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NOTICE TO APPLICANTS

VETERINARY MEDICINAL PRODUCTS

VOLUME 6A
Procedures for marketing authorisation

CHAPTER 1

Marketing authorisation

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CHAPTER 1 Marketing authorisation

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1. INTRODUCTION

1.1. Objectives

The primary purpose of the rules governing veterinary medicinal products is to safeguard public and animal health as well as the environment. However, this objective must be achieved by means which do not hinder the development of the veterinary pharmaceutical industry or trade in veterinary medicinal products within the Union. Thus, the pharmaceutical legislation of the European Union has consistently pursued the twin objectives: the protection of public and animal health and the free movement of veterinary medicinal products.

General principles of the Union veterinary pharmaceutical legislation are given in this Chapter. More detailed explanations concerning the different procedures for marketing authorisation are provided in the relevant chapters of the Notice to Applicants Volume 6A and by the Veterinary Coordination Group for Mutual Recognition and Decentralised Procedures (CMDv) [1].

1.2. Status

This Notice to Applicants has been prepared in accordance with Article 31 of Regulation (EC) No 726/2004[2] and Annex I of Directive 2001/82/EC[3] on the Union code relating to veterinary medicinal products. It is intended to facilitate the interpretation and application of the Union pharmaceutical legislation. It is not legally binding and, in case of doubt, reference should be made to the appropriate Union Directives and Regulations. It is important when reading this text to appreciate that the legal requirements of the Union pharmaceutical legislation must be met and that this Notice to Applicants represents the harmonised view of the Member States, the European Medicines Agency (EMA) and the Commission services on how those requirements may be met.

Guidelines and other interpretative documents to which references are included within this document represent the views of their authors.

References throughout the Notice to Applicants to provisions of Directive 2001/82/EC and Regulation (EC) 726/2004 must be read as references to the directive and the regulation as last amended, unless it is otherwise expressly stated.

2. MARKETING AUTHORISATION

A veterinary medicinal product may only be placed on the market in the European Economic Area (EEA) when a marketing authorisation has been issued by the competent authority of a Member State for its own territory (national authorisation) or when an authorisation has been granted in accordance with Regulation (EC) No 726/2004 for the entire Union (a Union authorisation). The marketing authorisation holder must be established within the EEA.

Immunological veterinary medicinal products may be denied access to the market, according to an individual Member State's national legislation. Indeed, Article 71 of Directive 2001/82/EC, provides that the manufacture, import, possession, sale, supply and/or use of immunological veterinary medicinal products may be prohibited, if the administration of the concerned immunological product

[1] http://www.hma.eu/veterinarymedicines.html
[2] OJ L 136, 30.4.2004, p.1
[3] OJ L 311, 28.11.2001, p. 1

conflicts with the implementation of a national programme for the diagnosis, control or eradication of animal disease or if the disease against which the immunological product conveys immunity is largely absent from the whole or a defined part of the Member State. Such a prohibition may apply to the whole or only to part of the territory of the Member State.

Article 54 of the Treaty of the functioning of the European Union (Chapter 2 Right of establishment) reads:

> *'Companies or firms formed in accordance with the law of a Member State and having their registered office, central administration or principal place of business within the Union must, for the purposes of this Chapter, be treated in the same way as natural persons who are nationals of Member States.*
> *"Companies or firms" means companies or firms constituted under civil or commercial law, including co-operative societies, and other legal persons governed by public or private law, save for those which are non-profit-making'.*

For the purpose of applying this definition in the context of the pharmaceutical legislation it should be clarified that 'non profit-making' organisations can be marketing authorisation holders.

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

(i) a decision granting the marketing authorisation issued by the relevant authority; and
(ii) a technical dossier with the data submitted by the applicant in accordance with Articles 12(3) to 14 of Directive 2001/82/EC and Annex I thereto, or Article 31(2) of Regulation (EC) No 726/2004.

European Economic Area (EEA)

Norway, Iceland and Liechtenstein form the EEA with the 28 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 the Union procedures. Where in this Chapter reference is made to Member States of the Union this should be read to include 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° 74/1999 of the EEA Joint Committee when decisions on approval of medicinal products are taken by the Union, Norway, Iceland and Liechtenstein will take corresponding decisions on the basis of relevant acts. Consequently, these States are concerned with the single European market for medicinal products. Therefore, where in Article 2 of Regulation (EC) No 726/2004 and Article 12 of Directive 2001/82/EC, reference is made to the applicant being established in the Union, this is extended to include Norway, Iceland and Liechtenstein.

The marketing authorisations granted by Norway, Iceland and Liechtenstein are eligible for the mutual recognition procedure in the same way as the marketing authorisations granted by Member States.

Liechtenstein

Since 1st December 2010 the treaty between Liechtenstein and Austria about automatic recognition of the Marketing Authorisations granted via Mutual Recognition Procedure (MRP) or Decentralised

Procedure (DCP) is operational[4]. This allows Liechtenstein to use Marketing Authorisations granted by Austria provided the applicants have identified Liechtenstein as CMS in the application form submitted with MRP or DCP applications. 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 EU legislation and in particular can be considered as a starting point for the purposes of data exclusivity/market protection in the EU.

Further, in application of a bilateral agreement between Switzerland and Liechtenstein, a Swiss marketing authorisation is automatically effective in Liechtenstein. 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, while Switzerland does not apply the EU pharmaceutical acquis, cannot be considered as a marketing authorisation granted in accordance with the pharmaceutical acquis for the purpose of EU legislation and in particular cannot be considered as a starting point for the purposes of data exclusivity/market protection in the EU (see part 6 on data exclusivity/market protection).

Monaco

An agreement between the Union and the Principality of Monaco entered into force on 1 May 2004, 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[5]. On the basis of this agreement and the special arrangements agreed between France and the Principality of Monaco in an agreement of 6 January 2003, the French authorities assume the role of competent authorities as far as the application of the medicinal products legislation to products manufactured in Monaco is concerned. The French authorities are responsible for the issue of marketing authorisations for Monaco and conduct inspections on manufacturing sites of 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 may be regarded as released in France, though the place of manufacturing sites is in Monaco.

2.1. National authorisations

The competent authorities of the Member States are responsible for granting marketing authorisations for veterinary medicinal products which are placed on their markets, except for veterinary medicinal products which are authorised under Regulation (EC) No 726/2004 (“Union Authorisations”).

In order to obtain a national marketing authorisation, an application must be submitted to the competent authority of the Member State.

In cases where national authorisations are requested for the same veterinary medicinal product[6] in more than one Member State and the marketing authorisation holder has received a marketing authorisation in a Member State, the applicant/marketing authorisation holder shall submit an application in the Member

[4] 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).
[5] O.J. 19.12.03 L 332/42
[6] For an explanation of what constitutes the “same medicinal product” in this context, see section E.3 of Commission communication on the Community marketing authorisation procedures for medicinal products (Official Journal C 229, 22/7/1998 p. 4 - 17).

States concerned using the procedure of mutual recognition. The Member States concerned should then recognise the marketing authorisation already granted by the Reference Member State and authorise the marketing of the product on their national territory.

If no marketing authorisation has been granted in the Union, the applicant may make use of a decentralised procedure and submit an application in all the Member States where it intends to obtain a marketing authorisation at the same time, and choose one of them as Reference Member State. Based on the assessment report prepared by the Reference Member State and any comments made by the Concerned Member State marketing authorisation should be granted in accordance with the decision taken by the Reference Member State and Concerned Member State in this decentralised procedure.

The marketing authorisation must contain the summary of product characteristics according to Article 14 of Directive 2001/82/EC and the labelling and/or the package leaflet according to Articles 58 to 61.

2.2. Union authorisations

The Union will grant marketing authorisations for veterinary medicinal products:

- referred to in the Annex to Regulation (EC) No 726/2004, which may only be authorised via the centralised procedure (mandatory scope);

- referred to in Article 3(2) of Regulation (EC) No 726/2004, relating to products containing new active substances, products which constitute a significant therapeutic, scientific or technical innovation or products for which the granting of a Union authorisation would be in the interest of patients or animal health at Union level. The applicant has to request confirmation that the product is eligible for evaluation through the centralised procedure (optional scope) and the EMA will decide on the matter; and

- a generic veterinary medicinal product of a centrally authorised veterinary medicinal product if not using the option in Article 3(3) of Regulation (EC) No 726/2004.

In order to obtain a Union authorisation, an application must be submitted to the EMA. See also section 3.1 of this Chapter.

The scientific evaluation of the application is carried out within the Committee for Medicinal Products for Veterinary Use (CVMP) of the EMA, and a scientific opinion is prepared. The opinion is sent to the European Commission which drafts a Decision. Having consulted the Member States through the relevant Standing Committee, the Commission adopts the Decision and grants a marketing authorisation.

Such a 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.

The marketing authorisation shall contain the summary of product characteristics according to Article 14 of Directive 2001/82/EC and the labelling and the package leaflet according to Articles 58 to 61.

Once a central marketing authorisation has been issued, the maintenance of existing national marketing authorisation or the issuing of new national marketing authorisations for the same veterinary medicinal product could be envisaged only as long as the therapeutic indications are different in national and central marketing authorisations. However, the same marketing authorisation holder can have a national generic of their centrally authorised veterinary medicinal product.

Indeed, if a product falls under the optional scope of the centralised procedure (Article 3(2) of Regulation (EC) No. 726/2004), the applicant has the choice of using either the centralised or the national (decentralised/mutual recognition) procedure for the same veterinary medicinal product. The *"Communication on the Community marketing authorisation procedures for medicinal products"*[7] clarifies that this choice does not allow both a central and a national marketing authorisation to co-exist simultaneously for the same product and that once a central marketing authorisation has been issued, there is no room for an additional scientific evaluation and regulatory decision for the same medicinal product (see in particular point A.2 and conclusion of the Communication). If such situation would occur the Commission would consider the need for a referral procedure.

The only exception for possible co-existence of central and national marketing authorisation that the Communication provides concern cases where there are different therapeutic indications (see point A.2.b).

2.3. Notion of 'global marketing authorisation'[8]

Article 5(1) second subparagraph of Directive 2001/82/EC provides that when a veterinary medicinal product has been granted an initial marketing authorisation, any additional species, strengths, pharmaceutical forms, administration routes, presentations as well as any variations and extensions shall also be granted an authorisation or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 13(1) of the Directive, which relates to the procedure for the authorisation of generic veterinary products and lays down rules on data and market exclusivity and on the so-called European Reference Product.

Thus, the global marketing authorisation contains the initial authorisation and all variations and extensions thereof, as well as any additional species, strengths, pharmaceutical forms, administration routes or presentations authorised through separate procedures, including in different Member States within the EU and under a different name, granted to the marketing authorisation holder of the initial authorisation. Where a product is initially authorised nationally and, subsequently, an additional strength, pharmaceutical form, administration route or presentation is authorised through the centralised procedure, this is also be part of the same global marketing authorisation.

The implications of the notion of global marketing authorisation for the purpose of the application of rules on data and market exclusivity are referred to in section 6 below.

Multiple applications of the same marketing authorisation holder are covered by the notion of 'global marketing authorisation'.

To determine the notion of same marketing authorisation holder or applicant in this context, see section 2.8.

1. If the veterinary medicinal product being assessed contains a modification of an existing active substance, it should be clarified during the marketing authorisation procedure whether the product contains a new active substance or not. This clarification impacts on the existence or not of a global marketing authorisation if the veterinary medicinal products belong to the same marketing

[7] Commission Communication 98/C229/03

[8] Global Marketing Authorisation has to be read in the light of Article 5(1) of Directive 2001/82/EC; it does not mean a 'worldwide Marketing Authorisation'.

authorisation holder. Request for a new active substance claim should be submitted within the initial marketing authorisation application for veterinary medicinal product containing the modified substance and will not be considered retroactively. This assessment is to be done in accordance with the definition of a new active substance provided in Annex I[9] at the end of this Chapter and the conclusion should be reflected at least in the assessment report. If the assessment report does not indicate that the product contains a new active substance, it will be considered that the product at stake contains the same active substance and belongs to the global marketing authorisation of the already authorised medicinal product(s) as described in Article 5(1) of Directive 2001/82/EC.

Example: Active substance A in VMP 1→ active substance A' in VMP 2

2. If the veterinary medicinal product being assessed contains within the same pharmaceutical form a combination of active substances, it will form a new and unique veterinary medicinal product requiring a separate marketing authorisation, regardless whether all of the active substances contained therein were already authorised in a veterinary medicinal product or not. In its application for the new combination, the applicant must demonstrate that each active substance has a documented therapeutic contribution within the combination and therefore all compounds are different active substance[10]. The authorisation for this new combination veterinary medicinal product is not considered to fall within the scope of the global marketing authorisations of the already authorised veterinary medicinal product(s) as described in Article 5(1) of Directive 2001/82/EC.

   Examples:

   Active substance A in VMP1, active substance B in VMP2 → Active substances A+B in VMP3

   Active substances A+B in VMP1, Active substances C+D in VMP2→ Active substances A+C in VMP3

   Active substances A+B in VMP1, Active substance C in VMP2 → Active substances A+C in VMP3

   Active substances A+B in VMP1→ Active substance A+C in VMP2

3. If the veterinary medicinal product being assessed contains only one active substance which was part of an authorised combination product, the new veterinary medicinal product will form a new and unique veterinary medicinal product requiring a separate marketing authorisation. Considering that during the assessment procedure of the already authorised combination product, the marketing authorisation holder had demonstrated that each substance of the fixed combination has a documented therapeutic contribution within the combination and therefore all compounds are different active substances[10], the authorisation for the new veterinary medicinal product is not considered to fall within the scope of the global marketing authorisations of the already authorised combination veterinary medicinal product as described in Article 5(1) of Directive 2001/82/EC.

[9] Annex I at the end of this Chapter applies for the purposes of application of Article 5 and Article 13 of Directive 2001/82/EC. However, for the purposes of Article 3(2) of Regulation (EC) No 726/2004 a "new active substance" is defined in paragraph 3 of the Annex of that Regulation.

[10] See DRAFT Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of New Active 5 Substance (NAS) status of chemical substances [http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/04/WC500186193.pdf].

Example: Active substances A+B in VMP 1 → Active substance A in VMP2

2.4. Validity of the marketing authorisation

2.4.1 Renewal

Marketing authorisations granted in the Union shall have an initial duration of five years (Articles 39(1) of Regulation (EC) No 726/2004 and 28(1) of Directive 2001/82/EC). After these five years, the marketing authorisation may be renewed on the basis of a re-evaluation of the benefit/risk balance. To this end, the marketing authorisation holder shall provide the EMA or the national competent authority with an application form together with a consolidated list of all documents submitted in respect of quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, at least six months before the marketing authorisation ceases to be valid (Articles 39(2) of Regulation (EC) No 726/2004 and 28(2) of Directive 2001/82/EC). Once renewed, the marketing authorisation shall be valid for an unlimited period unless the Commission or the national competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal (Articles 39(3) of Regulation (EC) No 726/2004 and 28(3) of Directive 2001/82/EC).

While the submission of the file should take place at least six months prior to the expiry of the marketing authorisation, premature submissions should be avoided. In this regard, it is noted that the renewal should take place upon the expiry of the period of five years and that such decision will be based on the consolidated file submitted by the marketing authorisation holder for this purpose, demonstrating that the benefit/risk is positive. A submission that is made too prematurely may not be sufficiently up to date for the Commission/Competent Authorities to adopt a decision on the renewal.

When marketing authorisations are issued using the repeat use mutual recognition procedure where the original marketing authorisation has not undergone a renewal, the reference member state, the concerned member states involved in the repeat use procedure and the applicant could agree the renewal period of the new marketing authorisation to be shortened in order to align it with the initial marketing authorisation.

Recommendations regarding the content of the consolidated application for the renewal are provided in the Guideline on the Processing of Renewals in the Centralised Procedure[11] and CMDv Best Practice Guide for handling renewals in the MRP/DCP[12].

2.4.2 Cessation of the marketing authorisation if the veterinary medicinal product is not marketed

According to Article 28(4) to (6) of Directive 2001/82/EC and Article 39(4) to (6) of Regulation (EC) No 726/2004 any authorisation which within three years of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State or on the Union market shall cease to be valid. When an authorised product previously placed on the market in the authorising Member State or in the Union is no longer actually present on the market for a period of three consecutive years, the authorisation for that product shall cease to be valid. The competent authority

[11] http://ec.europa.eu/health/files/eudralex/vol-6/ne_en_doc/v6c_renewals_12_2005_en.pdf
[12] http://www.hma.eu/fileadmin/_migrated/content_uploads/151214_CMDv_BPG-007_Renewals.pdf

may, in exceptional circumstances and on human or animal health grounds grant exemptions. Such exemptions must be duly justified.

The determination of the start of the three year period from the granting of the marketing authorisation should be the date when the veterinary medicinal product can be marketed by the marketing authorisation holder, taking into account, e.g. the market exclusivity and other protection rules which have to be respected.

The absence of the veterinary medicinal product from the market must be for three consecutive years, therefore in case the veterinary medicinal product would be put back on the market, the period of three years would restart. This situation may occur several times.

The marketing authorisation will remain valid if at least one presentation of the veterinary medicinal product is placed on the market and if at least one pack-size of the existing pack-sizes for that presentation is marketed. For the purposes of the application of these rules, a marketing authorisation comprises the initial authorisation and all variations and extensions granted to the marketing authorisation holder under the same name.

For the purposes of the application of Article 28(4) to (6) of Directive 2001/82/EC and Article 39(4) to (6) of Regulation (EC) No 726/2004, a veterinary medicinal product is “placed on the market” at the date of release into the distribution chain. It is the date when the product comes out of the control of the marketing authorisation holder.

For centrally authorised veterinary medicinal products “placed on the Union market” means that the veterinary medicinal product is at least marketed in one Member State of the Union. For nationally authorised products “placed on the market in the authorising Member State” means that the veterinary medicinal product is on the market of the Member State which has granted the marketing authorisation.

This is independent of the authorisation procedure used (decentralised, mutual recognition or purely national procedure). A veterinary medicinal product ceases to be placed on the market when the marketing authorisation holder ceases to release it into the distribution chain. Information regarding the placing of a veterinary medicinal product on the market should be provided in accordance with Article 27a of Directive 2001/82/EC and Article 38 of Regulation EC No 726/2004. After a marketing authorisation has been granted, the holder of the authorisation shall inform the competent authority of the authorising Member State or the EMA of the date of actual marketing of the veterinary medicinal product in that Member State or in the Union, taking into account the various presentations authorised. The holder shall also notify the national competent authority or the EMA if the product ceases to be placed on the market, either temporarily or permanently. Such notification shall, otherwise than in exceptional circumstances, be made no less than 2 months before the interruption in the placing on the market of the product. The marketing authorisation holder must inform the national competent authorities or the EMA of the reasons for such action. Upon request by the national competent authority or the EMA, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the national competent authority or the EMA with all data relating to the volume of sales of the veterinary medicinal product, and any data in his possession relating to the volume of prescriptions.´

2.4.3 Suspension or withdrawal of veterinary medicinal product and voluntary withdrawal of marketing authorisation

A marketing authorisation holder must notify respectively the Member States concerned/EMA of any decision taken to suspend the marketing or to withdraw a veterinary medicinal product from the market, together with the reasons for such decision.

A marketing authorisation holder must also notify its intention to withdraw a marketing authorisation, or not request the renewal of a marketing authorisation together with the reasons for such a decision.

2.5. 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 trade mark or the name of the marketing authorisation holder.

See also revised "Guideline on the acceptability of invented names for veterinary medicinal products processed through the centralised procedure"[13].

For applications through the mutual recognition or decentralised procedure, it is recommended whenever feasible that the same name for a given veterinary medicinal product should be used in all Member States. If a different name is to be used, it should be quoted in a covering letter from the applicant to the relevant competent authorities.

Where a generic of a veterinary medicinal product authorised through the centralised procedure is authorised by the competent authorities of the Member States in accordance with Article 13(1) of the Directive 2001/82/EC, the generic veterinary medicinal product has to be authorised under the same name in all the Member States where the application has been made. For these purposes, all the linguistic versions of the international non-proprietary name shall be considered to be the same name (Article 3(3) of Regulation (EC) No 726/2004).

2.6. Transparency

In accordance with Article 25 of Directive 2001/82/EC, the national competent authority is obliged to make publicly available the marketing authorisation together with the summary of product characteristics and any possible conditions to the marketing authorisation for each veterinary medicinal product that it has authorised and the assessment report and its reasons for the opinion after deleting any information of a commercially confidential nature.

As regards products authorised through the centralised procedure, notification of the marketing authorisation shall be published in the Official Journal of the European Union and the EMA shall publish the assessment report of the CVMP together with the reason for its opinion, after deletion of any information of a commercially confidential nature (Article 38 of Regulation (EC) No 726/2004).

2.7. Multiple applications

In the framework of the centralised procedure only one marketing authorisation may be granted to an applicant for a specific veterinary medicinal product. However, according to Article 82(1) 2nd subparagraph of Regulation (EC) 726/2004 the same applicant can submit more than one application for the same medicinal product when there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health-care professionals and/or patients or for co-marketing reasons. In such case, the Commission will inform the applicant whether the conditions are met before he submits his application to the EMA. For further details see the Commission services note on the handling of Duplicate Marketing Authorisation Application[14].

There are no corresponding provisions in Directive 2001/82/EC that apply to the mutual recognition and decentralised procedures. In such circumstances, the acceptance of multiple applications in mutual recognition and decentralised procedures should, however, not be used to undermine harmonisation at Union level or to circumvent the application of Union legislation. In particular, multiple applications should not lead to applications for the same veterinary medicinal product being submitted in different Member

[13] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500005231.pdf
[14] https://ec.europa.eu/health/sites/health/files/files/latest_news/2011_09_duplicates_note_upd_01.pdf

States and handled outside the principles of mutual recognition laid down in chapter 4 of Directive 2001/82/EC.

To avoid such an effect, the following principles should be observed:

- reference to any authorisation obtained for that veterinary medicinal product should be provided with the application for a marketing authorisation;

- as far as possible, the same Reference Member State should be used in case of multiple applications;

- Article 22 should be relied on to avoid that multiple applications are used to obtain marketing authorisations for the same veterinary medicinal product in different Member States outside the procedural framework of chapter 4 of Directive 2001/82/EC; the applicant may decide whether the mutual recognition procedure or the decentralised procedure is used for obtaining the multiple marketing authorisations.

See CMDv Recommendation on duplicate applications in mutual recognition and decentralised procedures available at CMDv website (http://www.hma.eu/veterinarymedicines.html).

2.8. Concept of "applicant" and "marketing authorisation holder"

The concept of "applicant" and "marketing authorisation holder" are important for the application of the global marketing authorisation definition and also in other contexts, such as the submission of applications under Directive 2001/82/EC, the submission of variations under work-sharing procedures or the submission of multiple marketing authorisations under Article 82(1) of Regulation (EC) No 726/2004 as well as the submission of multiple applications in mutual recognition and decentralised procedures. The definition of "applicant" provided for in the 1998 Commission Communication remains applicable.

An "applicant" and "marketing authorisation holder" can be a physical or legal entity. However, for the purposes of the application of the pharmaceuticals rules, having a distinct legal personality does not necessarily entail that each entity can be considered as a distinct applicant or marketing authorisation holder to the other one.

In particular, it is noted:

- 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.

- 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 for the purposes of the application of the pharmaceuticals rules regarding that 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.

3. MARKETING AUTHORISATION PROCEDURES

3.1. Centralised procedure

A marketing authorisation granted under the centralised procedure is valid for the entire EU market, which means the medicinal product may be put on the market in all Member States. For veterinary medicinal products which fall within the mandatory scope of the centralised procedure in accordance with the Annex to Regulation (EC) No 726/2004, the application is submitted to the EMA.

An application may likewise be submitted to the EMA for veterinary medicinal products which fall within the optional scope of the centralised procedure in accordance with Article 3(2) and 3(3) of Regulation (EC) No 726/2004 where the applicant wishes to obtain a Union marketing authorisation.

In particular, applications on the basis of Article 13 of Directive 2001/82/EC, where the reference veterinary medicinal product is centrally authorised may be submitted via the centralised procedure. Alternatively, they may be authorised by the competent authorities of the Member States through a national, mutual recognition procedure or decentralised procedure provided that the conditions, laid down in Article 3(3) of the Regulation (EC) No 726/2004 are met (e.g. summary of product characteristics is consistent with that of the centrally authorised medicinal product, same name in all the Member States).

Those Similar biological ("biosimilar") medicinal products which are developed by means of one of the biotechnological processes listed in the Annex to Regulation(EC) No 726/2004 must however be authorised via the centralised procedure.

Following the scientific evaluation and upon receipt of the opinion, the European Commission drafts a decision on a Union marketing authorisation and, after consulting the Standing Committee for Veterinary Medicinal Products, grants a marketing authorisation. The Commission Decision shall, based on the scientific recommendation of the CVMP, specify in its Annexes the conditions or restrictions regarding supply and use, including the following sub-categories: medicinal product subject to medical prescription, medicinal product not subject to prescription. Any restriction foreseen in supply and use reflected in Section 4.2 of the Summary of Product Characteristics will be translated into the legal status in Annex II.

3.2. Decentralised procedure and mutual recognition procedure

Both the decentralised and the mutual recognition procedures are based on the recognition by national competent authorities of an assessment performed by the authorities of one Member State.

According to the European Court of Justice, *"[…] Article 28 of Directive 2001/83/EC […] confers a Member State in receipt of an application for mutual recognition only a very limited discretion in relation to the reasons for which that Member State is entitled to refuse to recognise the marketing authorisation in question. In particular, as regards any assessment going beyond the verification of the validity of the application with regard to the conditions laid down in Article 32, the Member State concerned, except where there is a risk to public health, must rely on the assessments and scientific evaluations carried out by the Reference Member State"*[15].

Although the facts of the case relate to a MRP under Directive 2001/83/EC, the ECJ is interpreting Article 28(4) of Directive 2001/83/EC which applies both to MRP and DCP [16]. It is *mutatis mutandis* applicable to MRP and DCP under Directive 2001/82/EC.

To allow operation of the system, applicants for marketing authorisation are obliged to include in their applications copies of any authorisation previously obtained in other Member States as well as a list of those Member States in which an application for authorisation is under examination (Article 12(3)(n) of Directive 2001/82/EC). In addition, the dossier on which the marketing authorisation is based must be regularly updated (see section 5.1.1 below).

[15] §41 of ECJ C-452/06
[16] ECJ C-145/11, (cf. para. 39).

3.2.1. Decentralised procedure

For veterinary medicinal products not falling within the mandatory scope of the centralised procedure, the applicant may request one or more Concerned Member State(s) to approve a draft assessment report, summary of product characteristics, labelling and package leaflet as proposed by the chosen Reference Member State. An application is submitted to the competent authorities of the Reference Member State and the Concerned Member State(s), together with the information and particulars referred to in Articles 12, 13, 13a, 13b, 13c, 13d and 14 of Directive 2001/82/EC. The applicant must give an assurance that the dossier, including the proposed summary of product characteristics, labelling and package leaflet, is identical as submitted in all Member States concerned (Reference Member State and Concerned Member State). Differences in proposed prescription status and names of the veterinary medicinal product are acceptable, in line with national rules in force.

At the end of the decentralised procedure with a positive agreement, a national marketing authorisation will be issued in the Reference Member State and the Concerned Member State. The harmonisation is maintained through the procedures of Regulation (EC) No 1234/2008 for the examination of variations and the use of the decentralised and mutual recognition procedures for extensions.

3.2.2 Mutual recognition procedure

This procedure is based on the mutual recognition by Concerned Member State of a national marketing authorisation granted by the Reference Member State. The Concerned Member State refers to the Reference Member State that issued the national marketing authorisation on which the mutual recognition procedure is based. At the end of the mutual recognition procedure, a national marketing authorisation will be issued in the Concerned Member State.

The harmonisation is maintained through the procedures of Regulation (EC) No 1234/2008 for the examination of variations and the use of the decentralised and mutual recognition procedures for extensions and renewals.

3.3. Procedure for homeopathic veterinary medicinal products

According to Article 16 of Directive 2001/82/EC, Member States have to ensure that homeopathic veterinary medicinal products placed on the market within the Union are registered according to Article 17 and 18 or authorised according to Article 19 of that directive.

It follows from Article 1(8) of Directive 2001/82/EC, as amended that a homeopathic veterinary medicinal product is any medicinal product prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia[17] or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States. A homeopathic medicinal product may contain a number of principles.

Based on the particular characteristics of homeopathic veterinary medicinal products, Articles 17 and 18 of Directive 2001/82/EC provide for a simplified registration procedure for those homeopathic medicinal products which are placed on the market without therapeutic indication, administered by a route described in the European Pharmacopoeia or a pharmacopoeia of a Member State and where a sufficient degree of dilution can guarantee the safety of the product (no more than 1 part per 10 000 of the mother tincture) . Furthermore, according to Article 16(2) of Directive 2001/82/EC, the Member States are obliged to establish the abovementioned simplified registration procedure for the homeopathic

[17] See section 5.1.2

medicinal products referred to in Article 17.

However, if a veterinary homeopathic medicinal product is not eligible for the simplified registration procedure, before placing the product on the market of a Member State, it has to be authorised, regardless of the marketing authorisation procedure in accordance with Articles 12, 13a, 13b, 13c and 14 of Directive 2001/82/EC, as amended as appropriate.

Nevertheless, in accordance with Article 19(2) of Directive 2001/82/EC, in case of a national procedure, a Member State may introduce or retain in its territory specific rules for the safety tests and pre-clinical tests and clinical trials of homeopathic medicinal products intended for pet species and non-food-producing exotic species *other than those referred to in Article 17(1)* in accordance with the principles and characteristics of homeopathy as practised in that Member State. Accordingly, if the homeopathic veterinary medicinal product is eligible for the simplified registration procedure, the Member State cannot introduce other requirements than the ones following from Articles 17 and 18 of Directive 2001/82/EC.

An application under the simplified registration procedure may cover a series of veterinary medicinal products derived from the same homeopathic stock or stocks. The simplified registration procedure allows the registration of homeopathic veterinary medicinal products, provided that they are administered by a route described in the European Pharmacopoeia, that no specific therapeutic indication appears on the labelling of the medicinal product or in any information relating thereto, and that there is a sufficient degree of dilution to guarantee the safety of the medicinal product.

In addition, in order to demonstrate, in particular, the pharmaceutical quality and the batch-to batch homogeneity of the products concerned, the applicant has to provide the documents set up by Article 18 of Directive 2001/82/EC.

According to Article 17(2) of Directive 2001/82/EC the criteria and rules of procedure provided for in chapter 3 (except article 25) of that directive apply by analogy to the special, simplified registration procedure for homeopathic veterinary medicinal products. Hence, an application under the simplified registration procedure must be assessed within 210 days after the submission of a valid application.

However, it follows from Article 43 of Directive 2001/82/EC that Article 33(4), (5) and (6) and Articles 34 to 38 do not apply to the homeopathic veterinary medicinal products registered under the simplified registration procedure. Consequently, if a Member State cannot approve the assessment under the simplified registration procedure conducted by the Reference Member State, on the grounds of potential serious risk to public health, and the Member States fail to reach an agreement in the coordination group, the case will not be submitted to the EMA for arbitration. Each Member State will therefore take its own decision.

According to Article 64 of Directive 2001/82/EC, homeopathic veterinary medicinal products must be labelled in accordance with the provisions of title V of Directive 2001/82/EC on the labelling and package leaflet, and be identified by a reference on their labels, in clear and legible form, to their homeopathic nature. However, it follows from Article 64(2) of Directive 2001/82/EC that in addition to the clear mention of the words *"homeopathic veterinary medicinal product without approved therapeutic indications"*, the labelling and, where appropriate, the package leaflet for homeopathic veterinary medicinal products authorised under the simplified registration procedure must bear no other information than those mentioned in Article 64 of that Directive.

3.4. Independent national procedures

Independent national procedures will continue, but are strictly limited to veterinary medicinal products which are not to be authorised in more than one Member State.

Independent national procedures can also be used for extensions of authorised veterinary medicinal products as far as no a priori harmonisation has been achieved for the initial marketing authorisation (see section 7 of this Chapter).

4. UNION REFERRALS

In certain circumstances in the framework of marketing authorisations granted by the competent authorities of the Member States, a Union procedure, involving a scientific opinion by the CVMP leading to the adoption of a Commission decision addressed to the Member States can be triggered. These are the commonly called Union “referrals”, which may be triggered in the following situations:

1. in accordance with Article 33(4) of Directive 2001/82/EC (‘Mutual Recognition and Decentralised referral’);
2. in accordance with Article 34 of Directive 2001/82/EC (‘Harmonisation referral’);
3. in accordance with Article 35 of Directive 2001/82/EC (‘Union interest referral’);
4. in accordance with Article 78 of Directive 2001/82/EC (‘Urgent Union procedure’);
5. in accordance with Article 45 of Regulation (EC) No 726/2004 (‘Procedure for centrally authorised products only’);
6. in accordance with Article 13 of Commission Regulation (EC) No 1234/2008 (‘Referral when there is disagreement between Member States on a type II variation procedure’).

For further details see Notice to Applicants Volume 6A Chapter 3.

5. APPLICATION TYPES

The legal requirements and the procedures for making an application for a marketing authorisation are set out in Directive 2001/82/EC and in Regulation (EC) No 726/2004.

A brief description of these requirements and procedures is set out in this Chapter for applications:

1. according to Article 12(3) of Directive 2001/82/EC (see section 5.2 below);
2. according to Article 13 of Directive 2001/82/EC, relating to generic veterinary medicinal product, "hybrid" veterinary medicinal products and similar biological veterinary medicinal products (see section 5.3 below);
3. according to Article 13a of Directive 2001/82/EC, relating to applications relying on well-established veterinary use supported by bibliographic literature (see section 5.4 below);
4. according to Article 13b of Directive 2001/82/EC relating to applications for new fixed combination products (see section 5.5 below);
5. according to Article 13c of Directive 2001/82/EC relating to informed consent from a marketing authorisation holder for an authorised veterinary medicinal product (see section 5.6 below);
6. according to Article 13d of Directive 2001/82/EC concerning the derogation for immunological veterinary medicinal products; the applicant shall not be required to provide the results of certain

field trials on the target species if these trials cannot be carried out for duly substantiated reasons, in particular on account of other Union provisions (see section 5.7 below).

It is important, however, that the requirements and procedures are not confused with the presentation of the application dossier, on which guidance is given in "The Rules Governing Medicinal Products in the European Union, Volume 6B Notice to Applicants: Presentation and content of the dossier".

It must be stressed that, irrespective of the legal basis of the application, assessment reports such as the EPAR for EU marketing authorisations or similar summary reports from competent authorities inside and outside the EU which are made publicly available by competent authorities for reasons of transparency cannot be considered to meet the requirements of Annex I of Directive 2001/82/EC.

5.1. Basic requirements

5.1.1. Continuous update of marketing authorisation

The main principle underlying Union pharmaceutical legislation is the protection of human and animal health and the environment. Marketing authorisations for veterinary medicinal products are dynamic and not static and the dossier underlying a marketing authorisation must be regularly updated in order to ensure that scientific progress and new regulatory requirements are respected, in accordance with Article 27 of Directive 2001/82/EC, Annex I to Directive 2001/82/EC and Article 41 of Regulation (EC) No 726/2004. In particular, any information which may influence the evaluation of the benefits and the risks of the veterinary medicinal product must be promptly supplied. In this regard, holders of marketing authorisations granted in accordance with Article 13 or 13c of Directive 2001/82/EC should, where applicable, introduce variations swiftly whenever the marketing authorisation of the reference veterinary medicinal product or of the "original" veterinary medicinal product is changed to address a safety or efficacy concern and such changes have relevance for the 'generic' or 'informed consent' product respectively.

In addition, the marketing authorisation holder should inform the competent authorities relating to any pharmacovigilance concerns according to Article 75 of Directive 2001/82/EC.

5.1.2. Standardised nomenclatures and quality standards

The European Directorate for the Quality of Medicines (EDQM) of the Council of Europe provides standardised nomenclatures and quality of standards for medicinal substances and products which are published in the European Pharmacopoeia.

5.1.3. Standard Terms

The standard terms for pharmaceutical forms and routes of administration are contained in the “List of Standard Terms for pharmaceutical dosage forms, routes of administration and containers” published by the European Directorate for the Quality of Medicines (EDQM) of the Council of Europe.

5.1.4. Evaluation of the potential environmental risk

Article 12(3)(j) of Directive 2001/82/EC requires the evaluation of the potential environmental risks posed by the veterinary medicinal product. In fulfilling this all applicants/marketing authorisation holders should take into account the Guidelines on environmental impact assessment (EIA) for veterinary medicinal products – phase I and II http://www.ema.europa.eu/ema (Veterinary Regulatory > Research and development > Scientific guidelines > Safety and residues > Pharmaceuticals > Environmental risk assessment).

5.2. Applications according to Article 12(3) of Directive 2001/82/EC

5.2.1 Stand-alone application

An application for marketing authorisation must be accompanied by the particulars and documents set out in Article 12(3) of Directive 2001/82/EC and therefore the following documentation must be included in the dossier:

- administrative,
- pharmaceutical (physico-chemical, biological or microbiological) tests,
- safety tests and residue tests,
- preclinical and clinical trials,
- tests assessing the potential risk posed by the veterinary medicinal product to the environment.

For such applications, the relevant published literature also has to be submitted and these scientific publications can be used as supportive data.

5.2.2 "Mixed application"

Where Part 3 and/or 4 of the application for marketing authorisation consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references this kind of application has also to be submitted according to Article 12(3) of Directive 2001/82/EC. See also Annex I to Directive 2001/82/EC, Title III, section 7 on mixed marketing authorisation application.

5.3. Applications according to Article 13 of Directive 2001/82/EC

5.3.1 General concepts

5.3.1.1 Reference veterinary medicinal product

For data exclusivity and market protection period of the reference veterinary medicinal product, see section 6.

A definition of reference veterinary medicinal product is given in Article 13(2)(a) of Directive 2001/82/EC, which provides that the reference veterinary medicinal product means a veterinary medicinal product authorised under Article 5, in accordance with the provisions of Article 12. Article 5 lays down the principle that no veterinary medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued. In turn, Article 12 provides that in order to obtain a marketing authorisation an application must be made to the competent authority by an applicant established in the Union and containing the particulars and documents listed in that provision.

Besides, Article 5(1) contains the notion of global marketing authorisation as the initial marketing authorisation and any additional target species, strengths, pharmaceutical forms, administration routes or presentations, as well as any variations and extensions. Each product within the global marketing authorisation may be chosen as the reference veterinary medicinal product notwithstanding the requirement of articles 13.

Reference can be made to the dossier of a reference veterinary medicinal product for which a marketing authorisation has been/is granted in the Union in accordance with Articles 12(3), 13a, 13b or 13c of Directive 2001/82. The application form in part IA of the dossier for the generic product should clearly identify the reference product in order for the Reference Member State, in case of MRP/DCP, to prepare the assessment report.
On the contrary, reference cannot be made to the dossier of a veterinary medicinal product for which a marketing authorisation has been granted in the Union in accordance with Article 13(1).

Data supporting applications approved under Article 13(3) (e.g. new target species, indications, strength, route of administration, pharmaceutical form) do not benefit from periods of exclusivity, except when specifically provided for new target species in Article 13(5). For example, Product B (Company 2) was approved according to Article 13(3) based on additional preclinical and/or clinical studies (e.g. supporting a new target species, indication, strength, pharmaceutical form or route of administration) to those submitted in support of the reference product (Product A, Company 1). A subsequent application may be submitted for Product C (Company 3), which refers to data supporting the reference product (Product A) and also to the data submitted in support of Product B (approved according to Article 13(3)), provided that any data exclusivity awarded in respect of a possible new target species for Product B has elapsed. The application for Product C may be accepted irrespective of whether Products A and B belong to the same global marketing authorisation. In such case Product A would be the reference medicinal product in support of the application for Product C. Applicants proposing such a marketing authorisation application are advised to contact the competent authorities in advance of the submission. The same principle applies if Product B was approved according to Article 13(1), but where the marketing authorisation was subsequently amended to include a new species post-authorisation.

Reference must be made to a veterinary medicinal product which is or has been authorised in the Union, (i.e. a marketing authorisation has been granted for the reference veterinary medicinal product, but it may have ceased to exist) and in accordance with the Union law[18].

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.

Application in accordance with Article 13 refers to information that is contained in the dossier of the authorisation of the reference veterinary medicinal product. These authorisations for these veterinary medicinal products are therefore linked to the 'original' authorisation. This does not however mean that withdrawal of the authorisation for the reference product leads to the withdrawal of the authorisation for the generic product. However, where the reference veterinary medicinal product has been withdrawn, it is noted that public health concerns linked for instance to the lack of pharmacovigilance data may prevent the granting of such marketing authorisation (case C-223/01, AstraZeneca, judgment of the European Court of Justice of 16 October 2003).

An application according to Article 13 of Directive 2001/82/EC cannot be filed simultaneously with an application for a reference product (case C-223/01, AstraZeneca, judgment of the European Court of Justice of 16 October 2003).

The marketing authorisation holder of the reference veterinary medicinal product can file an application on the basis of Article 13 to his own veterinary medicinal product, provided that the requirements of Article 13 are fulfilled, for example the data exclusivity period has expired. It should be noted that in case of centralised application, Article 82(1) of Regulation 726/2004 applies.

5.3.1.2 "European reference veterinary medicinal product"

In case a medicinal product having the same qualitative and quantitative composition in active substance(s) and the same pharmaceutical form than the generic medicinal product which is the subject of the application is authorised in the reference Member State, it is not possible for the applicant to refer

[18] Case C-527/07, ECJ 18/06/2009

to a European reference medicinal product. This applies regardless of who is the marketing authorisation holder of the potential reference medicinal product in the reference Member State.

In the framework of Mutual recognition/Decentralised Procedures, the situation that must be considered concerns the identification of a reference medicinal product in the reference Member State. In case there is no product authorised in the reference Member State for the target species, then a medicinal product authorised in another Member State can be chosen by the applicant as reference product, i.e. the European reference medicinal product. According to Article 13(1) third subparagraph of Directive 2001/82/EC 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 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 data exclusivity has expired in the Member State of the reference veterinary medicinal product (see section 6).

At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State should transmit within a period of one month, a confirmation that the reference veterinary medicinal product is or has been authorised together with the full composition of the reference product and if necessary other relevant documentation.

The documentation requested must be relevant for the assessment of the application submitted on the basis of Article 13 [see the Guidance for Exchange of documentation relating to a Reference Veterinary Medicinal Product between Member States[19]].

5.3.1.3 Reference veterinary medicinal product not harmonised in the European Union

For historical reasons, the reference product identified in the procedure may have national marketing authorisations with different SPCs across the EU (horizontal disharmony of the reference veterinary medicinal product). This should not prevent that the veterinary medicinal product authorised on the basis of Article 13 has the same SPC across the EU (horizontal harmonisation of the generic veterinary medicinal product). Concerned Member States 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 the user, consumer, target species or the environment as regards the content of application considered.

5.3.2 Particularities for application according to Article 13

Article 13 constitutes a single legal base for the submission of applications. The content of such applications must comply with the requirements set out therein.

5.3.2.1 Application in accordance with paragraph 1 of Article 13 (generic veterinary medicinal product)

Directive 2001/82/EC defines a generic veterinary medicinal product in Article 13(2)(b) as a veterinary medicinal product which has:

- the same qualitative and quantitative composition in active substances as the reference product;
- the same pharmaceutical form as the veterinary reference veterinary medicinal product;

[19] http://www.hma.eu/veterinarymedicines.html

- and whose bioequivalence with the veterinary reference veterinary medicinal product has been demonstrated by appropriate bioavailability studies.

The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters, ethers, isomers or mixtures thereof or derivatives of an authorised active substance must be supplied by the applicant. If 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 then it would be necessary to submit the results of appropriate safety and residue tests and pre-clinical tests and clinical trials in accordance with the requirements of Article 13(3).

To the extent that the active substance may be considered as a new active substance as defined in Annex I at the end of this Chapter, the applicant may consider the submission of an application in accordance with Article 12(3) of Directive 2001/82/EC.

The various immediate release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic veterinary medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines (see also Annex II at the end of this Chapter).

The competent authorities will determine the validity of such applications on a case by case basis and will rely upon the summary evidence provided in Part 1 of the application dossier and, if available, on the assessment report of another competent authority.

‘Same qualitative and quantitative composition’

This requirement that the generic and reference products have the same qualitative and quantitative composition extends only to the active substance(s) and not to the other ingredients of the product. However, differences in excipient composition or differences in impurities must not lead to significant differences as regards safety and efficacy. The competent authorities will evaluate these differences in the light of all scientific knowledge at their disposal. See also ruling of the European Court of Justice in case C-74/03, Smithkline Beecham, judgement of 20 January 2005. The decision whether a different form of the active substance is to be regarded as a new active substance should be taken by the competent authorities on a case-by-case basis.

‘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. A generic veterinary product and a veterinary reference product may be considered to have the same pharmaceutical form if they have the same form of administration as defined by the Pharmacopoeia. Furthermore, Article 13(2)(b) of the directive 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 for the purposes of Article 13.

According to the European 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 which are presented in the form of a solution to be mixed in drinking water for administration to the animal are to be treated as having the same pharmaceutical form, provided that the differences in the form of administration are not significant in scientific terms. (See Case C-106/01, Novartis, judgment of 29 April 2004).

‘Bioequivalence’

The definition and demonstration of bioequivalence should be made in accordance with the published “Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products”, (EMA/CVMP/016/00-corr-FINAL) or "Bioequivalence: blood level bioequivalence study" (EMA/CVMP/VICH/751935/2013 – Corr.) depending on the time of application.

Article 13(2)b last sentence of Directive 2001/82/EC states: *"[…]Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines".*

Such exemptions from the need to demonstrate *in vivo* bioequivalence should be justified in the part 4 of the dossier and in the detailed and critical summaries (part 1).

Where bioequivalence cannot be demonstrated through bioavailability studies, for example for locally applied and locally acting medicinal products, Article 13(3) requires that the results of appropriate safety and residue tests and pre-clinical tests or clinical trials shall be provided and this Article provides the correct legal basis for the application.

5.3.2.2 Application in accordance with paragraph 3 of Article 13 ("hybrid” veterinary medicinal product)

Article 13(3) of Directive 2001/82/EC requires that, in certain circumstances in the framework of an application under Article 13, the results of the appropriate safety and residue tests and preclinical tests or clinical trials shall be provided. These applications will thus rely in part on the results of the appropriate safety and residue tests and pre-clinical tests and clinical trials for a reference product and in part on new data.

The extent of the additional studies required in the framework of an article 13(3) application depends on the changes introduced in the reference medicinal product (e.g. new strength, new route of administration, new therapeutic indication, new target species) and will be a matter of scientific assessment by the relevant competent authority.

Article 13(3) considers three circumstances where such additional data will be necessary:

- where the strict definition of a ‘veterinary generic veterinary medicinal product’ is not met;
- where bioavailability studies cannot be used to demonstrate bioequivalence (for example where the new product is supra-bioavailable or locally acting medicinal products);
- where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference product, etc.

Some guidance on the appropriate additional studies required is indicated in the table given in Annex II at the end of this Chapter.

In any event Article 13(3) should not be used as a legal basis for applications for products for which it is possible to demonstrate bioequivalence through bioavailability studies but the applicant failed to submit results of such studies demonstrating bioequivalence.

5.3.2.3 Application in accordance with paragraph 4 of Article 13 ("Similar biological veterinary medicinal product")

Article 13(4) of Directive 2001/82/EC requires that in the framework of an application under Article 13, it is stated that where a biological veterinary medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic veterinary medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the similar biological veterinary medicinal product and the reference biological veterinary medicinal product, the results of appropriate safety and residue tests and pre-clinical tests or clinical trials relating to these conditions must be provided.

5.4. Applications according to Article 13a of Directive 2001/82/EC

According to Article 13a of Directive 2001/82/EC it is possible to replace results of the safety and residue tests or of pre-clinical and clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substances of a new veterinary medicinal product have 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 I of Directive 2001/82/EC shall apply.

Being a derogation, the well-established use provision must be interpreted strictly. The well-established veterinary use legal basis is to be used only in cases where all aspects of the safety and efficacy are demonstrated by reference to published scientific literature.

It would derive that it should not be considered as an alternative to other legal basis such as Article 13 of Directive 2001/82/EC. The adequacy of the bibliographic evidence has to be assessed on a case by case basis in the understanding that applications under Article 13a does not lower the requirements of safety and efficacy that must be met.

Well-established medicinal use

Annex I to Directive 2001/82/EC lays down specific rules for the demonstration of a well-established medicinal use, with recognised efficacy and an acceptable level of safety. The adequacy of the bibliographic evidence has to be assessed on a case by case basis in the understanding that an application under Article 13a does not lower the requirements of safety and efficacy that must be met.

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, taking into account
- 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;
- the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments.

Therefore, different periods of time may be necessary for establishing well-established use of different substances. In any case, 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. Although “veterinary use” does not exclusively mean “use as an authorised veterinary medicinal product”, it could constitute a proof of veterinary use. In particular, for an active substance used in veterinary medicinal products authorised before a 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 13a even if it has partly or fully occurred before accession of that State.

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

Marketing authorisation applications for a product containing combination of active substances can be submitted on the basis of Article 13a. 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 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 in the detailed and critical summaries why.

The reference must refer to ‘published scientific literature’. The term ‘published’ literature implies that the text 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.

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 of Annex I of Directive 2001/82/EC.

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

If an applicant makes use of scientific literature to obtain authorisation for a food-producing species, and submits, in respect of the same veterinary medicinal product and with a view to obtaining authorisation

for another food-producing species, new residue studies in accordance with Regulation (EC) No 470/2009, together with further clinical trials, it shall not be permissible for a third party to use such studies or trials pursuant to Article 13, for a period of three years from the granting of the authorisation for which they were carried out.

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 considered on a case by case basis by the competent authorities.

5.5. Application according to Article 13b of Directive 2001/82/EC related to fixed combination

In accordance with Article 13b of Directive 2001/82/EC, in the case of veterinary medicinal products containing active substances used in the composition of authorised veterinary medicinal products in combination for therapeutic purposes, the results of new safety and residue tests, pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with point (j) of the first subparagraph of Article 12(3), but it shall not be necessary to provide scientific references relating to each individual active substance.

The combination of active substances within a single formulation according to this provision is a so-called 'fixed combination'.

A key principle of the acquis is that there must be a marketing authorisation for each medicinal product that is put on the EU market. Therefore, the fixed combination definition is limited to active substances contained in a same pharmaceutical form of administration, the so-called 'fixed-combination'. The combination of active substances, where active substances are included in separate pharmaceutical forms and presented in a combination pack cannot be considered as a fixed combination.

In very exceptional circumstances, which must be considered on a case by case basis, the marketing of distinct medicinal products in the same package may be indispensable for public or animal health reasons. Such reasons cannot be related to convenience or commercial purposes.

Strictly speaking, any combination of active substances is a new and unique veterinary medicinal product requiring a separate marketing authorisation and Summary of Products Characteristics. Therefore a new 'combination' veterinary medicinal product will have an independent period of data exclusivity and market protection from its first authorisation within the Union. Consequently, applications in accordance with article 13 and 13c referring to "combination" dossiers are acceptable.

An authorisation for a 'combination' veterinary medicinal product is not considered to fall within the scope of the global marketing authorisations of the individual active substances as described in Article 5 of Directive 2001/82/EC.

Applications for fixed-combination veterinary medicinal products can be accepted and validated under Article 13b on condition that the individual substances have been the object of a marketing authorisation in the EEA via a Union or national procedure, even though it is not in the same Member State.

5.6. Applications according to Article 13c of Directive 2001/82/EC related to "informed consent"

It follows from the wording of Article 13b that a full dossier comprising all the information of Parts 1 to 4 of Annex I has to be provided in relation to the fixed-combination. As with any application for a new veterinary medicinal product such a full dossier can be either a dossier based solely on own tests and

trials performed by the applicant or on a mixed dossier. Any absence of specific fixed-combination data should be duly justified by the applicant with reference to scientific and regulatory considerations. Article 13b does not contain a requirement for the inclusion of data on the individual active substances. It is nevertheless possible to include information on the individual 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. Such information could consist of literature or actual data. Applications according to Article 13c of Directive 2001/82/EC related to 'informed consent'

A derogation from the requirements to submit all of the information required in Article 12(3)j is provided by Article 13c of Directive 2001/82/EC for so-called 'informed consent' marketing authorisation applications. Despite the fact that the provision contains some criteria that are common to the definition of a generic veterinary medicinal product in Article 13, Article 13c does not concern generic medicinal products.

According to Article 13c: *"After the marketing authorisation has been granted, the authorisation holder may allow use to be made of the pharmaceutical, safety and residues, pre-clinical and clinical documentation contained in the file for the veterinary medicinal product, with a view to examining a subsequent application for a veterinary medicinal products having the same qualitative and quantitative composition in active substances and the same pharmaceutical form."*

An informed consent application does not have to cover all presentations/indications of the veterinary medicinal product with regard to which consent is given. Consent may be given to use the documentation contained in the file of the relevant veterinary medicinal product for a given presentation/indication provided that the application relies on that consent as regards all three parts of the dossier. It is a prerequisite for the use of Article 13c that consent has been obtained for all three parts containing the pharmaceutical, safety and residues and pre-clinical and clinical data. It is not possible to use Article 13c as a legal basis for an application consisting of the applicant's own Part II and for which consent has been given for Parts III and IV. In such cases the legal basis for the application is Article 12(3).

An informed consent application cannot cover more presentations or indications than the veterinary medicinal product with regard to which consent is given. Additional presentations or indications can only be added after the issuing of the marketing authorisation through variation. However, an informed consent application can cover fewer presentations or indications than the veterinary medicinal product from which consent is given.

The concept of "European reference veterinary medicinal product" is laid down by Article 13 and is applicable in case of application in accordance with Article 13. It does not apply in the context of applications under Article 13c. In addition, it should be noted that an informed consent application is only possible if there is still a valid marketing authorisation to which consent is given.

Furthermore, informed consent applications need to respect the following:

- for a central marketing authorisation the informed consent application has to follow the centralised procedure;
- for a national marketing authorisation the informed consent application has to follow a national procedure (either pure national or MRP or DCP). A prerequisite is that the marketing authorisation is granted in this /these MS.

It follows that an application under Article 13c can only be submitted to a Member State where the veterinary medicinal product with regard to which consent is given is authorised.

The applicant must show proof that marketing authorisation holder of the reference product has consented that the dossier of that product is used for the purpose of examining the application in question. It is up to the contracting parties to consider, as a term of their contractual agreement, whether

the ‘informed consent’ can be withdrawn by the consenting parties and what the consequences of the withdrawal of the informed consent would be.

The ‘informed consent’ product applicant must have permanent access to the documentation in order to fully carry out his responsibilities. For the information contained in the Active Substance Master File a new letter of access in connection with the informed consent application should be included, without prejudice to the restrictions on access to the Manufacturer Restricted Part of the Active Substance Master File.

For competent authorities, demonstration of the ‘informed consent’ is a formal condition which must be fulfilled, when the ‘informed consent’ application is submitted.

An authenticated letter from the party granting consent is required and must specify the name of the benefiting party and the products concerned. A withdrawal of the informed consent at a later stage has no direct consequences on the existence/validity of the marketing authorisation but the marketing authorisation holder is to take appropriate steps having regard to the requirement of permanent access to the file.

For more information on regulatory issues concerning a submission of informed consent applications in mutual recognition and decentralised procedures see CMDv Best Practice Guide - CMDv/BPG/012 available at CMDv website (http://www.hma.eu/veterinarymedicines.html);

5.7. Applications according to Article 13d of Directive 2001/82/EC

According to Article 13d of Directive 2001/82/EC concerning the derogation for immunological veterinary medicinal products; the applicant shall not be required to provide the results of certain field trials on the target species if these trials cannot be carried out for duly substantiated reasons, in particular on account of other Union provisions.

6. DATA EXCLUSIVITY AND MARKET PROTECTION

6.1. Data exclusivity and market protection period for reference veterinary medicinal products

6.1.1 Principles on data exclusivity and market protection of 'reference veterinary medicinal product'

The veterinary medicinal product, once authorised on the basis of Article 13, can however only be placed on the market 10, 11, 12 or 13 years after the authorisation of the reference veterinary medicinal product, depending on the protection period applicable for the reference veterinary medicinal product. The protection period in the Concerned Member State must also be taken into consideration before placing the veterinary medicinal product on its market.

For products authorised by the national competent authorities, according to the first subparagraph of Article 13(1) of Directive 2001/82/EC as amended, the applicant is not required to provide the results of safety and residues tests or pre-clinical tests and of clinical trials if he can demonstrate that the veterinary medicinal product is a generic of a reference veterinary medicinal product which is or has been authorised under Article 5 for not less than eight years in a Member State or in the Union.

According to the second subparagraph of Article 13(1), generic products authorised in this way must not be placed on the market until ten years have elapsed from the initial authorisation of the reference product. (This ten year period may be extended up to thirteen years if the conditions of Article 13(5) are fulfilled, see section 6.2 below).

Products for bees and fish automatically have a thirteen year protection period.

The period of eight years from initial authorisation of the reference product provides a period of so-called “data exclusivity”, after which valid applications for generic products can be submitted and lead to the granting of a marketing authorisation. The period of ten years from initial authorisation of the reference product provides a period of so-called “market protection” after which generic products authorised in this way can be placed on the market.

The same periods of protection apply in the case of centrally authorised products pursuant to Article 39(10) of Regulation (EC) No 726/2004.

It should be noted, however, that these periods of protection will only apply to applications for reference veterinary medicinal products submitted once the provisions of Directive 2004/28/EC and Regulation (EC) No 726/2004 start to apply; see section 6.1.2.

6.1.2 Data exclusivity and market protection for applications submitted before the implementation of the amended legislation

According to Article 89 of Regulation (EC) No 726/2004, the new periods of protection do not apply to those reference veterinary medicinal products for which the initial application for authorisation was submitted before 20 November 2005.

Equally, Directive 2004/28/EC makes it clear that the new periods of protection do not apply to those reference veterinary medicinal products for which an application for authorisation has been submitted before the date of transposition (i.e. 30 October 2005).

Products for which the initial submission was made prior to the dates referred above continue to benefit from the previous periods of protection (except in Croatia where the new periods of protection apply for all products) which are:

- 10 years for national authorisations granted by the following Member States: Belgium, Germany, France, Italy, the Netherlands, Sweden, United Kingdom, Luxemburg;
- 6 years for national authorisations granted by the following Member States: Austria, Denmark, Finland, Ireland, Portugal, Spain, Greece, Poland, Czech Republic, Hungary, Lithuania, Latvia, Slovenia, Slovakia, Malta, Estonia, Cyprus, Bulgaria, Romania and also Norway, Liechtenstein and Iceland;
- 10 years for all veterinary medicinal products authorised through the centralised procedure;
- 10 years for all veterinary medicinal products authorised following an opinion of the CVMP in accordance with Article 4 of Directive 87/22/EEC (ex-concertation procedure).

For the purposes of the application of the mentioned provisions, the date of submission of an application, and not the date of validation by the competent authority, determines the periods of protection applicable.

Evidence of the date of authorisation of the reference product should be provided where possible in the application for the generic marketing authorisation.

In mutual recognition or decentralised procedures if the protection period in a Concerned Member State is longer than in the Reference Member State, mutual recognition in the Concerned Member State is not possible before the expiry of the longer period.

The data exclusivity rules applicable before adoption of the current legislation allowed the coexistence of periods of six and ten years of protection in different Member States for the same product. In other

words, the generic of a reference product was allowed access to the market at different points in time in different Member States.

The new harmonised data exclusivity and market protection periods in Article 13(1) of Directive 2001/82/EC do not apply retroactively. It follows that:

- An application in accordance with Article 13 of Directive 2001/82/EC can only be processed via the centralised procedure after expiry of the period of protection of the Member State where the reference veterinary medicinal product was authorised (e.g., if the reference product is authorised in a Member State where a ten-year period of protection applies, the application under the centralised procedure may only be submitted after the 10 year period);
- An application in accordance with Article 13 of Directive 2001/82/EC can only be submitted under the decentralised/mutual recognition procedure after expiry of the period of protection of the reference veterinary medicinal product in the Reference Member State and the Concerned Member States. It follows that, if the period of protection in the Reference Member State and in three Concerned Member States is six years, a decentralised procedure to obtain a marketing authorisation in accordance with Article 13 of Directive 2001/82/EC is only possible regarding these four Member States. A mutual recognition procedure can be triggered a posteriori to cover other Concerned Member States once the protection period therein expires also.

6.1.3 Relevant periods of protection in the case of the reference veterinary medicinal product/"European Reference veterinary medicinal product"

As stated above (section 5), Article 13(1) of Directive 2001/82/EC allows a generic application to be submitted only if the reference product has been authorised for a given period of time. In addition, a generic application is possible under that provision even "if the reference veterinary medicinal product was not authorised in the Member State in which application for the generic product is submitted". In that case, a reference product authorised in another Member State must be identified. It should be noted that the use of this provision will only be possible if the reference product is out of data exclusivity in the Member State where it is authorised.

A veterinary medicinal product could be used as reference veterinary medicinal product if three cumulative conditions are met:

- The reference veterinary medicinal product has been authorised in the EU (through a centralised or national procedure);
- The reference veterinary medicinal product is or has been authorised in accordance with the pharmaceutical acquis,
- The relevant data exclusivity period has expired.

Therefore, the starting date for calculating the data exclusivity period is the date of authorisation in accordance with the pharmaceutical acquis of the reference veterinary medicinal product in the territory of the European Union. The data exclusivity period must have expired in the Member States concerned on the date at which the application for the generic veterinary medicinal product is submitted.

6.1.4 Protection periods and global marketing authorisation

For the notion of global marketing authorisation, see section 2.3. The global marketing authorisation contains the initial authorisation and all variations and extensions thereof, as well as any additional species, strengths, pharmaceutical form, administration routes or presentations authorised through separate procedures and under a different name, granted to the marketing authorisation holder of the initial authorisation.

In accordance with Article 5(1) of Directive 2001/82/EC, all these presentations of a given product are considered to be part of the same marketing authorisation for the purposes of applying the rules on data exclusivity and marketing protection.

This means that for a reference veterinary medicinal product, the start of the data exclusivity and market protection periods is the date when the first marketing authorisation was granted in the Union in accordance with the pharmaceutical acquis. New additional species, strengths, pharmaceutical form, administration routes, presentations as well as any variation and extensions do not restart or prolong this period. All additional species, strengths, pharmaceutical forms, administration routes, presentations as well as any variation and extensions have the same end point of the data exclusivity and market protection periods, namely 8 and 10 years after the first marketing authorisation was granted, respectively. This will apply even if the new presentation has been authorised to the same marketing authorisation holder through a separate procedure, national or centralised procedure (see section 2.3), irrespective of the legal basis and under a different name.

This ten-year period can only be prolonged in the case of addition of new food-producing species, as described in section 6.2.

6.1.5 Reliance on safety and efficacy data contained in the dossier of a reference veterinary medicinal product under data exclusivity

During the period of data exclusivity of a veterinary medicinal product, the data contained in parts 3 and 4 of that product and obtained through access to documents or freedom of information legislation within the EU or in third countries, cannot be relied on by other applicants or the authorities in a subsequent application to ascertain the safety and efficacy of other products. As long as a product authorised in the EU is under data exclusivity, the reliance on published or unpublished pre-clinical and clinical data contained in the dossier of that product within the EU or in third countries by the competent authorities to grant a marketing authorisation would lead to a circumvention of the data exclusivity rules. Therefore, such application cannot be accepted.

6.2 Extension of the ten year period in Article 13(1) in the case of addition of new food-producing species

6.2.1 Extension of the ten year period in Article 13(5)

Article 13(5) of Directive 2001/82/EC reads: *“In the case of veterinary medicinal products intended for one or more food-producing species and containing a new active substance that has not been authorised in the Union by 30 April 2004 the ten-year period provided for in the second sub-paragraph of paragraph 1 shall be extended by one year for each extension of the marketing authorisation to another food producing species, if it is authorised within the five years following the granting of the initial marketing authorisation.”*

The extra protection is only possible for new active substances, i.e. substances that have not been authorised in the Union by 30 April 2004. One extra year protection for the marketing authorisation shall be added for each additional food-producing species. However, this period shall not exceed a total of 13 years, for a marketing authorisation for four or more food producing species.

The additional year(s) of protection do not cover only the data submitted in support of the application for authorisation, but all the preclinical and clinical data of the veterinary medicinal product concerned.

6.2.2 Data protection for new studies under Article 13a(3)

Article 13a(3) of the directive states:

"If an applicant makes use of scientific literature to obtain authorisation for a food-producing species, and submits, in respect of the same medicinal product and with a view to obtaining authorisation for another

food-producing species, new residue studies in accordance with Regulation (EEC) No 2377/90, together with further clinical trials, it shall not be permissible for a third party to use such studies or such trials pursuant to Article 13, for a period of three years from the grant of the authorisation for which they were carried out. "
Article 13a(3) provides for 3-year data protection for new residue studies and clinical trials directly associated with the data that had to be submitted for the establishment of MRLs for these food-producing species for the pharmaceutical active substance and extending a veterinary medicinal product to these additional food-producing species. The period of data protection starts at the moment of the granting of the marketing authorisation for which they were carried out.

7. VARIATIONS AND EXTENSIONS

Throughout the life of a veterinary medicinal product, the marketing authorisation holder is responsible for the product which is placed on the market and is also required to take into account technical and scientific progress, and to make any amendments that may be required to enable the veterinary medicinal product to be manufactured and checked by means of generally accepted scientific methods.

Such amendments may involve changes to the product information or changes to the technical dossier submitted by the marketing authorisation holder. The procedures for the approval of such amendments have been set out in Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.

Regardless of the legal basis of the initial marketing authorisation, a marketing authorisation holder can submit an application in relation to further developments or uses of its medicinal product, including new therapeutic indications, in accordance with the provisions and requirements set out in Commission Regulation (EC) No 1234/2008 and the below mentioned Commission Guidelines.

Commission Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures provide additional information about procedures to amend marketing authorisations as well as the classification of variations.

Only the European Commission and the European Medicines Agency respectively are responsible for any variations relating to centrally authorised products.

Urgent safety restrictions

The Variation Regulations also include provisions for the marketing authorisation holder or the competent authority to take provisional urgent safety restrictions in the event of a risk to public health, animal health or the environment.

Where the marketing authorisation holder takes urgent safety restriction, he must forthwith inform the relevant national competent authority or the EMA (in the case of authorisations granted by the Member States or the Union, respectively). If the national competent authority/EMA has not raised any objections within 24 hours of the receipt of that information, the urgent safety restriction is deemed accepted. The corresponding variation application reflecting the urgent safety restriction must be submitted immediately to the national competent authority/EMA and in any case no later than 15 days after the initiation of the urgent safety restriction.

Where the national competent authority/Commission imposes provisional urgent safety restriction, the marketing authorisation holder must be obliged to implement the urgent safety restrictions. The

corresponding variation application reflecting the urgent safety restriction, must be submitted immediately to the national competent authority/EMA and in any case not later than 15 days after the initiation of the urgent safety restriction.

In all cases the appropriate documentation in support of the change must be included in the application.

8. SPECIAL REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS INTENDED FOR FOOD-PRODUCING ANIMALS

8.1. Background

Pharmacologically active substances administered to food-producing animals may leave residues harmful to human health in foodstuffs of animal origin. Therefore, the safety of the residues of veterinary medicinal products remaining in foodstuffs of animal origin has to be scientifically assessed in accordance with the procedure laid down in Regulation (EC) No 470/2009.

In accordance with Article 6 of Directive 2001/82/EC, the pharmacologically active substance(s) included in a veterinary medicinal product subject to a marketing authorisation for the purpose of administering it to a food-producing animal, must be included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 which sets out the pharmacologically active substances and their classification regarding MRLs in foodstuffs of animal origin[20].

For excipients that are not included in Table 1 of the Annex to Commission Regulation 37/2010, it may be possible to demonstrate that the excipients are not considered to have pharmacological activity when used as proposed in accordance with the guideline on data to be provided in support of a request to include a substance in the list of substances considered as not falling within the scope of Regulation (EC) No 470/2009 (EMA/CVMP/516817/2009). Application for such consideration should be submitted to the Agency and in case of a favourable outcome, the excipient(s) will be added to the list of substances considered as not falling within the scope of Regulation (EC) No. 470/2009, with regard to residues of veterinary medicinal products in foodstuffs of animal origin (EMA/CVMP/519714/2009).

8.2. Preconditions for granting a marketing authorisation

A veterinary medicinal product intended for administration to food-producing animals can only be authorised, if the pharmacologically active substance(s) contained in the product are mentioned in Table 1 of the Annex to Commission Regulation (EU) No 37/2010. All substances contained in the product may be subject to this requirement if they are pharmacologically active whether they are included as active substances or as excipients.

Before an application is made for a marketing authorisation for a veterinary medicinal product intended for administration to food producing animals, the maximum residue limit (MRL) status of all pharmacologically active substances contained in that veterinary medicinal product needs to be checked.

Table 1 of the Annex to Commission Regulation (EU) No 37/2010 includes substances for which MRLs have been established. The MRLs, and any provision where applicable, are fixed for specified target species and relevant target tissues.

Pharmacologically active substances listed in Table 2 of the Annex to Commission Regulation (EU) No 37/2010 are considered hazardous to the health of the consumer when present in foodstuffs obtained from treated animals. Therefore, veterinary medicinal products intended for administration to food-producing animals containing those substances cannot be authorised.

[20] OJ L 15, 20.1.2010, p. 1).

Excipients that are not included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 can still be used in veterinary medicinal products intended for administration to food-producing animals if they are included in the list of substances considered as not falling within the scope of Regulation (EC) No. 470/2009, with regard to residues of veterinary medicinal products in foodstuffs of animal origin (EMA/CVMP/519714/2009) or they have otherwise been demonstrated not to be pharmacologically active at the dose to be administered.

8.2.1 Requirements for applications for marketing authorisations for new pharmacologically active substances

The evaluation of the safety of the residues of pharmacologically active substances is a Union procedure. The application for establishment of MRLs for a substance contained in a product to be authorised shall therefore be submitted in all cases (national procedure, mutual recognition procedure or centralised procedure) to the Agency for assessment.

Such an application shall be assembled according to the requirements as laid down in Regulation (EC) No 470/2009 and further specified in Commission Implementing Regulation (EU) 2017/12[21].

In order to avoid any unnecessary delay in the procedure concerning the application for a marketing authorisation, applicants are strongly advised to submit the application for the establishment of MRLs as soon as the relevant documentation is ready and well in advance of the submission of the application for the marketing authorisation to the Member State(s) concerned or, in the case of a centralised procedure, to the EMA.

In accordance with Directive 2001/82/EC, a minimum of 6 months should elapse between a valid application for the establishment of MRLs and an application for marketing authorisation.

The application for granting a marketing authorisation for a veterinary medicinal product intended for administration to food-producing animals must always include a reference to the MRL status of all pharmacologically active substances contained therein as well as the specific data on safety and residues as required by Article 12 and Annex I of Directive 2001/82/EC.

8.2.2 Requirements for new target species and/or foodstuffs of animal origin

When an application for the granting of a marketing authorisation is to be made and the pharmacologically active substances contained in that product is (are) listed in Table 1 of the Annex to Commission Regulation (EU) No 37/2010, but are intended for different target species and/or target tissues/foodstuffs, an MRL application for the extension of the existing entry in Table 1 has to be made prior to the application for the marketing authorisation. Such an application for the extension of MRL shall be compiled in accordance with the Commission Implementing Regulation (EU) 2017/12 and be submitted to the EMA.

9. SPECIAL REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS FOR HORSES NOT INTENDED FOR HUMAN CONSUMPTION

A derogation of the Maximum Residue Limit principle for horses not intended for human consumption has been introduced with Article 6(3) of Directive 2001/82/EC.

This article provides the possibility to authorise a veterinary medicinal product containing pharmacologically active substances not included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 for particular animals of the equidae family.

[21] Commission Implementing Regulation (EU) 2017/12 of 6 January 2017 regarding the form and content of the applications and requests for the establishment of maximum residue limits in accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council OJ L 4, 7.1.2017, p. 1

These animals have to be declared as not being intended for slaughter for human consumption in accordance with Regulation (EC) 504/2008[22] and Regulation (EU) 2015/262[23]. Such veterinary medicinal products shall not include active substances that appear in Table 2 of the Annex to Commission Regulation (EU) No 37/2010.

Additionally, it is not allowed to authorise such a product for use in the treatment of conditions for which a veterinary medicinal product is authorised for animals of the equidae family in the EEA. In this case the cascade provisions of Article 11 of Directive 2001/82/EC should be used (i.e. including import from other EEA countries).

According to Article 12(1) subparagraph 3 of Directive 2001/82/EC a marketing authorisation for a veterinary medicinal product referred to in Article 6(3) may be applied for without a valid application in accordance with Regulation (EC) No 470/2009. All the scientific documentation necessary for the demonstration of the quality, safety and efficacy of the veterinary medicinal product, as provided for in paragraph 3, shall be submitted.

[22] OJ L 149, 7.6.2008, p. 3.
[23] OJ L 59, 3.3.2015, p. 1.

ANNEX I DEFINITION OF A NEW ACTIVE SUBSTANCE

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

- a chemical, biological or radiopharmaceutical substance not previously authorised in a veterinary medicinal product in the European Union;
- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised 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;
- a biological substance previously authorised 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;
- a radiopharmaceutical substance which is a radionuclide, or a ligand not previously authorised in a veterinary medicinal product in the European Union, or the coupling mechanism to link the molecule and the radionuclide has not been authorised previously in the European Union.

ANNEX II GUIDANCE ON THE APPROPRIATE ADDITIONAL STUDIES REQUIRED FOR APPLICATIONS UNDER ARTICLE 13 OF DIRECTIVE 2001/82/EC OR EXTENSION APPLICATIONS

	With regard to:	Additional data usually required:
a)	different salt/ester complex/derivative (with the same therapeutic moiety)	Evidence that there is no change in the pharmacokinetics of the moiety, pharmacodynamics and/or in toxicity which could significantly change the safety/efficacy profile (otherwise, to be considered as a new active substance)
b)	different route/pharmaceutical form (For parenteral administration, it is necessary to distinguish between intra-arterial, intravenous, intramuscular, subcutaneous and other routes) i) new route of administration ii) new pharmaceutical form (same route) (conventional to modified)	Safety and residue tests, pre-clinical and clinical data (safety/efficacy), pharmacokinetics, if justified
c)	different strength same route/ pharmaceutical form and posology	Bioavailability (cf. guideline), user safety, and residue tests (if justified)
d)	suprabioavailable products i) same dosage intervals but reduced doses intended to achieve same plasma/blood concentrations as a function of time	Bioavailability studies may suffice (see Bioequivalence guideline).
e)	active substances associated in a different proportion/different posology or if one or more is intended for modified release.	Clinical studies comparing existing/new proportion or dosage regimen, including bioavailability studies, user and environmental safety, residue tests, if justified
f)	Addition of target species (non-food)	Safety (user safety), environmental risk assessment (ERA), pre-clinical and clinical data
g)	Addition of target species (food producing)	Safety (user safety) and residues data, ERA as well as pre-clinical and clinical data