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Guideline on the application of Article 34 of Regulation (EU) 2019/6

Classification of veterinary medicinal products (prescription status) - Draft

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Guideline on the application of Article 34 of Regulation (EU) 2019/6

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Executive summary

This guideline elaborates on the scientific criteria within the various provisions of Article 34 of Regulation (EU) 2019/6 and provides assessors and stakeholders with clear guidance for its consistent and predictable application.

1. Introduction (background)

Consideration of whether a product is subject to veterinary prescription or not is an outcome of product assessment[1] and therefore requires detailed consideration. Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC establishes, in Article 34, the legal framework for the classification of veterinary medicinal products.

Whilst some of the provisions in Article 34 of Regulation (EU) 2019/6 are relatively clear-cut, some others will benefit from further elaboration. The HMA Task Force on Coordination of the Implementation of the Veterinary Regulation (TFCIVR) agreed that guidance was needed to ensure a harmonised EU approach to classification of veterinary medicinal products. The CVMP subsequently confirmed that it would develop guidance for the application of Article 34 of Regulation (EU) 2019/6.

It is the intention of the guideline to provide clear guidance for the practical application of the provisions in Article 34 of Regulation (EU) 2019/6. To ensure a consistent implementation and a harmonised EU approach, the assessment principles for the various provisions of Article 34 of Regulation (EU) 2019/6 are laid out. However, it is acknowledged that for some provisions the guidance provided is general and a case-by-case approach will be needed.

2. Scope

The objective of this guideline is to elaborate on the scientific criteria within the various provisions of Article 34 of Regulation (EU) 2019/6 and so enable a consistent decision-making process, both for initial marketing authorisation applications as well as for variations to change the prescription status of a veterinary medicinal product.

This guideline aims to provide assessors and stakeholders across the regulatory network with clear guidance for a consistent and predictable application of Article 34 of Regulation (EU) 2019/6. It is, however, not within the scope of this guideline to elaborate on considerations regarding harmonisation of prescription status for veterinary medicinal products that are not authorised through the centralised procedure, or on the impact, if any, from the application of Article 34 of Regulation (EU) 2019/6 to veterinary medicinal products authorised in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004.

3. Legal basis

Regulation (EU) 2019/6 lays down rules for the placing on the market, manufacturing, import, export, supply, distribution, pharmacovigilance, control and use of veterinary medicinal products in the EU.

Article 33(1)(b) of Regulation (EU) 2019/6 specifies that in case of a favourable assessment, the outcome of a competent authority's assessment on an initial marketing authorisation application shall include the classification of a veterinary medicinal product in accordance with Article 34.

[1] With reference to Article 33(1)(b) of Regulation (EU) 2019/6

Article 34 of Regulation (EU) 2019/6 sets out criteria according to which veterinary medicinal products shall be subject to a veterinary prescription. The article is structured in three paragraphs:

- In paragraph 1, the eight categories (a-h) of veterinary medicinal products that shall be classified as subject to veterinary prescription by the competent authority or the Commission, as applicable, are listed.
- Paragraph 2 provides discretion to competent authorities to, notwithstanding paragraph 1, classify a veterinary medicinal product as subject to veterinary prescription if it is classified as a narcotic drug in accordance with national law or where special precautions are contained in the summary of product characteristics referred to in Article 35 of Regulation (EU) 2019/6.
- Finally, paragraph 3, by way of derogation from paragraph 1, lists the seven conditions (also known as 'exemption criteria') (a-g) which must all be fulfilled for a veterinary medicinal product falling within the scope of paragraph 1 before it may be classified as not subject to veterinary prescription, noting the exception for veterinary medicinal products referred to in points (a), (c), (e) and (h) of paragraph 1 which must always be subject to veterinary prescription.

According to section I.2.1. of the Annex II to Regulation (EU) 2019/6, an application proposing the classification of a veterinary medicinal product as "not subject to veterinary prescription" shall include a critical review of the product characteristics in order to justify the suitability of such classification taking into consideration target and non-target animal safety, public health as well as environmental safety, as outlined in the criteria given in Article 34(3), points (a) to (g). Such critical review shall be provided for veterinary medicinal products falling under Article 34(1) categories (b), (d), (f) and (g), and for products not falling within any category of those listed in Article 34(1) but likely to contain special precautions in the summary of product characteristics referred to in Article 35 of Regulation (EU) 2019/6.

4. Application of Article 34 of Regulation (EU) 2019/6.

Classification of a veterinary medicinal product (VMP) in accordance with Article 34 of Regulation (EU) 2019/6 is an outcome of product assessment[2] of any new marketing authorisation application. The application of this article is foreseen as depicted below (see figure 1).

In this section, the criteria for the application of the various provisions of Article 34 are laid out. For some provisions, in addition to the guidance provided, expert judgement would be needed in a case-by-case approach. Therefore, with reference to the dossier requirement in section I.2.1 of the Annex II to Regulation (EU) 2019/6, applicants are strongly advised to justify a "not subject to veterinary prescription" status accordingly. Note for veterinary medicinal products not listed in Article 34(1), the competent authority's classification of the veterinary medicinal product under assessment will take into account the justification provided by the applicant according to section I.2.1 of Annex II but will ultimately be based on the provisions of Article 34(2).

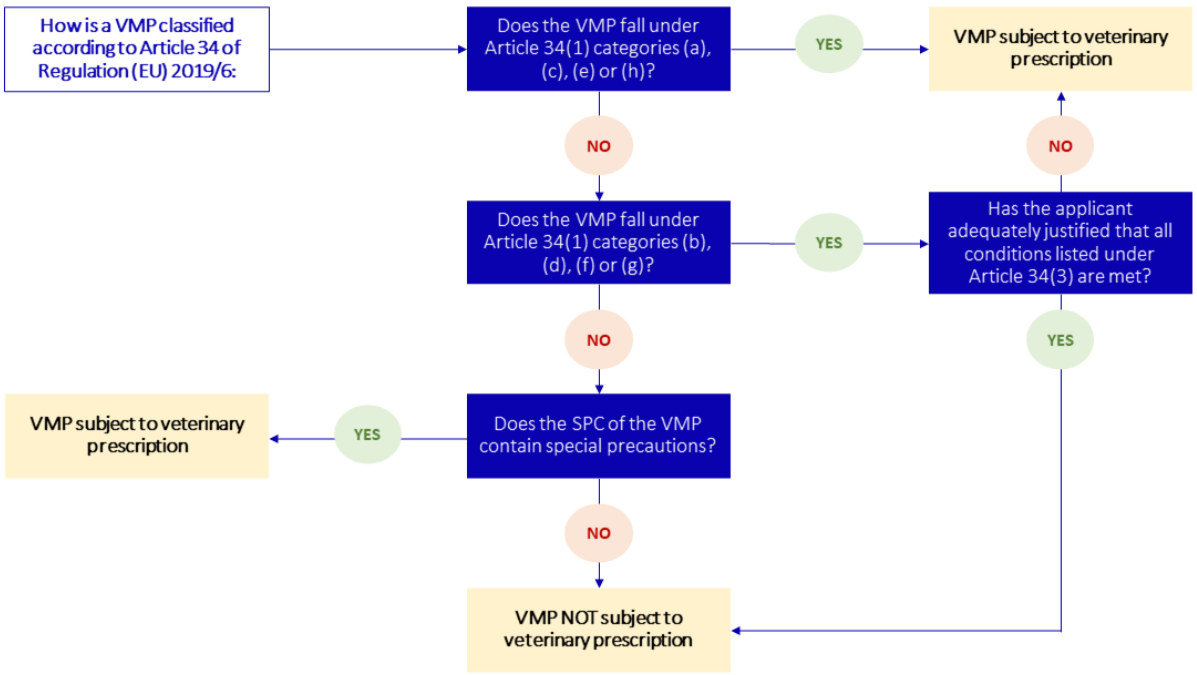

Figure 1. Schematic representation depicting application of Article 34 of Regulation (EU) 2019/6.

4.1. Article 34, paragraph 1, of Regulation (EU) 2019/6.

Article 34(1) sets out which veterinary medicinal products shall be classified as subject to veterinary prescription, as follows:

The competent authority or the Commission, as applicable, granting a marketing authorisation as referred to in Article 5(1) shall classify the following veterinary medicinal products as subject to veterinary prescription:

a) veterinary medicinal products which contain narcotic drugs or psychotropic substances, or substances frequently used in the illicit manufacture of those drugs or substances, including those covered by the United Nations Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol, the United Nations Convention on Psychotropic Substances of 1971, the

[2] With reference to Article 33(1)(b) of Regulation (EU) 2019/6

United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988 or by Union legislation on drug precursors;

b) veterinary medicinal products for food-producing animals;

c) antimicrobial veterinary medicinal products;

d) veterinary medicinal products intended for treatments of pathological processes which require a precise prior diagnosis or the use of which may have effects which impede or interfere with subsequent diagnostic or therapeutic measures;

e) veterinary medicinal products used for euthanasia of animals;

f) veterinary medicinal products containing an active substance that has been authorised for less than five years in the Union;

g) immunological veterinary medicinal products;

h) without prejudice to Council Directive 96/22/EC (23), veterinary medicinal products containing active substances having a hormonal or thyrostatic action or beta-agonists.

It shall be noted that veterinary medicinal products listed in Article 34(1)(a), (c), (e) and (h) will always be classified as subject to veterinary prescriptions as they are excluded from the derogation in Article 34(3).

The CVMP's scientific elaboration of the criteria in Article 34(1)(d) is provided below:

4.1.1. Article 34 (1)(d)

It is necessary to define when a "precise prior diagnosis" of a pathological process is required and to identify when the use of a VMP might impede or interfere with subsequent diagnostic or therapeutic measures.

Concerning the requirement for a "precise prior diagnosis", the term "precise" is understood as clearly implying that the diagnostic skills and knowledge of a veterinarian are required. The term "prior" implies that the (precise) diagnosis must be determined by a veterinarian before the VMP in question can be used. This is considered relevant for pathological processes that could lead to negative consequences on the animal's health and welfare if not adequately diagnosed by a veterinarian and thereby managed appropriately. Therefore, VMPs intended to treat such pathological processes shall remain under veterinary prescription.

Determining "a precise prior diagnosis" is not relevant for VMPs with exclusive preventive claims or indicated for symptomatic treatment of nonspecific conditions or indicated for diseases that can be easily diagnosed by a non-veterinarian and where no threatening consequences for the animal's health and welfare could be identified in case of delayed precise diagnosis. However, Article 34(1)(d) may still apply if the treatment has the potential to impede or interfere with subsequent diagnostic or therapeutic measures.

With "(…) effects which impede or interfere with subsequent diagnostic or therapeutic measures", it is understood that this refers to those VMPs that can mask clinical signs (e.g. lameness) or that could interfere with diagnostic results (e.g. blood samples), potentially critical for a veterinarian to determine an accurate diagnosis and the appropriate treatment.

Additionally, symptomatic treatment of non-specific conditions that could mask potentially severe underlying disease should also be considered under this criterion and such VMPs should therefore remain under veterinary prescription. In those cases, a non-prescription status may prevent the animal

being assessed by a veterinarian and the underlying disease diagnosed and treated correctly, and thereby could lead to negative consequences for the animal's health and welfare (e.g. antiemetics masking nausea and vomiting caused by a gastrointestinal foreign body, or pain treatment in the case of lameness caused by osteosarcoma).

4.2. Article 34, paragraph 2, of Regulation (EU) 2019/6.

Article 34(2) sets out which veterinary medicinal products may be classified as subject to veterinary prescription in addition to the categories listed in Article 34(1):

The competent authority or the Commission, as applicable, may, notwithstanding paragraph 1 of this Article, classify a veterinary medicinal product as subject to veterinary prescription if it is classified as a narcotic drug in accordance with national law or where special precautions are contained in the summary of product characteristics referred to in Article 35.

Therefore, a VMP not covered by Article 34(1) could, at the discretion of the competent authority, still be classified as subject to veterinary prescription according to Article 34(2) if it is classified as narcotic drug according to national law or if the SPC referred to in Article 35 of Regulation (EU) 2019/6 contains "special precautions". As provided for in section I.2.1 of the Annex II to Regulation (EU) 2019/6, applicants are strongly advised to justify a "not subject to veterinary prescription" status according to the dossier requirement.

The term "special precautions" within Article 34(2) is to be understood as any information contained in the SPC that could be reasonably considered as a special precaution (e.g. special precautions relating to information on potential adverse events or the route of administration can be considered to imply special precautions in certain cases).

The special precautions should be of such a nature that not complying with them could lead to negative consequences for the treated animal, the user, or to the environment.

4.3. Article 34, paragraph 3, of Regulation (EU) 2019/6.

Article 34(3) sets out criteria for when veterinary medicinal products mentioned in Article 34(1), by way of derogation from the latter, may be classified as not subject to veterinary prescription, i.e. the possible exceptions from the rule established in Article 34(1). It reads as follows:

By way of derogation from paragraph 1, the competent authority or the Commission, as applicable, may, except as regards veterinary medicinal products referred to in points (a), (c), (e) and (h) of paragraph 1, classify a veterinary medicinal product as not subject to veterinary prescription if all of the following conditions are fulfilled:

- *a) the administration of the veterinary medicinal product is restricted to pharmaceutical forms requiring no particular knowledge or skill in using the products;*
- *b) the veterinary medicinal product does not present a direct or indirect risk, even if administered incorrectly, to the animal or animals treated or to other animals, to the person administering it or to the environment;*
- *c) the summary of the product characteristics of the veterinary medicinal product does not contain any warnings of potential serious adverse events deriving from its correct use;*
- *d) neither the veterinary medicinal product nor any other product containing the same active substance has previously been the subject of frequent adverse event reporting;*

e) *the summary of the product characteristics does not refer to contra-indications related to the use of the product concerned in combination with other veterinary medicinal products commonly used without prescription;*

f) *there is no risk for public health as regards residues in food obtained from treated animals even where the veterinary medicinal product is used incorrectly;*

g) *there is no risk to public or animal health as regards the development of resistance to substances even where the veterinary medicinal product containing those substances is used incorrectly.*

The CVMP's scientific elaboration of the abovementioned criteria are provided below:

4.3.1. Article 34 (3)(a)

a) *the administration of the veterinary medicinal product is restricted to pharmaceutical forms requiring no particular knowledge or skill in using the products;*

Pharmaceutical forms that are considered to require no particular knowledge or skill include those administered orally, rectally, or topically. Such products therefore could potentially be exempted from veterinary prescription. On the other hand, it is generally considered that pharmaceutical forms administered by injection require particular knowledge and skills. Injectables should therefore be subject to prescription. VMPs administered via specific device requiring knowledge and skills should also be under veterinary prescription.

It should be noted that a VMP subjected to prescription could sometimes be administered by a person different from the prescribing veterinarian. Nevertheless, the prescription step would allow to the veterinarian to provide to the person administering the VMP the necessary instructions to ensure a correct administration.

4.3.2. Article 34 (3)(b)

b) *the veterinary medicinal product does not present a direct or indirect risk, even if administered incorrectly, to the animal or animals treated or to other animals, to the person administering it or to the environment;*

Article 34(3)(b) does not make reference to the relevance of the risk identified. Nevertheless, it is considered that only relevant risks with potential serious consequences to animals, users or to the environment should be considered under this paragraph.

This article also refers to direct and indirect risks that may occur even if the VMP is administered incorrectly, i.e. not according to the provisions in the SPC. Further elaboration of these concepts is given below.

Risks to the animal or animals treated or to other animals:

The direct risks are considered risks that are identified for the target animal species and generally appear in section 3.5 of the SPC under the heading "special precautions for safe use in the target species" and under section 3.11, that refers to resistance development (QRD v.9). Indirect risks are considered risks that are identified for animals not intended to be treated with the VMP and whose risks (if identified) would appear in section 3.3 of the SPC (i.e. contraindications).

In relation with the incorrect use of the VMP in the target species, section 3.10 of the SPC (i.e. "symptoms of overdose") should be checked in order to ensure that the VMP shows a good tolerance.

VMPs that demonstrate good tolerance in the target species are considered not likely to pose a significant risk for the treated animal in case of unintentional overdose. Also, the section 3.7 of the SPC (i.e. "use during the pregnancy, lactation or lay") should be checked in order to ensure that there are no major risks for the treated animals. In relation to risks to other animals, these risks include accidental exposure and subsequent relevant risk of animals that share the treated animal's environment (e.g. an untreated cow licking the site of application of a pour-on medicine from the back of a treated animal).

Risks to the person administering the VMP:

The direct and indirect risks for users are identified within the user risk assessment in the authorisation process and appear in section 3.5 of the SPC under the heading "special precautions to be taken by the person administering the veterinary medicinal product to animals". Direct risks are those for the person administering the VMP (including pregnant women). Indirect risks are those that are identified for people not administering the VMP but in close contact with treated animals (e.g. persons living in the same household including children and/or pregnant women, farmers or pet owners, taking specific consideration for immunocompromised individuals).

Regarding incorrect use, such risks for users should be related to relevant effects (e.g. in case of self-injection) and/or the need for personal protective equipment (PPE). In case safe use of a VMP requires wearing PPE, a risk for the user should be considered possible because PPE might be used incorrectly by non-professional users and in such cases the user would not be sufficiently protected. Nevertheless, it should be considered whether the need of PPE is simply a standard and prudent statement (e.g. in certain cases, the requirement to use gloves can be considered as a precautionary measure that would not automatically warrant a veterinary prescription status), or whether exposure due to incorrect use including failing to wear PPE could potentially cause serious health effects to the person administering the VMP (e.g. teratogenic effects, neurotoxicity).

Risks for the environment:

The direct risks for the environment appear in section 3.5 of the SPC under the heading "special precautions for the protection of the environment" and are those identified in the environmental risk assessment (ERA). Indirect risks would be those related to the consequences of an improper disposal of the VMP. Reference to these indirect risks (if any) can be found in the section 5.5 of the SPC.

The risks for the environment could be higher than determined in the ERA if there is a significant risk of incorrect use. Nevertheless, a conclusion on potential risks for the environment due to incorrect use would be taken on a case-by-case basis and depending on the nature of the VMP and on the environmental safety profile of the VMP.

Size of secondary packaging:

Certain veterinary medicinal products may be presented in large containers that are intended for partial dispensing to ensure the quantity supplied is limited to the amount required for the number of animals. Even if smaller container sizes of the same product could be considered for supply without a veterinary prescription, these large containers must be restricted to supply only on veterinary prescription, in order to avoid any risk of misuse or overdosage.

4.3.3. Article 34 (3)(c)

c) the summary of the product characteristics of the veterinary medicinal product does not contain any warnings of potential serious adverse events deriving from its correct use;

It is acknowledged that Regulation (EU) 2019/6 does not include a definition of "serious adverse events". In order to provide guidance on what is considered a serious adverse event, the following should be taken into account, whilst also applying expert judgement: an event that either results in death, is life-threatening, results in significant disability or incapacity, is a congenital anomaly/birth defect, or results in permanent or prolonged signs in the animals treated is considered serious.

Serious adverse events should take into account the clinical signs in the list of Medically Important (MI) terms developed (Appendix 1 of the Guideline on veterinary good pharmacovigilance practices (VGVP) (EMA/522332/2020)), noting this is not an exhaustive list. Furthermore, the nature of potential adverse events in relation to the intended use of the product in the target species (e.g. if adverse events have been reported for products indicated for prophylactic use in healthy animals) should also be taken into consideration.

4.3.4. Article 34 (3)(d)

d) neither the veterinary medicinal product nor any other product containing the same active substance has previously been the subject of frequent adverse event reporting;

Article 34(3)(d) is not linked to the occurrence of a specific adverse event. Instead, the term "frequency" is related to the number of adverse events reported following use of a VMP or other similar products containing the same active substance. Whilst it is acknowledged that frequency categories are used in section 3.6 of the SPC (i.e. adverse events in QRD v.9) these should not be used prescriptively to determine a threshold for determining whether an adverse event is reported 'frequently' for the purposes of applying Article 34(3)(d).

It is acknowledged that it would be useful to have clear guidance to differentiate what is frequent. However, the numbers of reports received are subject to considerable biases not related to the safety of the active substance(s). For example, innovative molecules, new therapeutic indications or VMPs indicated for companion animals, are likely to receive a higher number of reports than other VMPs, simply as there is more focus on the occurrence of potential adverse events in these cases. In addition, it is acknowledged that under-reporting of adverse events impacts frequency calculations, which are generally considered 'underestimates'. Therefore, classifying a total number of adverse reporting as "frequent" would depend on the expert's judgement that should take into account these and other biases. In addition, it should be noted that the total number of adverse events reported cannot be interpreted solely without taking into consideration the total sales of the VMP, as a proxy for estimated use in the reporting period. Incidence of adverse events shall be taken into account to analyse the frequency.

4.3.5. Article 34 (3)(e)

e) the summary of the product characteristics does not refer to contra-indications related to the use of the product concerned in combination with other veterinary medicinal products commonly used without prescription;

It is acknowledged that the current prescription status of individual VMPs authorised via the national or decentralised marketing authorisation procedures may vary across Member States. Therefore, it is not possible set an exhaustive list of VMPs that are used without prescription. Nevertheless, for the purposes of interpretation of this paragraph the following types of VMPs are considered as commonly used without prescription:

- Certain antiparasitic VMPs for companion animals providing that they are not intended to be used for the treatment or prevention of diseases requiring a prior diagnosis.

- Products for bees whose active substances are natural extracts.
- VMPs used for sealing the teat canal during the dry-off period.
- Topic antiseptics.
- Vitamins, minerals, trace elements and electrolytes for all species administered orally.
- Homeopathic VMPs administered orally.
- Propylene glycol to be administered orally.

It should be noted that the list above is not exhaustive and only reflect VMPs commonly not subject to prescription, meaning that some of the VMPs above might be subject to prescription in some countries in the EU.

4.3.6. Article 34 (3)(f)

f) there is no risk for public health as regards residues in food obtained from treated animals even where the veterinary medicinal product is used incorrectly;

For the purposes of the interpretation of Article 34(3)(f) it might be considered that a VMP does not pose a risk for public health, even if it is used incorrectly, when the VMP in question has a withdrawal period of "zero days/hours" in all food commodities and the active substance has a "No MRL required" status listed in Table 1 of Annex to Regulation (EU) No. 37/2010, as amended, for the concerned target specie(s). However, expert judgment is needed on a case-by-case basis to consider other safety aspects such as whether a health-based reference value (e.g. ADI, ARfD) has been established.

4.3.7. Article 34 (3)(g)

g) there is no risk to public or animal health as regards the development of resistance to substances even where the veterinary medicinal product containing those substances is used incorrectly.

The selection of resistance occurs when microbes or parasites are subjected to a high selective pressure due to the presence of antimicrobials or antiparasitic agents in the environment of the animal. Please note that antimicrobials shall, according to Article 34(1)(c) always be used under veterinary prescription as they are excluded from the derogation in Article 34(3). Consequently, the interpretation of this paragraph would only affect to antiparasitic VMPs.

The guideline EMA/CVMP/AWP/706442/2013[3] provides guidance on how to carry out an assessment of risk to public health due to the use of antimicrobials. One of the last steps in this process is the consequence assessment where "[t]he potential consequences (adverse health effects) of exposure of humans to the hazard and the severity and probability of the consequences occurring" should be considered. For the interpretation of Article 34(3)(g), the same principle should be followed: the hazard of the potential of development of resistances due to the use of the VMP in question should be defined, and the consequences of this hazard occurring should be integrated in the likelihood of appearance of resistance that could lead to a therapeutic failure, and the severity of the disease that one is aiming to treat. Regarding the likelihood of appearance of resistance, any reported cases of resistance to the active substance in respect of parasites should be taken into account. Regarding the severity of the disease being treated, the zoonotic potential of the diseases treated by the VMP in question and the seriousness of the diseases in animals should be considered.

[3] Guideline on the assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food producing animals

5. Application of Article 34 of Regulation (EU) 2019/6 to a variation application to change the classification (prescription status) of a veterinary medicinal product.

For variations to change the terms of marketing authorisations as regards the classification (prescription status) of the veterinary medicinal product, the schematic representation depicting the foreseen application of Article 34 of Regulation (EU) 2019/6 (see figure 1) as well as the criteria for the application of the various provisions of this article as detailed in section 4, should be considered. As provided for in section I.2.1 of the Annex II to Regulation (EU) 2019/6, applicants for such variations are strongly advised to justify a "not subject to veterinary prescription" status according to the dossier requirement. Note for veterinary medicinal products not listed in Article 34(1), the competent authority's conclusion on the variation requesting a change to the existing classification will take into account the justification provided by the applicant according to section I.2.1 of Annex II but will ultimately be based on the provisions of Article 34(2).

References

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC

QRD veterinary product-information annotated template version 9.0

Appendix 1 of the Guideline on veterinary good pharmacovigilance practices (VGVP) (EMA/522332/2020)

Guideline on the assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food producing animals (EMA/CVMP/AWP/706442/2013 – Draft 2)