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Reflection paper on criteria for determining that an active substance is essential when considered in the context of Article 37(2)(j) of Regulation 2019/6

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1. Introduction

Persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances are associated with specific concerns because of their persistence, their ability to accumulate in the environment and in living organisms, as well as their toxicity. Due to the combination of these intrinsic properties and possible redistribution across environmental compartments, PBT/vPvB substances can give rise to toxic effects over a longer time and a greater spatial scale than substances without these properties. The effects of persistence/bioaccumulation are unpredictable in the long-term. In the case of vPvB substances specifically, even if limited toxicity is demonstrated in laboratory testing, there is a concern that long-term effects may be possible since, over time, high concentrations may be reached in the environment or in animals at the top of the food chain.

Under different European legislation relating to the regulation of chemical substances, it is recognised that substances that are either PBT or vPvB must be considered hazardous for the environment due to their potential for eliciting long-term adverse effects. However, while the goal of identifying and preventing exposure of humans and the environment to PBT and vPvB substances is shared among different EU regulatory frameworks, the mandatory measures imposed for a substance identified as a PBT or vPvB vary between the different regulatory frameworks. Indeed, unlike the situation for industrial chemicals, biocides and plant protection products, recent veterinary medicines legislation (Directive 2001/82/EC, as amended) did not have any legal provisions relating specifically to the assessment/authorisation of veterinary medicinal products (VMPs) containing PBT/vPvB substances. That changed, however, with Regulation (EU) 2019/6 (application date of 28 January 2022), which introduced a legal provision to refuse an application for marketing authorisation where the active substance in the VMP meets the criteria for being considered PBT or vPvB, and the VMP is intended to be used in food-producing animals, unless it is demonstrated that the active substance is essential to prevent or control a serious risk to animal health.

Therefore, the purpose of this reflection paper is to establish criteria for determining that an active substance is essential when considered in the context of Article 37(2)(j) of Regulation (EU) 2019/6.

2. Discussion

2.1. The requirements for an environmental risk assessment under Regulation (EU) 2019/6

According to Regulation (EU) 2019/6 and Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6, an environmental risk assessment (ERA) is mandatory for all new applications for marketing authorisation for VMPs submitted in accordance with Article 8(1), independent of the application procedure (central or national marketing authorisation).

The ERA is an evaluation of the possible fate, exposure and effects of the product in/on the environmental compartments of concern. This assessment consists of two phases. The first phase (phase I) of the assessment shall always be performed and shall indicate the potential exposure of the environment to the product and the level of risk associated with any such exposure. Depending on the potential environmental exposure, second phase (phase II) assessment may be required. In this phase, further specific investigation of the fate and effects of the product on particular ecosystems must be conducted. For VMPs requiring a phase II assessment, the risk evaluation is structured around the risk quotient (RQ) approach as described in VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) guideline (GL) 38 ("Environmental impact assessment for veterinary medicinal products — Phase II"

[CVMP/VICH/790/03-FINAL]). The RQ is defined as the ratio between the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC), with a potential risk identified when the RQ > 1 (i.e., PEC > PNEC). For non PBT/vPvB substances, the risk assessment may be concluded and a decision on the need for risk mitigation measures may be reached based on the RQ approach. However, the properties of PBT/vPvB substances lead to an increased uncertainty in the estimation of risk when applying quantitative risk assessment (i.e. the RQ). For these substances, a safe concentration in the environment cannot be established with sufficient reliability. Therefore, this approach is not fully applicable for these substances and a separate hazard-based PBT/vPvB assessment is required, which focuses on intrinsic properties of substances. In section II.3A6 (4) of Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6, it is stated that "[f]or products intended for food producing species, persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances shall be classified according to the criteria in Annex XIII to Regulation (EC) No 1907/2006 of the European Parliament and of the Council (REACH Regulation) and assessed according to the guidance for PBT and vPvB assessment of substances in veterinary medicines published by the Agency".

Current CVMP guidance states that a PBT assessment is performed for all substances that enter phase II and have an octanol/water partition coefficient (log K_{ow}) ≥ 4 ("Guideline on the assessment of persistent, bioaccumulative and toxic [PBT] or very persistent and very bioaccumulative [vPvB] substances in veterinary medicinal products [EMA/CVMP/ERA/52740/2012]). However, in this guidance document it is also stated that a PBT assessment could be required for substances in products that do not enter phase II assessment if there is evidence, or strong indications, that the active substance has PBT properties. For example, this could be the case for substances with a valid log K_{ow} ≥ 4 or that have been assessed as PBT/vPvB in other regulatory frameworks.

It should be noted that, under Regulation (EU) 2019/6, an ERA is not a standard requirement for certain applications for marketing authorisation. In particular, according to Article 18(7) of this regulation, an ERA for a generic application may be required only where the marketing authorisation for the reference VMP was granted before 1 October 2005 (see reflection paper on the interpretation of Article 18[7] of Regulation [EU] 2019/6 [EMA/CVMP/ERA/622045/2020]).

2.2. Understanding Article 37(2)(j)

> *Article 37*
>
> ***Decisions refusing marketing authorisations***
>
> *1. Decisions refusing marketing authorisations referred to in Article 5(1) shall be taken on the basis of the documents prepared in accordance with Article 33(1) and shall be duly justified and include the reasons for refusal.*
>
> *2. A marketing authorisation shall be refused if any of the following conditions are met:*
>
> *[...]*
>
> *(j) the active substance within the veterinary medicinal product meets the criteria for being considered persistent, bioaccumulative and toxic or very persistent and very bioaccumulative, and the veterinary medicinal product is intended to be used in food-producing animals, unless it is demonstrated that the active substance is essential to prevent or control a serious risk to animal health.*

When deciding on whether or not this provision applies, the principal questions to be addressed are:

- Does the active substance meet the criteria for classification as PBT/vPvB? and,

- is the product (containing that active substance) intended for use in food-producing animals[1]?

A decision to refuse a marketing authorisation based on PBT/vPvB properties relates to VMPs intended for food-producing animals only. Products intended for use in non-food-producing species will not be refused on the basis of PBT/vPvB status, where the overall benefit-risk assessment is adjudged to be positive.

It is important to note that the legal text does not allow for the extent of environmental exposure to be taken into account when applying this provision.

In relation to the first question, a PBT assessment will only be required as part of an ERA when considered necessary in accordance with current guidance, i.e. a PBT assessment is performed for all substances that enter phase II and have log $K_{ow} \geq 4$. Also, as acknowledged above, a PBT assessment could be required for substances in products that do not enter phase II assessment if there is evidence, or strong indications, that the active substance has PBT properties. In the event that a substance is classified as PBT/vPvB by the relevant competent authority, then, regardless of extent of use, this article will apply.

Where an ERA is not required in support of an application for marketing authorisation for a product intended for use in food-producing species, it follows that a PBT assessment will not be required as part of that regulatory submission (see section 2 above). However, given that PBT/vPvB status is a characteristic of the active substance (independent of the product formulation in which the substance is included), it follows that if an active substance is determined to be PBT/vPvB (during a marketing authorisation [MA] procedure or in the context of a Union interest referral), then this determination will have implications for all existing marketing authorisations for products intended for use in food-producing species and containing that active substance. In this scenario, it is possible that a Member State or the Commission may trigger a review of all relevant products by referring its concern to the Agency in accordance with Article 82 of Regulation (EU) 2019/6 (Union interest referral).

Given that:

- the extent of environmental exposure is not taken into account when applying Article 37(2)(j),
- current CVMP guidance does not exclude the possibility that a PBT assessment may be requested for substances in VMPs that would not ordinarily require phase II assessment,
- classification of an active substance as PBT/vPvB will have implications for existing marketing authorisations for products intended for use in food-producing species and containing that active substance (regardless of the underlying legal basis), and
- this specific restriction results in refusal of the marketing authorisation,

it is advisable that an applicant when developing a new product intended for a food-producing species, regardless of its intended use, screens the substance for potential PBT properties at an early timepoint in the product development process and takes the findings into consideration in its approach to product development. This is an important consideration for both new and existing active substances and for both full and abridged applications given that Article 37(2)(j) applies to all active substances and is not restricted to specific application types. Again, in the event that a substance is classified as PBT/vPvB and is included in a product intended for a food-producing species, then this article will apply.

[1] According to Regulation 2019/6, Article 4(38) "food-producing animals" mean food-producing animals as defined in point (b) of Article 2 of Regulation (EC) No 470/2009. The definition included in article 2(b) of Regulation (EC) No 470/2009 is as follows: "food-producing animals" means animals bred, raised, kept, slaughtered or harvested for the purposes of producing food. Regulation (EC) No. 854/2004 established that horses are considered to be food-producing animals.

For the purposes of applying Article 37(2)(j), it should be noted that:

- the authorisation of products intended for use in food animals containing substances classified as PBT/vPvB should be considered exceptional,
- persistent, bioaccumulative and toxic or very persistent and very bioaccumulative substances should not be used in place of alternative treatments or management strategies.
- the essentiality of a substance is only to be considered in the context of "a serious risk to animal health". That is, where the condition/disease to be treated does represent a serious risk to the health of the animal. Concepts such as use of VMPs for zootechnical[2] purposes are not covered by this provision. Products that play a role in preventing zoonotic disease or otherwise protecting public health may fall under the exemption as laid down in Article 37(2)(j) where the condition/disease to be treated also poses a serious risk to animal health.

For those substances that are classified as PBT/vPvB and are deemed to satisfy the criteria for essentiality, the final decision to grant the marketing authorisation will still need to be taken based on a positive benefit-risk balance overall and where none of the other reasons for refusal detailed in Article 37(2) apply.

2.3. How to define "essential"

For the purposes of applying Article 37(2)(j), a substance should only be considered essential in exceptional circumstances where no satisfactory alternative treatment for a therapeutic indication is authorised and where the condition would, if untreated, create unnecessary suffering for the animal.

Therefore, when defining a product as essential, two criteria are of importance: therapeutic use and availability of alternatives.

A. Therapeutic use

The medicinal product is used to prevent or control a serious risk to animal health associated with a disease, which is life-threatening or irreversibly progressive, or without which animal health could be severely harmed. This could be in acute situations (e.g. emergency situations), or chronic situations/maintenance of stable conditions, or disease with a fatal outcome where the product has been shown to affect the progression of the disease or survival.

B. Availability of alternative veterinary medicinal products

While a product may satisfy the criteria for therapeutic use (defined above), it would not be classified as being essential in case appropriate alternatives are available.

Essential substances may be used for specific disease conditions or treatment needs, where there is an unmet medical need. In this context, unmet medical need is defined as "no authorised VMP in the Union that would yield equally satisfactory results in terms of successfully treating the animal or avoiding unnecessary suffering for the animal". It should be noted that off-label use (use under the "cascade") of an approved veterinary or human medicinal product does not qualify as addressing a medical need because safety and efficacy have not been established for the off-label use.

For substances that are intended for the prevention or control of disease caused by bacteria, viruses, fungi or parasites, it is recognised that there may be a need for substances with different pharmacological properties to address the threat of resistance. In this context, and noting that the authorisation of products for use in food-producing animals containing PBT/vPvB substances should be

[2] Of or relating to the science of breeding animals.

under exceptional circumstances only, a substance may be considered essential where there is clear evidence for a need of an alternative active substance in order to limit the selection and development of resistance and to be able to successfully treat the specific condition where resistance to authorised products has been documented. For example, where the substance is acting at a different site of action and/or with a different mode or mechanism of action compared to authorised products.

For those situations where a PBT/vPvB substance may be required to successfully treat (a) specific pathogen(s), consideration of "essential status" will relate to those specific pathogens only (that is, use of the substance for other purposes/other pathogens would not be considered essential and, therefore, would not form part of the authorised indication).

As advised above, for those substances that are classified as PBT/vPvB and are deemed to satisfy the criteria for essentiality, the final decision to grant the marketing authorisation will still need to be taken based on a positive benefit-risk balance overall and where none of the other reasons for refusal detailed in Article 37(2) apply. In the context of the overall benefit-risk assessment, the competent authority may consider it appropriate to restrict the authorised conditions of use of the product with a view to limiting the potential for environmental exposure (that is, authorise subject to appropriate risk-mitigation measures to ensure that exposure of the environment to those active substances is minimised). As part of this assessment, consideration should be given to the appropriateness of the pharmaceutical form and product presentation (pack size) for the intended target population with a view to facilitating targeted treatments and precise dosing. Further, prior to issuing a marketing authorisation for such products, the competent authority may require the applicant to propose measures to ensure that the authorised conditions of use, including risk mitigation measures (RMMs)[3] to minimise environmental exposure, are clearly communicated to the prescriber/end-user. In addition to highlighting potential environmental effects, the competent authority may require steps to be taken to promote alternative approaches to prevent or control disease with a view to minimising reliance on, and reducing the use of, PBT/vPvB substances by targeting treatment to those animals that require it.

2.4. Determining whether or not an active substance is considered essential

While it is stated that it is the essential status of the active substance that requires consideration, it is clear that this determination is to be made by the competent authority or the Agency in the context of a specific marketing authorisation application. Therefore:

- Determination of essentiality of a substance will be specific to the product in question and its intended use (target species, proposed indication) in the context of preventing or controlling a serious risk to animal health. That said, it is clear that classification of an active substance as PBT/vPvB in the context of a MA application will have implications for existing MAs for products intended for the same or similar use (see the section *"Understanding Article 37(2)(j)"* above).
- A separate evaluation of essentiality of a substance should be carried out when the substance is included in VMPs intended for a different purpose (different target species and/or proposed indication). In this case, the conclusion on essential status of the substance may be different to the original determination.
- Further, while a harmonised approach to determining the essentiality of an active substance would be desirable, it would be possible for different competent authorities to come to different

[3] EMA/CVMP/ERA/52740/2012 Guideline on the assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicinal products https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-assessment-persistent-bioaccumulative-toxic-pbt-very-persistent-very-bioaccumulative-vpvb_en.pdf

conclusions regarding the essential status of an active substance taking account of, among others, availability needs in different Member States.

It should be noted that, in order to facilitate targeted treatments and to minimise the potential for unnecessary environmental exposure to a PBT/vPvB substance, determination of essentiality of a PBT/vPvB substance will only be considered for VMPs formulated as single active substance products. That is, a PBT/vPvB substance will not be considered essential if presented in combination with (an)other active substance(s), where the primary purpose of the combination is to broaden the spectrum of activity of the product.

Also, when determining the essential status of a vPvB substance specifically, existing guidance of the CVMP (EMA/CVMP/ERA/52740/2012) will be taken into account. This guidance states that "[...] given the potential significant impacts on human health and the environment it seems unlikely that an authorisation for a vPvB substance in a veterinary medicinal product where the substance will be released to the environment could be granted". Therefore, the additional hazard considerations posed by these substances should be taken into account when considering the overall benefit-risk assessment.

While, ultimately, the decision on whether or not an active substance is considered essential will be taken in the context of an application for marketing authorisation, it appears appropriate, that a mechanism is provided whereby it would be possible for an applicant to seek advice on the "essential" status of an active substance (suspected to be PBT/vPvB) before proceeding to full product development. For example, this could be conducted in the context of Scientific Advice using a procedure similar to that put in place for "preliminary risk profiling" of new antimicrobials. The advice given in the context of such a procedure will be based on the questions and documentation submitted, without prejudice to evolution and state of the art developments and the subsequent assessment of a MA application by the relevant competent authority. EMA will consider putting such a procedure in place.

In the event that an active substance is deemed essential in the context of an application for marketing authorisation, it is possible that the conditions under which the determination was made will change subsequently, for example with the authorisation of a non-PBT alternative. While there is no explicit legal mechanism whereby the "essential" status of the substance is to be reconsidered subsequent to its original determination, this aspect will form a critical element of the overall benefit-risk assessment and, therefore, could be revisited when re-evaluating the benefit-risk balance in the context of any post-authorisation regulatory activity relating to that product or at the request of the Member States or the Commission in the context of a Union interest referral (Article 82 of Regulation [EU] 2019/6). A possible outcome of a subsequent re-examination is that it may lead to revocation of such marketing authorisation (due to the fact that the product is not considered essential anymore in the meaning of Article 37[2][j]).