaczonej przez drogę nr S51 biegnącą od wschodniej granicy gminy do miejscowości Ameryka oraz na zachód od linii wyznaczonej przez drogę biegnącą od skrzyżowania z drogą S51 do północnej granicy gminy, łączącej miejscowości Mańki – Mycyny – Ameryka w powiecie olsztyńskim,

— powiat ostródzki,

— powiat olecki,

— powiat giżycki,

— powiat braniewski,

— powiat kętrzyński,

— gminy Lubomino i Orneta w powiecie lidzbarskim,

— gmina Nidzica i część gminy Kozłowo położona na północ od linii wyznaczonej przez linię kolejową w powiecie nidzickim,

— gminy Dźwierzuty, Jedwabno, Pasym, Szczytno i miasto Szczytno i Świętajno w powiecie szczycieńskim,

— powiat mrągowski,

— gminy Lubawa, miasto Lubawa, Zalewo, miasto Iława i część gminy wiejskiej Iława położona na wschód od linii wyznaczonej przez drogę nr 521 biegnącą od zachodniej granicy gminy do skrzyżowania z drogą łączącą miejscowości Szymbark - Ząbrowo - Segnowy – Laseczno – Gulb, a następnie na wschód od linii wyznaczonej przez drogę łączącą miejscowości Szymbark - Ząbrowo - Segnowy – Laseczno - Gulb biegnącą do południowej granicy gminy w powiecie iławskim,

— część gminy wiejskiej Nowe Miasto Lubawskie położona na północ od linii wyznaczonej przez drogę biegnącą od zachodniej granicy gminy do miejscowości Lekarty, a następnie na północny -wschód od linii wyznaczonej przez drogę łączącą miejscowości Lekarty – Nowy Dwór Bratiański biegnącą do północnej granicy gminy miejskiej Nowe Miasto Lubawskie oraz na północ od linii wyznaczonej przez drogę nr 538, część gminy Grodziczno położona na północ od linii wyznaczonej przez drogę nr 538 w powiecie nowomiejskim,

— powiat węgorzewski,

— część gminy Rybno położona na północ od linii kolejowej, część gminy wiejskiej Działdowo położona na północ od linii wyznaczonej przez linie kolejowe biegnące od wschodniej do zachodniej granicy gminy w powiecie działdowskim,

w województwie podlaskim:

— powiat bielski,

— powiat grajewski,

— powiat moniecki,

— powiat sejneński,

— gminy Łomża, Piątnica, Jedwabne, Przytuły i Wizna w powiecie łomżyńskim,

— powiat miejski Łomża,

— powiat siemiatycki,

— powiat hajnowski,

— gminy Ciechanowiec, Klukowo, Szepietowo, Kobylin-Borzymy, Nowe Piekuty, Sokoły i część gminy Kulesze Kościelne położona na północ od linii wyznaczonej przez linię kolejową w powiecie wysokomazowieckim,

— gmina Rutki i część gminy Kołaki Kościelne położona na północ od linii wyznaczonej przez linię kolejową w powiecie zambrowskim,

— gminy Mały Potok i Stawiski w powiecie kolneńskim,

— powiat białostocki,

— powiat suwalski,

— powiat miejski Suwałki,

— powiat augustowski,

— powiat sokólski,

— powiat miejski Białystok,

w województwie mazowieckim:

— gminy Domanice, Korczew, Kotuń, Mordy, Paprotnia, Przesmyki, Siedlce, Skórzec, Wiśniew, Wodynie, Zbuczyn w powiecie siedleckim,

— powiat miejski Siedlce,

— gminy Ceranów, Jabłonna Lacka, Kosów Lacki, Repki, Sabnie, Sterdyń w powiecie sokołowskim,

— powiat łosicki,

— powiat sochaczewski,

— gminy Policzna, Przyłęk, Tczów i Zwoleń w powiecie zwoleńskim,

— powiat kozienicki,

— gminy Chotcza i Solec nad Wisłą w powiecie lipskim,

— gminy Gózd, Jastrzębia, Jedlnia Letnisko, Pionki z miastem Pionki, Skaryszew, Jedlińsk, Przytyk, Zakrzew, część gminy Iłża położona na zachód od linii wyznaczonej przez drogę nr 9, część gminy Wolanów położona na północ od drogi nr 12 w powiecie radomskim,

— gminy Bodzanów, Słubice, Wyszogród i Mała Wieś w powiecie płockim,

— powiat nowodworski,

— gminy Czerwińsk nad Wisłą, Naruszewo, Załuski w powiecie płońskim,

— gminy: miasto Kobyłka, miasto Marki, miasto Ząbki, miasto Zielonka w powiecie wołomińskim,

— gminy Borowie, Garwolin z miastem Garwolin, Miastków Kościelny, Parysów, Pilawa, część gminy Wilga położona na północ od linii wyznaczonej przez rzekę Wilga biegnącą od wschodniej granicy gminy do ujścia do rzeki Wisły, część gminy Górzno położona na północ od linii wyznaczonej przez drogę łączącą miejscowości Łąki i Górzno biegnącą od wschodniej granicy gminy, następnie od miejscowości Górzno na północ od drogi nr 1328W biegnącej do drogi nr 17, a następnie na północ od linii wyznaczonej przez drogę biegnącą

— od drogi nr 17 do zachodniej granicy gminy przez miejscowości Józefów i Kobyla Wola w powiecie garwolińskim,

— gminy Boguty – Pianki, Zaręby Kościelne, Nur i część gminy Małkinia Górna położona na południe od rzeki Brok w powiecie ostrowskim,

— gminy Chlewiska i Szydłowiec w powiecie szydłowieckim,

— gminy Cegłów, Dębe Wielkie, Halinów, Latowicz, Mińsk Mazowiecki i miasto Mińsk Mazowiecki, Mrozy, Siennica, miasto Sulejówek w powiecie mińskim,

— powiat otwocki,

— powiat warszawski zachodni,

— powiat legionowski,

— powiat piaseczyński,

— powiat pruszkowski,

— powiat grójecki,

— powiat grodziski,

— powiat żyrardowski,

— powiat białobrzeski,

— powiat przysuski,

— powiat miejski Warszawa,

w województwie lubelskim:

— powiat bialski,

— powiat miejski Biała Podlaska,

— gminy Batorz, Godziszów, Janów Lubelski, Modliborzyce i Potok Wielki w powiecie janowskim,

— gminy Janowiec, Kazimierz Dolny, Końskowola, Kurów, Markuszów, Nałęczów, Puławy z miastem Puławy, Wąwolnica i Żyrzyn w powiecie puławskim,

— gminy Nowodwór, miasto Dęblin i część gminy Ryki położona na południe od linii wyznaczonej przez linię kolejową powiecie ryckim,

— gminy Adamów, Krzywda, Stoczek Łukowski z miastem Stoczek Łukowski, Wola Mysłowska, Trzebieszów, Stanin, Wojcieszków, gmina wiejska Łuków i miasto Łuków w powiecie łukowskim,

— powiat lubelski,

— powiat miejski Lublin,

— gminy Niedźwiada, Ostrówek, Ostrów Lubelski, Serniki, Uścimów i Lubartów z miastem Lubartów w powiecie lubartowskim,

— powiat łęczyński,

— powiat świdnicki,

— gminy Fajsławice, Gorzków, Izbica, Krasnystaw z miastem Krasnystaw, Kraśniczyn, Łopiennik Górny, Siennica Różana i część gminy Żółkiewka położona na północ od linii wyznaczonej przez drogę nr 842 w powiecie krasnostawskim,

— gminy Chełm, Ruda – Huta, Sawin, Rejowiec, Rejowiec Fabryczny z miastem Rejowiec Fabryczny, Siedliszcze, Wierzbica, Żmudź, Dorohusk, Dubienka, Kamień, Leśniowice, Wojsławice w powiecie chełmskim,

— powiat miejski Chełm,

— powiat kraśnicki,

— powiat opolski,

— powiat parczewski,

— powiat włodawski,

— powiat radzyński,

— powiat miejski Zamość,

— gminy Sitno, Skierbieszów, Stary Zamość, Zamość w powiecie zamojskim

w województwie podkarpackim:

— powiat stalowowolski,

— gminy Oleszyce, Lubaczów z miastem Lubaczów, Wielkie Oczy w powiecie lubaczowskim,

— część gminy Kamień położona na zachód od linii wyznaczonej przez drogę nr 19, część gminy Sokołów Małopolski położona na północ od linii wyznaczonej przez drogę nr 875 w powiecie rzeszowskim,

— gminy Cmolas i Majdan Królewski w powiecie kolbuszowskim,

— gminy Grodzisko Dolne, część gminy wiejskiej Leżajsk położona na południe od miasta Leżajsk oraz na zachód od linii wyznaczonej przez rzekę San, w powiecie leżajskim,

— gmina Jarocin, część gminy Harasiuki położona na północ od linii wyznaczona przez drogę nr 1048 R, część gminy Ulanów położona na północ od linii wyznaczonej przez rzekę Tanew, część gminy Nisko położona na zachód od linii wyznaczonej przez drogę nr 19 oraz na północ od linii wyznaczonej przez linię kolejową biegnącą od wschodniej granicy gminy do skrzyżowania z drogą nr 19, część gminy Jeżowe położona na zachód od linii wyznaczonej przez drogę nr 19 w powiecie niżańskim,

— powiat tarnobrzeski,

— część gminy wiejskiej Przeworsk położona na zachód od miasta Przeworsk i na zachód od linii wyznaczonej przez autostradę A4 biegnącą od granicy z gminą Tryńcza do granicy miasta Przeworsk, część gminy Zarzecze położona na zachód od linii wyznaczonej przez drogę nr 1594R biegnącą od północnej granicy gminy do miejscowości Zarzecze oraz na południe od linii wyznaczonej przez drogi nr 1617R oraz 1619R biegnącą do południowej granicy gminy oraz na północ od linii wyznaczonej przez rzekę Mleczka w powiecie przeworskim,

w województwie pomorskim:

— gminy Dzierzgoń i Stary Dzierzgoń w powiecie sztumskim,

— gmina Stare Pole w powiecie malborskim,

— gminy Stegny, Sztutowo i część gminy Nowy Dwór Gdański położona na północny - wschód od linii wyznaczonej przez drogę nr 55 biegnącą od

— południowej granicy gminy do skrzyżowania z drogą nr 7, następnie przez drogę nr 7 i S7 biegnącą do zachodniej granicy gminy w powiecie nowodworskim,

w województwie świętokrzyskim:

— gmina Tarłów i część gminy Ożarów położona na północ od linii wyznaczonej przez drogę nr 74 w powiecie opatowskim,

— część gminy Brody położona na zachód od linii kolejowej biegnącej od miejscowości Marcule i od północnej granicy gminy przez miejscowości Klepacze i Karczma Kunowska do południowej granicy gminy oraz na wschód od linii wyznaczonej przez drogę nr 9 i na północny - wschód od linii wyznaczonej przez drogę nr 0618T biegnącą od północnej granicy gminy do skrzyżowania w miejscowości Lipie oraz przez drogę biegnącą od miejscowości Lipie do wschodniej granicy gminy i część gminy Mirzec położona na wschód od linii wyznaczonej przez drogę nr 744 biegnącą od południowej granicy gminy do miejscowości Tychów Stary a następnie przez drogę nr 0566T biegnącą od miejscowości Tychów Stary w kierunku północno – wschodnim do granicy gminy w powiecie starachowickim,

— gmina Gowarczów, część gminy Końskie położona na wschód od linii kolejowej, część gminy Stąporków położona na północ od linii kolejowej w powiecie koneckim,

w województwie lubuskim:

— powiat wschowski,

— gmina Kostrzyn nad Odrą i część gminy Witnica położona na południowy zachód od drogi biegnącej od zachodniej granicy gminy od miejscowości Krześnica, przez miejscowości Kamień Wielki - Mościce - Witnica - Kłopotowo do południowej granicy gminy w powiecie gorzowskim,

— gminy Gubin z miastem Gubin, Maszewo i część gminy Bytnica położona na zachód od linii wyznaczonej przez drogę nr 1157F w powiecie krośnieńskim,

— powiat słubicki,

— gminy Słońsk, Sulęcin i Torzym w powiecie sulęcińskim,

— gminy Bledzew i Międzyrzecz w powiecie międzyrzeckim,

— gminy Kolsko, część gminy Kożuchów położona na południe od linii wyznaczonej przez drogę 283 biegnącą od wschodniej granicy gminy do skrzyżowania z drogą nr 290 i na południe od linii wyznaczonej przez drogę nr 290 biegnącej od miasta Mirocin Dolny do zachodniej granicy gminy, część gminy Bytom Odrzański położona na północny zachód od linii wyznaczonej przez drogi nr 293 i 326, część gminy Nowe Miasteczko położona na zachód od linii wyznaczonych przez drogi 293 i 328, część gminy Siedlisko położona na północny zachód od linii wyznaczonej przez drogę biegnącą od rzeki Odry przy południowe granicy gminy do drogi nr 326 łączącej się z drogą nr 325 biegnącą w kierunku miejscowości Różanówka do skrzyżowania z drogą nr 321 biegnącą od tego skrzyżowania w kierunku miejscowości Bielawy, a następnie przedłużoną przez drogę przeciwpożarową biegnącą od drogi nr 321 w miejscowości Bielawy do granicy gminy w powiecie nowosolskim,

— gminy Nowogród Bobrzański, Trzebiechów, część gminy Bojadła położona na północ od linii wyznaczonej przez drogę nr 278 biegnącą od wschodniej granicy gminy do skrzyżowania z drogą nr 282 i na północ od linii

— wyznaczonej przez drogę nr 282 biegnącej od miasta Bojadła do zachodniej granicy gminy, część gminy Sulechów położona na wschód od linii wyznaczonej przez drogę nr S3 oraz na południe od linii wyznaczonej przez drogę łączącą miejscowości Kępsko - Buków biegnącą od zachodniej granicy gminy do miejscowości Buków, a następnie na wschód od linii wyznaczonej przez drogę łączącą miejscowości Buków – Miłkowo biegnącą od miejscowości Buków do północnej granicy gminy w powiecie zielonogórskim,

— powiat żarski,

— gminy Brzeźnica, Iłowa, Małomice, Szprotawa, Wymiarki, Żagań, miasto Żagań, miasto Gozdnica, część gminy Niegosławice położona na zachód od linii wyznaczonej przez drogę nr 328 w powiecie żagańskim,

— gmina Łagów, część gminy Lubrza położona na północ od linii wyznaczonej przez autostradę A2 i część gminy Świebodzin położona na północ od linii wyznaczonej przez autostradę A2w powiecie świebodzińskim,

w województwie dolnośląskim:

— gmina Pęcław, część gminy Kotla położona na północ od linii wyznaczonej przez rzekę Krzycki Rów, część gminy wiejskiej Głogów położona na wschód od linii wyznaczonej przez drogi nr 12, 319 oraz 329, część miasta Głogów położona na wschód od linii wyznaczonej przez drogę nr 12 w powiecie głogowskim,

— gminy Grębocice i Polkowice w powiecie polkowickim,

— gmina Rudna w powiecie lubińskim,

— część gminy Niechlów położona na południowy – zachód od linii wyznaczonej przez rzekę Barycz, część gminy Jemielno położona na zachód od linii wyznaczonej przez drogę nr 323 w powiecie górowskim,

w województwie wielkopolskim:

— gminy Przemęt i Wolsztyn w powiecie wolsztyńskim,

— gmina Wielichowo część gminy Kamieniec położona na zachód od linii wyznaczonej przez drogę nr 308 i część gminy Rakoniewice położona na zachód od linii wyznaczonej przez drogę nr 305 w powiecie grodziskim,

— gminy Wijewo, Włoszakowice, część gminy Lipno położona na zachód od linii wyznaczonej przez drogę nr S5 i część gminy Święciechowa położona na północ od linii wyznaczonej przez drogę nr 12 oraz na zachód od linii wyznaczonej przez drogę nr S5 w powiecie leszczyńskim,

— część gminy Śmigiel położona na zachód od linii wyznaczonej przez drogę nr S5, w powiecie kościańskim,

— powiat obornicki,

— część gminy Połajewo na położona na południe od drogi łączącej miejscowości Chraplewo, Tarnówko-Boruszyn, Krosin, Jakubowo, Połajewo - ul. Ryczywolska do północno-wschodniej granicy gminy w powiecie czarnkowsko-trzcianeckim,

— gmina Suchy Las, część gminy wiejskiej Murowana Goślina położona na północ od linii kolejowej biegnącej od północnej granicy miasta Murowana Goślina do północno-wschodniej granicy gminy oraz część gminy Rokietnica położona na północ i na wschód od linii kolejowej biegnącej od północnej

— granicy gminy w miejscowości Krzyszkowo do południowej granicy gminy w miejscowości Kiekrz w powiecie poznańskim,

— gmina Pniewy, część gminy Duszniki położona na północny – zachód od linii wyznaczonej przez drogę nr 306 biegnącą od północnej granicy gminy do miejscowości Duszniki, a następnie na północ od linii wyznaczonej przez ul. Niewierską oraz drogę biegnącą przez miejscowość Niewierz do zachodniej granicy gminy, część gminy Ostroróg położona na zachód od linii wyznaczonej przez drogę nr 186 i 184 biegnące od granicy gminy do miejscowości Ostroróg, a następnie od miejscowości Ostroróg przez miejscowości Piaskowo – Rudki do południowej granicy gminy, część gminy Wronki położona na południe od linii wyznaczonej przez drogi nr 182 i 186, część gminy Szamotuły położona na zachód od linii wyznaczonej przez drogę nr 306 oraz na wschód od wschodniej granicy miasta Szamotuły i na północ od linii kolejowej biegnącej od południowej granicy miasta Szamotuły do południowo-wschodniej granicy gminy oraz część gminy Obrzycko położona na wschód od drogi nr 185 łączącej miejscowości Gaj Mały, Słopanowo i Obrzycko do północnej granicy miasta Obrzycko, a następnie na wschód od drogi przebiegającej przez miejscowość Chraplewo w powiecie szamotulskim,

— część gminy Sieraków położona na wschód od linii wyznaczonej przez drogę nr 186 biegnącą od południowej granicy gminy do miejscowości Lutomek, a następnie na wschód od linii wyznaczonej przez drogę biegnącą od skrzyżowania z drogą nr 186 w miejscowości Lutomek biegnącą do skrzyżowania z ul. Leśną w miejscowości Lutom i dalej na wschód od ul. Leśnej biegnącej do wschodniej granicy gminy, część gminy Kwilcz położona na wschód od linii wyznaczonej przez drogę nr 186 biegnącą od północnej granicy gminy do skrzyżowania z drogą nr 24, następnie na północ od linii wyznaczonej przez drogę nr 24 biegnącą od skrzyżowania z drogą nr 186 do skrzyżowania z drogą w miejscowości Pólko, i dalej na wschód od linii wyznaczonej przez drogę biegnącą od miejscowości Pólko przez miejscowość Wituchowo do południowej granicy gminy w powiecie międzychodzkim

w województwie łódzkim:

— gminy Białaczów, Drzewica, Opoczno i Poświętne w powiecie opoczyńskim,

— gminy Biała Rawska, Regnów i Sadkowice w powiecie rawskim,

— gmina Kowiesy w powiecie skierniewickim,

w województwie zachodniopomorskim:

— gmina Boleszkowice i część gminy Dębno położona na zachód od linii wyznaczonej przez drogę nr 126 biegnącą od zachodniej granicy gminy do skrzyżowania z drogą nr 23 w miejscowości Dębno, następnie na zachód od linii wyznaczonej przez drogę nr 23 do skrzyżowania z ul. Jana Pawła II w miejscowości Cychry, następnie na południe od ul. Jana Pawła II do skrzyżowania z ul. Ogrodową i dalej na południe od linii wyznaczonej przez ul. Ogrodową, której przedłużenie biegnie do wschodniej granicy gminy w powiecie myśliborskim,

— gminy Mieszkowice, Moryń, część gminy Cedynia położona na południe od linii wyznaczonej przez drogę nr 124 biegnącą od zachodniej granicy gminy do miasta Cedynia, a następnie na południe od linii wyznaczonej przez drogę nr 125 biegnącą od miasta Cedynia do wschodniej granicy gminy w powiecie gryfińskim.

8. **Slovakia**

The following restricted zones II in Slovakia:

— the whole district of Gelnica,

— the whole district of Spišská Nová Ves,

— the whole district of Levoča,

— in the whole district of Michalovce,

— the whole district of Košice-okolie,

— the whole district of Rožnava,

— the whole city of Košice,

— the whole district of Sobrance,

— in the district of Vranov nad Topľou, the whole municipalities of Zámutov, Rudlov, Jusková Voľa, Banské, Cabov, Davidov, Kamenná Poruba, Vechec, Čaklov, Soľ, Komárany, Čičava, Nižný Kručov, Vranov nad Topľou, Sačurov, Sečovská Polianka, Dlhé Klčovo, Nižný Hrušov, Poša, Nižný Hrabovec, Hencovce, Kučín, Majerovce, Sedliská, Kladzany and Tovarnianska Polianka, Herrmanovce nad Topľou, Petrovce, Pavlovce, Hanušovce nad Topľou, Medzianky, Radvanovce, Babie, Vlača, Ďurďoš, Prosačov, Remeniny,

— Skrabské, Bystré, Petkovce, Michalok, Vyšný Žipov, Čierne nad Topľou, Zlatník, Hlinné, Jastrabie nad Topľou, Merník, Ondavské Maťašovce, Tovarné,

— in the district of Humenné the whole municipalities of Hudcovce, Brekov, Jasenov, Ptičie, Chlmec, Porúbka,

— the whole district of Prešov,

— in the whole district of Sabinov,

— in the district of Svidník, the whole municipalities of Dukovce, Želmanovce, Kuková, Kalnište, Lužany pri Ondave, Lúčka, Giraltovce, Kračúnovce, Železník, Kobylince, Mičakovce,

— the whole district of Bardejov,

— in the district of Stará Ľubovňa, the whole municipalities of Kyjov, Pusté Pole, Šarišské Jastrabie, Čirč, Ruská Voľa nad Popradom, Obručné, Vislanka, Ďurková, Plaveč, Ľubotín, Orlov,

— the whole district of Revúca,

— the whole district of Rimavská Sobota,

— in the district of Veľký Krtíš, the whole municipalities of Ľuboriečka, Muľa, Dolná Strehová, Závada, Pravica, Chrťany, Senné, Brusník, Horná Strehová, Slovenské Kľačany, Vieska, Veľký Lom, Suché Brezovo, Horné Strháre, Dolné Strháre, Modrý Kameň,Veľký Krtíš, Veľké Zlievce, Malé Zlievce, Veľké Stračiny, Malé Stračiny, Bušince, Čeláre, Gabušovce, Zombor, Olováry, Malý Krtíš, Nová Ves, Šuľa, Červeňany, Sucháň, Dačov Lom,

— the whole district of Lučenec,

— the whole district of Poltár

— in the district of Zvolen, the whole municipalities Lešť, Pliešovce

— in the district of Detva, the whole municipalities of Stará Huta, Vígľašská Huta,- Kalinka, Slatinské Lazy, Stožok, Klokoč, Vígľaš, Detva,

— in the district of Krupina the whole municipalities of Senohrad, Horné Mladonice, Dolné Mladonice, Čekovce, Lackov.

PART III

1. **Bulgaria**

The following restricted zones III in Bulgaria:

— the whole region of Gabrovo,

— the whole region of Lovech,

— the whole region of Montana,

— the Pleven region:

  — the whole municipality of Belene

  — the whole municipality of Gulyantzi

  — the whole municipality of Dolna Mitropolia

  — the whole municipality of Dolni Dabnik

  — the whole municipality of Iskar

  — the whole municipality of Knezha

  — the whole municipality of Nikopol

  — the whole municipality of Pordim

  — the whole municipality of Cherven bryag,

— the Ruse region:

  — the whole municipality of Dve mogili,

— the Shumen region:

  — the whole municipality of Veliki Preslav,

  — the whole municipality of Venetz,

  — the whole municipality of Varbitza,

  — the whole municipality of Kaolinovo,

  — the whole municipality of Novi pazar,

  — the whole municipality of Smyadovo,

  — the whole municipality of Hitrino,

— he Silistra region:

  — the whole municipality of Alfatar,

  — the whole municipality of Glavnitza,

- the whole municipality of Dulovo
- the whole municipality of Kaynardzha,
- the whole municipality of Tutrakan,

— the Sliven region:

- the whole municipality of Kotel,
- the whole municipality of Nova Zagora,
- the whole municipality of Tvarditza,

— the Targovishte region:

- the whole municipality of Antonovo,
- the whole municipality of Omurtag,
- the whole municipality of Opaka,

— the Vidin region,

- the whole municipality of Belogradchik,
- the whole municipality of Boynitza,
- the whole municipality of Bregovo,
- the whole municipality of Gramada,
- the whole municipality of Dimovo,
- the whole municipality of Kula,
- the whole municipality of Makresh,
- the whole municipality of Novo selo,
- the whole municipality of Ruzhintzi,
- the whole municipality of Chuprene,

— the Veliko Tarnovo region:

- the whole municipality of Veliko Tarnovo,
- the whole municipality of Gorna Oryahovitza,
- the whole municipality of Elena,
- the whole municipality of Zlataritza,
- the whole municipality of Lyaskovetz,
- the whole municipality of Pavlikeni,
- the whole municipality of Polski Trambesh,
- the whole municipality of Strazhitza,
- the whole municipality of Suhindol,

— the whole region of Vratza,

— in Varna region:

- the whole municipality of Avren,
- the whole municipality of Beloslav,
- the whole municipality of Byala,
- the whole municipality of Dolni Chiflik,
- the whole municipality of Devnya,
- the whole municipality of Dalgopol,
- the whole municipality of Provadia,
- the whole municipality of Suvorovo,

— the whole municipality of Varna,

— the whole municipality of Vetrino,

— in Burgas region:

— the whole municipality of Burgas,

— the whole municipality of Kameno,

— the whole municipality of Malko Tarnovo,

— the whole municipality of Primorsko,

— the whole municipality of Sozopol,

— the whole municipality of Sredets,

— the whole municipality of Tsarevo,

— the whole municipality of Sungurlare,

— the whole municipality of Ruen,

— the whole municipality of Aytos.

2. **Italy**

The following restricted zones III in Italy:

— tutto il territorio della Sardegna.

3. **Latvia**

The following restricted zones III in Latvia:

— Aizputes novada Kalvenes pagasta daļa uz austrumiem no ceļa pie Vārtājas upes līdz autoceļam A9, uz ziemeļiem no autoceļa A9, uz austrumiem no autoceļa V1200, Kazdangas pagasta daļa uz austrumiem no ceļa V1200, P115, P117, V1296,

— Kuldīgas novada, Laidu pagasta daļa uz dienvidiem no autoceļa V1296,

— Skrundas novada Rudbāržu, Nīkrāces pagasts, Raņķu pagasta daļa uz dienvidiem no autoceļa V1272 līdz robežai ar Ventas upi, Skrundas pagasts (izņemot pagasta daļa no Skrundas uz ziemeļiem no autoceļa A9 un austrumiem no Ventas upes), Skrundas pilsēta,

— Vaiņodes novada Embūtes pagasta daļa uz ziemeļiem autoceļa P116, P106.

4. **Lithuania**

The following restricted zones III in Lithuania:

— Jurbarko rajono savivaldybė: Seredžiaus ir Juodaičių seniūnijos,

— Kauno rajono savivaldybė: Čekiškės seniūnija, Babtų seniūnijos dalis į vakarus nuo kelio A1ir Vilkijos apylinkių seniūnijos dalis į rytus nuo kelio Nr. 1907,

— Kėdainių rajono savivaldybė: Pernaravos seniūnija ir Josvainių seniūnijos pietvakarinė dalis tarp kelio Nr. 229 ir Nr. 2032,

— Plungės rajono savivaldybė: Alsėdžių, Babrungo, Paukštakių, Platelių ir Žemaičių Kalvarijos seniūnijos,

— Raseinių rajono savivaldybė: Ariogalos ir Ariogalos miesto seniūnijos,

— Skuodo rajono savivaldybės: Barstyčių, Notėnų ir Šačių seniūnijos.

5. **Poland**

The following restricted zones III in Poland:

w województwie warmińsko-mazurskim:

— gminy Kiwity i Lidzbark Warmiński z miastem Lidzbark Warmiński w powiecie lidzbarskim,

— gminy Barczewo, Gietrzwałd, Jonkowo, Dywity, Dobre Miasto, Purda, Stawiguda, Świątki, część gminy Olsztynek położona na północ od linii wyznaczonej przez drogę nr S51 biegnącą od wschodniej granicy gminy do miejscowości Ameryka oraz na wschód od linii wyznaczonej przez drogę biegnącą od skrzyżowania z drogą S51 do północnej granicy gminy, łączącej miejscowości Mańki – Mycyny – Ameryka w powiecie olsztyńskim,

— powiat miejski Olsztyn,

w województwie mazowieckim:

— gminy Łaskarzew z miastem Łaskarzew, Maciejowice, Sobolew, Trojanów, Żelechów, część gminy Wilga położona na południe od linii wyznaczonej przez rzekę Wilga biegnącą od wschodniej granicy gminy do ujścia do rzeki Wisły, część gminy Górzno położona na południe od linii wyznaczonej przez drogę łączącą miejscowości Łąki i Górzno biegnącą od wschodniej granicy gminy, następnie od miejscowości Górzno na południe od drogi nr 1328W biegnącej do drogi nr 17, a następnie na południe od linii wyznaczonej przez drogę biegnącą od drogi nr 17 do zachodniej granicy gminy przez miejscowości Józefów i Kobyla Wola w powiecie garwolińskim,

— część gminy Iłża położona na wschód od linii wyznaczonej przez drogę nr 9 w powiecie radomskim,

— gmina Kazanów w powiecie zwoleńskim,

— gminy Ciepielów, Lipsko, Rzeczniów i Sienno w powiecie lipskim,

w województwie lubelskim:

— powiat tomaszowski,

— gmina Białopole w powiecie chełmskim,

— gmina Rudnik i część gminy Żółkiewka położona na południe od linii wyznaczonej przez drogę nr 842 w powiecie krasnostawskim,

— gminy Adamów, Grabowiec, Komarów – Osada, Krasnobród, Łabunie, Miączyn, Nielisz, Radecznica, Sułów, Szczebrzeszyn, Zwierzyniec w powiecie zamojskim,

— powiat biłgorajski,

— powiat hrubieszowski,

— gminy Dzwola i Chrzanów w powiecie janowskim,

— gmina Serokomla w powiecie łukowskim,

— gminy Abramów, Kamionka, Michów, Firlej, Jeziorzany, Kock w powiecie lubartowskim,

— gminy Kłoczew, Stężyca, Ułęż i część gminy Ryki położona na północ od linii wyznaczonej przez linię kolejową w powiecie ryckim,

— gmina Baranów w powiecie puławskim,

w województwie podkarpackim:

— gminy Cieszanów, Horyniec – Zdrój, Narol i Stary Dzików w powiecie lubaczowskim,

— gminy Kuryłówka, Nowa Sarzyna, miasto Leżajsk, część gminy wiejskiej Leżajsk położona na północ od miasta Leżajsk oraz część gminy wiejskiej Leżajsk położona na wschód od linii wyznaczonej przez rzekę San, w powiecie leżajskim,

— gminy Krzeszów, Rudnik nad Sanem, część gminy Harasiuki położona na południe od linii wyznaczona przez drogę nr 1048 R, część gminy Ulanów położona na południe od linii wyznaczonej przez rzekę Tanew, część gminy Nisko położona na wschód od linii wyznaczonej przez drogę nr 19 oraz na południe od linii wyznaczonej przez linię kolejową biegnącą od wschodniej granicy gminy do skrzyżowania z drogą nr 19, część gminy Jeżowe położona na wschód od linii wyznaczonej przez drogę nr 19 w powiecie niżańskim,

— gminy Chłopice, Jarosław z miastem Jarosław, Laszki, Wiązownica, Pawłosiów, Radymno z miastem Radymno, w powiecie jarosławskim,

— gmina Stubno w powiecie przemyskim,

— część gminy Kamień położona na wschód od linii wyznaczonej przez drogę nr 19 w powiecie rzeszowskim,

— gminy Adamówka, Sieniawa, Tryńcza, miasto Przeworsk, część gminy wiejskiej Przeworsk położona na wschód od miasta Przeworsk i na wschód od linii wyznaczonej przez autostradę A4 biegnącą od granicy z gminą Tryńcza do granicy miasta Przeworsk, część gminy Zarzecze położona na wschód od linii wyznaczonej przez drogę nr 1594R biegnącą od północnej granicy gminy do miejscowości Zarzecze oraz na północ od linii wyznaczonej przez drogi nr 1617R oraz 1619R biegnącą do południowej granicy gminy w powiecie przeworskim,

w województwie lubuskim:

— gminy Nowa Sól i miasto Nowa Sól, Otyń oraz część gminy Kożuchów położona na północ od linii wyznaczonej przez drogę nr 283 biegnącą od wschodniej granicy gminy do skrzyżowania z drogą nr 290 i na północ od linii wyznaczonej przez drogę nr 290 biegnącej od miasta Mirocin Dolny do zachodniej granicy gminy, część gminy Bytom Odrzański położona na południowy wschód od linii wyznaczonej przez drogi nr 293 i 326, część gminy Nowe Miasteczko położona na wschód od linii wyznaczonych przez drogi 293 i 328, część gminy Siedlisko położona na południowy wschód od linii wyznaczonej przez drogę biegnącą od rzeki Odry przy południowe granicy gminy do drogi nr 326 łączącej się z drogą nr 325 biegnącą w kierunku miejscowości Różanówka do skrzyżowania z drogą nr 321 biegnącą od tego skrzyżowania w kierunku miejscowości Bielawy, a następnie przedłużoną przez drogę przeciwpożarową biegnącą od drogi nr 321 w miejscowości Bielawy do granicy gminy w powiecie nowosolskim,

— gminy Babimost, Czerwieńsk, Kargowa, Świdnica, Zabór, część gminy Bojadła położona na południe od linii wyznaczonej przez drogę nr 278 biegnącą od wschodniej granicy gminy do skrzyżowania z drogą nr 282 i na południe od linii wyznaczonej przez drogę nr 282 biegnącej od miasta Bojadła do zachodniej granicy gminy i część gminy Sulechów położona na zachód od linii wyznaczonej przez drogę nr S3 oraz na północ od linii wyznaczonej przez

— drogę łączącą miejscowości Kępsko - Buków biegnącą od zachodniej granicy gminy do miejscowości Buków, a następnie na zachód od linii wyznaczonej przez drogę łączącą miejscowości Buków – Miłkowo biegnącą od miejscowości Buków do północnej granicy gminy w powiecie zielonogórskim,

— część gminy Niegosławice położona na wschód od linii wyznaczonej przez drogę nr 328 w powiecie żagańskim,

— powiat miejski Zielona Góra,

— gminy Skąpe, Szczaniec, Zbąszynek , część gminy Lubrza położona na południe od linii wyznaczonej przez autostradę A2 i część gminy Świebodzin położona na południe od linii wyznaczonej przez autostradę A2 w powiecie świebodzińskim,

— gminy Bobrowice, Dąbie, Krosno Odrzańskie i część gminy Bytnica położona na wschód od linii wyznaczonej przez drogę nr 1157F w powiecie krośnieńskim,

— część gminy Trzciel położona na południe od linii wyznaczonej przez drogę nr 92 w powiecie międzyrzeckim,

w województwie wielkopolskim:

— gmina Zbąszyń, część gminy Miedzichowo położona na południe od linii wyznaczonej przez drogę nr 92, część gminy Nowy Tomyśl położona na zachód od linii wyznaczonej przez drogę nr 305 w powiecie nowotomyskim,

— gmina Siedlec w powiecie wolsztyńskim,

— część gminy Rakoniewice położona na wschód od linii wyznaczonej przez drogę nr 305 w powiecie grodziskim,

w województwie dolnośląskim:

— gminy Jerzmanowa, Żukowice, część gminy Kotla położona na południe od linii wyznaczonej przez rzekę Krzycki Rów, część gminy wiejskiej Głogów położona na zachód od linii wyznaczonej przez drogi nr 12, 319 oraz 329, część miasta Głogów położona na zachód od linii wyznaczonej przez drogę nr 12 w powiecie głogowskim,

— gminy Gaworzyce, Radwanice i część gminy Przemków położona na północ od linii wyznaczonej prze drogę nr 12 w powiecie polkowickim,

w województwie świętokrzyskim:

— część gminy Brody położona na wschód od linii kolejowej biegnącej od miejscowości Marcule i od północnej granicy gminy przez miejscowości Klepacze i Karczma Kunowska do południowej granicy gminy w powiecie starachowickim.

6. **Romania**

The following restricted zones III in Romania:

— Zona orașului București,

— Județul Constanța,

— Județul Satu Mare,

— Județul Tulcea,

— Județul Bacău,

— Județul Bihor,

— Județul Bistrița Năsăud,

— Județul Brăila,

— Județul Buzău,

— Județul Călărași,

— Județul Dâmbovița,

— Județul Galați,

— Județul Giurgiu,

— Județul Ialomița,

— Județul Ilfov,

— Județul Prahova,

— Județul Sălaj,

— Județul Suceava

— Județul Vaslui,

— Județul Vrancea,

— Județul Teleorman,

— Județul Mehedinți,

— Județul Gorj,

— Județul Argeș,

— Județul Olt,

— Județul Dolj,

— Județul Arad,

— Județul Timiș,

— Județul Covasna,

— Județul Brașov,

— Județul Botoșani,

— Județul Vâlcea,

— Județul Iași,

— Județul Hunedoara,

— Județul Alba,

— Județul Sibiu,

— Județul Caraș-Severin,

— Județul Neamț,

— Județul Harghita,

— Județul Mureș,

— Județul Cluj,

— Județul Maramureş.

7. **Slovakia**

The following restricted zones III in Slovakia:

— the whole district of Trebišov.'.

DECISIONS

COUNCIL DECISION (EU) 2021/812

of 10 May 2021

on the position to be taken on behalf of the European Union within the Association Committee in Trade configuration and in the Association Council established by the Association Agreement between the European Union and the European Atomic Energy Community and their Member States, of the one part, and Georgia, of the other part, as regards a favourable opinion on the comprehensive roadmap approved by the Government of Georgia for the implementation of legislation related to public procurement and recognising the completion of Phase 1 of Annex XVI-B of that Association Agreement

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular the first subparagraph of Article 207(4), in conjunction with Article 218(9) thereof,

Having regard to the proposal from the European Commission,

Whereas:

(1) The Association Agreement between the European Union and the European Atomic Energy Community and their Member States, of the one part, and Georgia, of the other part ([1]) (the 'Agreement') was concluded by the Union by Council Decision (EU) 2016/838 ([2]) and entered into force on 1 July 2016.

(2) Article 145(1) of the Agreement stipulates that Georgia is to submit to the Association Committee in Trade configuration a comprehensive roadmap for the implementation of public procurement legislation in Georgia with time schedules and milestones, which is to include all reforms in terms of legislative approximation to the Union *acquis*.

(3) Pursuant to Article 145(2) of the Agreement, a favourable opinion by the Association Committee in Trade configuration is required in order for the comprehensive roadmap to become the reference document for the implementation of the legislative approximation of Georgia's public procurement legislation to the Union public procurement *acquis*.

(4) In accordance with Article 146(2) of the Agreement, the approximation to the Union *acquis* is to be carried out in consecutive phases as set out in the schedule in Annex XVI-B to the Agreement. The implementation of each phase is to be evaluated by the Association Committee in Trade configuration, as set out in Article 408(4) of the Agreement, and, following a positive assessment by that Committee, is to be linked to the reciprocal granting of market access as set out in Annex XVI-B to the Agreement.

(5) The Association Committee in Trade configuration is to adopt a decision in accordance with Article 11(2) of its rules of procedure, set out in Annex II to Decision No 1/2014 of the EU-Georgia Association Council ([3]), giving an opinion regarding the comprehensive roadmap approved by the Government of Georgia as well as an assessment of the approximation of Georgian legislation to the Union *acquis* so far in the completion of Phase 1 as set out in Annex XVI-B to the Agreement. That roadmap was approved by the Government of Georgia in Decree no 536 of 31 March 2016 of the Government of Georgia 'Concerning the planned changes in the Public Procurement field envisaged in compliance with the obligations between Georgia and the EU within the scope of the Deep and Comprehensive Free Trade Area (DCFTA) Agreement' as amended by Decrees no 154 of 22 January 2018 and no 974 of 12 June 2020 of the Government of Georgia.

([1]) OJ L 261, 30.8.2014, p. 4.

([2]) Council Decision (EU) 2016/838 of 23 May 2016 on the conclusion, on behalf of the European Union, of the Association Agreement between the European Union and the European Atomic Energy Community and their Member States, of the one part, and Georgia, of the other part (OJ L 141, 28.5.2016, p. 26).

([3]) Decision No 1/2014 of the EU-Georgia Association Council of 17 November 2014 adopting its Rules of Procedure and those of the Association Committee and of Sub-Committees [2015/2261] (OJ L 321, 5.12.2015, p. 60).

(6) After the acknowledgement of the completion of Phase 1 as set out in Annex XVI-B to the Agreement, the Association Council is to take a decision, in accordance with Article 11(2) of its rules of procedure, set out in Annex I to Decision No 1/2014 of the EU-Georgia Association Council, on granting reciprocal market access, in accordance with Annex XVI-B to the Agreement, for supplies for central government authorities.

(7) It is appropriate to establish the position to be taken on the Union's behalf in the Association Committee in Trade configuration and in the Association Council, as the envisaged decisions will be binding on the Union,

HAS ADOPTED THIS DECISION:

Article 1

The position to be taken on the Union's behalf within the Association Committee in Trade configuration as regards the comprehensive roadmap approved by the Government of Georgia, and the completion of Phase 1 as set out in Annex XVI-B to the Agreement, shall be based on the draft Decision of the Association Committee in Trade configuration ([4]).

Article 2

The position to be taken on the Union's behalf in the Association Council as regards the granting of reciprocal market access in accordance with Annex XVI-B to the Agreement shall be based on the draft Decision of the Association Council ([4]).

Article 3

This Decision shall enter into force on the date of its adoption.

Done at Brussels, 10 May 2021.

For the Council
The President
J. BORRELL FONTELLES

([4]) See document ST 7791/21 on http://register.consilium.europa.eu

COUNCIL DECISION (CFSP) 2021/813

of 20 May 2021

amending Decision 2014/486/CFSP on the European Union Advisory Mission for Civilian Security Sector Reform Ukraine (EUAM Ukraine)

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on European Union, and in particular Articles 42(4) and 43(2) thereof,

Having regard to the proposal from the High Representative of the Union for Foreign Affairs and Security Policy,

Whereas:

(1) On 22 July 2014 the Council adopted Decision 2014/486/CFSP on the European Union Advisory Mission for Civilian Security Sector Reform Ukraine (EUAM Ukraine) ([1]).

(2) On 13 May 2019 the Council adopted Decision (CFSP) 2019/761 ([2]), extending the mandate of EUAM Ukraine until 31 May 2021.

(3) In the context of a strategic review of EUAM Ukraine, the Political and Security Committee agreed that EUAM Ukraine should be extended until 31 May 2024 and that a strategic assessment should be conducted after two years, focused on the evolution in the political dimension.

(4) Decision 2014/486/CFSP should therefore be extended until 31 May 2024.

(5) EUAM Ukraine will be conducted in the context of a situation which may deteriorate and could impede the achievement of the objectives of the Union's external action as set out in Article 21 of the Treaty,

HAS ADOPTED THIS DECISION:

Article 1

Decision 2014/486/CFSP is amended as follows:

(1) in Article 14(1), the following subparagraph is added:

'The financial reference amount intended to cover the expenditure related to EUAM Ukraine for the period from 1 June 2021 to 31 May 2024 shall be EUR 88 500 000.';

(2) Article 18 is replaced by the following:

'*Article 18*

Strategic review

A strategic assessment of EUAM Ukraine shall be conducted after 31 May 2023, focused on the evolution in the political dimension.';

(3) in Article 19, the second paragraph is replaced by the following:

'It shall apply until 31 May 2024.'.

([1]) OJ L 217, 23.7.2014, p. 42.

([2]) Council Decision (CFSP) 2019/761 of 13 May 2019 amending Decision 2014/486/CFSP on the European Union Advisory Mission for Civilian Security Sector Reform Ukraine (EUAM Ukraine) (OJ L 125, 14.5.2019, p. 16).

Article 2

This Decision shall enter into force on the date of its adoption.

Done at Brussels, 20 May 2021.

For the Council
The President
A. SANTOS SILVA

COUNCIL DECISION (CFSP) 2021/814

of 20 May 2021

amending Decision (CFSP) 2017/915 on Union outreach activities in support of the implementation of the Arms Trade Treaty

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on European Union, and in particular Articles 28(1) and 31(1) thereof,

Having regard to the proposal from the High Representative of the Union for Foreign Affairs and Security Policy,

Whereas:

(1) On 29 May 2017, the Council adopted Decision (CFSP) 2017/915 ([1]).

(2) On 30 July 2020, the Council adopted Decision (CFSP) 2020/1134 ([2]), amending Decision (CFSP) 2017/915 and extending the implementation period for the activities referred to in Article 1 thereof until 30 June 2021.

(3) On 31 March 2021, the Bundesamt für Wirtschaft und Ausfuhrkontrolle, and on 6 April 2021, Expertise France, in their respective capacities as Implementing Agencies, requested the authorisation of the Union to extend for a second time the implementation of Council Decision (CFSP) 2017/915, until 31 January 2022, due to continuing challenges arising from the COVID-19 pandemic.

(4) The continuation of the activities referred to in Article 1 of Decision (CFSP) 2017/915 does not have any implication as regards financial resources until 31 January 2022,

HAS ADOPTED THIS DECISION:

Article 1

Article 5 of Decision (CFSP) 2017/915 is hereby replaced by the following:

'*Article 5*

This Decision shall enter into force on the date of its adoption.

It shall expire on 31 January 2022.'.

Article 2

This Decision shall enter into force on the date of its adoption.

Done at Brussels, 20 May 2021.

For the Council
The President
A. SANTOS SILVA

([1]) Council Decision (CFSP) 2017/915 of 29 May 2017 on Union outreach activities in support of the implementation of the Arms Trade Treaty (OJ L 139, 30.5.2017, p. 38).

([2]) Council Decision (CFSP) 2020/1134 of 30 July 2020 amending Decision (CFSP) 2017/915 on Union outreach activities in support of the implementation of the Arms Trade Treaty (OJ L 247, 31.7.2020, p. 24).

COUNCIL IMPLEMENTING DECISION (CFSP) 2021/815

of 20 May 2021

implementing Decision 2014/450/CFSP concerning restrictive measures in view of the situation in Sudan

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on European Union, and in particular Article 31(2) thereof,

Having regard to Council Decision 2014/450/CFSP of 10 July 2014 concerning restrictive measures in view of the situation in Sudan and repealing Decision 2011/423/CFSP [1], and in particular Article 6 thereof,

Having regard to the proposal from the High Representative of the Union for Foreign Affairs and Security Policy,

Whereas:

(1) On 10 July 2014 the Council adopted Decision 2014/450/CFSP.

(2) On 5 March 2021 the United Nations Security Council (UNSC) Committee established pursuant to UNSC Resolution 1591(2005) approved the removal of one person from the list of persons and entities subject to restrictive measures.

(3) The Annex to Decision 2014/450/CFSP should therefore be amended accordingly,

HAS ADOPTED THIS DECISION:

Article 1

The Annex to Decision 2014/450/CFSP is amended as set out in the Annex to this Decision.

Article 2

This Decision shall enter into force on the date of its publication in the *Official Journal of the European Union*.

Done at Brussels, 20 May 2021.

For the Council
The President
A. SANTOS SILVA

[1] OJ L 203, 11.7.2014, p. 106.

ANNEX

In the list set out in the Annex to Decision 2014/450/CFSP, the entry for the following person is deleted:

3. **SHAREIF, Adam**.

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