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Guidance to Applicants - Veterinary Medicinal Products

(Text with EEA relevance)

(C/2024/1443)

Contents

INTRODUCTION

Regulation (EU) 2019/6 ([1]) ('the Regulation') applies in the Union to veterinary medicinal products since 28 January 2022 ([2]). The Regulation, which repealed Directive 2001/82/EC, has substantially amended the regulatory framework for veterinary medicinal products with a view to better adapting the regulatory environment to the specific characteristics of the veterinary sector and to support the following objectives:

— ensure the protection of human and animal health and the environment;

— improve the functioning of the internal market;

— increase the availability of veterinary medicinal products;

— stimulate research and innovation;

— reduce administrative burden; and

— address the public health risk of antimicrobial resistance (AMR).

The above-referred objectives should, therefore, underpin the application and interpretation of the Regulation.

This document has been developed by the Commission in consultation with the competent authorities of the Member States and the European Medicines Agency ('the Agency') in order to assist stakeholders in complying with their obligations under the Regulation. Only the Court of Justice of the European Union is competent to authoritatively interpret Union law.

1. VETERINARY MEDICINAL PRODUCT

1.1. Definition

Pursuant to Article 4(1) of the Regulation, a substance -or combination of substances- is to be considered as a 'veterinary medicinal product' if at least one of the following conditions is fulfilled:

(a) it is presented as having properties for treating or preventing disease in animals;

(b) its purpose is to be used in, or administered to, animals with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action;

(c) its purpose is to be used in animals with a view to make a medical diagnosis;

(d) its purpose is to be used for euthanasia of animals.

It follows from the foregoing that the definition of 'veterinary medicinal product' in the Regulation corresponds to the definition provided for by Directive 2001/82/EC, with the exception of substances or combination of substances intended to be used for euthanasia of animals which are now considered as veterinary medicinal products under the Regulation and subject to the rules and procedures thereof. The inclusion of substances -or combinations of substances- intended for euthanasia within the definition of 'veterinary medicinal product' is the reason for which, in the context of the definition of 'benefit-risk balance', the Regulation refers to 'positive effects' instead of 'positive therapeutic effects', which was the term used in Directive 2001/82/EC. For the avoidance of doubt, it must be clarified that the concept of 'benefit' under the Regulation should continue to be interpreted in the light of the definition of 'veterinary medicinal product' as explained below.

Veterinary medicinal products by presentation

The presentation criterion set forth in point (a) of Article 4(1) of the Regulation intends to protect the buyer/user of the veterinary medicinal product by preventing that products that do not have therapeutic effects are, for commercial reasons, presented as veterinary medicinal products by the manufacturer or the seller ([3]).

([1]) 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 (OJ L 4, 7.1.2019, p. 43).
([2]) Subject to the transitional measures provided therein.
([3]) See, for example, judgement of 28 October 1992, Ter Voort, C-219/91, EU:C:1992:414.

In that context, a product is 'presented for treating or preventing disease' when it is expressly 'indicated' or 'recommended' as such, possibly by means such as labels, leaflets and/or oral representation. A product is also considered as 'presented for treating or preventing disease' whenever any averagely well-informed consumer gains the impression that the product in question should, having regard to its presentation, have the properties of a medicinal product ([4]).

However, the external form given to a product, although it may serve as strong evidence of the seller's or manufacturer's intention to market that product as a veterinary medicinal product, cannot be the sole or conclusive evidence, since otherwise certain food products which are traditionally presented in a similar form to medicinal products would also be covered and fall in the scope of the definition of a medicinal product ([5]).

Veterinary medicinal products by function

Contrary to the definition of veterinary medicinal product by presentation, the broad interpretation of which is intended to protect buyers/users from products which do not have the effectiveness that they are entitled to expect, the definition of veterinary medicinal product by function, set forth in point (b) of the Article 4(1) of the Regulation, is meant to cover only products which are designed to be used in animals to restore, correct or modify physiological functions and for which pharmacological, immunological and/or metabolic properties have been scientifically established.

In applying the definition of veterinary medicinal product by function, one should take into account the case law of the Court of Justice of the European Union:

— Therapeutic purpose: the fact that a product may be prescribed for 'therapeutic purposes' is a decisive factor with a view to its classification as veterinary medicinal product by function. Conversely, in the absence of any, even potential, use of the product concerned for the treatment of a recognised pathological condition, the condition relating to the existence of beneficial effects on health will not be met. Consequently, classification as a veterinary medicinal product by function requires that it be possible to establish that the product concerned is potentially capable of inducing a specific benefit to health. If that is not the case, that product cannot be regarded as veterinary medicinal product. In addition, it should be noted that, although that benefit may result from an improvement in appearance, such an assessment cannot be carried out by a subjective assessment but must be based on a scientific finding ([6]).

— Significant effect: Some products generally viewed as foodstuffs may have an effect on physiological functions or even serve some therapeutic purpose. In order to preserve the effectiveness of the functional criterion in the definition of 'veterinary medicinal product', it is not sufficient that a product has properties beneficial to health in general. Moreover, products whose effect on physiological functions is no more than the effect that a foodstuff consumed in a reasonable quantity may have on those functions, does not have a significant effect on the metabolism and cannot, therefore, be classified as products capable of restoring, correcting or modifying physiological functions ([7]).

Veterinary medicinal products for zootechnical purposes

A veterinary medicinal product for zootechnical purposes is a product that is administered to a healthy animal for an indication related to the reproductive system, including oestrus synchronisation, termination of unwanted gestation or the preparation of donors and recipients for the implantation of embryos. Products qualifying as such were covered by the Directive 2001/82/EC and continue to be covered by the Regulation as the definition of 'veterinary medicinal product' is unchanged in this regard.

Veterinary medicinal products used for making a medical diagnosis

In accordance with point (c) of Article 4(1) of the Regulation, products that are used in animals to make a medical diagnosis are classified as veterinary medicinal products.

([4]) See, for example, C-219/91, above-referred.
([5]) See, for example, judgement of 15 November 2007, Commission v. Germany, C-319/05, EU:C:2007:678.
([6]) See, for example, judgement of 13 October 2022, *M2Beauté Cosmetics*, C-616/20, EU:C:2022:781.
([7]) See, for example, C-319/05 above-referred.

Veterinary medicinal products used for euthanasia

In accordance with point (d) of Article 4(1) of the Regulation, products that are used for euthanasia are classified as veterinary medicinal products.

1.2. Classification

A prerequisite for the granting of a marketing authorisation under the Regulation is that the product at stake is a veterinary medicinal product.

Whether the product in respect of which a marketing authorisation is sought falls under the definition of veterinary medicinal product is not specifically examined during the validation phase. Therefore, prospective applicants having doubts as to whether a product can be considered as a veterinary medicinal product are advised to consult with the relevant competent authorities (in case of prospective applications under the centralised procedure, the Agency should be consulted).

Article 144 of the Regulation tasks the coordination group set up by Article 142 with the issuance of recommendations to Member States as to whether a specific veterinary medicinal product or a group of veterinary medicinal products is to be considered a veterinary medicinal product within the scope of the Regulation ([8]).Moreover, according to Article 3(2) of the Regulation, the Commission may adopt decisions on whether a specific product or group of products are to be considered as veterinary medicinal products. Such decisions are binding in all Member States.

1.3. Industrial production and industrial process

While Article 2(1) of the Regulation provides that it applies to veterinary medicinal products prepared industrially or by a method involving an industrial process, the concept of 'industrial preparation' or 'industrial process' does not form part of the definition of 'veterinary medicinal product'. Veterinary medicinal products that have not been prepared industrially or by a method involving an industrial process are not subject to the Regulation but may be subject to national provisions applicable to veterinary medicinal products.

In interpreting the concepts of industrial preparation and industrial process, account must be taken of the objectives pursued by the Union legislation on veterinary medicinal products and the need to avoid the development of unsafe or ineffective therapies. In particular, the Court of Justice has noted that the terms 'prepared industrially' and 'manufactured by a method involving an industrial process' cannot be interpreted narrowly and that those terms must therefore include, at the very least, any preparation or manufacture involving an industrial process. Such a process is characterised in general by a succession of operations, which may, in particular, be mechanical or chemical, in order to obtain a significant quantity of a standardised product ([9]).

It follows that standardisation is a feature typical of an industrial process. Moreover, while a one-off or a sporadic activity can be considered not to fall under the scope of the Regulation, the manufacturing of a veterinary medicinal product on a routine basis or promotional activities with a view to increasing the demand for a veterinary medicinal product are parameters that can indicate that significant amounts are being produced and that such activities fall under the scope of the Regulation.

Stakeholders that engage in the development and/or manufacturing of veterinary medicinal products and consider that their activities do not fall under the Regulation because neither an industrial preparation nor an industrial process are involved, are advised to consult with the national competent authorities of the Member State(s) where they intend to market the relevant veterinary medicinal product.

The preparation of an officinal formula or magistral formula in a pharmacy is only subject to the provisions laid out in Chapter VII of the Regulation ([10]).

([8]) See Article 144(d) of the Regulation.
([9]) See judgement of 16 July 2015, Abcur, C-544/13, EU:C:2015:481.
([10]) See Article 2(6) of the Regulation.

2. MARKETING AUTHORISATION

A veterinary medicinal product may only be placed on the Union market when a marketing authorisation has been granted by the competent authority of a Member State for its own territory (national marketing authorisation) or when an authorisation has been granted by the Commission (centralised marketing authorisation); the latter being valid in all Member States. The marketing authorisation holder must be established within the Union. Not-for-profit organisations can also be marketing authorisation holders.

A marketing authorisation lays down the terms under which the marketing of a veterinary medicinal product is authorised. A marketing authorisation is composed of:

(i) a decision granting the marketing authorisation issued by the relevant competent authority; and

(ii) a technical dossier with the data submitted by the applicant in accordance with Article 8 and Annex II of the Regulation.

The use of veterinary medicinal products outside the terms of the marketing authorisation is only permissible under the conditions laid down in Articles 112 to 114 of the Regulation.

National competent authorities may, under the specific circumstances foreseen in the Regulation, allow the use in their territory of veterinary medicinal products that have not been granted a marketing authorisation valid in their territory ([11]). In addition, the marketing of certain homeopathic veterinary medicinal products is subject to registration (instead of authorisation), as provided for in Chapter V of the Regulation ([12]).

Finally, Member States may prohibit the manufacture, import, distribution, possession, sale, supply or use of immunological veterinary medicinal products in their territory -or a part thereof- under certain circumstances ([13]).

European Economic Area (EEA)

Norway, Iceland and Liechtenstein form the EEA with the 27 Member States of the European Union. These countries have, through the EEA agreement, adopted the complete Union *acquis* on veterinary medicinal products and are consequently parties to Union procedures. Where in this Chapter reference is made to the Union or to Member States this should be read as to include Norway, Iceland and Liechtenstein. Therefore, *e.g.*, where reference is made to the applicant being established in the Union, this includes Norway, Iceland and Liechtenstein.

Legally binding acts from the Union (*e.g.* Commission decisions) do not directly confer rights and obligations but have first to be transposed into legally binding acts in Norway, Iceland and Liechtenstein. According to Decision N° 371/2021 of the EEA Joint Committee when decisions on approval of veterinary medicinal products are taken by the Union, Norway, Iceland and Liechtenstein will take corresponding decisions on the basis of relevant acts.

In addition, the marketing authorisations granted by Norway, Iceland and Liechtenstein are eligible for the mutual recognition and the subsequent recognition procedures in the same way as the marketing authorisations granted by Member States.

Liechtenstein

A treaty between Liechtenstein and Austria about automatic recognition of the Marketing Authorisations granted via the mutual recognition procedure or decentralised procedure applies since 1 December 2010 ([14]). This allows Liechtenstein to use marketing authorisations granted by Austria provided the applicants have identified Liechtenstein as a Member State concerned in the application form submitted with applications under the decentralised, mutual recognition or subsequent recognition procedures. At the end of the procedures, Austria will grant authorisations that will be recognised by Liechtenstein. This marketing authorisation can be considered as a marketing authorisation granted in accordance with the pharmaceutical *acquis* for the purpose of Union legislation and in particular can be considered as a starting point for the purposes of the application of the rules on protection of technical documentation in the Union.

([11]) See Articles 5(6), 110(2) and (3), and 116 of the Regulation.
([12]) See Article 2(5) in conjunction with Article 86 of the Regulation.
([13]) See Article 110(1) of the Regulation.
([14]) Abkommen zwischen der Österreichischen Bundesregierung und der Regierung des Fürstentums Liechtenstein betreffend die automatische Anerkennung von in Österreich zugelassenen bzw. registrierten Human- und Tierarzneimitteln in Liechtenstein (Federal Law Gazette BGBl. III Nr. 126/2010).

Pursuant to a bilateral agreement between Switzerland and Liechtenstein, a Swiss marketing authorisation is automatically effective in Liechtenstein. However, this recognition has no effects outside the customs union between Switzerland and Liechtenstein. Consequently, a marketing authorisation granted by the Swiss authorities and recognised by Liechtenstein, cannot be considered as a marketing authorisation granted in accordance with the pharmaceutical *acquis* for the purpose of the Union legislation and in particular cannot be considered as a starting point for the purposes of the application of the rules on protection of technical documentation in the Union.

Monaco

An agreement between the Union and the Principality of Monaco entered into force on 1 May 2004 ([15]). On the basis of this agreement and the special arrangements between France and the Principality of Monaco of 6 January 2003, the French authorities assume the role of competent authorities as far as the application of the veterinary medicinal products legislation to products manufactured in Monaco is concerned. The French authorities are responsible for the issuing of marketing authorisations for Monaco and conduct inspections on manufacturing sites of veterinary medicinal products in Monaco. Batches from Monaco have to be considered as batches which have already undergone controls in a Member State and are therefore exempted from further controls and retesting. The batches released in the manufacturing sites in Monaco can be regarded as released in France.

United Kingdom (Northern Ireland)

In accordance with the Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community, and in particular Article 5(4) of and point 20 of Annex 2 to the Windsor Framework ([16]), Regulation (EU) 2019/6, as well as legal acts of the Union implementing, supplementing, amending or replacing this legal act apply to and in the United Kingdom in respect of Northern Ireland.

2.1. **National marketing authorisations**

The competent authorities of the Member States are responsible for granting the marketing authorisations for veterinary medicinal products that are placed on the market in their territory, except for veterinary medicinal products that are granted an authorisation by the Commission ('centralised marketing authorisation').

In order to obtain a national marketing authorisation, an application must be submitted to the competent authority of a Member State. A marketing authorisation application, however, cannot be submitted in a Member State when the same marketing authorisation holder has submitted an application or been granted a marketing authorisation for the same veterinary medicinal product by another Member State or under the centralised procedure ([17]).

Where the holder of a marketing authorisation granted in a Member State wants to apply for authorisation for the same veterinary medicinal product in (an)other Member State(s), that marketing authorisation holder should submit an application in the Member States concerned using the mutual recognition procedure ([18]). A minimum of six months should elapse between the decision granting the national marketing authorisation and the submission of an application for mutual recognition ([19]).

If no marketing authorisation for the concerned veterinary medicinal product has been granted in the Union to the applicant, the applicant may make use of the decentralised procedure and submit an application in all the Member States where it intends to seek a marketing authorisation at the same time and choose one of them as reference Member State ([20]).

([15]) Council Decision 2003/885/EC of 17 November 2003 concerning the conclusion of the Agreement on the application of certain Community acts on the territory of the Principality of Monaco, OJ L 332, 19.12.2003, p. 42.

([16]) Joint Declaration No 1/2023 of the Union and the United Kingdom in the Joint Committee established by the Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community of 24 March 2023 (OJ L 102, 17.4.2023, p. 87).

([17]) See Article 8(6) of the Regulation.

([18]) See Articles 46(2), 48(2) and 51 of the Regulation.

([19]) See Article 52(3) of the Regulation.

([20]) See Articles 48 to 50 of the Regulation.

After completion of a decentralised procedure or a mutual recognition procedure, the marketing authorisation may be extended to additional Member States in accordance with the subsequent recognition procedure laid down in Article 53 of the Regulation.

2.2. **Centralised marketing authorisations**

The centralised marketing authorisation procedure is mandatory for the following veterinary medicinal products:

— veterinary medicinal products developed by means of recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotic and eukaryotic cells, and hybridoma and monoclonal antibody methods;

— veterinary medicinal products intended primarily for use as performance enhancers (growth promotion and yield increase);

— veterinary medicinal products containing a new active substance, not yet authorised as a veterinary medicinal product in the Union;

— veterinary medicinal products that contain or consist of engineered allogeneic tissues or cells, unless they consist exclusively of blood components; and

— novel therapy veterinary medicinal products ([21]), unless they consist exclusively of blood components.

In some cases, the determination as to whether a veterinary medicinal product falls under the mandatory scope of the centralised procedure may require a scientific assessment that is not carried out during the validation phase. However, if during the assessment procedure of an application submitted to the national competent authorities, it becomes apparent that the veterinary medicinal product falls under the scope of the centralised procedure, the national procedure cannot continue ([22]). Therefore, prospective applicants having doubts as to whether a veterinary medicinal product may fall under the scope of the centralised procedure are advised to consult the relevant competent authorities prior to submitting an application under the national procedure.

In addition, applicants may choose the centralised procedure for any other veterinary medicinal product, including for generics of nationally authorised products, provided that the applicant has not been granted a national marketing authorisation for the same veterinary medicinal product already in a Member State ([23]).

Under the centralised procedure, the marketing authorisation application is submitted to the Agency. The scientific evaluation is carried out by the Committee for Veterinary Medicinal Products ('CVMP') of the Agency and a scientific opinion is prepared. The opinion is sent to the Commission, which adopts a decision after consulting the Standing Committee on Veterinary Medicinal Products (which is composed of the representatives of the Member States and chaired by the Commission).

A centralised marketing authorisation is valid throughout the Union and confers the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State.

Interplay between the national and the centralised procedures

The use of the national and the centralised procedure for the same veterinary medicinal product by the same marketing authorisation holder/applicant is not possible ([24]).

([21]) Pursuant to Article 4(43) of the Regulation, a novel therapy veterinary medicinal product includes veterinary medicinal products specifically designed for gene therapy, regenerative medicine, tissue engineering, blood product therapy, phage therapy, as well as other products issued from nanotechnologies or any other therapy that is considered as a nascent field in veterinary medicine.

([22]) See Articles 46(2) and 48(2) of the Regulation.

([23]) See Article 42(4) of the Regulation.

([24]) Pursuant to Article 8(6), when submitting an application under a national procedure, the applicant is required to submit a declaration that it has not submitted an application in another Member State or in the Union and that no such marketing authorisation has been granted in another Member State or in the Union. In addition, pursuant to Article 42(4), a centralised marketing authorisation cannot be granted if a marketing authorisation has already been granted for the veterinary medicinal product in a Member State.

The following scenarios are, however, possible:

— Applications pursuant to Articles 18 and 19 can be submitted to the Agency for generic and hybrid veterinary medicinal products referring to a reference veterinary medicinal product that has been authorised nationally (including under the decentralised, mutual recognition or subsequent recognition procedures), provided that the applicant does not hold a marketing authorisation for the same veterinary medicinal product granted at national level.

— Applications pursuant to Articles 18 and 19 can be submitted to the national competent authorities (including under the decentralised, mutual recognition or subsequent recognition procedures) for generic and hybrid medicinal products referring to a reference veterinary medicinal product that has been authorised under the centralised procedure, except for veterinary medicinal products listed under Article 42 (2) (a), (b), (d) and (e) (where the holding of a marketing authorisation obtained through the centralised procedure is mandatory), provided that the applicant does not hold a centralised marketing authorisation for the same veterinary medicinal product.

— A duplicate marketing authorisation can be obtained under the centralised procedure if the original marketing authorisation was granted under the centralised procedure. Likewise, a duplicate marketing authorisation can be obtained under a national procedure if the original marketing authorisation was granted under a national procedure. However, it is not possible to apply for a duplicate under the centralised procedure when the original marketing authorisation has been granted by national competent authorities or to apply for a duplicate under a national procedure when the original marketing authorisation has been granted a centralised marketing authorisation.

2.3. **Concepts of 'applicant' and 'marketing authorisation holder'**

An 'applicant' and a 'marketing authorisation holder' can be a physical or a legal entity. However, for the purposes of applying the legislation on veterinary medicinal products, having a distinct legal personality does not necessarily entail that each entity can be considered as a distinct applicant or marketing authorisation holder. Thus, it is noted that:

— applicants and marketing authorisation holders belonging to the same company group or that are controlled by the same physical or legal entity are to be considered as one entity; and

— applicants and marketing authorisation holders that do not belong to the same company group and are not controlled by the same physical or legal entity are to be considered as one applicant/marketing authorisation holder if they have concluded tacit or explicit agreements concerning the marketing of the same veterinary medicinal product. This includes cases of joint marketing but also cases where one party licenses to the other party the right to market the same veterinary medicinal product in exchange for fees or other considerations.

2.4. **Invented name of a veterinary medicinal product**

A marketing authorisation is granted to a single marketing authorisation holder who is responsible for placing the veterinary medicinal product on the market. The marketing authorisation shall contain the name of the veterinary medicinal product, which may be either a single invented name, or a common or scientific name (when available, the International Non-Proprietary Name of the active substance(s)) accompanied by a trademark or the name of the marketing authorisation holder.

The invented name/trademark proposed should be appropriately chosen having regard to the objective of the Regulation to ensure the protection of human and animal health and the environment. Applicants should therefore avoid invented names/trademarks that may be detrimental to public, animal health, or the environment by *e.g.* misleading the user of the veterinary medicinal product as to the properties of the veterinary medicinal product.

Applicants are also advised to consider the 'Guideline on the acceptability of names for veterinary medicinal products processed through the centralised procedure' ([25]) and the most updated version of the 'QRD veterinary product-information annotated template' ([26]).

([25]) EMA/328/1998, as updated

([26]) See specifically the section in the SPC on name of the veterinary medicinal product (https://www.ema.europa.eu/en/veterinary-regulatory/marketing-authorisation/product-information/veterinary-product-information-templates).

The use of the same name for a veterinary medicinal product that is authorised in more than one Member State is beneficial *e.g.* from the standpoint of pharmacovigilance. Accordingly, for applications through the decentralised, mutual recognition or subsequent recognition procedures, it is recommended whenever feasible that the same name for a given veterinary medicinal product is used in all Member States. If a different name is used, it should be reflected in a covering letter from the applicant to the relevant competent authorities.

2.5. **Combination packs**

The marketing of distinct veterinary medicinal products as part of the same marketing authorisation or in the same package can only be accepted in exceptional circumstances, when it is demonstrated that there are overriding animal health reasons or in case of immunological veterinary medicinal products consisting of separate pharmaceutical forms that should be mixed before administration to the animal. A justification for the marketing of a combination pack cannot be related to convenience or commercial purposes.

The submission of an application for a single marketing authorisation in this scenario should be justified by the applicant and agreed by the national competent authorities or, in case of the centralised procedure, by the Agency prior to the submission of the application.

2.6. **Validity of the marketing authorisation**

Marketing authorisations for veterinary medicinal products are valid for an unlimited period, with the exception of marketing authorisations granted pursuant to Article 23 or 25, which are valid for a period of five years and of one year respectively ([27]). Marketing authorisations granted under Article 23 or 25 can be renewed (see Sections 4.3 and 4.4).

National competent authorities (for nationally authorised products) or the Commission (for centrally authorised products) may take decisions to suspend, revoke or amend a marketing authorisation in accordance with and under the conditions laid out in Article 130 of the Regulation. In addition, in case of a risk to public or animal health or to the environment, the relevant competent authority can prohibit the supply or order the recall of veterinary medicinal products under the conditions provided for in Article 134. Finally, temporary safety restrictions can be imposed in the circumstances foreseen in Article 129.

Voluntary withdrawal of applications

Applicants may decide to withdraw a marketing authorisation application before the assessment thereof has been completed but they are required to state the reasons for doing so ([28]). The same principle should apply when a marketing authorisation holder withdraws an application for a variation before the end of the assessment thereof.

The national competent authority or, as applicable, the Agency will make public the withdrawal of the marketing authorisation application and, if already drawn up, the relevant report or the opinion, after deletion of any commercially confidential information ([29]).

In the case of applications for marketing authorisation submitted to more than one Member State (under the decentralised, mutual recognition or subsequent recognition procedures), applicants may withdraw the application with regard to specific Member State(s) concerned only. However, the withdrawal of the application from the reference Member State ends the procedure as a change of reference Member State during the procedure is not possible.

Voluntary withdrawal of marketing authorisations

Should a marketing authorisation holder wish to seek the withdrawal of its marketing authorisation, it should submit a request to the competent authority that granted the marketing authorisation, stating the reasons for such request for withdrawal. For centralised marketing authorisations, the request should be submitted to the Agency. In case of marketing authorisations granted under the decentralised, mutual recognition or subsequent recognition procedures, the request should be made to the concerned Member States that are concerned by the voluntary withdrawal and to the reference Member State.

([27]) See Articles 5(2), 24 and 27 of the Regulation.
([28]) See Article 32(2) of the Regulation.
([29]) See Article 32(3) of the Regulation.

Duty to supply and duty to communicate cessation of marketing

Pursuant to Article 58(2) of the Regulation, marketing authorisation holders are required, within the limit of their responsibilities, to ensure appropriate and continued supplies of their veterinary medicinal products. When this obligation is not fulfilled, competent authorities may withdraw the marketing authorisation ([30]). Marketing authorisation holders should therefore notify the relevant competent authorities in case of difficulties related to supply.

In addition, marketing authorisation holders are required to record in the Union product database the dates when the authorised veterinary medicinal products are placed on the market and information on the availability of the veterinary medicinal products in each relevant Member State ([31]). Furthermore, marketing authorisation holders must inform the competent authority that granted the marketing authorisation of any action they intend to take to cease the marketing of a veterinary medicinal product prior to taking such action, together with the reasons ([32]).

3. MARKETING AUTHORISATION APPLICATIONS

3.1. General principles and requirements

Marketing authorisation applications should be submitted electronically and using the formats made available by the Agency ([33]).

Marketing authorisation applications should contain technical documentation necessary to demonstrate the quality, safety and efficacy of the relevant veterinary medicinal product in accordance with the specific requirements laid down in Annex II of the Regulation. In addition, all applications should contain the information required under Annex I of the Regulation as well as a summary of the pharmacovigilance system master file ([34]).

Additional information is required for applications concerning food-producing animals ([35]), applications concerning antimicrobial veterinary medicinal products ([36]), and applications concerning veterinary medicinal products containing or consisting of genetically modified organisms ('GMOs') ([37]).

The technical documentation may consist of safety and efficacy studies carried out by the applicant as well as bibliographical references.

Irrespective of the legal basis of the application, assessment reports such as the European Public Assessment Report ('EPAR') for centralised marketing authorisations, or similar reports drawn by national competent authorities that may be made public inside or outside the Union cannot be considered to meet the requirements set out in Annex II of the Regulation as such.

Marketing authorisations subject to obligations or conditions

Marketing authorisations for veterinary medicinal products can be subject to specific obligations and/or conditions where appropriate, including but not only in the case of marketing authorisations for antimicrobial veterinary medicinal products and marketing authorisations granted under Articles 23 (limited markets) and 25 (exceptional circumstances) of the Regulation.

In the case of marketing authorisations granted for novel therapy veterinary medicinal products, the imposition of post-marketing authorisation studies can be considered on a case-by-case basis. Regardless of whether post-authorisation studies are imposed, applicants for such products should submit a risk management plan detailing measures envisaged to ensure appropriate follow-up of treated animals with a view to detecting early and delayed adverse reactions and to gain information on the long-term efficacy and safety profile of the concerned novel therapy veterinary medicinal product ([38]).

([30]) See Article 130(3)(a) of the Regulation.
([31]) See Article 58(6) of the Regulation.
([32]) See Article 58(13) of the Regulation.
([33]) See Article 6(3) of the Regulation.
([34]) See Article 8(1) of the Regulation.
([35]) See Articles 5(5) and 8(3) of the Regulation.
([36]) See Article 8(2) of the Regulation.
([37]) See Article 8(5) of the Regulation.
([38]) See Section V.1.1.6 of Annex II of the Regulation.

3.2. **Applications based on comprehensive technical documentation**

In order to obtain a marketing authorisation, applications should contain comprehensive technical documentation demonstrating the quality, safety and efficacy of the product by means of required tests, preclinical studies and clinical trials. The standard data requirements are laid down in Sections II (for non-biologicals) and Section III (for biologicals) of Annex II; certain adaptations being applicable for specific type of products as set out in Section V. Throughout this document, the term 'comprehensive technical documentation' is used to refer to the data requirements laid down in these sections of Annex II.

Under certain circumstances, marketing authorisations may be granted on the basis of a dossier that does not contain comprehensive technical documentation (see Sections 4.3 and 4.4). Applications that rely -wholly or partly- on data submitted by a previous applicant are also acceptable under certain conditions (see Sections 4.5, 4.6 and 4.8).

3.3. **Applications under Article 23 ('Limited markets')**

When a veterinary medicinal product is intended for the treatment or prevention of a disease that occurs infrequently or in limited geographical areas, or is intended for animal species other than cattle, sheep for meat production, pigs, chickens, dogs and cats, an application for marketing authorisation in accordance with Article 23 can be submitted, provided that the applicant justifies that the benefits for public or animal health linked to the availability of the product outweigh the risks inherent to the lack of comprehensive safety and/or efficacy technical documentation ([39]).

3.3.1. ***The concept of limited markets***

The definition of limited market is provided for in Article 4(29) of the Regulation. Pursuant to this definition, the following non-cumulative criteria determine when veterinary medicinal products are intended for a limited market:

— criteria linked to the indication: a veterinary medicinal product that is intended for the treatment or prevention of diseases that occur infrequently or in limited geographical areas is considered to be intended for a limited market;

— criteria linked to the target species: a veterinary medicinal product that is intended for animal species other than cattle, sheep for meat production, pigs, chickens, dogs and cats is considered to be intended for a limited market.

While the criteria linked to the target species is straightforward, the criteria linked to the indication may be more difficult to apply in practice as the threshold for consideration as limited market is determined by the prevalence of the disease in combination with the specific indication that is claimed for the product.

The determination whether a veterinary medicinal product is intended for the treatment or prevention of disease that occurs infrequently or in limited geographical areas should be done on the basis of epidemiological criteria, scientific criteria and current veterinary practice. It follows that applications for artificially restrictive indications cannot be accepted by the competent authorities in the context of applications under Article 23. For example, an application with a claim relating to the treatment of gastric ulcer due to a specific and restricted cause is considered to be artificially restricted as the product could similarly be used in current veterinary practice for the treatment of gastric ulcer arising from underlying aetiologies other than the one proposed.

3.3.2. ***Requirements for a marketing authorisation under Article 23***

Pursuant to Article 23 of the Regulation, the following cumulative requirements should be met for a marketing authorisation to be granted for a limited market:

(i) The benefit to animal or public health of the availability on the market of the veterinary medicinal product outweighs the risks inherent in the lack of comprehensive documentation. In interpreting this requirement, a balance should be struck between facilitating the availability of veterinary medicinal products and limiting the risks that veterinary medicinal products may be authorised with an unfavourable benefit-risk balance (due to the uncertainties linked to the lack of comprehensive safety and/or efficacy documentation). Moreover, account should be taken of the main principle underpinning the Union regulatory framework for veterinary medicinal products, *i.e.*, the need to ensure a high level of public and animal health and environmental protection.

([39]) See Article 23 of the Regulation in conjunction with Article 4(29).

Having regard to the above, it can be considered that the requirement set in Article 23(1) (a) is met when the following cumulative criteria are fulfilled:

— the veterinary medicinal product is intended to treat, prevent or make a medical diagnosis of a seriously debilitating or life-threatening disease, and

— there is an unmet medical need (see Section 4.3.3).

These criteria may be adapted on the basis of accumulated experience.

(ii) A positive benefit-risk balance is demonstrated. The definition of benefit-risk balance set out in point 19 of Article 4 of the Regulation is applicable to all marketing authorisations, including those granted under Article 23.

3.3.3. ***Unmet medical need***

For the purposes of applying Article 23, 'unmet medical need' is to be understood as a disease for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Union or, even if such a method exists, in relation to which the veterinary medicinal product concerned brings a meaningful advantage. The concept of 'meaningful advantage' should relate to the intrinsic characteristics of the product and it should be clearly demonstrated that such intrinsic properties have a relevant and significant positive impact on the animal to be treated or on public health.

In general, a meaningful advantage should normally be based on meaningful improvement of efficacy or clinical safety, such as having an impact on the onset and duration of the disease or improving the morbidity or mortality. In exceptional cases, also major improvements to the care of the treated animals could be considered a meaningful advantage, *e.g.* if the new veterinary medicinal product is expected to address serious existing issues with treatment compliance. It is stressed that the concept of 'meaningful advantage' is to be interpreted strictly to ensure a high level of public and animal health.

Existence of other authorised products:

When one or more authorised veterinary medicinal products exist on the market to treat the relevant disease in the concerned target species, it cannot be considered that there is an unmet medical need. In such cases, a marketing authorisation application can only be granted pursuant to Article 23 if it is demonstrated that the product for which an authorisation is sought provides a meaningful advantage over the existing veterinary medicinal products.

In considering whether an authorised veterinary medicinal product exists on the market ([40]), account should be taken of the fact that, while centralised marketing authorisations are valid throughout the Union, national marketing authorisations are only valid in the territory of the Member State that has granted the marketing authorisation.

It follows that, if a veterinary medicinal product has only been authorised in one or a few Member State(s), an application for an Article 23 marketing authorisation could, in principle, be considered in Member States where no such marketing authorisation has been applied for. In this regard, one should note that an application under Article 23 cannot be used to circumvent the application of the mutual recognition/subsequent recognition procedure for existing marketing authorisations.

Moreover, when a veterinary medicinal product has already been authorised in one or more Member States for the relevant indication in the concerned target species, the submission of an application under Article 23 to such Member States or according to the centralised procedure is only possible if a meaningful advantage of the veterinary medicinal product that is the object of the application is demonstrated ([41]).

([40]) In this context, authorised veterinary medicinal product means a veterinary medicinal product that has been granted a marketing authorisation.

([41]) This applies also when the concerned veterinary medicinal product falls under the mandatory scope of the centralised procedure (such applications can only be submitted to the Agency).

Finally, considering the uncertainties that may exist for veterinary medicinal products authorised on the basis of less than comprehensive safety and/or efficacy documentation, including regarding the period of validity of such marketing authorisations, an unmet medical need cannot be considered to have been definitively fulfilled in case of marketing authorisations granted under Article 23 or Article 25. Accordingly, a marketing authorisation application under Article 23 should not be barred when the existing marketing authorisations relevant to the prevention, treatment or diagnosis of the disease at stake have been granted pursuant to Article 23 or Article 25.

3.3.4. ***Data requirements***

While some safety and/or efficacy data may be omitted, marketing authorisation applications submitted pursuant to Article 23 should contain comprehensive quality data and a summary of the pharmacovigilance system master file ([42]). Additional requirements applicable to specific types of veterinary medicinal products also remain applicable to marketing authorisations granted in accordance with Article 23 (*e.g.* additional requirements for applications concerning veterinary medicinal products intended for food-producing animals, applications concerning antimicrobial veterinary medicinal products, or applications concerning veterinary medicinal products containing or consisting of GMOs).

The type of technical documentation that should be provided to demonstrate a positive benefit-risk balance is to be determined case-by-case by the evaluating competent authority. Applicants are advised to contact the relevant authority as to the specific content of the dossier.

3.3.5. ***Product information***

Article 23(2) of the Regulation requires that the summary of product characteristics ('SPC') of veterinary medicinal products that have been authorised pursuant to Article 23 clearly state that only a limited assessment of safety or efficacy has been conducted due to the lack of comprehensive data. In addition, for those products, Article 35(1)(j) requires that the SPC contains the following statement 'marketing authorisation granted for a limited market and therefore assessment based on customised requirements for documentation'. With a view to convey the information foreseen in both Articles, applicants can use the following statement:

Marketing authorisation granted for a limited market and therefore assessment based on customised requirements for documentation. Only a limited assessment of safety or efficacy has been conducted due to the lack of comprehensive safety or efficacy data.

3.3.6. ***Validity of the marketing authorisation and re-examination***

Marketing authorisations granted pursuant to an Article 23 application have a validity of five years. The validity of such marketing authorisations can be extended by periods of five years for an unlimited number of times by means of a re-examination. Such re-examination applications should demonstrate that the relevant veterinary medicinal product continues to be intended for a limited market and that the benefits of availability of the veterinary medicinal product to animal or public health continue to outweigh the risks inherent in the lack of comprehensive safety and/or efficacy technical documentation in accordance with Article 23(1) (a) and (b). In addition, the applicant is required to submit an updated assessment of the benefit-risk balance.

The application for re-examination should be submitted to the competent authority that granted the initial marketing authorisation (in case of centralised marketing authorisations, the application should be submitted to the Agency), at least six months before the expiry date of the marketing authorisation. Further details on the procedure are set out in Article 24 of the Regulation.

3.3.7. ***Becoming a standard marketing authorisation***

A marketing authorisation granted under Article 23 can be amended to become a standard marketing authorisation (validity not limited in time) when the missing data on safety and/or efficacy are submitted ([43]). The submission of missing data should be done under a variation procedure.

([42]) See Article 8(1)(c), which is applicable to all marketing authorisation applications.
([43]) See Article 24(6) of the Regulation.

If and when, following the examination of the submitted data, the relevant competent authority concludes that comprehensive technical documentation has been duly submitted, the statement in the SPC referring to the lack of comprehensive data will be removed, and the legal basis of the marketing authorisation will be changed ([44]).

3.3.8. *Co-existence of indications authorised on the basis of a submission under Article 23 and indications granted pursuant to another legal basis*

In accordance with Article 23(2) of the Regulation, the SPC of veterinary medicinal products covered by marketing authorisations granted pursuant to Article 23 should specify that the assessment has been done on the basis of limited safety and efficacy data. It is therefore not possible for a limited market indication to be granted as a variation to a marketing authorisation granted under another legal basis based on comprehensive technical documentation. For example, if the holder of a marketing authorisation wants to expand the terms of an existing marketing authorisation for chickens to cover ducks on the basis of less than a comprehensive technical dossier, the application should be submitted as a separate stand-alone application pursuant to Article 23 and not as a variation to the first authorisation. If granted, the limited market authorisation will belong to the same marketing authorisation for the purposes of applying the rules of protection of technical documentation as the first authorisation.

3.4. **Applications under Article 25 ('Exceptional circumstances')**

In exceptional circumstances related to animal or public health, applicants may submit an application containing less than comprehensive quality, safety and/or efficacy technical documentation, provided that they demonstrate that, for objective and verifiable reasons, the missing information cannot be provided. In addition, the applicants should justify that the benefits for public or animal health linked to the immediate availability of the product outweigh the risks inherent in the lack of comprehensive technical documentation ([45]).

While some quality, safety and/or efficacy data may be omitted, marketing authorisation applications in exceptional circumstances should contain a summary of the pharmacovigilance system master file ([46]). Additional requirements applicable to specific types of veterinary medicinal products also remain applicable to marketing authorisations granted in accordance with Article 25 (*e.g.* additional requirements for applications concerning veterinary medicinal products intended for food-producing animals, applications concerning antimicrobial veterinary medicinal products, or applications concerning veterinary medicinal products containing or consisting of GMOs).

It is stressed that a marketing authorisation cannot be granted pursuant to Article 25 if it is not demonstrated that the benefit-risk balance is positive.

Marketing authorisations granted pursuant to Article 25 can be subject to the obligation to conduct post-authorisation studies and/or to specific reporting obligations. In addition, conditions or restrictions, in particular regarding the safety, may be imposed.

Article 26(2) requires that the SPC of veterinary medicinal products that have been authorised on the basis of an Article 25 application should state that only a limited assessment of quality, safety or efficacy has been conducted due to the lack of comprehensive quality, safety and/or efficacy data. In addition, Article 35(1)(j) requires that the SPC contains the following statement 'marketing authorisation in exceptional circumstances and therefore assessment based on customised requirements for documentation'. With a view to convey the information foreseen in both Articles, applicants can use the following statement:

Marketing authorisation in exceptional circumstances and therefore assessment based on customised requirements for documentation. Only a limited assessment of quality, safety or efficacy has been conducted due to the lack of comprehensive quality, safety or efficacy data.

([44]) In the Union Product Database, the marketing authorisation will become a full application - new active substance (Article 8 of Regulation (EU) 2019/6) or full application - known active substance (Article 8 of Regulation (EU) 2019/6).
([45]) See Article 25 of the Regulation.
([46]) See Article 8(1)(c) of the Regulation, which is applicable to all marketing authorisation applications.

Validity of the marketing authorisation and re-examination

Marketing authorisations granted pursuant to an Article 25 application have a validity of one year. The validity of such marketing authorisations can be extended by periods of one year for an unlimited number of times. Such applications should demonstrate that the exceptional circumstances related to animal or public health remain. In addition, the applicant is required to submit an updated assessment of the benefit-risk balance.

The application for re-examination should be submitted to the competent authority that granted the initial marketing authorisation (in case of centralised marketing authorisations, the application should be submitted to the Agency), at least three months before the expiry date of the marketing authorisation. Further details on the procedure are set out in Article 27 of the Regulation.

Becoming a standard marketing authorisation

A marketing authorisation granted pursuant to Article 25 can be amended to become a standard marketing authorisation (whose validity is not limited in time) when the missing data on quality, safety and/or efficacy are submitted ([47]). The submission of missing data should be done under a variation procedure.

When, following the examination of the submitted data, the relevant competent authority concludes that comprehensive technical documentation has been duly submitted, the statement in the SPC referring to the lack of comprehensive data will be removed and the legal basis of the marketing authorisation will be changed ([48]).

3.5. Applications under Article 18 (' Generic applications ')

3.5.1. *General considerations*

Article 4(9) of the Regulation defines 'generic veterinary medicinal product' as a 'veterinary medicinal product which has the same qualitative and quantitative composition of active substances and the same pharmaceutical form as the reference veterinary medicinal product, and with regard to which bioequivalence with the reference veterinary medicinal product has been demonstrated'.

'Same qualitative and quantitative composition of active substances'

The different salts, esters, ethers, isomers and mixtures of isomers, complexes or derivatives of an active substance shall be considered the same active substance, unless they differ significantly in properties with regard to safety or efficacy ([49]). It is incumbent upon the applicant to demonstrate that any such difference does not significantly affect the safety and efficacy of the active substance contained in the generic veterinary medicinal product that is the object of the application as compared with the safety and efficacy of the active substance in the reference veterinary medicinal product. When additional information concerning changes to the nature of the active substance cannot establish the absence of a significant difference with regard to safety or efficacy, an application in accordance with the requirements of Article 19 should be submitted.

There is no assessment of the properties of the active substance during the validation phase. Therefore, in cases when, during the assessment of an application submitted under Article 18, it becomes apparent that, due to differences in safety or efficacy, the active substance contained in the veterinary medicinal product that is the object of the generic application cannot be considered the same as in the reference veterinary medicinal product, the application cannot be assessed under Article 18.

Applicants should then withdraw the application or, if they are able to provide the required technical documentation to demonstrate the safety and efficacy of the veterinary medicinal product within the timespan of the ongoing procedure, request a change of the legal basis of their submission so that it can be assessed in accordance with Article 19. The possibility to request a change of legal basis can only be considered when the amount of technical data required to

([47]) See Article 27(6) of the Regulation.

([48]) In the Union Product Database, the marketing authorisation will become a full application -new active substance (Article 8 of Regulation (EU) 2019/6) or full application - known active substance (Article 8 of Regulation (EU) 2019/6).

([49]) See Article 18(2) of the Regulation.

demonstrate the safety and efficacy of the product is limited. In contrast, if the amount of additional technical documentation required to demonstrate the safety and efficacy is substantial, it will not be possible for the competent authorities to assess the new data within the timelines of the ongoing procedure and therefore a new application under Article 19 should be submitted. Moreover, a change of legal basis can only be considered by the competent authorities when such a request is submitted prior to the deadline to respond to the first list of questions.

Applicants should take into account that the marketing authorisation procedure will end with a negative outcome if the applicant fails to demonstrate the efficacy and safety of the product within the timespan of the ongoing procedure and it is stressed that the technical documentation to be submitted in the context of a marketing authorisation application under Article 19 can be significant. Moreover, applicants should also consider that, when the changes in the active substance are such that it has to be considered a different active substance, the assessment under Article 19 is not appropriate and an application in accordance with Article 8 and, as appropriate, Section II (for non-biologicals) or Section III (for biologicals) of Annex II should be submitted.

Accordingly, applicants are strongly advised to carefully consider any differences in the active substance of the veterinary medicinal product that is the object of the application -as compared with the active substance of the reference veterinary medicinal product- ahead of their submissions and to consult with the competent authorities as appropriate.

While the requirement that the generic and the reference veterinary medicinal product has the same qualitative and quantitative composition extends only to the active substance(s) and not to the other ingredients of the product, differences in excipient composition or differences in impurities must not lead to significant differences as regards safety and efficacy ([50]).

'Same pharmaceutical form'

This criterion relating to the same pharmaceutical form contained in the definition of generic veterinary medicinal product is evaluated with reference to the standard terms for pharmaceutical dosage forms established by the European Pharmacopoeia.

According to the Court of Justice, in determining the pharmaceutical form of a medicinal product, account must be taken of the form in which it is presented and the form in which it is administered, including the physical form. In that context, veterinary medicinal products presented in the form of a solution to be mixed in drinking water for administration can be considered as having the same pharmaceutical form, provided that the differences in the form of administration are not significant in scientific terms ([51]).

Furthermore, Article 18(3) of the Regulation provides that the various immediate release oral forms -which would include tablets, capsules, oral solutions and suspensions- are considered to be the same pharmaceutical form.

'Bioequivalence'

Guidance as to the definition and demonstration of bioequivalence is available in the 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' ([52]), or the 'VICH GL52 Bioequivalence: blood level bioequivalence study' ([53]).

In accordance with Article 18(1)(a) of the Regulation, bioavailability studies need not be provided if the applicant can provide a justification. Such exemptions from the need to demonstrate *in vivo* bioequivalence should be justified in the application. To assess the robustness of the justifications provided by the applicant, the competent authorities will also consider the relevant published guidelines, in particular the ones above referred to.

([50]) See, for example, judgement of 20 January 2005, Smithkline Beecham, C-74/03, EU:C:2005:39.
([51]) See, for example, judgment of 29 April 2004, *Novartis Pharmaceuticals*, C-106/01, EU:C:2004:245.
([52]) EMA/CVMP/016/2000, as updated.
([53]) EMA/CVMP/VICH/751935/2013 – Corr

Where bioequivalence cannot be demonstrated through bioavailability studies and a waiver is not applicable, a hybrid application under Article 19 should be submitted. The demonstration of safety and efficacy in the context of an Article 19 application where bioequivalence to a reference veterinary medicinal product cannot be demonstrated may require the submission of significant technical documentation. Applicants are advised to discuss with the competent authorities as to the appropriate technical documentation that should be provided in this scenario.

3.5.2. ***Biological veterinary medicinal products***

For applications submitted pursuant to Article 18, the safety and efficacy of the generic veterinary medicinal product is determined by reference to the dossier of a previously authorised veterinary medicinal product in respect of which bioequivalence is demonstrated.

Because the characterisation of biologicals is intrinsically linked to the raw and starting materials, as well as the production process and its controls, and considering that details about the production and control process of veterinary medicinal products are usually proprietary information that is not publicly available, for biological veterinary medicinal products (including immunologicals), generic applications are not considered appropriate. For these products, a hybrid application under Article 19 should in principle be submitted ([54]).

In this regard, it is stressed that an Article 18 application can only be considered with regard to a biological reference veterinary medicinal product if the raw and starting materials, as well as the production process and controls of the veterinary medicinal product concerned by the application are the same as those of the reference veterinary medicinal product. Where this cannot be demonstrated, an application under Article 19 should be submitted.

3.5.3. ***Generic applications submitted by the holders of the marketing authorisation of the reference veterinary medicinal product***

An application submitted pursuant to Article 18 cannot be filed simultaneously with an application for a corresponding reference veterinary medicinal product. Indeed, the marketing authorisation holder of the reference veterinary medicinal product can file an application on the basis of Article 18 for its own (generic) veterinary medicinal product, provided that all the requirements of Article 18 are fulfilled, including that the period of protection of the technical documentation has expired or is due to expire in less than two years.

In the above-referred scenario, the marketing authorisation of the reference veterinary medicinal product and the marketing authorisation of the generic version of the said veterinary medicinal product belong to the same marketing authorisation for the purposes of applying the rules of protection of technical documentation. Quality differences between the two products should be explained at the time when the request for the generic marketing authorisation application is submitted unless the quality dossier is the same.

By contrast, applications submitted pursuant to Article 21 can be submitted any time after the authorisation of the cross-referred veterinary medicinal product.

3.5.4. ***Reference veterinary medicinal product***

3.5.4.1. *Marketing authorisations that can be used as reference veterinary medicinal products*

The term 'reference veterinary medicinal product' is defined in Article 4 (8) of the Regulation as *'a veterinary medicinal product authorised in accordance with Article 44, 47, 49, 52, 53 or 54 as referred to in Article 5(1) on the basis of an application submitted in accordance with Article 8'*. Based on this definition, therefore, the reference veterinary medicinal product may have been authorised in accordance with the centralised procedure or a national procedure (including marketing authorisations granted in a single Member State, as well as marketing authorisations granted in multiple Member States pursuant to the decentralised, mutual recognition or subsequent recognition procedure).

([54]) See Section IV.1.1 of Annex II of the Regulation.

The reference veterinary medicinal product must have been authorised on the basis of an application submitted in accordance with Article 8. The concept of 'reference veterinary medicinal product' should be interpreted having regard to the goals of the Regulation to increase availability of veterinary medicinal products while ensuring that a high level of public and animal health protection is ensured. Further clarifications as to the interpretation on the concept of 'reference veterinary medicinal product' are provided below:

a) Marketing authorisations granted following the submission of comprehensive technical documentation

Any marketing authorisation that has been granted following the submission of a comprehensive technical documentation (see Section 4.2) may be used as reference veterinary medicinal product, provided that the period of protection of the technical documentation in the marketing authorisation of the reference veterinary medicinal product has elapsed or is due to elapse in less than two years. For the sake of clarity, it is noted that marketing authorisations for combination veterinary medicinal products granted in accordance with Article 20 of the Regulation can also be reference veterinary medicinal products.

b) Generic and hybrid marketing authorisations ([55])

In principle, the safety and efficacy of a veterinary medicinal product cannot be established by reference to a veterinary medicinal product that, in turn, roots its safety and efficacy in the demonstration of bioequivalence to a third product. This is because, in a 'generic to a generic' construction, it cannot be inferred that there is a sufficient degree of bioequivalence between the 'generic to the generic' and the original reference veterinary medicinal product ([56]).This is illustrated in the following example:

— Product A: reference veterinary medicinal product.

— Product B: 80 % bioequivalence with Product A is demonstrated ⇨ generic marketing authorisation.

— Product C: 80 % bioequivalence with Product B ⇨ bioequivalence between product C and A is 64 %, which is not sufficient to support the safety and efficacy profile of product C.

A veterinary medicinal product that is authorised on the basis of its bioequivalence to another product can only be accepted as reference veterinary medicinal product in the exceptional cases where the risk of generic drift can be discarded. In particular, this approach can be accepted in respect of products that have the same qualitative composition in active substances, are part of the same development and are held by the same marketing authorisation holder (or 'MAH') as illustrated in the following examples:

Example 1

— Formulations A and B are aqueous oral solutions having the same qualitative composition in active substance and no relevant differences in excipients. The only difference between the two formulations is the concentration of the active substance.

— Formulation A was authorised on the basis of submission of relevant technical documentation. Formulation B was authorised on the basis of bioequivalence with Formulation A. Both formulations are part of the same development and have always belonged to the same marketing authorisation holder.

— Formulation B may be used as reference veterinary medicinal product in an application by a third party.

Example 2

— The marketing authorisation holder of Product A (authorisation granted on the basis of submission of relevant technical documentation) subsequently applies for a generic marketing authorisation for Product B; Product A being the reference veterinary medicinal product.

([55]) This Section does not address the scenario of new indications, target species, strengths, pharmaceutical forms or administration routes developed by holders of a generic or a hybrid marketing authorisation and supported by relevant technical documentation. Prospective applicants intending to obtain a marketing authorisation by means of reference to the technical documentation developed by such holders (after the relevant data protection period has elapsed or is due to elapse in less than two years) should consider Section 4.6 and in particular the subsection on data requirements.

([56]) Bioequivalence between 80 % and 125 % is generally deemed acceptable, as explained in the Guideline on the conduct of bioequivalence studies for veterinary medicinal products.

— The quality dossiers for Products A and B are identical.

— Product B may be used as reference veterinary medicinal product in an application by a third party if batches of the Product A are no longer available in the Union to conduct bioequivalence studies.

Example 3

— Product A was developed by MAH A (authorisation granted on the basis of submission of relevant technical documentation). Product B, which contains the same active substance and has the same pharmaceutical form, was developed independently by MAH B (authorisation also granted on the basis of submission of relevant technical documentation).

— MAH A has acquired Product B. However, bioequivalence has never been demonstrated nor evaluated between Products A and B.

— Products A and B cannot automatically be considered bioequivalent and interchangeable products notably in view of a subsequent generic application for Product C. Whilst Products A and B may theoretically be bioequivalent, the difference in the product development and manufacturing history should be taken into account, unless the manufacturing and controls for Product B have been fully aligned with those of Product A subsequent to the acquisition.

— The reference veterinary medicinal product for generic Product C can only be either Product A or Product B against which bioequivalence has actually been demonstrated. It is not necessarily possible to make a combined reference to the terms of the marketing authorisation of Product A and B for the purpose of seeking an authorisation for Product C in the abovementioned scenario simply on the basis that Products A and B have the same qualitative composition in active substances and now belong to the same marketing authorisation holder, unless the risk of generic drift has been satisfactorily scientifically assessed.

Prospective applicants are strongly advised to consult the relevant competent authorities before submitting any application under Article 18 that relies on a reference veterinary medicinal product that, in turn, has been authorised on the basis of bioequivalence to a third product.

c) Limited market authorisations granted under Article 23

Marketing authorisations granted following an application submitted pursuant to Article 23 of the Regulation can be used as a reference veterinary medicinal product provided that all requirements for granting a generic marketing authorisation are fulfilled and that the requirement under Article 23(1) is met.

Any specific obligation imposed on the marketing authorisation of the reference veterinary medicinal product that is deemed appropriate also for the generic veterinary medicinal product should be imposed on the generic marketing authorisation. The product information of the generic veterinary medicinal product should also specify that the said product has been authorised on the basis of bioequivalence to a reference veterinary medicinal product that has been granted a limited market authorisation and that only a limited assessment of safety or efficacy has been conducted due to the lack of comprehensive technical documentation (see in this regard Section 4.3.5).

d) Marketing authorisations in exceptional circumstances

Marketing authorisations granted following an application submitted pursuant to Article 25 of the Regulation can be used as a reference veterinary medicinal product provided that all requirements for granting a generic marketing authorisation are fulfilled and that the requirements in Article 25 are met.

Any specific obligation imposed on the marketing authorisation of the reference veterinary medicinal product which is deemed appropriate also for the generic veterinary medicinal product should be imposed to the generic marketing authorisation. The product information of the generic veterinary medicinal product should also specify that the product has been authorised on the basis of bioequivalence to a reference veterinary medicinal product that has been granted a market authorisation in exceptional circumstances and that only a limited assessment of quality, safety or efficacy has been conducted due to the lack of comprehensive technical documentation (see in this regard Section 4.4).

e) Informed consent marketing authorisations

Veterinary medicinal products authorised on the basis of informed consent applications submitted pursuant to Article 21 of the Regulation can be used as reference veterinary medicinal products.

f) Bibliographic marketing authorisations

Veterinary medicinal products authorised on the basis of bibliographic applications submitted pursuant to Article 22 of the Regulation can be used as reference veterinary medicinal products. Pursuant to Article 18(1)(c) of the Regulation, the submission of a generic application cannot take place until the period of protection of the technical documentation of the reference veterinary medicinal product has elapsed or is due to elapse in less than two years. While the technical documentation in the public domain can be relied upon by any applicant to submit a distinct bibliographic marketing authorisation application, the specific bibliographic dossier submitted to obtain a marketing authorisation is to be considered technical documentation within the meaning of Article 38(1) of the Regulation. Therefore, the submission of a generic application pursuant to Article 18 is only possible after the period of protection of the technical dossier submitted has expired.

3.5.4.2. *Reference veterinary medicinal product not benefiting from protection*

Pursuant to Article 18(1)(c), a generic application should demonstrate that the period of protection of the technical documentation in the marketing authorisation of the reference veterinary medicinal product has elapsed or is due to elapse in less than two years. It follows that generic applications cannot be submitted until two years before the expiry date of the protection of the technical documentation of the reference veterinary medicinal product. Further details on the protection of technical documentation are provided in Section 6.

3.5.4.3. *Reference veterinary medicinal product no longer authorised in the Union*

Reference must be made to a veterinary medicinal product which is or has been authorised in the Union (*i.e.* it is possible to refer to a veterinary medicinal product that has been granted a marketing authorisation even if such marketing authorisation does no longer exist at the time when the generic application is submitted) and in accordance with the Union law ([57]).

In case the reference veterinary medicinal product is no longer produced and placed on the Union market, demonstration of the bioequivalence with the reference veterinary medicinal product through bioavailability studies should however be performed on batches which have been authorised within the Union, unless a waiver from bioequivalence studies applies (see heading 'Bioequivalence' under Section 4.5.1).

When batches of the reference veterinary medicinal product are no longer available in the Union territory, an application under Article 19 or Article 22 can be submitted.

However, as efficacy and safety in a marketing authorisation application in accordance with Article 18 is demonstrated on the basis of reference to information that is contained in the dossier of the authorisation of the reference veterinary medicinal product, if the reference veterinary medicinal product has been withdrawn for reasons related to public or animal health or the environment, a marketing authorisation under Article 18 cannot be granted. A similar principle applies in case of marketing authorisations submitted under Article 19.

Withdrawal of the marketing authorisation of the reference veterinary medicinal product

The withdrawal of a marketing authorisation at the request of the holder when the underlying period of protection of the technical documentation is coming to an end may hinder the entry of generics on the market. As explained in Section 3.6, any request for withdrawal of a marketing authorisation shall state the reasons. It is stressed that the withdrawal of a marketing authorisation which sole purpose is to prevent the entry of generics on the market may constitute a breach of the competition law rules, even if such a withdrawal is permissible under the Union legislation on veterinary medicinal products ([58]).

([57]) See Recital (34) of the Regulation.

([58]) See, for example, judgement of 6 December 2012, AstraZeneca v. Commission, Case C-457/10 P, EU:C:2012:770.

It has been observed that, at times, marketing authorisation holders of veterinary medicinal products authorised on the basis of tests, studies and clinical trials apply for a generic marketing authorisation of their own reference veterinary medicinal product (so-called 'autogeneric') and request the withdrawal of the marketing authorisation of that reference veterinary medicinal product, thereby hindering the access of other generics to the market. Aside from the possible breach of the competition law that these strategies may entail, from the standpoint of the Union legislation on veterinary medicinal products, the original reference veterinary medicinal product and the autogeneric have the same qualitative and quantitative composition in active substances and belong to the same marketing authorisation holder. It follows that marketing authorisation applications under Article 18 by third parties using the 'autogeneric' as reference veterinary medicinal product can be accepted if the risk of generic drift can be discarded as explained in Section 4.5.4.1.

3.5.4.4. *Changes affecting the safety or efficacy profile of the reference veterinary medicinal product*

If during the lifecycle of the generic veterinary medicinal product it is confirmed that the benefit-risk balance of the reference veterinary medicinal product is no longer positive, or that -where applicable- the conditions for extending the validity of a marketing authorisation of the reference veterinary medicinal product under Article 23 or Article 25 are no longer met, or otherwise the marketing authorisation of that reference veterinary medicinal product is withdrawn, suspended or revoked by the competent authorities in accordance with Article 130 or temporary safety restrictions are imposed in accordance with Article 129, appropriate action would be required also towards the generic veterinary medicinal products of that reference veterinary medicinal product.

By contrast, where the reference veterinary medicinal product is withdrawn at the request of the marketing authorisation holder for reasons that are not related to the quality, safety or efficacy thereof, an impact on the safety and efficacy profile of the generic veterinary medicinal product cannot be automatically assumed. However, appropriate action on the generic veterinary medicinal product may be required to ensure that the benefit-risk thereof continues to be positive in certain cases (*e.g.* if the marketing authorisation of the reference veterinary medicinal product foresees the conduct of a post-marketing study to confirm efficacy or safety). In general, any event having an impact on the safety and/or efficacy of the reference veterinary medicinal product that is relevant to the generic veterinary medicinal product should be considered new information affecting the benefit-risk balance of the generic marketing authorisation for the purposes of Article 58(10) of the Regulation.

3.5.4.5. *'European reference veterinary medicinal product'*

In the framework of the decentralised, mutual recognition or subsequent recognition procedures, a reference veterinary medicinal product should be identified in the reference Member State. In case there is no product authorised in the reference Member State, then a veterinary medicinal product authorised in another Member State can be chosen by the applicant as reference veterinary medicinal product, *i.e.* the European reference veterinary medicinal product. According to the paragraph (4) of Article 18, a generic application can also be submitted in a Member State although the reference veterinary medicinal product has never been authorised in that Member State. In that case, a reference veterinary medicinal product authorised in another Member State should be identified, so-called the European reference veterinary medicinal product.

In these cases, the applicant has to identify in the application form the name of the Member State in which the reference veterinary medicinal product is or has been authorised. It is also a prerequisite that the period of protection of the technical documentation has expired.

The competent authority of the Member State in which the application is submitted, or the Agency, may request information on the reference veterinary medicinal product from the competent authority of the Member State that granted the marketing authorisation. Such information should be transmitted to the requestor within 30 days of the receipt for the request ([59]).

([59]) See Article 18(5) of the Regulation.

3.5.4.6. *Reference veterinary medicinal product not harmonised in the European Union*

For historical reasons, the reference veterinary medicinal product identified in the procedure may have national marketing authorisations with different SPCs across the Union (horizontal disharmony of the reference veterinary medicinal product). This should not prevent that the veterinary medicinal product authorised on the basis of Article 18 has the same SPC across the Union (horizontal harmonisation of the generic veterinary medicinal product). The Member States concerned should recognise the assessment performed by the reference Member State, except where they have concerns as to the existence of a potential serious risk to human or animal health or the environment as regards the content of the application considered. In this case, those concerns should be raised and discussed in the context of the relevant assessment procedure.

Differences in SPCs across the Union might also be a trigger for competent authorities to propose the reference veterinary medicinal product for the procedure for harmonisation of the SPC according to Article 70 of the Regulation.

3.5.5. ***Other specificities of applications under Article 18***

3.5.5.1. *Additional information on environmental aspects*

Information about environmental impacts from the use of veterinary medicinal products was not required for veterinary medicinal products authorised prior to 1 October 2005. Where the reference veterinary medicinal product has been authorised prior to 1 October 2005, the competent authorities may require that a generic application contains safety data concerning the potential risks posed by the generic veterinary medicinal product to the environment ([60]).

3.5.5.2. *Additional information on antimicrobial or antiparasitic resistance*

The Regulation requires marketing authorisation applications submitted pursuant to Articles 18 or 19 concerning antimicrobial or antiparasitic veterinary medicinal products to provide information regarding the risk of development of antimicrobial or antiparasitic resistance respectively ([61]).

3.5.5.3. *Product information*

The product information of the generic veterinary medicinal product should be essentially similar to that of the reference veterinary medicinal product ([62]). However, the product information for the generic and the reference veterinary medicinal product may be different in the following cases:

— The generic of a reference veterinary medicinal product that has not been harmonised (see Section 4.5.4.6).

— Specific information linked to quality differences, in particular, the use of different excipients.

— Certain indications or pharmaceutical forms are still covered by patent law at the time when the generic veterinary medicinal product is authorised ([63]).

— The technical documentation supporting one or more indications in the marketing authorisation of the reference veterinary medicinal product still benefits from protection at the time when the generic veterinary medicinal product is authorised. Details on the protection of technical documentation submitted to support indications is provided for in Section 6.4.1.

— The technical documentation supporting certain pharmaceutical forms, administration routes or dosages in the marketing authorisation of the reference veterinary medicinal product still benefits from protection pursuant to Article 40(5) at the time when the generic veterinary medicinal product is authorised.

([60]) See Article 18(7) of the Regulation. See also the Reflection paper on the interpretation of Article 18(7) of Regulation (EU) 2019/6 (EMA/CVMP/ERA/622045/2020).
([61]) See Sections IV.1.3, IV.1.4 and IV.2.2 of Annex II of the Regulation.
([62]) See Article 18(6) of the Regulation.
([63]) See Article 18(6) of the Regulation.

— The technical documentation supporting the establishment of maximum residue limits ('MRLs') relevant to the marketing authorisation of the reference veterinary medicinal product still benefits from protection pursuant to Article 40(4) at the time when the generic veterinary medicinal product is authorised.

— Where a generic application concerns a reference veterinary medicinal product authorised prior to 1 October 2005, the product information of the generic marketing authorisation may be required to include -as appropriate- information about the environmental risks, including any necessary risk mitigation measures.

— Where a generic application concerns an antimicrobial or antiparasitic veterinary medicinal product, information about the risk of developing antimicrobial or antiparasitic resistance, including any necessary risk mitigation measures may be required (even if this information is not provided in the product information of the reference veterinary medicinal product because the authorisation thereof predates the application of the Regulation).

It is noted that, in the last two scenarios, the differences in the product information of the generic veterinary medicinal product and the reference veterinary medicinal product are expected to be temporary. Where, pursuant to the evaluation of the data on environmental risks or on the risk of development of antimicrobial/antiparasitic resistance, specific information is added to the product information of the generic veterinary medicinal product, holders of the reference veterinary medicinal product are required -pursuant to Article 58- to update the product information as appropriate (See Sections 5.1).

3.6. **Applications under Article 19 ('Hybrid applications')**

3.6.1. ***General considerations***

Applications based on Article 19 of the Regulation concern veterinary medicinal products that are similar to a reference veterinary medicinal product, but which do not meet the conditions for an Article 18 application. In particular, Article 19 concerns veterinary medicinal products that fail to meet the definition of 'generic veterinary medicinal product', or cases when the demonstration of safety and/or efficacy cannot be done exclusively by demonstration of bioequivalence with an already authorised veterinary medicinal product (*e.g.* in cases when an indication or target species not included in the terms of the marketing authorisation of the reference veterinary medicinal product is applied for).

Articles 18 and 19 are closely linked as evidenced by the fact that Article 19 sets out the conditions and requirements to submit an application 'by way of derogation from Article 18(1)' ([64]). The considerations regarding the 'reference veterinary medicinal product' set out in Section 4.5.4 herein are generally also relevant for applications submitted under Article 19. Likewise, considerations set out in Section 4.5.5 herein are also relevant to applications under Article 19, without prejudice to specific adaptations to the product information that may be required to reflect specific differences between the veterinary medicinal product authorised under Article 19 and the reference veterinary medicinal product.

It is stressed that, in cases where bioequivalence with a reference veterinary medicinal product cannot be demonstrated, an application under Article 19 can only be granted if sufficient data to demonstrate the safety and efficacy of the product is provided.

3.6.2. ***Data requirements***

The extent of the additional documentation required in the framework of an Article 19 application depends on *e.g.* the changes introduced vis-à-vis the reference veterinary medicinal product (*e.g.* new strength, new route of administration, new indication, new target species, differences in raw materials or manufacturing process in the case of biologicals, *etc*) and will be a matter of scientific assessment by the relevant competent authority. Section 7 herein addresses aspects related to the protection of the environment and human health considerations.

([64]) This is also relevant in connection with the application of Article 41 of the Regulation.

Applicants willing to introduce indications, target species, strengths, pharmaceutical forms or administration routes that are not part of the marketing authorisation of the reference veterinary medicinal product but have been included in the terms of a (different) marketing authorisation (after any applicable period of protection of the relevant technical documentation has elapsed or is due to elapse in less than two years) will be required to provide additional data supporting that the additional elements in the relevant marketing authorisation can also be added to their marketing authorisation. As the extent of the additional data required depends on the specific characteristics of the veterinary medicinal product concerned, applicants are encouraged to discuss this issue with the Agency (in the case of a prospective centralised marketing authorisation) or the relevant national competent authorities.

The pre-clinical studies or clinical trials for a hybrid veterinary medicinal product may be conducted with batches of the reference veterinary medicinal product authorised in the Union or in a third country. In the latter case, the applicant should demonstrate that the reference veterinary medicinal product authorised in a third country has been authorised in accordance with requirements equivalent to those established in the Union for the reference veterinary medicinal product and are so highly similar that they can substitute each other in the clinical trials ([65]).

3.7. **Applications for combination veterinary medicinal products ('fixed combinations')**

Pursuant to Article 20 of the Regulation, in the case of veterinary medicinal products containing active substances used in the composition of authorised veterinary medicinal products, applicants are not required to provide safety and efficacy data relating to each individual active substance. The combination of active substances within a single formulation according to this provision is known as 'fixed combination'. It is stressed that the combination of active substances, where the active substances are included in separate pharmaceutical forms and presented in a combination pack cannot be considered as a fixed combination.

Applications submitted pursuant to Article 20 should contain comprehensive technical documentation in relation to the fixed combination. As with any application for a new veterinary medicinal product, such dossier can either be a dossier based solely on tests, studies and clinical trials performed by the applicant or on a mixed dossier (*i.e.* dossier composed of tests, studies and/or trials and bibliographic data). Any absence of specific fixed-combination data should be duly justified by the applicant with reference to scientific and regulatory considerations.

While Article 20 does not require that data on individual active substances is provided, it is nevertheless possible to include such information in the application. This may occur when the applicant tries to justify the absence of certain specific data on the combination by reference to information available on the individual substances. Such information could consist of literature or actual data.

3.8. **Applications under Article 21 ('Informed consent applications')**

Pursuant to Article 21 of the Regulation, an applicant for a marketing authorisation for a veterinary medicinal product is not required to provide the technical documentation on quality, safety and efficacy if that applicant demonstrates permission, through a letter of access, to use the documentation submitted by another entity in respect of an already authorised veterinary medicinal product.

It is a prerequisite for the use of Article 21 that consent has been obtained for all parts of the application containing the pharmaceutical, safety and residues data, and preclinical and clinical data. It is thus not possible to refer to Article 21 as a legal basis for an application consisting of the applicants' own Part II of the application and for which consent has been given for Parts III and IV.

An informed consent application does not have to cover all the presentations/indications/target species/strengths/pharmaceutical forms of the cross-referred veterinary medicinal product. Consent may be given to use the technical documentation contained in the file of the cross-referred veterinary medicinal product for a given presentation/indication/target species/strength/pharmaceutical form only.

([65]) See Article 19(2) of the Regulation.

An informed consent application cannot cover more presentations/indications/target species/strengths/pharmaceutical forms than the cross-referred veterinary medicinal product. However, authorisation of additional presentations/indications/target species/strengths/pharmaceutical forms can be sought after the issuing of the marketing authorisation (through a variation procedure).

Cross-referred veterinary medicinal product

The cross-referred veterinary medicinal product is the veterinary medicinal product in respect of which a letter of consent is provided in an application pursuant to Article 21. The cross-referred veterinary medicinal product should have a valid marketing authorisation. It follows that it is not possible to submit an application under Article 21 together with the application for the cross-referred veterinary medicinal product.

When the cross-referred veterinary medicinal product has been granted a marketing authorisation under Article 23 or a marketing authorisation under Article 25, any specific obligation imposed on the cross-referred veterinary medicinal product that is deemed appropriate should be imposed also on the informed consent marketing authorisation. Where applicable, the product information of the veterinary medicinal product authorised pursuant to Article 21 should also draw attention to the fact that the product has been authorised on the basis of technical documentation of a veterinary medicinal product that has been granted a marketing authorisation under Article 23 or Article 25 and that only a limited assessment has been conducted due to the lack of comprehensive technical documentation (see in this regard Sections 4.3.5 and 4.4).

The following limitations apply regarding informed consent applications:

— When the cross-referred veterinary medicinal product has been granted a centralised marketing authorisation, the informed consent application should follow the centralised procedure.

— When the cross-referred veterinary medicinal product has been granted a national marketing authorisation, the informed consent application should follow a national procedure (either purely national procedure, decentralised procedure, mutual recognition procedure or subsequent recognition procedure).

Access to the quality, safety and efficacy data of the cross-referred veterinary medicinal product

The applicant should show proof that the marketing authorisation holder of the cross-referred veterinary medicinal product has given consent that the dossier of that product is used for the purpose of examining the application at stake. To this effect, an authenticated letter from the party granting consent should be provided. That letter should specify the name of the benefiting party and the products concerned (including -as appropriate- any applicable restrictions).

The applicant should have permanent access to the technical documentation in order to fully carry out its responsibilities. For information contained in the active substance master file, a new letter of access should be provided to the relevant competent authorities by the applicant, without prejudice to the restrictions on access to the manufacturer restricted part.

Changes affecting the safety or efficacy profile of the cross-referred veterinary medicinal product

If during the lifecycle of the veterinary medicinal product authorised under Article 21 it is confirmed that the benefit-risk balance of the cross-referred veterinary medicinal product is no longer positive, or that –where applicable- the conditions for extending the validity of the marketing authorisation of the cross-referred product under Article 23 or Article 25 are no longer met, or otherwise the marketing authorisation of the cross-referred veterinary medicinal product is withdrawn, suspended or revoked by the competent authorities in accordance with Article 130 or temporary safety restrictions are imposed in accordance with Article 129, appropriate action would be required also towards the veterinary medicinal products authorised in accordance with Article 21.

By contrast, where the cross-referred veterinary medicinal product is withdrawn at the request of the marketing authorisation holder for reasons that are not related to the quality, safety or efficacy thereof, an impact on the safety and efficacy profile of the veterinary medicinal product authorised under Article 21 cannot be automatically assumed. However, appropriate action on the veterinary medicinal product authorised under Article 21 may be required to ensure that the benefit-risk thereof continues to be positive in certain cases (*e.g.* if the marketing authorisation of the cross-

referred veterinary medicinal product foresees the conduct of a post-marketing study to confirm efficacy or safety). In general, any event having an impact on the safety and/or efficacy of the cross-referred veterinary medicinal product that is relevant to the veterinary medicinal product authorised under Article 21 should be considered as new information affecting the benefit-risk balance thereof for the purposes of Article 58(10) of the Regulation.

Environmental aspects

Pursuant to Article 21 and Annex II of the Regulation, informed consent applications are based on the letter of access to the dossier of an already authorised veterinary medicinal product. It follows that, as a general principle, the performance of an environmental risk assessment ('ERA') in connection with informed consent applications is not required.

The Regulation does not preclude cross-reference to marketing authorisations granted prior to 1 October 2005. In this regard, it is noted that marketing authorisation applications granted before 1 October 2005 are not likely to contain data that can be deemed adequate to assess environmental risks. It follows that, to the extent that an informed consent application is submitted by reference to a product that has been authorised before 1 October 2005, the authorities are not likely to be able to assess the environmental risks of the veterinary medicinal product by means of reference to the dossier of the cross-referred veterinary medicinal product.

Pursuant to Article 37(2)(i) of the Regulation, a marketing authorisation should be refused if the risks to public or animal health or to the environment are not sufficiently addressed.

In the case of applications submitted pursuant to Articles 18 and 19 of the Regulation, criteria have been developed to ensure that appropriate information is available in connection with the environmental risks of the veterinary medicinal products concerned, while avoiding duplication of studies. With a view to ensuring that environmental risks of newly granted marketing authorisations are duly assessed while avoiding duplication of studies and in particular animal studies, it is appropriate to apply the principles developed for the application of Article 18(7) of the Regulation to informed consent applications as well.

It follows that, to avoid having their marketing authorisation applications rejected pursuant to Article 37(2)(i) of the Regulation, prospective applicants are advised to verify that the dossier that is used as reference for an informed consent application contains relevant information about the environmental risks, unless such information is otherwise available to the authorities. Applicants are encouraged to discuss this issue with the Agency (in the case of a prospective centralised marketing authorisation) or the relevant national competent authorities.

3.9. Applications under Article 22 ('Bibliographic applications ')

According to Article 22 of the Regulation, instead of providing technical documentation on efficacy and safety, an applicant may provide detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substance(s) of the veterinary medicinal product has been in well-established veterinary use within the Union for at least ten years, with recognised efficacy and an acceptable level of safety for the proposed indications in the target species using the proposed route of administration and dosage regimen. In this regard, the provisions of Annex II of the Regulation apply.

Being a derogation, the well-established use provision must be interpreted strictly. The adequacy of the bibliographic evidence has to be assessed on a case-by-case basis, bearing in mind the fact that applications under Article 22 cannot lead to lower requirements of safety and efficacy.

Applications according to Article 22 of the Regulation are acceptable only in so far as the published scientific literature is relevant and sufficient to demonstrate the safety and efficacy profile of the veterinary medicinal product which is the object of the application. Therefore, when the safety and efficacy profile of the relevant veterinary medicinal product is determined by the manufacturing process and the starting materials (notably, for biologicals), only literature data that

refers to veterinary medicinal products manufactured according to the same procedure can be considered, provided that differences in the starting materials do not have an impact on the safety and/or efficacy. For example, for veterinary medicinal products containing cells subject to substantial manipulation, an application under Article 22 is not acceptable unless the manufacturing process of the product reported in the literature and the manufacturing process of the product covered by the application is the same.

Well-established medicinal use

Annex II of the Regulation lays down specific rules for the demonstration of a well-established medicinal use, with recognised efficacy and an acceptable level of safety ([66]). The following criteria should be taken into account:

— the time over which a substance has been used with regular application in the target species; quantitative aspects of the use of the substance;

— the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods; and

— the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and

— the coherence of scientific assessments.

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

Evidence must be supplied to demonstrate the systematic and documented use of the active substance, *i.e.* extensive and continued use over a period of at least 10-years in the Union. 'Veterinary use' does not exclusively mean 'use as an authorised veterinary medicinal product'. In particular, for an active substance used in veterinary medicinal products authorised before a Member State joined the Union or before an authorisation in a Member State was upgraded in accordance with Union law; the use in that territory is to be taken into account for the purpose of application of Article 22, even if it has partly or fully occurred before accession of that Member State. However, the use of an active substance under other legal frameworks (*e.g.* food, biocides) cannot be considered 'well-established use' for the purposes of applications under Article 22.

Well-established veterinary use refers to the use for a specific therapeutic purpose. If well-known substances are the object of an application for new indications, it is not possible to refer to a well-established veterinary use for the proposed new indication. Data on the new indication together with appropriate safety and residue tests and preclinical and clinical data should be provided and, in such a case, another legal basis should be used for the marketing authorisation application.

Marketing authorisation applications for a product containing a combination of active substances can be submitted on the basis of Article 22. In such cases, the detailed references to published scientific literature submitted must concern the systematic and documented use of the active substances in combination. It is nevertheless possible to include information on the individual active substances in the application for a fixed combination. This will typically occur where the applicant tries to justify the absence of certain specific data on the combination by reference to the information available on the individual substances.

Documentation

The applicant is encouraged to provide a detailed description of the strategy used for the search of published literature and the justification for inclusion of references in the application. The documentation and the detailed and critical summaries submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form

([66]) See Part IV.5.3.1 to IV.5.3.12.

of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, should be communicated. If documentation is lacking, a justification should be given. If parts of the dossier are incomplete, particular attention must be given to explain why in the detailed and critical summaries.

References provided must refer to 'published scientific literature'. The term 'published' implies that the literature must be freely available in the public domain and published by a reputable source preferably peer reviewed. Copies of the full text of the literature, including necessary translations must be submitted.

Scientific monographs may offer an overview on published scientific literature which - together with the full texts referred to- may be used in addition to other documents for a bibliographical application. These monographs can help to avoid duplication of work and bring about gradual harmonisation in the evaluation of veterinary medicinal products. Likewise, the assessment report published by the Agency following the evaluation of an application for the establishment of maximum residue limits in accordance with Regulation (EC) No 470/2009 may be used in an appropriate manner as literature, particularly for the safety tests.

However, it must be stressed that assessment reports such as the EPAR for Union marketing authorisations which are made publicly available by competent authorities for reasons of transparency cannot be considered to supply sufficient information to meet the requirements for applications under Article 22.

Post-marketing experience with other products containing the same constituents is of particular importance and should be reported and addressed adequately.

In certain cases, studies may be provided only to support the relevance of the literature (used to demonstrate safety and efficacy of the active substance(s)) to the product intended for marketing. These are to be considered on a case-by-case basis by the competent authorities.

4. **LIFECYCLE OF MARKETING AUTHORISATIONS**

4.1. **Continuous update**

Marketing authorisations for veterinary medicinal products are dynamic and not static and they must be updated to take due account of scientific and technical progress and available evidence, to ensure that the benefit-risk balance continues to be positive ([67]) and that new regulatory requirements are respected, as applicable.

In particular, marketing authorisation holders are required to update their marketing authorisations by means of a variation procedure in the following cases:

— to ensure that the product information (SPC, package leaflet and labelling) is kept up to date with current scientific knowledge ([68]);

— to ensure that manufacturing methods and controls are kept up to date with scientific and technical progress ([69]); and

— to submit without undue delay an application for variation -where necessary- following the assessment of the pharmacovigilance data ([70]).

Holders of marketing authorisations granted in accordance with Articles 18, 19 or 21 should, where relevant, submit variation applications swiftly after the marketing authorisation of the reference veterinary medicinal product or of the cross-referred veterinary medicinal product is amended to address a safety or efficacy concern, the risk of development of resistance or other risks to public health, animal health or the environment that is relevant to their marketing authorisations ([71]).

([67]) See Article 77(4) and 81(2) of the Regulation.
([68]) See Article 58(4) of the Regulation.
([69]) See Article 58(3) of the Regulation.
([70]) See Articles 77(10) and 81(2) of the Regulation.
([71]) The submission of a variation by the holder of marketing authorisations granted pursuant to Article 18, 19 or 21 is not required to align to changes in the pharmaceutical form, administration route or dosage that are introduced in the marketing authorisation of the reference veterinary medicinal product and that are covered by Article 40(5) in so far as the relevant technical documentation benefits from protection.

In addition to the above scenario, all marketing authorisation holders should consider whether new scientific information that becomes available in connection with similar veterinary medicinal products authorised in the Union is relevant in connection with their marketing authorisations and, where appropriate, take relevant measures, such as the submission of a variation application.

Furthermore, all marketing authorisation holders are required to swiftly communicate to the competent authorities that have granted the marketing authorisation (in the case of centralised marketing authorisations, the notification should be made to the Agency) the following:

— any new information that may influence the evaluation of the benefits and the risks of the veterinary medicinal product, including -but not limited to- information obtained through pharmacovigilance; and

— any prohibition or restriction that has been imposed by the competent authorities in the Union or in third countries ([72]).

At any time during the lifecycle of the marketing authorisation, the national competent authorities or the Agency may request the marketing authorisation holder to provide data demonstrating that the benefit-risk balance remains positive ([73]).

It is stressed that the evaluation of the risks of a veterinary medicinal product includes:

— risks relating to the quality, safety and efficacy as regards animal or human health;

— risks of undesirable effects on the environment; and

— risks relating to the development of resistance ([74]).

4.2. **Variations**

Marketing authorisations for veterinary medicinal products can be amended at the request of the marketing authorisation holder with a view to amending the terms of the marketing authorisation, *e.g.* to add or amend target species, indications, strengths or pharmaceutical forms. This possibility exists for all marketing authorisations, regardless of the legal basis thereof. The technical documentation that is required for the variation depends on the type of change that is envisaged.

In certain cases (*e.g.* when bioequivalence is demonstrated), it is also possible to request a variation on the basis of safety and efficacy data of a previously authorised veterinary medicinal product provided that any relevant period of protection has elapsed or is due to elapse in less than two years (or a letter of access is provided). The requirements for generic and hybrid applications explained in Section 4 are also applicable for variation applications.

Different scenarios are possible, including:

— A marketing authorisation holder that has been granted a marketing authorisation under Article 18 can submit proprietary technical information with a view to expanding the terms of the originally granted authorisation.

— A marketing authorisation holder that has been granted a marketing authorisation following the submission of comprehensive technical documentation can request a variation to expand the terms of the originally granted authorisation following a generic approach (*i.e.* by demonstrating bioequivalence with another veterinary medicinal product).

— A marketing authorisation that has been granted on the basis of bibliographic data can subsequently submit proprietary technical information with a view to expanding the terms of the originally granted authorisation.

Marketing authorisations granted before 28 January 2022

Variations of marketing authorisations granted before 28 January 2022 should be submitted in accordance with Regulation (EU) 2019/6.

([72]) See Article 58(10) of the Regulation.
([73]) See Article 58(9) of the Regulation.
([74]) See Article 4(19) of the Regulation.

5. PROTECTION OF TECHNICAL DOCUMENTATION

5.1. General principles

Under certain conditions, applicants for a new marketing authorisation or a variation may refer to technical documentation that has been developed by a third party with a view to obtaining a marketing authorisation or a variation for another veterinary medicinal product.

The rules on the protection of technical documentation aim at ensuring a fair balance between the protection of innovative companies and the general interests that are served by the marketing of generic veterinary medicinal products, as well as the interest in avoiding the repetition of tests on animals where not necessary.

Restrictions on the ability of generic applicants to refer to technical documentation of a reference veterinary medicinal product -thereby leading to differences in the product information of generic and reference veterinary medicinal products- are foreseen in the Regulation as a means to reward major investments in the development of tests, pre-clinical studies and clinical trials required to apply for a marketing authorisation or to establish a maximum residue limit for pharmacologically active substances of the veterinary medicinal product, as well as in connection with innovation on veterinary medicinal products with an existing marketing authorisation. Such protection should be limited in time in order to allow for competition ([75]).

Additionally, the need to ensure a high level of public and animal health and environmental protection -which is at the core of the Union legislation on veterinary medicinal products- should also be considered when applying the rules on protection of technical documentation. In this regard, it is important to ensure that products that are essentially similar in composition and also with regard to the authorised uses, have essentially similar product information, for example regarding conditions of use, duration of treatment, onset or duration of effect, concomitant treatments, precautions linked to environmental concerns, *etc* ([76]).

In sum, in applying the provisions on the protection of technical documentation of the Regulation account must be taken of the need to reward major investments by developers of veterinary medicinal products, the need to ensure fair access of generics to the market to increase availability of veterinary medicinal products, and the need to avoid -as much as possible- disharmonisation in the product information between reference veterinary medicinal products and generics, in particular on aspects of product information that are relevant to public or animal health or the environment.

Applicants relying on technical documentation developed in connection with another veterinary medicinal product

Technical documentation on quality, safety and efficacy submitted with a view to obtaining a marketing authorisation or a variation thereof can only be relied upon by other applicants in the following circumstances:

— the marketing authorisation holder has granted consent by means of a letter of access (application pursuant to Article 21); or

— the underlying period of protection has elapsed or is due to elapse in less than two years (applications pursuant to Articles 18 and Article 19) ([77]).

In case of applications pursuant to Article 21, the letter of access should be submitted as part of the application. In case of applications pursuant to Articles 18 and 19, the applicant is required to demonstrate that the application concerns a reference veterinary medicinal product for which the period of protection of the technical documentation laid down in Articles 39 and 40 has elapsed or is due to elapse in less than two years ([78]).

The protection of the technical documentation is applicable also in Member States where the reference veterinary medicinal product is not authorised or is no longer authorised ([79]).

([75]) See recitals (33) and (36) of the Regulation.
([76]) See Article 18(6) of the Regulation.
([77]) See Article 38(1) of the Regulation.
([78]) See Article 18(1)(c) of the Regulation.
([79]) See Article 38(2) of the Regulation.

Until the period of protection has elapsed or is due to elapse in less than two years, the protected technical documentation may not be referred to in the context of another application, even if this information is obtained through access to documents or freedom of information legislation within the Union or third countries. As long as a veterinary medicinal product authorised in the Union benefits from protection, the reliance on published or unpublished technical documentation contained in the dossier of that product within the Union or in third countries by the competent authorities to grant a marketing authorisation would lead to a circumvention of the rules on the protection of technical documentation. Therefore, such applications cannot be accepted.

Furthermore, holders of a generic or a hybrid marketing authorisation cannot place the relevant veterinary medicinal product on the market until the period of protection of the technical documentation of the reference veterinary medicinal product has elapsed ([80]).

Responsibility of applicants and role of competent authorities

Applicants relying on technical documentation on quality, safety and/or efficacy submitted in the context of a previously granted marketing authorisation should demonstrate that the period of protection of the technical documentation – as laid down in Articles 39 and 40- has elapsed or is due to elapse in less than two years (unless a letter of access is provided) ([81]). It follows that it is the responsibility of applicants to ensure that the period of protection of technical documentation relied upon in their applications has elapsed or is due to elapse in less than two years (unless a letter of access is provided).

While competent authorities should reject an application that is in breach of the period of protection of technical documentation, it is stressed that the assessment of marketing authorisation applications by the competent authorities is based on the content of the submission made by the applicant and focused on criteria of quality, safety and efficacy. Decisions adopted by national competent authorities on applications are without prejudice to the rights of owners of technical documentation to seek judicial remedy before national courts ([82]).

It is also important to highlight that the protection of public and animal health and the environment underpins the application of Regulation (EU) 2019/6. Accordingly, in making a decision on an application for marketing authorisation, competent authorities must examine the safety and efficacy of the veterinary medicinal product, and it is therefore permissible for that authority to take account of all data in its possession, from whatever source, to the extent that such data demonstrate that the product is harmful or that it lacks efficacy ([83]).

5.2. Same marketing authorisation for the purpose of applying the rules of the protection of technical documentation ('SMA')

Article 38(3) of the Regulation explains what is to be considered as same marketing authorisation for the purpose of applying the rules of the protection of technical documentation:

A marketing authorisation or a variation to the terms of a marketing authorisation differing from the marketing authorisation previously granted to the same marketing authorisation holder only with regard to target species, strengths, pharmaceutical forms, administration routes or presentations shall be regarded as the same marketing authorisation as the one previously granted to the same marketing authorisation holder for the purpose of applying the rules of the protection of technical documentation.

Modifications to the target species, strengths, pharmaceutical forms, administration routes or presentations initially included in a marketing authorisation can be made via a variation procedure or under a separate marketing authorisation procedure. The SMA contains the initial authorisation as well as subsequent changes thereto regarding target species, strengths, pharmaceutical forms, administration routes or presentations, also when the subsequent modifications are authorised under a separate marketing authorisation procedure and regardless of the legal basis of the respective applications.

([80]) Article 58(5) of the Regulation.
([81]) See Articles 18(1)(c) and 38(1) of the Regulation.
([82]) See judgment of 14 March 2018, Astellas Pharma, C-557/16, EU:C:2018:181.
([83]) See judgment of 29 April 2004, *Novartis Pharmaceuticals,* C-106/01, EU:C:2004:245.

The concept of SMA concerns variations and marketing authorisations granted to the same holder and is not applicable across different marketing authorisation holders. For example, the marketing authorisation of the reference veterinary medicinal product and the marketing authorisation of a generic product are not part of the SMA, unless they belong to the same marketing authorisation holder as explained in Section 3.3. By contrast, if the marketing authorisation holder of product A subsequently acquires from a third party the marketing authorisation of product B, the marketing authorisations of products A and B will be considered part of the SMA if both products contain the same active substance(s).

As explained in Section 6.1, the concept of SMA laid down in Article 38(3) should be interpreted as having regard to the overall objective of the Regulation to ensure a high level of protection of human and animal health and the environment and having due consideration to other provisions of the Regulation. In particular, Article 18(6) provides that the SPC of generic veterinary medicinal products should be essentially similar to that of the reference veterinary medicinal product and Article 58(4) requires marketing authorisation holders to update the SPC, package leaflet and labelling in accordance with current scientific knowledge.

Additional details regarding the protection of technical documentation supporting indications are provided in Section 6.4.1.

New active substance

If a marketing authorisation application concerns a modification of an existing active substance, it should be clarified during the assessment procedure whether the application concerns a new active substance or not.

Requests for a new active substance claim should be submitted with the application containing the modified substance. No such claims will be considered retroactively.

The decision is taken by the competent authorities on a case-by-case basis, taking into account the definition provided for in Annex herein and the conclusion should be reflected at least in the assessment report. If the assessment report does not consider that the product at stake contains a new active substance, it will be considered that the product at stake contains the same active substance as in a previously authorised veterinary medicinal product.

Combination of active substances

If the veterinary medicinal product being assessed contains a combination of active substances within the same pharmaceutical form, it will be regarded as a new veterinary medicinal product requiring a separate marketing authorisation, regardless of whether some or all of the active substances contained therein have been authorised in a veterinary medicinal product. The authorisation of a combination veterinary medicinal product is not considered to fall within the scope of the SMA of an already authorised veterinary medicinal product(s) containing one of the substances of the combination veterinary medicinal product.

If the veterinary medicinal product being assessed contains only one active substance, which was part of an authorised combination veterinary medicinal product, such veterinary medicinal product is to be considered a new veterinary medicinal product requiring a separate marketing authorisation. As the benefit-risk balance in the authorised combination product relates to the combination of active substances, the applicant for the new authorisation will have to demonstrate the positive benefit-risk balance of the veterinary medicinal product that contains only one substance. The authorisation of the new veterinary medicinal product is not considered to fall within the scope of the SMA of the already authorised combination veterinary medicinal product.

Changes to the marketing authorisation

Throughout the lifecycle of a marketing authorisation, changes to the terms of the marketing authorisation may give rise to additional periods of protection. In this regard, it is important to make a distinction between:

— *Changes that prolong the period of protection of the SMA*: In the scenarios foreseen in paragraphs (1) to (3) of Article 40, the protection period of the SMA is prolonged. Accordingly, no generic or hybrid application may be submitted until the end of the extended protection period.

— *Changes that give rise to a new (distinct) period of protection:* In the scenarios foreseen in paragraphs (4) and (5) of Article 40, as well as when new indications are added to the first marketing authorisation (as a variation or as a separate marketing authorisation), a distinct period of protection starts applying. This distinct period only concerns the specific technical documentation supporting the relevant change and it does neither restart or prolong the period of protection of the SMA, nor affect the existing generic marketing authorisations.

5.3. Counting the period of protection of the SMA

Starting date

The start of the period of protection of the SMA is the date when the first marketing authorisation was granted in the Union in accordance with the pharmaceutical *acquis* ([84]). New target species, strengths, pharmaceutical forms, administration routes or presentations that may be subsequently added through a variation procedure (or as a separate marketing authorisation) do no restart the period of protection.

The starting date for the periods of protection applicable to specific technical documentation submitted in support of new indications and in the scenarios foreseen in Article 40(4) and (5) is explained in Section 6.4.

Duration

Pursuant to Article 39(1), the duration of the period of protection is as follows:

a) 10 years for veterinary medicinal products for cattle, sheep for meat production, pigs, chickens, dogs and cats;

b) 14 years for antimicrobial veterinary medicinal products for cattle, sheep for meat production, pigs, chickens, dogs and cats containing an antimicrobial active substance which has not been an active substance in a veterinary medicinal product authorised within the Union on the date of the submission of the application;

c) 18 years for veterinary medicinal products for bees;

d) 14 years for veterinary medicinal products for animal species other than those referred to in points (a) and (c).

Moreover, paragraphs (1) to (3) of Article 40 provide that, when additional target species are included in -or are subsequently added to- the marketing authorisation, the above-referred periods can be extended up to a maximum period of 18 years. The extension of the period of protection only applies where the application for the additional target species is submitted at least three years before the expiration of the protection applicable in accordance with Article 39. The cut-off point for the three years period is the date of submission of the variation application.

The length of the extension of the protection period depends on the type of animal species that is included in/added to the marketing authorisation:

(i) ***Cattle, sheep for meat production, pigs, chickens, dogs and cats ('major target species'):*** An additional year is added per additional major target species included in the first marketing authorisation, or per major target species subsequently added to the marketing authorisation no later than three years before the end of the period of protection.

— Example 1: a veterinary medicinal product is granted a marketing authorisation for cattle and pigs (10+1) and five years later it is expanded to cats and dogs (+1+1); period of protection = 13 years.

— Example 2: an antimicrobial veterinary medicinal product (new active substance) is granted a marketing authorisation for cats and dogs; period of protection = 15 years (14+1).

(ii) ***Target species other than cattle, sheep for meat production, pigs, chickens, dogs, cats ('minor target species'):*** Four additional years are added per additional minor target species included in the first marketing authorisation (except if the first marketing authorisation includes bees), or per minor target species subsequently added to the marketing authorisation no later than three years before the end of the period of protection.

([84]) Article 39(2) of the Regulation.

— Example 1: a veterinary medicinal product is granted a marketing authorisation for ducks and turkeys = 18 years (14+4).

— Example 2: a veterinary medicinal product is granted a marketing authorisation for ducks and turkeys (14+4) and five years later it is expanded to goose; period of protection (+4) = 18 years ([85]).

Marketing authorisations concerning major and minor target species

Article 40(1) addresses the scenario of one or more major target species added to a marketing authorisation that already covers one or more major target species. In turn, Article 40(2) addresses the scenario of one or more minor target species added to a marketing authorisation that already covers one or more minor target species. However, the same marketing authorisation can refer to both major and minor target species.

When a marketing authorisation concerns both major and minor target species, the period of protection of technical documentation should be calculated as follows:

1) If the initial marketing authorisation concerns a mix of major and minor target species, the period of protection that should be applied first is the one set out in Article 39(1)(a).

2) The extension of protection set out in Article 40(1) and (2) should be added subsequently.

3) The maximum period of protection of 18 years set out in Article 40(3) applies.

The following examples are provided for illustration purposes:

— Example 1: A marketing authorisation application covers cattle and goats; period of protection = 14 years (10+4).

— Example 2: A marketing authorisation granted for goats and sheep for meat production (10+4) is subsequently expanded to cattle (+1); period of protection = 15 years.

— Example 3: A marketing authorisation granted for ducks and turkey (14+4) is subsequently expanded to chicken (+1); period of protection = 18 years ([86]).

Target species

For the purposes of applying the rules on the protection of technical documentation, the concept of target species is to be interpreted on the basis that sub-types (breeds) or subcategories within a given target species are not considered different target species. For example, the inclusion of laying hens in the SPC of a marketing authorisation that is already authorised for broilers (for the relevant indication) cannot be regarded as an addition of a target species. Likewise, the inclusion of piglets in the SPC of a marketing authorisation that is already authorised for adult pigs (for the relevant indication) cannot be regarded as an addition of a target species for the purposes of applying the rules on protection of technical documentation.

5.4. Protection of other technical documentation

5.4.1. *Indications*

The Regulation does not specifically provide for details on the application of the protection of technical documentation submitted in connection with indications. Neither the recitals that refer to the rules on protection of technical documentation mention indications, nor do Articles 39 and 40. However, in accordance with Article 38(3) of the Regulation, indications are not part of the SMA. Therefore, as a general rule, one should consider that technical documentation underpinning the addition of a new indication is entitled to a new, stand-alone period of protection.

([85]) Even though the periods of data protection resulting from the addition of all the target species is 22 years, the limit of 18 years set out in Article 40(3) applies.

([86]) Even though the periods of data protection resulting from the addition of all the target species is 19 years, the limit of 18 years set out in Article 40(3) applies.

However, it would be contrary to the objectives of ensuring a high level of public and animal health and environmental protection and to the principle that the product information of a reference and generic veterinary medicinal product should be essentially similar, as laid out in Article 18(6) of the Regulation, if the submission of technical documentation to confirm, update or modify the product information of a reference veterinary medicinal product concerning an existing indication led to disharmonisation of the product information between the SPC of reference and the generic products on aspects regarding the use of the veterinary medicinal product for the relevant indication.

Accordingly, it must be considered that technical documentation submitted to support changes to the product information that are intrinsically linked to a given indication, such as new dosage, ([87]) duration of treatment, place in therapy (*e.g.* first line, second line), as well as other aspects of the product information relevant to the safe and efficacious use of the product within the relevant indication (*e.g.* information on concomitant treatments or onset or duration of effect) are captured by the period of protection of the relevant indication. It follows that such changes can be reflected - as appropriate - in the marketing authorisation of generic veterinary medicinal products.

This can be illustrated with the following examples:

— Example 1:

  — A marketing authorisation is granted on 15 January 2023 for a veterinary medicinal product for the treatment of biliary spasms in dogs. The posology for the biliary spasms is amended in December 2026, following the submission of proprietary data.

  — The protection of the technical documentation regarding the indication treatment of biliary spasms ends on 15 January 2033, including for the technical documentation submitted to change the posology.

— Example 2:

  — A marketing authorisation is granted on 10 June 2026 for a veterinary medicinal product for the symptomatic treatment of diarrhoea in dogs. In September 2030 the duration of treatment for the treatment of symptomatic treatment of diarrhoea is amended, following the submission of proprietary data.

  — The protection of the technical documentation regarding the indication symptomatic treatment of diarrhoea ends on 10 June 2036, including for the technical documentation submitted to change the duration of treatment.

— Example 3:

  — A marketing authorisation is granted on 10 March 2025 for an antiparasitic veterinary medicinal product for cats. Following the outcome of a post-marketing study imposed as obligation in the marketing authorisation, a restriction of use is introduced on 3 September 2032 in the indication previously granted out of environmental concerns.

  — The protection of the technical documentation ends on 10 March 2035, including with regard to the restriction of use introduced in 2032.

— Example 4:

  — A marketing authorisation is granted on 5 April 2024 for a veterinary medicinal product authorised for the treatment of lymphoma in dogs. Following a signal management, the applicant conducts a post-marketing study. In light of the outcome of the study the marketing authorisation holder requests a variation to amend the product information regarding precautions of use by the veterinarians administering the product. The marketing authorisation is amended on 25 November 2030.

  — The protection of the technical documentation for the indication lymphoma ends on 5 April 2034, the variation introduced on 25 November 2030 does not trigger any period of protection and should be swiftly reflected in the product information of generic veterinary medicinal products as appropriate.

([87]) Except when the conditions in Article 40(5) apply, in which case the four years of protection would only apply to the technical documentation that supports the new dosage.

Period of protection

It is important to note that, because new indications are not part of the SMA, the granting of a new indication does not expand the protection of the previously granted marketing authorisation, nor does it restart the protection period for the underlying SMA. The period of protection afforded to the new indication concerns exclusively the technical documentation on quality, safety and efficacy related to the granting of the new indication. This period starts applying from the date of adoption of the decision granting the new indication (regardless of when the original marketing authorisation was granted).

Having regard to the overarching objective of the rules on protection of technical documentation as well as the specific wording of paragraphs (1) to (3) of Article 40, which links the extension of the period of protection to the granting of the first marketing authorisation, it should be considered that the additional extension periods foreseen in these articles do not apply to technical documentation that has been submitted to support a new indication after the first marketing authorisation is granted.

Accordingly, the period of protection of the technical documentation that is submitted in support of a new indication (after the marketing authorisation is granted) is determined by the periods foreseen in Article 39 alone. This is illustrated with the following examples:

— Example 1:

  — On 30 June 2023, Company A obtains a marketing authorisation for Product A, the SPC of which includes indication X in sheep for meat production. Subsequently the same company submits relevant technical documentation to expand the marketing authorisation to include the new indication Y in goats; the variation is authorised on 15 September 2025.

  — The addition of the target species goats in 2025 concerns an indication that is not covered by the SMA and therefore cannot expand the period of protection of the SMA. Therefore, Company B can submit a generic application for the indication X in sheep for meat production using Product A as reference veterinary medicinal product as from 30 June 2031 (*i.e.* two years before the 10 year protection period elapses).

  — Company B can submit a generic application for a variation covering the new indication Y in goats using Product A as reference veterinary medicinal product as from 15 September 2037 (*i.e.* two years before the 14 year protection period elapses).

— Example 2:

  — On 30 June 2023, Company A obtains a marketing authorisation for Product A, the SPC of which includes indication X in sheep for meat production and goats. Subsequently the same company submits relevant technical documentation to expand the marketing authorisation to include the new indication Y in sheep for meat production and goats; the variation is authorised on 15 September 2025.

  — The period of protection for the indication X is 14 years (10+4). Therefore, Company B can submit a generic application for indication X in sheep for meat production and goats using Product A as reference veterinary medicinal product as from 30 June 2035 (*i.e.* two years before the period of protection elapses).

  — The period of protection for the new indication Y is 10 years ([88]). Therefore, Company B can submit a generic application for indication Y in sheep for meat production and goats using Product A as reference veterinary medicinal product as from 15 September 2033 (*i.e.* two years before the period of protection elapses).

([88]) Subsection 'Marketing authorisations concerning major and minor target species' in Section 6.3 explains how to count the period of protection when a marketing authorisation is granted for a major and a minor target species. In the example at stake, the period of protection that should be counted first is the one applicable to sheep for meat production. In addition, as the example relates to a new indication, the period of protection for the relevant technical documentation supporting the indication is not extended with the addition of target species (goats).

Finally, it is noted that the period of protection of the technical documentation as explained above applies regardless of whether the new indication is applied for as a separate marketing authorisation or as a variation to an existing marketing authorisation. To make a distinction between developments authorised through the granting of a separate marketing authorisation and developments authorised through the variation of the terms of an initial marketing authorisation would elevate form over substance and would create an easy route for applicants to gain additional periods of protection ([89]).

5.4.2. *Safety and residues tests, pre-clinical studies and clinical trials concerning maximum residues limits ('MRL')*

Article 40(4) provides for five years of protection for safety and residue tests, studies and trials associated with the data submitted to establish an MRL in accordance with Regulation (EC) No 470/2009 in the context of a marketing authorisation application or in the context of a variation. The period of protection starts counting from the date of adoption of the decision granting the marketing authorisation for which they were carried out.

The protection afforded by Article 40(4) of the Regulation is exclusively limited to the tests, studies and trials concerned and it does not prolong the period of protection of the SMA.

5.4.3. *Changes to the pharmaceutical form, administration route or dosage that have demonstrated a reduction in the antimicrobial or antiparasitic resistance or an improvement in the benefit-risk balance*

Pre-clinical studies and clinical trials submitted to support such changes benefit from four years of protection, during which other applicants may not refer to the relevant studies and trials, unless they have obtained a letter of access.

Pursuant to Article 40(5), the change to the pharmaceutical form, administration route or dosage must be a factor leading to (a) a reduction in antimicrobial or antiparasitic resistance, or (b) an improvement of the benefit-risk balance of the veterinary medicinal product. It is not excluded that a change of pharmaceutical form, administration route or dosage may also be associated with another variation. In such cases, for the protection of technical documentation foreseen under Article 40(5) to apply, it will always be necessary to justify how the change to the pharmaceutical form, administration route or dosage contributes to the claimed improvement of the benefit-risk balance and/or the reduction of resistance.

The specific protection afforded by Article 40(5) is dependent upon the assessment by the authorities that a change in the pharmaceutical form, administration route or dosage has demonstrated a reduction in the antimicrobial or antiparasitic resistance or an improvement in the benefit-risk balance. It is noted that the assessment whether the conditions set out in Article 40(5) are met is distinct from the assessment of the quality, safety and efficacy profile of the veterinary medicinal product and the benefit-risk balance thereof. For example, it is possible for a variation to change the dosage to be granted even if the relevant competent authority does not uphold the applicant's claim in connection with Article 40(5). When the conditions set out in Article 40(5) are met, an explicit statement will be added to the public assessment report.

The protection afforded by Article 40(5) of the Regulation is exclusively limited to the preclinical studies or clinical trials concerned and it does not expand the period of protection of the SMA. The period of protection starts applying from the moment when the relevant variation is granted (regardless of when the original marketing authorisation was granted).

5.5. **Innovation by holders of marketing authorisations granted pursuant to Articles 18 and 19**

Stimulation of innovation by a reinforced system of protection of technical documentation is one of the objectives in the Regulation. Innovation in the veterinary medicinal products sector may come from developers that submit a marketing authorisation application supported by pre-clinical studies and clinical trials, but it may also come from holders of generic marketing authorisations that invest in innovation to their products and develop the product further *e.g.* by adding new indications or new target species. Recital (36) confirms that the legislator not only wanted to reward innovation in new veterinary medicinal products but also innovation brought to veterinary medicinal products with an existing marketing authorisation.

([89]) See judgement of 28 June 2017, *Novartis Europharm v. Commission*, C-629/15 P, EU:C:2017:498.

The protection of technical documentation set out in Articles 39 and 40 of the Regulation is not linked or restricted to specific types of applications ([90]). Accordingly, innovation that is introduced in a marketing authorisation and that is supported by technical documentation may benefit from protection, regardless of the legal basis thereof, provided that the relevant conditions set out in the Regulation are met.

Having regard to Article 38(3) of the Regulation, the period of protection set out in Articles 39 and 40 should be calculated as explained in sections 6.5.1 and 6.5.2.

5.5.1. *Technical documentation supporting a new strength, pharmaceutical form, route of administration or target species*

It is open to holders of a marketing authorisation originally granted under Article 18 (or Article 19) to generate the required technical documentation to add new strengths, pharmaceutical forms, routes of administration or target species that are not authorised for the reference veterinary medicinal product. Such innovation can be made through a variation to the existing marketing authorisation or by means of the submission of a separate application. The consequences in terms of protection of the relevant technical documentation should be the same.

When holders of a marketing authorisation granted under Article 18 (or Article 19) obtain a new strength, pharmaceutical form, route of administration or target species on the basis of technical documentation generated by them, the periods of protection of Article 39 apply to the relevant technical documentation, having regard to the concept of SMA. Because the concept of SMA does not apply across different holders, it is appropriate to make a distinction between the following two scenarios:

— Scenario 1*: The holder of a marketing authorisation granted under Article 18 (or Article 19) is not the same as the marketing authorisation holder of the reference veterinary medicinal product*: the technical documentation that is submitted to add a new strength, pharmaceutical form, route of administration or new target species benefits from the periods of protection set out in Article 39. The period of protection starts counting from the time of the granting of the relevant variation (or -as applicable- the granting of the new marketing authorisation).

  It is noted that, once the holder has benefited from the period of protection laid down in Article 39, any subsequent addition of more target species to the SMA can only benefit from the period of protection set out in Article 40 (regardless of whether that extension to new species is done by means of a variation or by means of a new marketing authorisation application). The concept of SMA is likewise applicable to the subsequent addition of more strengths, pharmaceutical forms or routes of administration (whether by means of a variation or a new application).

  Example:

  — Company A holds a generic marketing authorisation for a veterinary medicinal product authorised for the treatment of gastric ulcer in dogs (same as the reference veterinary medicinal product). Following the submission of the required technical documentation, company A expands the marketing authorisation to treat gastric ulcer in cats. The technical documentation generated by company A is entitled to 10 years of protection (application of the period of protection in Article 39(1)(a)).

  — If five years after the variation above-referred, Company A develops additional technical information to expand the indication to horses, the technical documentation generated by company A to support the authorisation of the veterinary medicinal product for the treatment of gastric ulcer in cats and horses would be entitled to 14 years of protection (10+4).

([90]) See Article 38(1) of the Regulation.

— Scenario 2: *The holder of a marketing authorisation under Article 18 (or Article 19) is the same as the marketing authorisation holder of the reference veterinary medicinal product ('autogeneric'):* Because the marketing authorisation of the reference veterinary medicinal product and the generic marketing authorisation belong to the SMA, it is not possible for such holder to circumvent the periods of protection of Article 39 by submitting a new application under Article 18 (or Article 19). Thus, the addition of new strengths, pharmaceutical forms and routes of administration cannot give rise to periods of protection under Article 39 as they are covered by the SMA of the reference veterinary medicinal product. However, the addition of new target species gives rise to the additional period of protection set out in Article 40 (provided the relevant conditions provided therein are met).

Example:

— Company B holds a marketing authorisation for a veterinary medicinal product authorised for the treatment of gastric ulcer in dogs. Three years after having obtained the marketing authorisation, Company B expands the marketing authorisation to treat gastric ulcer in cats. Four years after the above-referred variation, Company B expands the marketing authorisation to horses. The technical documentation supporting the marketing authorisation for the treatment of gastric ulcer in dogs, cats and horses benefits from a period of protection of 15 years (10+1+4).

5.5.2. *Technical documentation supporting a new indication*

The period of protection starts counting from the date of the amendment of the marketing authorisation to include the new indication.

Example:

— The holder of a generic marketing authorisation for a veterinary medicinal product intended for the treatment of chickens submits additional studies and trials with a view to adding a new indication (also for the treatment of chickens) five years after the generic marketing authorisation was granted.

— Period of protection = 10 years from the granting of the additional indication (the protection concerns the technical documentation submitted in support of the additional indication only).

5.6. Protection of technical documentation for marketing authorisations granted before 28 January 2022

Technical documentation supporting marketing authorisations granted prior to 28 January 2022 benefits from the data exclusivity and market protection periods provided for under Directive 2001/82/EC.

However, technical documentation supporting variations to those marketing authorisations can benefit from the protection periods foreseen under Regulation (EU) 2019/6 if the relevant conditions foreseen therein are met. Different scenarios can arise, including:

— ***Terms of existing marketing authorisations:*** Article 152(3) provides that the periods of protection set out in Article 39 shall not apply to reference veterinary medicinal products for which an authorisation has been granted before 28 January 2022. This article aims at maintaining the periods of protection applicable under Directive 2001/82/EC in respect of technical documentation submitted to support the terms of marketing authorisations approved prior to 28 January 2022.

It follows that the protection periods foreseen in Article 39 do not apply to technical documentation submitted to support the terms of marketing authorisations approved prior to 28 January 2022. For example, the protection period for the technical documentation submitted in support of a marketing authorisation for a minor animal species granted in January 2019 does not become automatically extended to 14 years.

— ***New indications:*** The concept of SMA set out in Article 38(3) is applicable to marketing authorisations granted prior to 28 January 2022 ([91]). Given that, under the Regulation, the SMA no longer encompasses new indications, technical documentation submitted in support of a new indication that is granted after 28 January 2022 is entitled to a protection period.

([91]) See Article 152(1) of the Regulation.

While the Regulation does not specifically establish the protection periods applicable in the above-referred scenario, the following considerations support that the periods provided for in Article 39 should apply:

— the new indication is not part of the SMA existing prior to 28 January 2022; and

— it would be inconsistent to apply different periods of protection depending on whether the new indication is submitted as variation to an existing marketing authorisation or as a new marketing authorisation.

It is stressed that the period of protection only applies to the technical documentation submitted in support of the relevant indication and that it does not extend the protection applicable to the remaining aspects of the marketing authorisation.

— ***New target species***: Article 40 is applicable since 28 January 2022 to all marketing authorisations, including those granted in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004 ([92]). While the wording of Article 40 is construed by reference to the protection periods laid down in Article 39, in the scenario where a new target species is added to a marketing authorisation granted prior to 28 January 2022, account must be taken also of Article 152(3).

Given that Article 152(3) of the Regulation prevents the reopening of the protection periods in respect of technical documentation submitted to support the terms of marketing authorisations approved prior to 28 January 2022, it should be inferred that, in the scenario at stake, the periods of protections laid down in Article 40 should be applied as follows:

— New target species as foreseen in paragraph (1) of Article 40 (major target species): an additional period of one year to the existing protection period under Directive 2001/82/EC would apply per each additional target species, provided that -in the case of a variation- the application was submitted at least three years before the expiration of the period of protection pursuant to Directive 2001/82/EC.

— New target species as foreseen in paragraph (2) of Article 40 (minor target species): an additional period of four years to the existing protection period under Directive 2001/82/EC would apply per each additional target species, provided that -in the case of a variation- the application was submitted at least three years before the expiration of the period of protection pursuant to Directive 2001/82/EC.

The maximum period of 18 years foreseen in Article 40(3) would apply to the two scenarios above referred.

— ***New pharmaceutical forms, routes of administration or dosage meeting the requirements in Article 40(5):*** After 28 January 2022, the additional protection period of four years afforded to the studies and trials concerned applies - as from the date of the decision approving the corresponding variation or marketing authorisation- to all marketing authorisations, including those granted in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004 ([93]).

It is stressed that the period of protection only applies to the technical documentation submitted in support of the establishment of the relevant pharmaceutical form, route of administration or dosage and that it does not extend the protection applicable to the remaining aspects of the marketing authorisation.

— ***Technical documentation supporting MRLs:*** After 28 January 2022, the additional protection period of five years afforded to the tests, studies and trials concerned as set out in Article 40(4) applies -as from the date of the decision approving the corresponding variation or marketing authorisation- to all marketing authorisations, including those granted in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004 ([94]).

([92]) See Article 152(1) of the Regulation.
([93]) See Article 152(1) of the Regulation.
([94]) See Article 152(1) of the Regulation.

It is stressed that the period of protection only applies to the technical documentation submitted in support of the establishment of the relevant MRL and that it does not extend the protection applicable to the remaining aspects of the marketing authorisation.

6. PROTECTION OF THE ENVIRONMENT AND HUMAN HEALTH CONSIDERATIONS

6.1. Environmental risk assessment

Risks of undesirable effects on the environment are part of the risk profile of veterinary medicinal products ([95]). It follows that a marketing authorisation will be refused if it is considered that the environmental risks, when assessed against the benefits, render the benefit-risk of the veterinary medicinal product negative. Moreover, the Regulation requires that marketing authorisations be refused if the risks to the environment are not sufficiently addressed ([96]).

An environmental risk assessment is part of the safety information that should be provided in the marketing authorisation application.

Applications submitted under Articles 18, 19 or 21 of the Regulation refer to data submitted in support of the marketing authorisation of a previous veterinary medicinal product. In such cases, as the environmental risks have already been assessed for the previously authorised veterinary medicinal product, the submission of an ERA is not required, unless the reference/cross-referred veterinary medicinal product has been authorised prior to 1 October 2005 (See Section 4.5.5.1 and Section 4.8).

6.2. Product information and risk mitigation measures

Environmental risks of veterinary medicinal products are linked to the product composition and the estimated level of exposure which, in turn, is determined by the pharmaceutical form, dose and administration route as well as the intended use (indication and target species). Unless duly justified (*e.g.* different route of administration with significant impact on shedding), information about environmental risks and, where appropriate, risk-minimisation measures for veterinary medicinal products with similar composition should be similar.

In cases where the product information of the reference/cross-referred veterinary medicinal product does not contain information on environmental risks but such information becomes available subsequently (*e.g.* following the assessment of marketing authorisations for similar veterinary medicinal products), the marketing authorisation holder of the relevant reference/cross-referred veterinary medicinal product should update the product information as appropriate ([97]).

6.3. Active substances that are PBTs or vPvBs

Pursuant to Article 37(2)(j), competent authorities cannot grant a marketing authorisation to a veterinary medicinal product intended to be used in food-producing animals if it contains an active substance that is persistent, bioaccumulative and toxic ('PBT') or very persistent and very bioaccumulative ('vPvB'), unless the active substance at stake is essential to prevent or control a serious risk to animal health.

The identification of a given substance as PBT or vPvB should be done in accordance with the identification criteria defined in Annex XIII to Regulation (EC) No 1907/2006 of the European Parliament and of the Council (REACH Regulation) ([98]). Thus, when a substance has been determined to be PBT/vPvB according to REACH identification criteria, such determination is relevant for the purposes of applying Article 37(2)(j).

([95]) See definition of benefit-risk balance set out in Article 4(19) of the Regulation.
([96]) See Article 37(2)(i) of the Regulation.
([97]) See Article 58(4) of the Regulation.
([98]) 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).

The determination of whether the active substance is essential to prevent or control a serious risk to animal health is done in the context of the assessment of the application.

Applications submitted under the Regulation

Article 37(2)(j) is applicable to marketing authorisation applications or to variation applications intended to expand an existing marketing authorisation to a food-producing species. It is stressed that this provision applies also to marketing authorisation applications submitted under Article 18, 19 or 21.

The Regulation does not require an update of the assessment as to whether the active substance continues to be essential after a marketing authorisation is granted. However, holders of marketing authorisations granted after 28 January 2022 are required to comply with the obligations set out in Article 58. Therefore, the considerations in the section below apply *mutatis mutandis* to this scenario.

Marketing authorisations granted prior to the application of the Regulation ([99])

Holders of marketing authorisations granted before Article 37(2)(j) became applicable are not required to demonstrate that PBT or vPvB active substances contained in products intended for food-producing animals are essential. However, as environmental risks and risks to human health are part of the risk profile of veterinary medicinal products, the determination that an active substance is PBT or vPvB may have an impact on the overall benefit-risk of authorised veterinary medicinal products.

While the identification of an active substance as PBT or vPvB does not automatically affect the validity of the existing marketing authorisations, marketing authorisation holders should assess the risk profile of the veterinary medicinal products concerned in light of new evidence and inform the competent authorities if such new information affects the benefit-risk profile of the product ([100]).

In addition, Article 58(4) requires marketing authorisation holders to update their product information according to the latest scientific knowledge. This obligation encompasses also any new information relevant to the impact of the veterinary medicinal product on the environment or public health.

Competent authorities may also request marketing authorisation holders concerned to provide data demonstrating that the benefit-risk balance continues to be positive. Furthermore, the benefit-risk balance could also be re-evaluated in the context of post-authorisation activities or in the context of a Union interest referral.

([99]) This Section is applicable also to marketing authorisations granted after 28 January 2022 the assessment procedure of which has been completed in accordance with Regulation (EC) No 726/2004 or Directive 2001/82/EC.

([100]) See Article 58(10) of the Regulation.

ANNEX

GLOSSARY

1. **Same veterinary medicinal product:**

   Section E3 of the Commission communication on the Community marketing authorisation procedures for medicinal products ([1]) explains that any medicinal product with the same qualitative and quantitative composition in active substances (*i.e.* the same strength) and the same pharmaceutical form is to be considered as the same medicinal product. This definition is relevant to the interplay between the centralised and the national procedures as well as in connection with the operation of the decentralised, mutual recognition or subsequent recognition procedures. In this context, account should be taken also of the definition of 'applicant' and 'marketing authorisation holder' as explained in Section 3.3.

2. **Indication:**

   It is the use that is claimed for a veterinary medicinal product. It can include the treatment, prevention or diagnosis of a disease, zootechnical uses or use for euthanasia.

3. **Presentation:**

   Different pack sizes are considered different presentations; for example, a 30-tablet box and a 60-tablet box of a given veterinary medicinal product are two distinct presentations.

4. **New active substance**:

   A new chemical, biological or radiopharmaceutical veterinary active substance includes:

   (i) a chemical, biological or radiopharmaceutical substance not previously authorised as active substance in a veterinary medicinal product in the European Union, and

   (ii) a chemical, biological or radiopharmaceutical substance previously authorised as active substance in a veterinary medicinal product in the European Union provided that the following conditions are met:

   — For chemical substances: an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as active substance in a veterinary medicinal product in the European Union but differing significantly in properties with regard to safety and/or efficacy from that chemical substance previously authorised.

   — For biological substances: a biological substance previously authorised as active substance in a veterinary medicinal product in the European Union but differing significantly in properties with regard to safety and/or efficacy which is due to differences in one or a combination of the following: in molecular structure, nature of the source material or manufacturing process.

   For immunological veterinary medicinal products: The replacement or addition of a new antigen or a new strain in the case of already authorised immunological veterinary medicinal products should not be considered as replacing/adding a new active substance. New isolates or variants of microorganisms that have been authorised in an immunological veterinary medicinal product are likewise not to be considered as new active substances.

([1]) Official Journal C 229, 22/7/1998 p. 4