14 October 2022
EMA/CVMP/352510/2022
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on "Reflection paper on criteria for determining that an active substance is essential when considered in the context of Article 37(2)(j) of Regulation (EU) 2019/6" (EMA/CVMP/116512/2021)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	AnimalhealthEurope (AhE)
2	Access VetMed
3	Norwegian Environment Agency
4	Federation of Veterinarians of Europe (FVE)
5	Friends of the Earth Germany (BUND)

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	AnimalhealthEurope welcomes the opportunity to comment to this draft reflection paper. This document sends a clear message that very careful consideration by companies is required before developing a new product which contains a PBT/vPvB substance classified as such by the criteria and extrapolations set out under REACH.	The fact that the content of the reflection paper is seen by AhE as providing a "clear message" is noted. The CVMP welcomes the comment that the "message" has been clearly received.
2	Access VetMed welcomes the opportunity to comment on this reflection paper. According to the Reflection paper on the interpretation of Article 18(7) of Regulation (EU) 2019/6 and as stated in lines 92-96 in this consultation: *"The VMP-Reg no longer requires that an ERA is provided routinely with a generic application, effectively bringing the ERA in line with the rest of the safety aspects in part 3 of the dossier."* In line with the Regulation 2019/6, no ERA is required for generic products of which the reference product (RP) was registered after 1 October 2005. Therefore generics fulfilling the above stated fall out of the restrictions of the current reflection paper and that of the Article 37(2)(j) of Regulation 2019/6.	Notwithstanding the exemption from the requirement to furnish environmental risk assessment (ERA) data for generics provided for in Article 18(7) of Regulation (EU) 2019/6, this does not imply that generics may be considered exempt from (or, out-of-scope of) Article 37(2)(j). To clarify, if a generic product is intended for food producing species and the substance included in the product has been identified as persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB), then such a product should not be granted a marketing authorisation (MA) unless that substance is determined to be essential to prevent or control a serious risk to animal health. No change to text proposed.
3	**Specific comments** The Chemicals Strategy for Sustainability Towards a Toxic-Free Environment proposes the development of a horizontal essential use concept to apply across chemicals legislation. The Chemicals Strategy commits to "define criteria for essential uses to ensure that	Comments, in particular those relating specifically to aquaculture, are noted. However, the reflection paper is very clear that marketing authorisation applications for veterinary medicinal products (VMPs) intended for food animals containing substances

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	the most harmful chemicals are only allowed if their use is necessary for health, safety or is critical for the functioning of society and if there are no alternatives that are acceptable from the standpoint of environment and health". To our understanding, the primary objective of an essential use concept is to reduce the use and exposure of hazardous substances, such as PBT and vPvB substances, by allowing only a limited use of a harmful substance in certain selected essential applications, while a secondary objective is to make the process of regulating hazardous substances simpler and more efficient. The introduction of too broad and unspecific derogations to restrictions under an essential use concept should be avoided to meet these objectives. In the Biocidal Products Regulation (BPR), PBT and vPvB active substances meet the exclusion criteria and shall not be approved. Article 5(2) opens for derogations to this rule, one of which is if: "not approving the active substance would have a disproportionate negative impact on society when compared with the risk to human health, animal health or the environment arising from the use of the substance." The phrase essential use is not used in the BPR, but the objective is the same. A comparative assessment including the availability of suitable and sufficient alternative substances or technologies is fundamental to see if the criteria for derogation are met. The use of a biocidal product containing PBT and/or vPvB substances that are approved in accordance with this derogation shall be subject to appropriate risk-mitigation measures to ensure that exposure of humans, animals and the environment to those active substances is minimised. A similar approach should/could be used for the VMPs.	identified as PBT/vPvB should be refused unless that substance is determined to be essential to prevent or control a serious risk to animal health. When considering essential status, the text is clear that a substance should only be considered essential in exceptional circumstances where no satisfactory alternative treatment exists and where the condition would, if left untreated, create unnecessary suffering for the animal (section 2.3 – criteria A and B). Further, the text is clear that, where such products are authorised, appropriate risk mitigation measures (RMMs) should be applied to limit potential environmental exposure and that measures should be taken to clearly communicate risks to the prescriber/ user (lines 203-215). No change to text proposed.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Specific comments related to aquaculture Use and discharge of substances with PBT/vPvB properties is highly concerning and it is important to develop new pharmaceuticals without such substances. Therefore, the ban of active ingredients with PBT/vPvB properties for pharmaceuticals applying for a marketing authorisation is very important. This ban is especially important in the fish farming industry where fish are farmed in open fish pens. Most medicines in aquaculture are administered through fish feed or as a bath treatment in the fish pens. Hence, the medicines have a much higher potential to spread to the marine environment than if the medicine was administered directly in each fish. It is of great importance that the interpretation of "essential" in article 37 will be harmonised with the essential use concept elaborated under the chemical strategy for sustainability. We recommend that such exceptions should only be possible during a transmission period until better alternatives without PBT/vPvB properties, are available. With regard to aquaculture of fish there are already alternative medicines without such properties on the market and there are also alternative non-pharmaceutical methods available.	The concern highlighted is noted; however, CVMP, in drafting this reflection paper, must operate within the legal parameters set. To propose an absolute ban on use for certain species would go beyond what is provided for in the legislation. No change to text proposed. While Article 37(2)(j) itself does not provide for a "transition", the reflection paper is clear that the essential status of a substance can be revisited if there is a change to the circumstances under which the original determination was made (lines 257-267). No change to text proposed.
4	FVE considers that protection of environment is of utmost importance and welcomes the CVMP initiative to look into criteria for determining conditions under which an active substance could be considered essential. FVE highlights however that these conditions should not hamper availability of treatment options and risk to withdrawal of certain important substances or products, e.g. antiparasitic, from the market. In that respect, a thorough	Comment noted. A "satisfactory alternative" is where the medical need is satisfied. The concept of unmet medical need is addressed in section 2.3(B). The CVMP accepts that a parasitic disease, if left untreated could be a cause of serious, potentially life-threatening,

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	consideration of certain aspects is necessary and appropriate clarifications need to be part of the guidance on these criteria, i.e. - Define what is considered a **satisfactory alternative** treatment for a therapeutic indication - Define what a **serious risk associated with a life-threatening or irreversibly progressive disease** is, for example a parasitic disease has several stages and if it remains untreated could be life-threatening in the long term. - Clarification on the mechanism and definition of acceptable alternatives is necessary on which revocation of the MA of an essential substance can be based. Since there is not clear legal provision for reconsideration of the "essential" status of the substance this is an important point for consideration. - **mitigation measures** have to be considered as part of the overall assessment for the characterisation of a essential PBT/vPvB substance. Since the process for licensing a veterinary medicinal product changes to use characterization as 'essential substance' as the starting point for further development of a product, aspects that may apply to mitigate potential risks, e.g. formulation or route of administration, have to be considered as part of the characterization process. - the guidance to be developed should as much as possible ensure **a harmonised approach throughout the Union**, especially in cases where different authorities may have different assessment results.	disease. This is addressed in section 2.3(B), where reference is made to substances "that are intended for the prevention and control of disease caused by bacteria, viruses, fungi or parasites….". Regarding the definition of acceptable alternatives, it is unclear how the stakeholder wishes to have the text amended. Again, the concept of unmet medical need (satisfactory alternatives) is addressed in section 2.3(B). In the context of Article 37(2)(j), the starting point for consideration is: • Does the product contain a substance identified as PBT/vPvB? and, • Is the product intended for use in food animals? If the answer to both questions is "yes", then marketing authorisation applications for such products should be refused unless that substance is determined to be essential to prevent or control a serious risk to animal health. The essential status of a substance is something that needs to be considered early in the product development process. Notwithstanding the fact that a substance may be considered essential, the reflection paper is clear that, where products containing such substances are authorised, appropriate RMMs should be applied to limit potential environmental exposure and a MA will only be granted based on a positive benefit-risk assessment which will take into account the appropriateness of the pharmaceutical form, product presentation and proposed conditions of use.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	FVE strongly supports the need for environmental risk assessment as part of marketing authorisation procedure, but highlights the need for a science-based assessment that applies a holistic approach, whereby mitigation measures and availability of efficient treatment options for both terrestrial and aquatic animals are thoroughly considered.	This is an aspect that an applicant needs to be conscious of during product development. Regarding the need for a harmonised approach throughout the EU, the comment is noted. Indeed, one of the objectives of developing a reflection paper is to arrive at a common understanding of how the provision should be implemented. However, relevant competent authorities (CAs) (EMA and National competent authorities (NCAs)) are ultimately responsible for taking decisions to authorise and as noted in line 230-233, it is possible for different CAs to come to different decisions depending on specific availability needs.
5	FoE Germany (BUND) welcomes EMA's draft to define "essential uses" of veterinary medicinal products with PBT/vPvB properties. In general, PBT/vPvB substances are particularly hazardous to the environment and should only be approved in a few exceptional cases when alternative treatment methods are not available. In the context of the upcoming revision of REACH Regulation (EC) No 1907/2006, the criteria for "essential uses" are currently being discussed in detail. In principle, the Montreal Protocol is to be followed, which defines essential as "necessary for health, safety or critical for functioning of society" and "no available technically and economically feasible alternatives" exist. The criteria should therefore be set very strictly so that the use of VMPs with PBT/vPvB properties is limited to a few indispensable applications. The present Reflection paper, in part, still leaves options open to a rather generous interpretation of the criteria.	Comment noted. However, the reflection paper is very clear that marketing authorisation applications for veterinary medicinal products intended for food animals containing substances identified as PBT/vPvB should be refused unless that substance is determined to be essential to prevent or control a serious risk to animal health. Further, it is stated that the authorisation of such products should be exceptional and that, where such products are authorised, appropriate RMMs should be applied to limit potential environmental exposure. No change to text proposed.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	In general, bioaccumulating VMPs are problematic in food-producing animals because they are excreted only slowly and, due to their persistence, are metabolized only to a limited extent. For this reason, the fact that they are consumed by humans must be taken into particular account in the authorization process. Due diligence is necessary when setting maximum residue limits. The limitation of the PBT/vPvB assessment provided for in Regulation 2019/6 is to be criticized. In special cases, e.g. external treatment of pets such as dogs against lice or feeding VMPs to wild animals such as pigeons, can lead to significant environmental exposures to hazardous substances. Drugs with PBT/vPvB properties should not be authorised. An additional requirement should be to exclude PBT substances in aquaculture totally. Pharmaceuticals in aquaculture cannot be administered without contamination of the water body. An important measure to avoid misuse is a documentation requirement. Therefore, the necessity to use essential VMPs must be justified in writing by veterinarians and authorities should develop statistics in order to document the amount of application of PBT/vPvB substances.	This is a criticism of the legal provision itself. The CVMP, in drafting this reflection paper, must operate within the legal parameters set. To include a consideration of products for non-food animals in this reflection would go beyond the scope of the provision. Similarly, to propose an absolute ban on use for certain species would go beyond what is provided for in the legislation. No change to text proposed. There is no recording requirement as a condition of use attached to this provision. However, it should be noted that the products in question will be subject to prescription and related controls. Further, it should be noted that there is a requirement for marketing authorisation holders (MAHs) to record sales data in the Union Product Database. This may allow the regulatory authorities to document the amount of use of the products in question.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
76	1	Comment: This refers to a "hazard" based assessment. However, in the final assessment the risk of the product needs to assessed and managed linked to the benefit (unmet medical need).	Comment noted. However, the initial assessment is essentially hazard based. The legislation requires that a marketing authorisation for a product containing a substance identified as PBT/vPvB and intended for use in food animals should be refused unless that substance is determined to be essential to prevent or control a serious risk to animal health. The product-specific benefit risk assessment is only relevant where the substance is determined to be essential. No change to text proposed.
84-91	3	Comment: For a risk assessment, hazard is compared to exposure. There seems to be agreement that a risk assessment is not reliable for PBT/vPvB substances. This is especially obvious for vPvB substances, which may have no hazard data for the environment, but have persistence and bioaccumulative properties of concern. It is therefore hard to grasp the logic of requiring a risk to be demonstrated in phase 1 before the PBT/vPvB properties are assessed in phase 2. This could lead to PBT/vPvB substances not being addressed and granted marketing authorisation. Proposed change: PBT/vPvB assessment should be performed in phase 1.	Not accepted. The text as presented in lines 84-91 reflects current CVMP guidance.
87-89	2	Comment: In the Reflection paper it is stated that according to the PBT guideline	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(EMA/CVMP/ERA/52740/2012 effective in 2016) 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 January 2020 a supportive Q&A document to the PBT guideline (EMA/593989/2019) was published by EMEA, where it was confirmed that PBT assessment is not required for products where the ERA can stop in phase I. In this case, the PBT hazards should be reflected in the SPC. Proposed change: For substances in products that stop in phase I, no further PBT assessment is required, despite the evidence, or strong indications, that the active substance has PBT properties. Potential PBT properties of the API should be reflected in SPC of the product.	Ordinarily, for a product ERA that stops at phase I, a PBT assessment is not required. However, given: • the legal requirement to refuse a MA where the product contains a substance identified as PBT/vPvB and intended for use in food animals, and • that the extent of environmental exposure is not taken into account, it is appropriate that the regulatory authorities may require a PBT assessment for a substance where there is strong evidence that it has PBT/vPvB properties even when an ERA for a product containing that substance may stop in phase I. This is in line with the guidance provided in the 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). The CVMP acknowledges that the supporting Q&A document advises that known PBT hazards of a substance should be reflected in the summary of product characteristics (SPC) of products where the ERA stops at phase I (without requiring that a PBT assessment be repeated and submitted as part of the data package); however, with the change in legislation (specifically the new PBT provision), it would not be appropriate to label a product intended for use in food animals as containing a substance identified as PBT and leave it on the market without confirming PBT status and, in

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			case PBT/vPvB was confirmed, without making a determination of essential status.
90-91	2	Comment: The criteria for triggering PBT assessment should be defined more precisely. REACH guidance (ECHA, Chapter R7a) states that "*The value for the dissociated molecule determined around a Ph of 7 (sometimes referred to as Dow) is considered more realistic for PBT and chemical safety assessment*". Proposed change: According to this, the trigger for PBT assessment should be logKow ≥ 4 at Ph 7 ± 0.5.	Not accepted. While is recognised that the stakeholder makes a valid comment, it is not the purpose of this reflection paper to update existing guidance on PBT assessment. That said, it is noted that the existing guidance does cross-reference the relevant REACH guidance, where the more precise requirements for Kow determination can be found.
111	3	Comment: In the document reference is given to criteria for classification as PBT/vPvB substances. Annex XIII of REACH describes criteria for the identification but not the classification of PBT , vPvB substances. Classification criteria for PBT, vPvB according to CLP have not been established yet. Proposed change: use the term identification instead of classification for PBT/vPvB.	Accepted.
113-116	3	Comment: The release of PBT compounds to the environment is no less problematic if it comes from veterinary medicines used on a non-food producing or food-producing animal. Having already stated in this document that the risk assessment is not entirely applicable to PBT/vPvB substances, it seems odd to be able to conclude so broadly that the use of PBT/vPvB substances in non-	Not accepted. The proposed change goes beyond what is provided for in the legislation. The CVMP, in drafting this reflection paper, must operate within the legal parameters set. To include a consideration of products for non-food producing animals in this reflection would go beyond the scope of the provision.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		food animals will have a positive benefit-risk assessment. Emission of VMP with PBT/vPvB properties can lead to unpredictable long-term adverse effects on the environment and human health. Therefore, emission of PBT/vPvB veterinary medicines should be minimized as much as possible. Proposed change: The use of PBT/vPvB substances should not be dependent on whether the animal is used for food production, but instead be equally applied to all animals.	
119-121	3	Comment: The limit value is set to a log K_{OW}≥ ≥ 4 or higher as a proxy for the potential for bioaccumulation. While we agree that this is an important parameter in aquatic animals, it's reliability as a screening level tool is limited for air breathing animals. The A log K_{OW}≥ 2 and a Log K_{OA} ≥ 5 is now commonly referenced as a set of screening values for air-breathing animals. Proposed change: Add log K_{OW}≥ 2 and a Log K_{OA} ≥ 5 as screening values in terrestrial animals, alongside the Log K_{OW} ≥ 4 for aquatic animals	Not accepted. The limit value included in the document reflects what is stated in current CVMP guidance.
128-133	2	Comment: Access VetMed is concerned about the wording: 'it follows that if an active substance is determined to be PBT/vPvB (during a marketing authorisation [MA] procedure..'	Accepted. The text in question will be amended to read: "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

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The statement implies that an API may be classified as PBT/Vpbt substance based on the results of studies for a single application. It should be clarified that whilst an API may appear to potentially be a PBT/Vpbt substance based on the studies submitted with a single Marketing Authorisation application, a conclusive designation of PBT/Vpbt for an API across all products should only be made on the basis of the weight of evidence of all available data as described in the REACH/ECHA guidelines. Proposed change: The reflection paper should make it clear that a PBT/Vpbt designation can only be made for APIs in already authorised products following consideration of all available evidence, most likely following an Article 82 of Regulation (EU) 2019/6 (Union interest referral) procedure.	active substance is determined to be PBT/vPvB (for example, in the context of an assessment conducted by ECHA, during a marketing authorisation [MA] procedure or in the context of a Union interest referral where all available evidence is considered), then this determination might ~~will~~ have implications for all existing marketing authorisations for products intended for use in food-producing species and containing that active substance, in particular regarding possible changes to the benefit-risk balance of VMPs concerned.”
133-135	2	Comment: it should be ensured that, if an API is demonstrated as being PBT/vPvB during a marketing authorisation procedure, a referral should then be triggered to assess all existing marketing authorisations of the same API used in food producing species. At present, the proposed wording ‘may’ only infers a possibility and that could lead to not scientifically sound situations while not providing a level playing field to all marketing authorisation holders. Proposed change: “…In this scenario, ~~it is possible that~~ a Member State or the Commission **shall** ~~may~~	Not accepted. Noting that the document in question is a reflection paper and that CVMP is not in a position to place obligations on Member States or the Commission, it is not considered appropriate to use the word “shall”. However, following further reflection, the text in question has been amended as follows: “…then this determination might have implications for all existing marketing authorisations for products intended for use in food-producing species and containing that active substance, in particular regarding possible changes to the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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)".	benefit-risk balance of the VMPs concerned. This topic is, however, outside the scope of this reflection paper. ~~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)~~".
143	1	Comment: this specific restriction results in refusal of the marketing authorisation, "unless there is an otherwise unmet essential medical need" should be added. Proposed change: please add "unless there is an otherwise unmet essential medical need"	Partially accepted. Reflecting the text of the Regulation, the text has been amended to read: "~~this specific restriction results in~~ Article 37(2)(j) requires the refusal of the marketing authorisation (unless it is demonstrated that the active substance is essential to prevent or control a serious risk to animal health)"
154-155	1	Comment: There is no definition of "management strategies", nor criteria under which any such strategies could be regarded as successful with regards to animal health. An applicant would not be able to predict which alternative management strategy CVMP may consider to be preferential compared with a product containing a PBT (or vPvB) substance with a proven safety and efficacy profile. Proposed change: Please consider adding example criteria under which such strategies could be regarded as successful.	Proposed change not accepted. It will be for the applicant to argue that the disease/condition that the PBT substance is intended to treat cannot be successfully controlled by non-chemotherapeutic means (that can be implemented under practical farm conditions).
155	1	Comment: Not all management strategies are capable of reducing or eliminating the need for treatments.	Proposed change not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: please consider expanding text as follows "… or management strategies <u>that have demonstrated to significantly reduce the need of treatments</u>."	It will be for the applicant to argue that the disease/condition that the PBT substance is intended to treat cannot be successfully controlled by non-chemotherapeutic means (that can be implemented under practical farm conditions).
167	3	Comment: For the definition of "essential "the development under the essential use concept needs to be taken into account. For VMP with PBT /vPvB properties their long-term adverse effects can be unpredictable. Therefore, it will be difficult to assess the benefit risk balance of the VMP as required in article 37(2).	The essential nature of the substance is addressed in section 2.3. No change in text proposed.
168	4	Comment: Please clarify what "no satisfactory alternative treatment for a therapeutic indication" means and how a characterisation may affect existing treatment options. Proposed change: Add clarifications in the reflection paper and/or a provision for clear definitions in the following guidance.	A "satisfactory alternative" is where the medical need is satisfied. The concept of unmet medical need is addressed in section 2.3(B). No change in text proposed.
173-177	5	Comments: The definition of "therapeutic needs" leaves considerable room for interpretation. Concrete examples may help to make clear and exemplify when an exceptional application is justified.	The CVMP accepts that the definition of "therapeutic needs" leaves room for interpretation. However, it is clear from the definition that we are talking about diseases/conditions that have the potential to cause serious harm, unnecessary animal suffering and be life threatening. It is considered that the inclusion of specific examples may not add further value.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
173-177	4	Comment: With regard to the criterion about therapeutic use and the impact of a disease, it needs to be clarified how the balance of an alternative against the PBT/Vpbt in question would be assessed. What happens if an alternative exists and it is not that efficient as the proposed PBT/Vpbt? How the existence of mitigation measures can impact decision in such case? Proposed change: Add clarifications in the reflection paper and/or a provision for clear definitions in the following guidance.	A "satisfactory alternative" is where the medical need is satisfied. The concept of unmet medical need is addressed in section 2.3(B). No change in text proposed.
187-195	5	Comments: We appreciate the comments on resistance management. Here in particular, the need for mandatory documentation should be highlighted. Regarding antimicrobials, it should be pointed out that emergency antibiotics (with PBT properties) for human therapy must not be authorized.	Comment noted. Regarding the need for mandatory documentation, there is no recording requirement as a condition of use attached to this legal provision. However, it should be noted that the products in question will be subject to prescription and related controls. Regarding antimicrobials specifically, any antimicrobial resistance (AMR) risks to public health will be addressed within the context of the assessment of the application for marketing authorisation and will be taken into account as part of the overall benefit risk assessment. This requirement has to be met for all antimicrobials, irrespective of their importance to public health (categorisation). No change in text proposed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
187-195	2	Comment: The essentiality of retaining a wide range of APIs to counteract resistance is identified. In a similar manner the whole range of environmental effects should be considered when considering the essentiality of a PBT API since the removal of one product simply based on its PBT status may inadvertently result in increased adverse effects in some environmental compartments where the alternative treatments show higher toxicity than the PBT API. Proposed change: Proposed additional text*: The decision on essentiality of an API should also consider the whole range of environmental effects of both the API and alternatives since the removal of one product simply based on its PBT status may inadvertently result in increased adverse effects in some environmental compartments where the alternative treatments show higher toxicity than the PBT API.*	Not accepted. According to Article 37(2)(j), the decision on essentiality must be based on the need to prevent or treat a serious risk to animal health. It should be assumed that any alternatives will, by virtue of the fact that they are authorised, have a positive benefit/risk balance based on the proposed conditions of use (that is, documented benefits that outweigh the risks, including environmental risks, associated with their use).
187-189	1	Comment: Please note that resistance is dynamic in nature and alternatives that were once appropriate may lose their effectiveness. It is important to have sufficient alternatives available even in the case of reduced sensitivity as this may reduce selection pressure. Proposed change: Please specify how necessity would need to be documented when referring to reduced sensitivity/resistance.	CVMP agrees with the comment. Indeed, the need to have sufficient alternatives available is recognised and acknowledged in the text (lines 187-195). However, noting that the authorisation of products containing substances identified as PBT should be exceptional, the text advises that anti-infectives that are PBT may be considered essential only "where there is clear evidence of a need for an alternative". The text goes on to

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			state "where resistance to authorised products has been documented". The CVMP is of the view that the advice on this point is clear, while not being overly prescriptive. No change to text proposed.
196-199	1	Comment: This statement is counterintuitive and limiting. If a PBT/vPvB VMP has been shown to treat a wider range of pathogens beyond that which is regarded as essential, that extended claim should be authorised. If not, that would theoretically require the use of an additional product to treat the other pathogens if these are also present in the animal – which is often the case with parasites. This may trigger issues with target animal safety and would unnecessarily expose the environment to an additional substance. By recognising efficacy against all pathogens, an alternative therapy would be immediately available should resistance to a new pathogen develop, as well as reducing the likelihood of the development of resistance. Proposed change: Please reconsider.	Change not accepted. While the CVMP acknowledges the concern raised, the following text was agreed following regulatory advice: The last arm of point (j) ("unless it is demonstrated that the active substance is essential to prevent or control a serious risk to animal health") provides a derogation to the general rule that a marketing authorisation shall be refused when the veterinary medicinal product is intended to be used in food-producing animals and it contains an active substance considered PBT/vPvB. Being a derogation from the general rule, it should be interpreted restrictively. In other words, a strict interpretation would only allow the authorisation of a veterinary medicinal product intended to be used in food-producing animals containing an active substance considered PBT/vPvB when the therapeutic claim made in the application is strictly falling within the limits of the derogation, i.e. essential to prevent or control a serious risk to animal health. Therefore, for such VMP, the acceptance of (non-essential) indications which would fall outside the limits of the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			derogation appear to be contrary to the wording of the provision.
200-205	4	Comment: Whereas the reflection paper suggests that the MA process for of PBT/Vpbt substances that starts from the characterisation of a PBT/Vpbt substance as essential before it is considered within a product that may additionally subject to mitigation measures, we see that this may be disproportional in practice. Many PBTs/vPBTs change characteristics depending on the formulation or the administration rout, therefore mitigation measures should become part of the criteria for characterisation of a PBT/Vpbt substance as essential. Proposed change: Add additional criterion on assessment of mitigation measures as part of the characterisation process.	Not accepted. The comment is acknowledged; however, the reflection paper includes a clear message that pharmaceutical form and product presentation will be considered during the authorisation process when the proposed conditions of use are more clearly defined. So, while determination of essentiality is based on the need to prevent or treat a serious risk to animal health, it is clear that the product containing the substance should be presented in a form and pack size and for administration by a route that is appropriate to keeping environmental exposure to a minimum.
203	3	Comment: Giving marketing authorisations for VMP with PBT/vPvB properties should only be granted for a limited time period and revaluated regularly.	Not accepted. The issuing of time-limited authorisations is not provided for in Article 37. To introduce the concept in this reflection paper would go beyond what is provided for in the legislation.
205-215	5	Comments: We welcome the comments on risk mitigation measures that should be part of the authorization. For example, there should be no grazing during the treatment period or animal excreta should be disposed of in an orderly manner rather than spread as manure.	Comment noted. However, RMMs to be applied to a specific product will be determined in the context of an assessment of an application for marketing authorisation and will be tailored to the product in question.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			No change in text proposed.
212-215	1	Comment: This statement is not clear and possibly beyond the control of the applicant/MAH. Proposed change: Please clarify whether this is referring to label statements.	Comment has been accepted. On further reflection, it is agreed that certain elements of the statement are beyond the control of the MAH. Noting that the MAH can only be responsible for its product, the text has been modified to focus on communicating product-specific information relating to hazard, risk mitigation and appropriate use. The text has been amended as follows: "Further, prior to issuing a marketing authorisation for such products, the competent authority may require the applicant to propose measures to ensure that potential environmental effects and the authorised conditions of use, including risk mitigation measures (RMMs) 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.~~"
224-225	4	Comment: It is necessary to include in the guideline a criterion assessing the impact on availability of treatment options if an active substance is characterised as PBT/vPvB. If such characterisation is to have implications for existing MAs for products intended for the same or similar use, could that mean	Not accepted. The point about "satisfactory alternatives" is adequately addressed in section 2.3(B).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		that several existing products for multiply species will have to be withdrawn? Proposed change: Add additional criterion on impact to overall availability treatment options for this or other target species.	
230-233	2	Comment: The reflection paper recognises that 'essentiality' may differ between member states. As the legislation stands in a centralised or DCP application the refusal by one or some states to accept an API as essential would result in the refusal of a Marketing Authorisation across the whole region. Provision needs to be made for member states identifying the API as essential to be able to authorise the product. Proposed change: The reflection paper must recognise that provision needs to be made for member states identifying an API as essential to be able to authorise the product.	Not accepted. One of the objectives of developing a reflection paper is to arrive at a common understanding of how the provision should be implemented. However, relevant competent authorities (EMA and NCAs) are ultimately responsible for taking decisions to authorise and as noted in line 230-233, it is possible for different CAs to come to different decisions depending on specific availability needs. While noting the concern of the stakeholder, it is beyond the scope of this reflection paper to propose regulatory mechanisms that facilitate the authorisation of such products in individual MSs. No change to text proposed.
230-233	4	Comment: It is important that this guidance ensures a harmonised approach in the Union and considers availability of treatment options at core.	Noted
230-236	1	Comment: A new substance would need to follow the centralised procedure. How will decisions on essentiality be made when it is seen as essential for some MS in their situation and not essential by	As noted in the comment, Regulation (EU) 2019/6 requires that applications for MA for products containing new active substances are submitted via the centralised procedure. In this case, a marketing authorisation is granted when a majority of the CVMP support a positive opinion. In a

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		others? Likewise, a referral will lead to a centralised opinion, where the same question may arise. Proposed change: Please consider clarifying how such situations will be dealt with in practice.	scenario where a majority of the CVMP do not support a positive opinion, the application is refused. In the absence of a marketing authorisation issued centrally, it will not be permitted to market the product in any EU MS, even in individual MS that may consider the substance essential. No change to text proposed.
235-236	1	Comment: Similar to the comment on line 196-199, if multiple pathogens are present, that is the condition for using such a combination product. In the interests of animal welfare, it is preferable to administer a single dose to livestock rather than increasing the time the animal is handled during administration of separate VMPs (and generating additional waste containers from separate products for disposal). Broadening the spectrum of activity by using a combination product ensures that the health and welfare of the animal is paramount. Proposed change: Please reconsider.	Not accepted. To facilitate targeted treatment, CVMP is of the opinion that products containing PBT/vPvB substances should be formulated as single active substance products. No change to text proposed.
236	5	Comments: We strongly support that the VMPs administered must be single active substances products.	Comment noted. No change to text proposed.
247-256	2	Comment: The paper mentions the possibility of seeking Scientific Advice regarding the essentiality of a substance prior to an application; however there is concern that the issue of divergent opinion between member states could result in no consensus opinion	In the absence of consensus, a CVMP decision on essentiality of a substance will require support from a majority of the Committee. In a scenario where a majority of the committee do not agree that a substance can be considered essential (in

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		or the outcome being dependent on the composition of the committee making the decision.	the context of Article 37(2)(j)), it will not be deemed essential. No change to text proposed.
251	1	Comment: Whilst the opportunity for scientific advice is most welcome, we fail to see how this can offer an applicant necessary guidance. CVMP would not be able to comment on whether a novel alternative product from a competitor was being developed; this would only become apparent at the time of dossier review of the PBT/vPvB VMP.	Concern acknowledged. However, no change to text proposed.
256-267	1	Comment: Please include some wording to clarify the process for the re-examination of a product that has had an authorisation when an alternative is brought to the market place.	The original text is as clear as it can be on this point. While the legislation does not provide for a specific "re-examination procedure", it is possible that the essential status of a substance could be revisited in the context of any post-authorisation assessment procedure. Where the essential status of a substance is questioned and that substance is included in multiple different products, the "re-examination" would be best conducted in the context of a Union Interest Referral. No change to text proposed.
257-259	4	Comment: While we understand that in the light of new scientific data there may be a need for reconsideration of the "essential status" of some substances, such decision should encompass more considerations and clear definitions of what could be considered as efficient alternative options.	The point about "satisfactory alternatives" is adequately addressed in section 2.3(B). No change to text proposed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
257-267	1	Comment: while understandable, this will lead to a much increased regulatory uncertainty and further dissuade companies from developing products that are PBT/vPvB even for unmet medical needs.	Comment noted. No change to text proposed.
260-267	5	Comments: We emphasize the need to grant authorizations of PBT/vPvB substances only for a limited period of time and to revoke the authorizations As soon as an alternative treatment method is available that does not justify further exceptional use. To this end, an exchange of information between the EU states must be ensured.	The issuing of time-limited authorisations is not provided for in Article 37. To introduce the concept in this reflection paper would go beyond what is provided for in the legislation. No change to text proposed.