11 May 2017
EMA/CVMP/401418/2016
Committee for Medicinal Products for Veterinary Use

Overview of comments received on 'Reflection paper on the authorisation of veterinary medicinal products containing (potential) persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances' (EMA/CVMP/448211/2015)

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

Stakeholder no.	Name of organisation or individual
1.	IFAH-Europe
2.	Pestizid Aktions-Netzwerk e.V. (PAN Germany)
3.	Pharmaq AS
4.	National Institute for Public Health and the Environment, the Netherlands
5.	German Environment Agency (Umweltbundesamt), *Expert group for PBT assessment of pesticides, biocides, REACH chemicals (Member of ECHA PBT Expert group) and pharmaceuticals*

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1. General comments

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1.	IFAH-Europe welcomes the opportunity to comment on this Reflection Paper and the intention by CVMP to provide further and clearer guidance on this topic as requested. A primary comment from IFAH-Europe is a request that the paper should be a lot clearer about what steps or processes are intended and how these fit into the authorisation process. Our comments below reflect the fact that currently we remain unclear about the intentions of CVMP and we are highly concerned about the potential impact on the registration process for veterinary medicinal products (VMPs). For example, following comparisons with environmental regulations of chemicals, biocides and plant protection products, CVMP appears to propose to add another assessment step to the authorisation of VMPs in the EU, at the active pharmaceutical ingredient (API) level rather than the product level. This would require additional legislation and seems to comprise a PBT-assessment based on REACH-requirements, but without the exposure or volume-based exemptions within that Regulation. In essence, the process would appear to be: • For products with new APIs: submission of data prior to application for a MA. • For products with existing APIs: submission of data in a process which is not yet developed. • The data to be submitted: a soil degradation study, chronic toxicity studies in aquatic organisms, Log Kow and if > 4, a bioaccumulation study in fish • These data are required for all APIs, even when dealing with APIs/products for companion	Thank you for your comments. It is acknowledged that the purpose of the reflection paper (RP)/objective was not clearly stated at the beginning of the document. The document has been revised so that the objective is clear from the outset. It is accepted that additional legislation is required in order to appropriately address concerns regarding the use of PBT substances in VMPs. The need for legislative change is a clear recommendation of the RP. In terms of 'process', the IFAH-Europe is not entirely correct. The RP is clear on the following: - There is a need to determine the PBT status of substances used in VMPs (line n. 258-259) - A PBT assessment will not be required for all substances.

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	animals, MUMs, natural substances, extensively metabolised substances and products for which the exposure is low etc., for which the assessment currently stops in Phase I. • If confirmed PBT or vPvB, the API will not be allowed and all products containing it are taken off the market. The API will be put on a list. • In exceptional cases, a product could be allowed, at least temporarily, until a substitute has been found.	Indeed, this is recognised in the CVMP PBT Guideline (EMA/CVMP/ERA/52740/2012). The intention would be to follow the approach outlined in that document: "*As the Phase I assessment does not require any specific environmental data the PBT screening can only be conducted as part of the Phase II assessment. However, there are provisions as set out as in the last paragraph of the introduction of VICH GL 6 (CVMP/VICH 2000), that allows further assessment of environmental risk if there are particular concerns over the activity and use of the product or active substance (the so called 'however clause'). Therefore, where a competent authority has evidence, or strong indications that an active substance of a product that would otherwise stop in phase I potentially has PBT/vPvB properties, a PBT/vPvB assessment could be required.*" The CVMP PBT GL states specifically, "a PBT/vPvB assessment should not be requested

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		for products for non-food producing species, for products containing natural substances, or if the substance is shown to be extensively metabolized in the animal, as defined in the Phase I decision tree." The RP has been updated accordingly. - Classification as a PBT substance does not mean that it would automatically be excluded from use in a VMP. At several points in the RP, it is clear that such substances could be considered for authorisation where environmental exposure is expected to be limited and/or there is a clear therapeutic need (e.g. see 421-432). - Regarding the proposal for a 'phase out', this relates to authorised products containing confirmed PBT substances for which conditions for maintaining the substance on

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	<u>In our view this approach presents several challenges:</u> • How to create this legislation. • Purpose of the list and how it will be used. • How to deal with risk/benefit, as mandated by the current legislation. • How to set the conditions for a MA for a product containing an API that is confirmed PBT. • How to make comparative assessments between products (not mandated by the current legislation). • How to phase-out a product in the meantime. • How to manage environmental exposure (called “emission”). • How to manage the consequences (such as on medicines availability and therapeutic gaps). Also, recommendations from the Guideline on PBT-substances (EMA/CVMP/ERA/52740/2012) such as consideration of other relevant data in the dossier, should allow the possibility of further studies and a thorough risk assessment.	the market are not met (rather than abruptly removing them from the marketplace, see 350-355). The CVMP would suggest that, on careful reading of the draft RP, the challenges highlighted by IFAH-Europe are for the most part acknowledged in the document. One point to note is that it is not the intention of the CVMP that this approach will lead to availability concerns. As stated repeatedly in the RP, one of the conditions for authorising/maintaining a MA would be where there is a clear therapeutic need that is not met by available VMPs (e.g. 428-431, 299-303). It is accepted that a decision to authorise will be based on a consideration of all data in the dossier. Overall, a decision to authorise or maintain a Marketing Authorisation for a VMP containing a PBT will be taken on the basis of an

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		overall B/R assessment (370-379)
1.	**<u>Proportionality and appropriateness of the policy proposals</u>** IFAH-Europe has several concerns with the approach that is described within the draft reflection paper: 1. The proposals from the AHEG appear to move the authorisation process from product based to, at least, a partially substance based one. This appears to be a fundamental change in the legal basis for the authorisation of a VMP. 2. These proposals single out 3 to 4 studies from the environmental part of the safety documentation, which is completely disproportionate in comparison with the other aspects from the safety file. VMPs are developed first of all to treat animals, not to be applied directly to the environment and to cause environmental effects (c.f. pesticides). 3. The proposal appears to start a move of the authorisation process from regulatory authorities to environmental agencies. 4. Approval of a substance would be purely hazard-based, since any risk assessment can only be done based on products. Furthermore, it would completely rule out any benefit-risk assessment (in the document, it is clearly stated in a number of instances that PBT substances should be non-approvable). 5. A hazard based assessment and refusal of permission to undertake ATC studies on this basis would prevent field data on the benefits being gathered, contrary to CVMP guidance. 6. It seems disproportionate to, after 25 years, completely alter the principles of authorisation of VMPs for approximately (a potential) 20 substances, particularly considering 1 additional study (a bioconcentration study in fish) that can readily be required in Tier B under the current system (Log K_{ow}, aquatic toxicity and soil degradation are included in the Tier A	Thank you for your comments. The concerns expressed are, for the most part, based on a misconception that the proposal is to have a formal 'substance approval' based on PBT status. That is not the proposal. What is being proposed is, simply, to determine the PBT status of substances used in VMPs and, for confirmed PBT substances, to determine the conditions under which products containing those substances can be authorised. For existing products, if the conditions for maintaining the authorisation (yet to be elaborated) are not met, it is proposed that these products would be removed (phased out) from the market (350-355). In addition, the following should be noted: - Point 3 - The CVMP does not accept that the "proposal appears to start a move of the

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	package). 7. Making VMP approvals substance-based also for example ignores the substantial overlap with active ingredients also used in human medicine. What would be the consequences? 8. "Replacement" may be a feasible option for chemicals, but this is not the case for a veterinary or human medicine requiring at least 10 years of development time. • Anthelmintic resistance is an issue of growing importance. Therefore, there is a need for new anthelmintic classes together with refined strategies for parasite control.[1, 2] As described by Woods and Knauer (2010), discovery and development of antiparasitic agents is particularly challenging, since one has to balance efficacy, persistent activity and stability with safety for the target animal, consumers and the environment.[3] It is therefore not surprising that over the past decade, hardly any new classes have been developed for use in food-producing species. • These challenges are an issue in human medicine as well.[4] • It should be noted that substitution of a substance in this context is hardly possible; at least maintaining the currently available treatment options and encouraging the development of new classes will be key actions to ensure appropriate and effective treatment of parasitic infestations in food-producing animals in the EU. 9. A move to a substance-based approval system will certainly impact medicines availability. 10. Exposure is important: The current legislation, from 1992 until present, requires an assessment in two steps, with an exposure assessment as the first step. For VMPs this makes sense; this is a fragmented market with a variety of species, and there are many products that are so limited in volume of use, that exposure is negligible. Such an assessment allows for focus on the products of potential concern, i.e. those where exposure	authorisation process from regulatory authorities to environmental agencies". Indeed, the CVMP would suggest that the contrary is the case. The proposal aims to ensure that, for individual products, the risks to the environment are appropriately considered in the context of the overall B/R assessment (370-379). - Point 4 - It is stated "in the document, it is clearly stated in a number of instances that PBT substances should be non-approvable". This is incorrect. See above. - Point 5 - Regarding the potential concern about conducting ATC studies, the CVMP would suggest that PBT status is only one of a number of factors that would have to be considered when submitting an application to conduct such

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	of the environment might be important. 11. Note that REACH uses an exposure-based limit as well: substances imported or manufactured in the EU at less than 10 tonnes per year do not require a CSA and PBT-assessment. If full datasets will be required for all, including low volume VMPs, these will disappear or never reach the European market. This would also include companion animal products. 12. For (veterinary) pharmaceuticals, the formulation and route of administration are crucial factors determining efficacy and environmental, consumer, user and target animal safety of a product – not just the substance. Therefore, and on scientific grounds, an MA for a VMP will always need to be product-based, and environmental hazards of an active ingredient should not be the only factors to be taken into consideration when deciding on authorisation of a VMP. Veterinary medicinal products require a considerable amount of studies during their development to ensure their quality, safety and efficacy; the latter are almost entirely linked to a product and not just a substance. The scope of the safety file alone for food producing animals is much wider than what is required under REACH.	studies. The CVMP is of the opinion that an applicant shouldn't be proceeding to ATC studies without being aware of the potential hazards associated with use of the substance in question. - Point 7 - The current reflection relates to VMPs only. For human medicines, a PBT assessment is always performed in Phase I of the ERA if the log Kow is ≥ 4.5 irrespective of any exposure considerations. In Phase II, the experimental data are assessed against the PBT criteria in case log Kow is ≥ 3. Therefore, classification of a substance that is used in both veterinary and human medicinal products as PBT is not expected to have significant consequences for human use of that substance. - Point 8 - While the RP

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		acknowledges the concept of 'replacement'/substitution (in case 2 out of 3 PBT criteria are met), as it applies in the areas of PPPs and Biocides, it is not proposed as an option for VMPs. Again, what is being proposed is, simply, to determine the PBT status of substances used in VMPs and, for confirmed PBT substances, to determine the conditions under which products containing those substances can be authorised. For existing products, if the conditions for maintaining the authorisation (yet to be elaborated, see 304-338) are not met, it is proposed that these products would be removed (phased out) from the market (350-356). - Point 9 – The intention of the proposals in the RP is to comprehensively address the

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		PBT issue without impacting on availability. - Points 10 & 11 – It is acknowledged that exposure is an important consideration. As noted in the RP as originally drafted, "Consideration needs to be given to whether or not a PBT assessment should be required for (any) substances that would normally stop in Phase I" (273-284). Indeed, the intention would be to follow the approach outlined in section 1.2 of the CVMP PBT Guideline: "*As the Phase I assessment does not require any specific environmental data the PBT screening can only be conducted as part of the Phase II assessment. However, ……."* In addition, as mentioned in the draft RP (lines 346-351), two of the proposed conditions under which substances containing

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		PBTs could be authorised are: "[where there is] limited potential for environmental exposure" and "[where] effective risk mitigation measures (RMMs) can be applied to reduce or prevent environmental exposure". - Point 12 – The CVMP agrees that the PBT status of a substance is just one of a number of considerations when deciding on the authorisation of a VMP. This is recognised in the RP. On the general point that a decision to authorise should be taken at a product level and not at the level of the substance, the CVMP agrees. However, while substance level assessment resulting in a list of "allowed" substances is not proposed in this reflection (see comments above), the CVMP would like to point out that 'substance level' assessment

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		resulting in a list of “allowed” substances is already a feature of the EU VMP authorisation process – in order for an active substance to be included in a VMP for food animals, this must have undergone an MRL assessment (essentially, appear on a list of allowed substances).
1.	**Comparisons with frameworks for other substances** Industry has commented on the PBT-guideline, with many of the comments being rejected. The GL brings in the PBT assessment for industrial chemicals under REACH, but without the exposure considerations based on annual volumes (*no PBT-assessment is required for substances imported or manufactured in the EU in annual volumes of less than 10 tonnes*). Pharmaceuticals are not just industrial chemicals; they have a very specific therapeutic purpose and as such they are rightly exempt from REACH. While there is no exposure consideration for PPPs and biocides it has to be acknowledged that use of these substances cause a direct exposure of the environment, which is not the case for the vast majority of VMPs. Furthermore, the PBT-assessment for industrial chemicals, biocides and PPPs is concerned with the direct entry of these substances into the aquatic compartment. For the B criterion for chemicals and pesticides aquatic routes of entry are more important, hence the test species is fish. Unlike chemicals and pesticides, in most instances VMPs undergo a passage through the animal and their route of entry is indirectly to soil via manure, not to water.	The text relating to the approach to PBT assessment under other legal frameworks was included as relevant background information. Please note the following: - The issue of “exposure considerations” is addressed in the comments above. - While it is acknowledged that the majority of VMPs enter the environment indirectly (via the treated animal), that may not be the case for all potential PBT substances. For example, some may be present in VMPs

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	For VMPs, main test species include the target animal species and laboratory species, usually the rat. We perform detailed ADME studies in these species using radiolabelled material and characterise the fate of the active ingredient and its metabolites in a very detailed manner, over a period of time, and mimicking worst-case use conditions. This goes far beyond what is tested in an OECD 305 test and as such provides at least equal, if not more weight. Therefore, the classification as “B” based on a study in fish only can be severely questioned for VMPs not delivered directly to the aquatic environment. Even where the product is used to treat fish, and it might be perceived that there is greater potential for aquatic bioaccumulation, current test protocols ignore the reduction in accumulation found due to adsorption of the molecule to particulates and thus present an unrealistic scenario. In essence, APIs used in VMPs for food-producing animals can be P or T, but never truly B. In food-producing animals, bioaccumulative substances have no future as a VMP by default, since it would be impossible to set an appropriate withdrawal time to ensure consumer safety. As persistence can be factored in when modelling, a quantitative assessment is possible. The absence of any comparison with human pharmaceuticals is notable, the more so since they serve similar purposes, but in a different species.	used as dip washes or administered directly into the freshwater/marine environments. In addition, entry via manure should not be confused with reduced environmental exposure. - The comments on the determination of the PBT status (criteria for classification as PBT) are noted. They are however not within the scope of the reflection paper. The approach to PBT assessment has been described in the CVMP PBT GL (EMA/CVMP/ERA/52740/2012). and the reflection paper has been updated to cross-reference the CVMP PBT guideline when needed. - That said, the following points should be noted: • Pesticides and biocides are generally also not directly applied to the aquatic

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		compartment and the same processes as for veterinary medicines (runoff, leaching) can result in an exposure of the aquatic compartment. For all frameworks, the PBT assessment is performed irrespective of the compartment primarily exposed and based on standardised laboratory studies to generate comparable results and to allow a comparison with the PBT classification criteria. That is, regardless of the framework under which a substance is evaluated, the approach to PBT assessment is comparable. • Once a substance has entered the environment, it makes no difference if the source is from its use as a biocide, pesticide or pharmaceutical and

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		therefore the PBT assessment is harmonised for all substance groups. Some of the substances used in veterinary medicine are also used as a biocide or pesticide. • While the classification of a substance as PBT should be the same irrespective of its intended use, the regulatory consequences may differ, i. e. non-approval in case of pesticides or, as now proposed for veterinary medicines, the option to authorise a product containing a PBT substance where the overall benefit risk assessment is judged to be positive.
1.	**<u>Scientific considerations regarding exposure</u>** From a scientific point of view, I-E is concerned that the component of exposure has not been thoroughly considered. In the case of the large majority of terrestrial animal parasiticides, entry into the environment is largely via soil, not water. Many of the potential PBT-substances are	- While it is acknowledged that the majority of VMPs enter the environment indirectly (via the treated animal), that may not

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	immobile and show an irreversible binding to and into soil particles, typically have a very low water solubility and are lipophilic– hence a higher K_{ow} by default.[5, 6] Usually, aquatic toxicity studies with these substances require non-representative test designs (such as the use of carrier solvents, semi-static or flow-through systems) to ensure adequate exposure of the test organisms. The same is true for bioconcentration studies in fish: an exposure is created that is impossible to occur under even worst-case environmental conditions. Yet, the PBT-assessment in this reflection paper is concerned with just the aquatic compartment. This brings the PBT issue with the majority of VMPs to a hypothetical and unrealistic level, but with serious impact on the future availability of effective treatments for animals.	be the case for all potential PBT substances. For example, some may be present in VMPs used as dip washes or administered directly into the freshwater/marine environments. In addition, entry via manure should not be confused with reduced environmental exposure. - The questions/comments on how the PBT status is determined and the reasoning for using fish as the model organism to determine B is not within the scope of the reflection paper. The approach to determining PBT status is described in the CVMP GL (EMA/CVMP/ERA/52740/2012), Part I. The CVMP PBT guideline has been included in the RP as the appropriate reference. - As advised previously, the intention of the proposals in the RP is to comprehensively

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		address the PBT issue without impacting on availability.
1.	**<u>Reflections on parasiticides</u>** Our understanding is that this is intended to be a general reflection paper on the authorisation of substances qualifying as PBT. Some parasiticides may become classified as PBT, but the document also mentions the possibility for PBT classification for substances of other therapeutic groups. Therefore, all specific sections on the use of parasiticides are out of context and may be better placed in a paper dealing specifically with parasiticides. Statements on responsible use of these products are also out of context of this paper. The use of medicines in what are considered as sensitive environments in some member states are already restricted on MAs and the disposal of excreta and effluent arising from treatment of food animals regulated by the appropriate government agencies, and so the processes already exist and are in use.	Contrary to the view of IFAH-Europe, the purpose of the reflection on parasiticides was to provide some context to the consideration of PBT. Noting that all potential PBTs identified to date are parasiticides, it was thought useful to reflect on the benefits of such products, the conditions of use (in general terms), the route of entry of the active substance into the environment and whether or not any RMMs or restrictions on use could be usefully applied to reduce emissions of individual products in the event that the active substance is classified as PBT. The reflection on parasiticides feeds into other aspects of the reflection paper, including: seeing the direct and indirect (combating resistance emergence) benefits of products and consideration of options to

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		reduce emissions to the environment. The rate of application of slurry/manure is regulated in the EU based on maximum accepted spreading limits of nitrogen. This does not eliminate the risks and hazards associated with the active substances used in VMPs. The purpose of the refection on parasiticides has been clarified in the RP.
1.	**Conclusions and proposed change** In view of the relatively small number of active ingredients potentially of concern, there should be no need for major changes to the regulatory system and a move to a substance-based approval approach, with the sole purpose of screening for active ingredients that may qualify as PBT. The current product-based assessment and the internationally agreed principle of screening of environmental exposure as a first step (Phase I-assessment - EMEA/CVMP/ERA/418282/2005-Rev.1) should remain in place; this is not contradictory to the approach taken under REACH, where not all substances go through a PBT-assessment based on exposure. For products entering Phase II, an environmental risk assessment including determination of the PBT-status is to be performed. This PBT-assessment should not end with a decision on the hazard alone; a thorough risk assessment should follow, as set forth in guideline	Thank you for your comments. - The concerns expressed are based on a misconception that the proposal is to have a formal 'substance approval' based on PBT status. That is not the proposal. What is being proposed is, simply, to determine the PBT status of substances used in VMPs and, for confirmed PBT substances, to determine the conditions under

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	EMA/CVMP/ERA/52740/2012. The latter is only possible on a product-basis, since the product and the way it is used are key elements to derive exposure and subsequent risk. Finally, and taking all other elements of the product dossier into account, a decision should be made weighing benefits and risks. Should the proposals set forth in the Reflection Paper be adopted, implemented and mandatory for all active ingredients regardless of their use, this will have a profound impact on existing and future medicines availability in the EU – in an era where investment and innovation in this region is already declining steadily. In the context of the general comments above, we urge the entire CVMP to reconsider the proposals in the reflection paper.	which products containing those substances can be authorised. For existing products, if the conditions for maintaining the authorisation (yet to be elaborated, see 304-338) are not met, it is proposed that these products would be removed (phased out) from the market (350-356). - The intention of the proposals in the RP is to comprehensively address the PBT issue without impacting on availability. The CVMP does not accept that the proposals in this document will have a "*profound effect on availability*". - It is acknowledged that exposure is an important consideration. As noted in the RP as originally drafted, "Consideration needs to be given to whether or not a PBT assessment should be required for (any) substances that would

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		normally stop in Phase I" (273-284). Indeed, the intention would be to follow the approach outlined in section 1.2 of the CVMP PBT Guideline: "*As the Phase I assessment does not require any specific environmental data the PBT screening can only be conducted as part of the Phase II assessment. However, ……."* In addition, as mentioned in the draft RP (lines 346-351), two of the proposed conditions under which substances containing PBTs could be authorised are: "[where there is] limited potential for environmental exposure" and "[where] effective risk mitigation measures (RMMs) can be applied to reduce or prevent environmental exposure". - The CVMP agrees that the PBT status of a substance is just one of a number of considerations

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		when deciding on the authorisation of a VMP.
2.	Veterinary pharmaceuticals are a major achievement. They are needed to cure animal illnesses and reduce their pain. But once released in the environment they interact with the ecosystem and cause environmental problems due to their substance properties and become pollutants. Substances which are persistent, bioaccumulative and toxic (PBT) or which are very persistent and very bioaccumulative (vPvB) specifically affect the environment and there is an urgent need to keep them from the environment. PAN Germany therefor welcomes that the high environmental concern of veterinary medical products (VMP) with persistent, bioaccumulative and toxic substances or properties (PBTs) and VMPs with very perstistent and very bioaccumulative (vPvBs) substances or properties are taken seriously. We agree that the current legislation is not securing the environment from adverse effects from VMPs containing PBT/vPvB substances. PAN Germany sees an urgent need to revise the legislation in the field of veterinary pharmaceutical policies to ensure that the environment and human health will more effectively be protected from adverse effects of veterinary medicinal products that enter the environment. We welcome the decision to develop a strategic approach for marketing authorisations for VMPs containing (potential) PBT substances. We agree that it is difficult to predict fate/environmental concentrations and the effects of PBT/vPvB substances in the environment, and that therefore conventional quantitative risk assessment is not an appropriate approach to protect the environment from such substances. Therefore it is necessary to conduct risk management measures based on the identified hazard.	Thank you for your comment.

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	Due to PBT substance's ability to persist in the environment, to accumulate in organisms and due to their toxicity, PBT properties have been recognised as criteria for exclusion from authorisation in other legislative frameworks (e.g., BPR and PPP). While the reflection paper is meant to refer to PBT and vPvB substances, the discussion (chapter 3) and the recommendations (chapter 4) only focuses on PBT and do exclude vPvBs. This is irritating. We strongly suggest including vPvBs in the discussion and the recommendations. vPvB substances resist environmental degradation, persist in the environment, bioaccumulate in human and in animal tissue, and bioconcentrate. EMA stated 2015 that *"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."* (see EMA (2015) Guideline on the assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicinal products . Page 9/16 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/09/WC500193826.pdf). But counting on the «unlikeliness» is not enough. Only if there was a legal obligation to exclude VMP with vPvBs substances this would explain why vPvB are not considered in chapter 3 and 4. In order to protect the environment and the health of todays and future generations this should in general also apply to VMPs. Authorisation for vPvB or PBT substances should generally be denied (with very limited derogations see below) (see PAN Germany 2013: Recommendations for Enhanced Protection of the Environment from Adverse Effects of Veterinary Medicinal Products. Position Paper. http://www.pan-germany.org/download/veterinary_pharmaceuticals/Enhanced_Protection_of_Environment_from_Veterinary_Medicinal_Products.pdf).	Comment noted. The RP has been updated so that vPvB is appropriately captured in the document. The CVMP is of the opinion that the PBT status of a substance is just one of a number of considerations when deciding on the authorisation of a VMP (that is, the PBT status of a substance alone should not be the determining factor when deciding on the authorisation of a VMP).

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	The best risk prevention measure for PBT and vPvB substances is to not authorise them. Because once realised in the environment the substances cannot be removed. This is especially the case for vPvBs – therefore we propose a general ban of those substances. As counter-exceptions, authorisation of VMPs with PBT substances must only be granted for a limited authorisation period following defined narrow derogations and only when there are no less harmful alternative products on the market or treatment methods or sufficient prophylactic measures available if (a) it is shown that the exposure to the environment, under realistic worst case conditions of use, is negligible, in particular where the product is used in closed systems or under other conditions which aim at excluding the release into the environment; (b) it is shown by evidence that the active substance/product is essential to prevent or control a serious danger to animal health. At present, marketing authorisation for a veterinary medicinal product is valid for an unlimited period of time and a regular environmental review of the approval decision that secures an environmental assessment based on the current state of scientific knowledge is not in place. PAN Germany strongly recommends that any market authorisation for a VMP that contains PBT substances shall be limited to 7 years and that this authorisation is linked to the establishment of a binding substation plan in order to use this period to invest in the search of alternative VMPs without PBT substances and in the search of alternative treatment methods and prevention methods. PAN Germany recommends a clear exclusion provision for vPvBs without derogations.	For confirmed PBT/vPvB substances, the conditions under which products containing those substances can be authorised/maintained would need to be elaborated (conditions for authorisation to be considered are detailed in the RP, 304-338). Where the established conditions are not met, it is proposed that these products would be removed (phased out) from the market (350-356). An absolute exclusion for such substances is suggested in the CVMP Guideline on the assessment of PBT/vPvB substances in veterinary medicinal products

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		(EMA/CVMP/ERA/52740/2012). However, at the moment, PBT and vPvB substances fall within the same group/type of hazardous substances (i.e, within the current veterinary framework and other EU frameworks the regulatory consequences do not differ) and thus there are no legal grounds as yet to address concerns regarding vPvB substances specifically. An absolute exclusion for vPvB substances is not captured in the RP but the paper has been revised to clarify that additional hazard considerations posed by these substances should be taken into account when considering the overall B/R assessment.
4.	We welcome this reflection paper,that contains many useful suggestions. The focus on harmonisation of the assessment and management options with the other EU chemicals legislative frameworks is highly supported. Current focus is on active substances, while the VMP may contain excipients that may also have PBT/vPvB properties. This needs to be addressed in the reflection paper.	Thank you for your comments. It is correct that the focus of this reflection is on active substances. This is in line with the standard approach to ERA assessment for

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		VMPs. A specific PBT assessment for excipients is not foreseen in the CVMP GL on PBT assessment of veterinary medicines (EMA/CVMP/ERA/52740/2012). However, if an excipient happens to be a known PBT substance, it is expected that this will be discussed/addressed during the authorisation process. No change to the reflection paper required.
	Any developments touched upon in this paper that might ultimately lead to phasing out or restricting the use of VMP products containing PBT/vPvB substances may also be taken to stimulate innovation of more environmentally friendly, yet effective alternatives (products). Coupling of proposed measures with stimulation of innovation could be addressed in the reflection paper. We encourage the authors to do so.	Comment noted. Stimulation of innovation is touched on in section 4.2 ("*a need for increased research into non-chemical approaches to parasite control*", "*consideration should be given to incentivise products of low risk to the environment*" and "*to the development of treatment delivery methods that are more effective*". No change to the reflection paper required.
	For reasons of consistency throughout the paper reference should made to PBT/vPvB and not to	Final comment regarding PBT/vPvB is noted. The RP has been updated

Stakeholder number	General comment (if any)	Outcome (if applicable)
	PBT alone.	so that vPvB is appropriately captured in the document.
5.	Thank you for the well-structured reflection paper on authorisation of VMP's containing PBT or vPvB substances which will be helpful for further authorisation procedures.	Comment noted.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
41-43	1.	**Comment:** Spatial distribution of material is more a function of the geographic range of use of a product and its potential mobility – where is it used, how it is used, how often, how mobile it might be, etc. This is true regardless of whether a compound is PBT or not. It also ignores the fact that many such compounds do not remain in the same bioavailable state as determined under unnatural laboratory testing conditions. **Proposed change:** please revise, or provide references to back up the statement.	Noted. This text is in line with the ECHA documents on PBT assessment and the CVMP GL on PBT assessment. Guideline citation added at the end of the paragraph.
43-49	1.	**Comment:** This statement appears to exclude the option of generating data tailor-made for a given product/active ingredient to address a specific concern, even though EMA/CVMP/ERA/52740/2012 mentions the concept of additional studies. **Proposed change:** Please revise to include the option to generate data to address specific concerns.	Noted. The text referred to in the comment is general, background text. It highlights a concern. How that concern can be addressed is covered later in the document.
44-46	3.	**Comment:** The concern that stopping emission of such substances into the environment may not necessarily result in a reduced concentration of the substance in the environment is hard to accept. The persistence criterion is met when degradation half life is more than 180 days (marine sediment). Although degradation at this rate is slow, it is hard to imagine that organic molecules do not degrade at all, which would need to be the case if reduced environmental concentrations would not be achieved by stopping exposure. It is unrealistic that organic molecules will not degrade at all.	Comment accepted. However, for certain substances, it is the case that half-lives may be much longer than the trigger for classification as persistent.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: ~~There is a concern that even if the emission of such substances into the environment is stopped, this may not necessarily result in a reduced concentration of the substance in the environment and, subsequently, in biota.~~	
50	4.	**Comment:** For all technical details, please refer to the CVMP PBT guideline and not directly to REACH. In the CVMP PBT guideline, the correct references to the criteria and assessment methods of REACH are included. These references to REACH in the CVMP PBT guideline are made dynamic, which means that when the REACH legislation changes, the CVMP documents do not have to be amended. This refers specifically also to Annex I, which is not necessary to include in the reflection paper when reference to the CVMP PBT guideline is made. Please also include the CVMP PBT guideline in the references section.	Accepted. The text has been revised to refer to the CVMP PBT guideline and not REACH. Accordingly the Annex I proposed for the original version of the reflection paper has been deleted.
53-59	1.	**Comment:** The document makes statements about quantitative risk assessments being inappropriate and also 'Hazard-based assessment only' quite freely in the Background. This is misleading and is in conflict with the remainder of the document, where tiered assessment and benefit-risk considerations are discussed – which is also the case in the guideline EMA/CVMP/ERA/52740/2012 referred to. Furthermore, the statements are not backed up by any references. **Proposed change:** Please adapt the text to better represent the overall context of the document and the options mentioned in the guideline.	The concern is not entirely clear. The central point of this paragraph is that the conventional approach to ERA assessment (risk quotient approach) is not appropriate for determining impact on the environment due to PBT/vPvB substances. This is generally accepted. A reference to relevant ECHA guidance has been added.
57	4.	**Comment:** Include a regular reference to the CVMP PBT guideline.	Accepted.
62-64	1.	**Comment:** Further claims are made about the potential to elicit long term effects, but	Not accepted. The text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		without the possibility of further analysis of data or tests to determine whether this potential is indeed confirmed, or purely theoretical based on limited knowledge. **Proposed change:** Please include the possibility of further data gathering and analysis to enable risk assessment as opposed to simple hazard-based decision making, which is not in accordance with guideline EMA/CVMP/ERA/52740/2012.	referred to in the comment is general, background text. It highlights a concern. How that concern can be addressed is covered later in the document.
66	1.	**Comment:** For plant protection products, normalisation is done to 20°C instead of 12°C. There and also in REACH, the limit for Log K_{ow} is 4.5 instead of 4 for VMPs. Hence, while the assessment might be shared, the methodology differs. **Proposed change:** this should be specified in the text.	The proposed change is not accepted. While the differences in certain technical elements of PBT assessment between substance categories is acknowledged, a reconsideration of technical requirements is outside the scope of the current document. For each of the substance categories, the RP includes a reference to the relevant criteria for determining PBT status. Further detail, in particular specifying the differences in criteria between the different substance categories is

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			considered not necessary. That said, the RP acknowledges that there needs to be “a coordinated/harmonised approach to PBT classification across all legislative frameworks”. (294-303). Further, while in other frameworks the trigger for PBT screening is log Kow ≥ 4.5, it should be noted that the trigger for bioaccumulation studies is a log Kow ≥ 3. As the aim is to perform the PBT assessment in line with the studies available within the assessment according to the VICH GL, it was considered most appropriate to use the log Kow action limit from the VICH GL. In addition, the technical determination of the PBT

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			classification is addressed in the CVMP GL EMA/CVMP/ERA/52740/2012 and it was not intended that such technical aspects would be revisited in the context of this RP.
71-75	1.	**Comment:** The aim of the REACH regulation is not only substitution but also the determination of appropriate risk management measures. This should be reflected in the text. In addition, the paragraph goes beyond what is underlined in REACH guidelines and we suggest deleting the last sentence. **Proposed change:** The REACH Regulation pays specific attention to the PBT/vPvB susbtances, with the aim to **identify risk management measures and exposure scenarios that minimise the releases and exposures in the whole life-cycle of the substance and ultimately** substituting these if technically and economically viable alternatives are available. ~~The process of substitution of an individual substance may take several years, and until this is achieved the regulation has processes in place to minimise the release of and exposure to PBT and vPvB substances~~	Partially accepted. The text has been re-drafted for clarification.
71	4.	**Comment:** 'the PBT/vPvB substances' is too focused **Proposed change:** change the PBT/vPvB substances into PBT/vPvB substances	Not applicable. Paragraph has been re-drafted.
71	4.	**Comment:** incorrect Regulation number for REACH **Proposed change:** (EC) 1997/2007 into: (EC) 1907/2006, as amended.	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
75-76	1.	**Comment:** The criteria for PBT/ vPvB assessment under REACH have a minimum annual volume limit **reflecting** what is considered to be safe as this will not result in a relevant environmental exposure. This should be specified for a better understanding of the process. This concept also corresponds to what is intended by a Phase I evaluation for VMPs: filter out products of potential concern based on exposure. **Proposed change:** A PBT/vPvB assessment must be conducted for all substances for which a chemical safety assessment (CSA) is required under REACH. **These are, according to Article 14(1) of the REACH Regulation, in general all substances manufactured or imported in amounts of 10 or more tonnes per year that are not exempted from the registration requirement under the Regulation.**	Partially accepted. The text has been re-drafted for clarification. Note: The RP is clear that there is a need to determine the PBT status of substances used in VMPs. The draft RP indicates that consideration needs to be given to whether or not a PBT assessment should be required for (any) substances that would normally stop in Phase I of the VICH GL 6 (CVMP/VICH/592/1998). See RP, section 3.1, paragraph 3. The reflection paper has now been updated to clarify that the intention would be to follow the approach outlined in section 1.2 of the CVMP PBT Guideline (EMA/CVMP/ERA/52740/2012): "*As the Phase I*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			assessment does not require any specific environmental data the PBT screening can only be conducted as part of the Phase II assessment. However, ……."
78-87	1.	**Comment:** in contrast to the REACH-approach, refusal of authorisation seems to be the direction taken by some MSs (e.g. Germany – moxidectin).	Noted. However, in the RP it is stated that, in accordance with existing VMP legislation, "*it is not possible to refuse a MA on the basis of PBT status alone. The decision to authorise, or not, a product is taken on the basis of the overall benefit risk balance*." (Section 3.2, 4th bullet point).
82-85	5.	**Comment** from the REACH experts: Please include "Authorisation for the use of PBT/vPvB substances is granted only if there are no suitable alternatives and if the socio-economic benefits of their use outweigh the (high) socio-economic costs." **Proposed change:** "Authorisation for the use of PBT/vPvB substances is granted only if there are no suitable alternatives and if the socio-economic benefits of their use outweigh the (high) socio-economic costs."	Partially accepted. The paragraph has been re-drafted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
88-102/122-126	1.	**Comment:** Plant protection products are designed to be deliberately released into the environment in large volumes, and intended to have environmental effects. VMPs are in the first place intended to heal and they are administered to the animal. A comparison between PPP and VMP is therefore not appropriate. It is understood that for PPPs there are no considerations regarding exposure, since they are applied directly to the environment at a large scale. However given the substantial differences with VMPs this should not be the reason to eliminate exposure considerations for VMPs in a Phase I assessment.	Noted. However, the text referred to in the comment is to be regarded as background information only (that is, to outline the approach to PBT assessment for other chemical substances). No other comparison was intended.
90-91	4.	**Comment:** 'Step 1' which here is the approval process of active substances of PPPs at EU level is not only 'assessment of properties of the active substance'. The text seems to suggest this. The active substance approval process entails a complete hazard (PBT, classification and labelling) as well as risk assessment of all relevant aspects (phys-chem, efficacy, human health, environment, target, non-target species, etc.) The same holds for the BPR framework. **Proposed change:** The first step is an assessment of hazard and risk of the active substance (for inclusion etc.)	Accepted.
90-102	5.	**Comment:** Our PPP experts have included some clarifications and rewrote the text passage. **Proposed change** of paragraph: … For all substances intended to be used in PPPs, the environmental risk assessment (ERA) follows a two-step process. First, the active substance needs to be approved on EU level. Therefore, a risk assessment of all intended uses of the active substance in the EU will be performed. Only substances for which safe uses can be proven in the EU, an	Partially accepted. A number of amendments have been made to the text in question.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		approval will be granted and the active substance can enter the second step which is centred on a risk assessment of plant protection products (PPP) containing the approved active substance and will be performed on zonal and national level. As a first measure of the EU approval procedure of an active substance, the properties of the substance will be assessed against certain criteria ('cut-off criteria'), which include an assessment with regard to the PBT and the vPvB criteria. When a substance is identified as a PBT or vPvB, it will not be approved as an active substance in the EU and no further risk assessment will be performed on EU level and it cannot be used in a PPP in any of the EU Member States. There are no derogations that will allow for its use as a PPP. Further, substances that meet two out of three PBT criteria are classified as 'candidates for substitution' (CfS). CfS will be approved for only seven years instead of 10 years, and thus also a PPP containing the substance can only be authorised for seven years. In addition, prior to authorisation of each intended use of PPP containing a CfS, a comparative assessment with alternative PPPs by the competent authority is required. A PPP containing a CfS will only be authorized for a certain use if no methods or PPPs of lesser risk are already available provided there is no significant economic impact and no practical disadvantages for agriculture (SANCO/11507/2013 rev. 12, 2014).	
93	4.	**Comment:** active substances under Regulations 1107/2009 and 528/2012 are not 'authorised', but approved. Please change wording at several locations accordingly. E.g. lines 94, 108, 109. Note: products ('step 2') are indeed authorised according to legal wording. **Proposed change:** change authorised (in case of active substances) into approved.	Accepted.
93-94	4.	**Comment:** "the substance cannot enter the second step" Substances do not go from step 1 to step 2. These are separate processes. In both steps a	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		full risk and hazard assessment is performed. For the active at EU level, for the product at product authorisation level. Products can only be authorised with approved active substances. Consider also generally changing 'steps' into processes or alike. **Proposed change:** When a substance is identified as a PBT it will not be approved as an active substance. Seeking market authorisation for products containing that active substance is not possible. That is, there are no…	
105-106	4.	**Comment:** see comment for lines 90-91. **Proposed change:** see proposal at comment for lines 90-91.	Accepted.
103-121/122-126	1.	**Comment:** Biocides are also applied directly to the environment in large volumes, with the intention to exert effects, and therefore there are no considerations regarding exposure. Given the substantial differences with VMPs this should, however, not be the reason to eliminate exposure considerations for VMPs in a Phase I assessment. Note the concept of societal aspects in the BPR, which implies a benefit-risk assessment.	Noted. However, the text referred to in the comment is to be regarded as background information only (that is, to outline the approach to PBT assessment for other chemical substances). No other comparison was intended.
107-108	4.	**Comment:** the second step is centred…this can be much more precise. In addition: prefer to omit 'steps' as indeed substance approval is a prerequisite for product authorisation, but these are not necessarily steps that follow in time. It concerns different processes.	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Replace sentence 108 by: Market authorisation of biocidal products can only be sought for products containing approved active substances. Add (if desirable): a risk and hazard assessment of the product is also part of the product authorisation procedure.	
117-118	4.	**Comment:** make text on candidates for substitution on article 10d of the BPR of equal strength as that in PPP section. The implications are equal. Now the text states 'is encouraged'. **Proposed change** (if any): Further, as in Regulation (EC) No 1107/2009, as amended, active substances that meet two out of three PBT criteria are classified as 'candidate for substitution'.	Accepted.
124-125	4.	**Comment:** this is not correctly stated. There is no step 1 with only the evaluation of intrinsic properties and step 2 with risk assessment for the environment. There is the process of active substance approval at EU level. A full hazard assessment and risk assessment is performed. When applicants apply for a market authorisation, a product specific dossier is submitted and again a full risk assessment as well as hazard assessment need to be performed. Prerequisite is that the actives in the product have been approved. Proposed change (if any): adapt text accordingly.	Accepted.
129-131	1.	**Comment:** Please note that the requirement to conduct an environmental risk assessment has been in the legislation since 1992, with Dir 92/18/EEC specifying that the assessment needs to be conducted in 2 phases, with an exposure assessment as the first step. **Proposed change:** please include a reference to Dir 92/18 in the text for completeness.	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
129-145	5.	**Comment:** The principles of general risk assessment and PEC/PNEC approach are also implemented for PPP, biocides and REACH chemicals. They should be mentioned in a general part of chapter 'Introduction'. **Proposed change:** Please shift the paragraph and revise the text.	Noted. However, the proposed change is considered unnecessary. The purpose of the reflection on ERA for other chemical substances was simply to make the point that there is a requirement for PBT assessment which is conducted in the context of a 'substance approval' process. Additional detail on the approach to assessment is not required.
138	5.	**Comment:** a potential risk is identified if the RQ > or = 1, not if RQ > 1 **Proposed change:** please change in 'when the RQ ≥ 1'	Accepted.
139-141	1.	**Comment:** These sentences are declarative and not necessarily true; e.g. a PNEC can be established; that aspect is based upon ecotoxicological data and is wholly independent of PEC. Other environmental fate data can assist in determining a longer-term PEC; modelling can take potential build-up of a substance into account. **Proposed change:** Please revise this paragraph, or include scientific references supporting these statements.	Not accepted. The PNEC is based EC/LC50 or NOEC values, which relate to the external effective concentration of the substance measured in the test medium (e. g. water). The internal concentration causing the effect on the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			organism is not determined in ecotoxicology tests. If the substance accumulates, the effective internal concentration can already be reached even if the concentration in test medium is lower. Therefore, no PNEC can be determined. It should be noted that the purpose of the reflection paper is how to address concerns regarding the use of PBT substances in veterinary medicine, not to revisit the approach to PBT assessment and/or the PBT criteria, which has been addressed in the CVMP PBT Guideline (see EMA/CVMP/ERA/52740/2012)
140-141	5.	**Comment:** For PBT/vPvB substances, a safe concentration in the environment cannot be established. We suggest to delete the term “with sufficient reliability”.	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Delete the term “with sufficient reliability” in line 141.	
152	4.	**Comment:** typo **Proposed change** (if any): delete “46”	Accepted.
154-157	1.	**Comment and proposed change:** Please state the sources of the data used for this exercise.	Accepted.
157-158	4.	**Comment:** ‘make a definitive determination’ can only be done after assessment **Proposed change** (if any): the necessary data to perform a PBT assessment and conclude on PBT status is….	Accepted.
158-161	1.	**Comment:** There is a Community referral ongoing for all products containing moxidectin to be administered to cattle, sheep and horses. This should be reflected in the text, and highlights the fact that procedures exist to include several products in the review when a risk is identified on a substance. **Proposed change:** ~~However, in the context of an assessment of an application for marketing authorisation submitted via decentralised procedure, national competent authorities concluded that one of the substances identified in the screening process (moxidectin, a parasiticide used in cattle, sheep and horses) fulfilled the criteria for PBT classification.~~ In the frame of a decentralized procedure, Germany referred to the Committee under Article 35 of Directive 2001/82/EC, due to concerns that moxidectin, one of the substances identified in the screening process, may have persistent, bioaccumulative and toxic (PBT) properties. The Committee started a procedure to examine all veterinary medicinal products containing moxidectin to be administered to cattle, sheep 1.and horses. This	Partially accepted. The RP has been updated to include a section on the ongoing referral (up to the time of writing, April 2017), in which a Member State considered that action should be taken at a European level (Community (Article 35) referral procedure) for all VMPs containing moxidectin to be administered orally, topically or subcutaneously to cattle, sheep or horses.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		referral procedure is currently ongoing.	
158-161	4.	**Comment:** why give a substance specific example in a reflection paper. A general statement may describe the situation as well. For cypermethrin a similar conclusion was reached between the RMS, CMS and applicant.	Noted. The substance specific example is significant in that it emphasises that concerns relating to PBT is a real issue that the network is currently attempting to address.
162-164	1.	**Comment:** By the same token, unless bioconcentration / bioaccumulation / bioavailability data are available then the classification of the 20 candidate substances as B/vB on the basis of log K_{OW} >4.0 might be erroneous. **Proposed change:** Please revise the sentence to reflect this point and identify the need for generation of appropriate data.	Not accepted. The RP is clear on the following: - The 20 substances in question are potentially PBT, - For the majority, the data to make a definitive determination are not available.
162-163	4.	**Comment:** or have not been determined in an appropriate manner **Proposed change**: after "medicines; "or have not been determined in an appropriate manner.	Partially accepted. Text amended to: "It should be noted that reliable log K_{ow} values….."
165-168	1.	**Comment and proposed changes:** If parasiticides are the scope of the present document, please reflect that in the title of the reflection paper, but then it no longer deals with PBT-substances in veterinary medicine in general.	Not accepted. The RP is on the use of PBT substances in veterinary medicinal in general. However, the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			purpose of the reflection on parasiticides was to provide some context to the consideration of PBT. Noting that all potential PBTs identified to date are paraciticides, it was thought useful to reflect on the benefits of such products, the conditions of use (in general terms), the route of entry of the active substance into the environment and whether or not any RMMs or restrictions on use could be usefully applied to reduce emissions of individual products in the event that the active substance is classified as PBT. The reflection on parasiticides feeds into other aspects of the reflection paper, including: seeing the direct and indirect (combating resistance emergence)

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			benefits of products and consideration of options to reduce emissions to the environment.
172 ff.	5.	**Comment:** The change from the general part to the specific product types (parasiticides for terrestrial animals and in aquaculture) is a little abrupt and should be explained more detailed.	Accepted. The RP has been amended and the section on parasiticides is presented in an Annex and the purpose of the reflection on parasiticides is presented more clearly.
173 - 292	1.	**Comment and proposed changes:** This document is intended to deal with PBT-substances in general. The whole section 2.2 focuses solely on parasiticides, which is inappropriate in the general context, and lines 167-168 already refer to potential PBT-substances from other therapeutic classes. A reflection paper on parasiticides is a different issue which has nothing to do with PBT-assessments. Therefore, please delete section 2.2. If section 2.2 is to be maintained, review and editing by (a) parasitologist(s) would be highly recommended as we believe this would result in an improved text. The general recommendations on appropriate use also belong in a RP on parasiticides, not in this document.	Partially accepted. The section on parasiticides is now presented in an Annex and the purpose of the reflection on parasiticides is presented more clearly.
176-177	1.	**Comment:** This is speculation, qualitative but not quantitative and not supported by any data or references. **Proposed change:** please delete the sentence or support with references.	Not accepted. It is accepted that the statement is qualitative; however, all substances identified as

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			potential PBTs are used as parasiticides for major food-producing species. As such, it is not unreasonable to suggest that their use is likely to be extensive.
178-180	1.	**Comment:** An overview of the value of parasiticides and their contribution to animal health and welfare has been elaborated by parasitologists and is provided in Annex 1. *Copied below*: "In lines 178 to 180 the authors rightly state the need to control internal parasites in livestock especially in pasture-based enterprises; external parasites should also be included. Both internal and external parasites of grazing livestock are ubiquitous and therefore all grazing livestock should be considered an at-risk or an exposed population to infection and infestation [1.] Even light to moderate infections and infestations negatively impact the welfare, thrift and production efficiency of grazing animals. Consequently, where animal welfare and production efficiency is an objective, a parasite control program and intervention methods should be implemented [2]. **All grazing life-stock should be considered an exposed and at-risk animal population for sub-clinical and clinical gastroenteritis. Therefore, where animal welfare and resource stewardship is an objective, husbandry practices should include a parasite control program that minimizes the confounding effects of sub-clinical and clinical gastroenteritis and ectoparasite infestations on the welfare of the animal.**	Noted. See comments next to the boxes. In the absence of a specific proposal for amendment to the text, and given that the major points of this submission are already addressed in the RP, no changes have been made to the text. This specific point is addressed in the Annex of the RP (576-578).

[1] Rinaldi L. et. al. Mapping and modelling helminth infections in ruminants in Europe: experience from GLOWORM. Geospatial Health 9(2), 2015, pp. 257-259.
[2] Charlier J. et. al. ECONOHEALTH: Placing helminth infections of livestock in an economic and social context. Vet. Parasitol. 212, (2015), pp. 62-67.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Approaches to minimize parasite infections and infestations include husbandry practices founded on an understanding of the epidemiology of the organism, chemotherapeutic interventions to prevent or remove the effect of the organism on the host or a combination of both. Prior to the 1960's the use of chemotherapeutic agents to achieve modern-day societal expectations for animal welfare and production efficiency was virtually nil. Livestock producers were essentially dependent on the genetic resistance and resiliency of the host to sustain body growth and reproduction, most often at a high cost to the welfare and production efficiency of the animal. Moreover, little was known about the epidemiology and biology of internal and external parasites, relative to current day, that could assist management decisions to mitigate parasite infections and infestations. Even with the current knowledge-base of parasite epidemiology and host genetics and breeding techniques, improved husbandry and hygiene practices and genetic selection as stand-alone methods for parasite control are far from achieving the level of animal welfare and production efficiency expected from modern livestock producers and society.[3]	This specific point is addressed in the RP (429-432, and Annex 579-587).

[3] Sutherland I. and Leathwick D. Anthelmintic resistance in nematode parasties of cattle: a global issue? Trends in Parasitol. 27 (4), 2011, pp. 176 -181.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		There is currently not a commercial-scale alternative to chemotherapeutics that provides comparable mitigation of the deleterious effects of internal and external parasites to the welfare of livestock species. It is essential for existing classes of anthelmintics to remain available to the livestock producer to sustain the level of animal welfare and resource stewardship expected by modern livestock producers and society. In the 1960's the benzimidazole class of anthelmintics became available that provided a broad spectrum of efficacy against internal parasites along with a wide margin of target animal and user safety. Subsequently in 1968, the imidazothiazole / tetrahydropyrimidine class of anthelmintic, levamisole, was introduced and also provided a broad spectrum of efficacy against internal parasites. In the 1980's the macrocyclic lactone (ML's) class of anthelmintic revolutionized parasite control and enabled a higher level of animal welfare for livestock that was afforded by the broad spectrum activity against internal and external parasites combined with wide margin of target animal and user safety[4]. Approximately thirty five years later, a new class of anthelmintic, the aminoacetonitrile derivatives (AAD) was introduced to the market in 2009 but only in an oral dose formulation for use in small ruminants in New Zealand and the United Kingdom. The AAD class of compound has a narrower spectrum of efficacy compared to the older benzimidazoles, imidazothiazoles and macrocyclic lactones. Subsequent to the introduction the AAD's, the spiroindole class of anthelmintic, derquantel, was introduced to the market as a fixed-dose combination oral formulation; also only for use in small ruminants. The current options for cattle producers and non-ruminant food animal producers still remain limited to three drug classes of anthelmintics (benzimidazoles, imidazothiazoles and the macrocyclic lactones). There is no indication that a new broad-spectrum chemical class of compound will be available to these producers in the coming years or decades and hence will remain reliant upon existing drug classes.	Noted.

[4] Woods, D.J., *et. al.* Anthelmintic discovery and development in the animal health industry. Expert Opin. Drug Discov. (2007) 2(Suppl. 1) : S25-S33.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		It has been 35 years since a new broad-spectrum class of anthelmintic has been introduced to the large ruminant and non-ruminant food animal producers and there is little indication that a new class will be introduced in the coming years. Parasite control will continue to be limited to the three classes of anthelmintics (benzimidazoles, imidazothiazoles and the macrocyclic lactones). Since the 1960's, global beef production has more than doubled and carcass weights have increased by approximately 30 percent[5]. It is without question that improvements in animal welfare that have been gained from effective parasite control by these three classes of anthelmintics (benzimidazole, imidazothiazole / tetrahydropyrimidines and macrocyclic lactones) have contributed to the efficiency of livestock production. The endectocidal attribute of the macrocyclic lactones have also enabled livestock producers to depart from the once common use of plunge dipping or bath treatments for external parasite control; now limited primarily to tropical and subtropical regions of the world. Also, livestock managed under effective internal and external parasite control programs founded on chemotherapeutic control are more efficient converters of forage to meat enabling more efficient utilization of land and forage resources. **The macrocyclic lactone class of endectocide has marginalized and virtually eliminated the practice of dip baths for external parasite control in livestock and has revolutionized the welfare of livestock species in modern grazing systems. The health and well-being afforded by this class has translated into improved production efficiency of livestock and stewardship of land and forage resources.**	Noted.

[5] FAO 2010 Food and agriculture organization of the United Nations statistical databases. See http://faostat.fao.org

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		Given the limited number of anthelmintic drug classes available to the livestock producer, alternatives to chemotherapeutic control of livestock parasites have been and continue to be explored. One alternative pursued for several decades and considered the ultimate approach to control is a broad spectrum internal parasite vaccine for livestock. To date there are approximately 14 parasite vaccines produced and/or manufactured or distributed by governmental organizations[6]. However, only one is a nematode vaccine (*Dictyocaulus viviparus*) another is a tapeworm vaccine and one is a tick vaccine (*Rhipicephalus [Boophilus] microplus*); all others are vaccines with protozoa-derived antigen. Other alternatives explored, also with little success and commercial/large-scale application, have included various plant extracts with nematocidal activity, nematophagous fungi and various metals, mineral and other natural element or feed additives. The classes of anthelmintics, especially macrocyclic lactone class, remain essential to the health and welfare of pasture-based livestock and the resulting improvement in resource utilization and production efficiency. The global cattle population is estimated to increase from 1.5 billion to 2.6 billion by 2050 and ruminant rangeland grazing intensity is projected to increase[7] and hence the need for internal and external parasite control will increase proportionally. It is important therefore to maintain the longevity and availability of these compounds. **Commercial-scale vaccination as a means of internal and external parasite control in livestock remains a scientific goal but is many years, if not decades, away from becoming a reality.** Inherent with the administration of any anthelmintic is the genetic selection of the subpopulation of organisms that are genetically refractive, tolerant or resistant to the active ingredient[8]. Anthelmintic resistance, at least to the major classes of compounds, is conferred by multiple alleles (variant form of a gene) and therefore constitutes a small	Noted.

[6] Vercruysse J. *et. al.* Control of parasitic disease using vaccines: an answer to drug resistance? Rev. sci. tech. Off. Int. Epiz. 2007, 26(1), pp 105 -115.
[7] Thornton PK, Livestock Production: recent trends, future prospects. Philos Trans R Soc Lond B Biol Sci. 2010 Sep 27; 365(1554):2853-2867.
[8] Sargison N. Pharmaceutical treatments of gastrointestinal nematode infections of sheep – Future of anthelmintic drugs. Vet. Parasitol. 189 (2012) 79-84.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		percentage of a naïve parasite population. As selection pressure is increased on a parasite population the proportion of resistant or refractive parasites increases until they are the dominant genotype in the parasite population. In addition to the frequency of exposure / selection pressure, under dosing (exposing parasites to sub-therapeutic levels of a drug) will also increase the resistant population by further selecting refractive parasites[9]. This phenomenon has been observed for all classes of anthelmintics and will likely be the case if other classes of anthelmintics compounds become commercially available. The greatest prevalence of anthelmintic resistance in livestock has been observed in the sheep industry where frequent anthelmintic administrations were common to internal parasite control programs. The frequency of administration was driven primary by high mortality and clinical morbidity associated with parasitic gastroenteritis and enema due to the hematophagous parasite *Haemonchus contortus*. *Haemonchus contortus* is often the most prevalent internal parasite in sheep due to its high fecundity (egg shedding) relative to other species. The practice of frequent anthelmintic application and resistance development in sheep has often been erroneously extrapolated to characterize the use pattern of anthelmintics and endectocides in cattle parasite management programs as well. This is an unfortunate and erroneous characterization of the industry as whole. There are likely cases of misuse, overuse or erroneous application of anthelmintics, but without empirical evidence demonstrating common practice, such statements are mere generalizations. It would not be possible to have 30 years of effective use of these compounds in the cattle industry if frequent indiscriminate or misuse was an industry norm. A cursory review of the scientific literature will demonstrate that anthelmintic resistance is occurring in all species of livestock that are exposed to the current classes of compounds[10]. Industry and scientific leaders in conjunction with veterinarians and producers are working toward solutions to maintaining the longevity of existing anthelmintics. For example there is a slow shift in some market segments away from	

[9] Gasbarre, L. et. al. Anthelmintic resistance in cattle nematodes in the US. Vet. Parasitol. 2014 Jul 30;204(1-2):3-11.

[10] Papadopoulos E et. al. Anthelmintic resistance in sheep in Europe: A selected review. Vet. Parasitol. 189 (2012) 85-88.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		pour-on formulations to injectable formulations to ensure proper dose rate and application (proprietary marketing data). The goal is to continue this trend. The introduction and proper use of combination products or concurrent use of anthelmintics with disparate modes of action are being introduced to producers along with education on use patterns. **Genotypic selection for resistance is a natural outcome of chemotherapeutic-based parasite control if excessive selection pressure is placed on the parasite population. Relative to their initial use, the knowledge-base of anthelmintic resistance has increased significantly. The focus of modern parasite control programs is to implement use patterns at the farm level that balance the objectives of effective control with minimal selection pressure on parasites to extend the usefulness of the limited pool of available anthelmintics.** In summary the availability of all of the existing classes of anthelmintics is vital to maintaining the current level of health and welfare of livestock in modern production systems. “	This specific point is addressed in the Annex of the RP (619-637 and 661-696)
178-180	1.	**Comment:** Mortality is possible; certainly with a number of helminth species in sheep, horses and cattle. Note that some also have a zoonotic potential, with a possible impact on public health. **Proposed change:** add: “**and may even result in mortality**”	Accepted.
179-180	5.	**Comment:** The paper should not focus on economy. **Proposed change:** Delete the second part of the sentence beginning with “and may cause significant economic losses to farmers…..”	Not accepted. The RP does not focus on economy. What is stated is an accepted fact and is a consideration when deciding on the need to use parasiticides.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
186-191	1.	**Comment:** This paragraph does not relate to the problem addressed in this reflection paper. In addition, all the risks mentioned in this paragraph are evaluated and appropriately addressed as part of the marketing authorisation process. All necessary mitigation measures are implemented. **Proposed change:** Suggest deletion of the sentence "Related to the use…"	Partially accepted. The sentence "Related to the use……." is deleted. However, the following sentence ("In addition, emerging resistance……") will be retained with minor modification. The purpose of this sentence is to make the point that emerging resistance is an increasing concern. This is considered a significant and relevant point in that it emphasises the need for a range of effective anthelmintic treatments and it leads on to the point that there is a need for a more sustainable approach to parasite control (from the point of view of both resistance emergence and environmental safety).
187	5.	**Comment:** The use of VMPs might also cause unwanted effects to the consumers. **Proposed change:** "…there are potential unwanted environmental effects **as well as**	Sentence has been deleted as per comment above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		hazards for occupational (user) **and consumers**."	
190-191	1.	**Comment:** Not only animal welfare, but animal health is threatened – parasites can induce serious disease and may even cause mortality (especially in sheep and horses). Note that for this reason, multiple pharmacologic options with different efficacy spectra and mechanisms of action are needed for robust parasite management programs. **Proposed change:** add: "**and animal health**"	Accepted.
203-206	1.	**Comment:** While there may be potential for substances to move between compartments, the usually very low mobility in soil/sediment and low water solubility of P/vP molecules are such that they are unlikely to move from soil/sediment to water and such molecules will be of reduced bioavailability with less potential to bioaccumulate. **Proposed change:** Please revise the lines to reflect this point.	Not accepted. Sorption coefficients are partition coefficients and part of the substance will always be in the water phase. Desorption processes occur as well. The substances may be transferred to surface water via runoff (partially with particulate matter) and they may be present in aquatic sediments and suspended matter. It has been agreed in the REACH framework that PBT classification is always independent of the compartment.
207-209	1.	**Comment:** These are very general statements and assumptions, but not substantiated by data. The relevance to a general reflection paper on PBT substances is also unclear.	Not accepted. The statements in question are

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Please reconsider, or include scientific references in support of statements made.	of a general nature. However, the main point of this paragraph is to highlight that there is practically no information on the toxicological profile of metabolites/degradation products. Given the gaps in information relating to active substances, this is not an unreasonable assumption.
209	4.	**Comment:** move 'unchanged' **Proposed change:** …a large proportion of the administered dose is excreted unchanged into the environment.	Accepted.
210	5.	**Comment:** 'extensively metabolised' in the context of VMP authorisation means each metabolite and parent are less than 5%. Is this what is meant here or is it rather metabolism in general and formation of main metabolites? **Proposed change:** Delete 'extensively'	Accepted. Text has been modified to "….in general not ~~extensively~~ metabolised <u>to a great extent</u> in the body…."
211-213	1.	**Comment:** This is again an assumption and very general; MA holders may actually have such data or could in some instances be prepared to generate them. For example, excretion profiles (which are product-specific) are typically part of a product dossier and are often discussed in the ERA. **Proposed change:** Please revise or delete.	Not accepted. It is accepted that such data could be generated. However, given the gaps in information relating to active substances, it is a

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			reasonable assumption that even less information is available for metabolites/ degradation products.
214-222	1.	**Comment:** In fact, for all the reasons specified in this paragraph, this is exactly why veterinary medicines need to be considered as unique and deserve a robust risk assessment specific to product and means of use as opposed to by chemical compound and hazard. This is why a substance-based assessment for VMPs is flawed and subject to misuse and misinterpretation, because it does not take this important information into proper context.	Noted. The CVMP wishes to emphasise that the concerns expressed are, for the most part, based on a misconception that the proposal is to have a formal 'substance approval' based on PBT status. That is not the proposal. What is being proposed is, simply, to determine the PBT status of substances used in VMPs and, for confirmed PBT substances, to determine the conditions under which products containing those substances can be authorised. The proposal is that the decision to authorise, or not, will be

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			taken on a product basis. (299-356).
217-218	1.	**Comment:** The assumption about exposure from pour-ons and injectables (what about boluses, premixes?) is clearly not informed by any data. This will be formulation and substance-dependent. **Proposed change:** Please include scientific references in support of statements made.	Not accepted. As clearly stated in the text, this is an assumption (which for the most part, is expected to be true). However, clearly, it is not a critical detail – it only serves to make the point that one factor to consider when discussing options to limit environmental emissions is the product administration route.
219-220	1.	**Comment:** The major factor for dosing precision is a correct estimation or determination of the animal's body weight; topical pour-on products can be administered as precisely as injectables. The direct exposure due to wash-off seems to be overestimated. **Proposed change:** Please include scientific references in support of statements made.	Not accepted. Again, this is not a critical detail – it only serves to make the point that certain substances can only be formulated in products that must be administered by a particular route. That is, when discussing options to limit environmental emissions of a particular substance, alternative

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			administration routes may not be an option.
227	1.	**Comment:** Persistent efficacy minimises treatments and is a desired feature for an antiparasitic, but that implies a certain persistence. Without that feature, frequent treatments (such as every 3 weeks to interrupt the parasite life cycle) are inevitable, resulting in a high and frequent environmental exposure. The more efficacious, the greater the potential for toxicity to non-target environmental species. These simply are conflicting goals. **Proposed change:** Please take this into account in your considerations.	While long acting products (persistent efficacy) may limit the number of treatments, there are growing concerns that persistent efficacy may be a significant factor in resistance emergence[11]. As reflected in the RP, what is needed is a more sustainable approach to parasite control (more judicious use of products), not longer-acting products.
233	4.	**Comment:** reducing use of medicinal treatments will potentially reduce the risk (e.g. as exposure decreases), however, the hazard remains as long as the substance is being used. **Proposed change**: remove 'hazard and'	Accepted.

[11] Leathwick DM, Besier RB, 2014. The management of anthelmintic resistance in grazing ruminants in Australasia--strategies and experiences. Vet Parasitol. 204(1-2):44-54.
Leathwick DM, Miller CM, Fraser K, 2015. Selection for anthelmintic resistant Teladorsagia circumcincta in pre-weaned lambs by treating their dams with long-acting moxidectin injection. Int. J. Parasitol. 5, 209-214.
le Jambre LF, Dobson RJ, Lenane IJ, Barnes EH, 1999. Selection for anthelmintic resistance by macrocyclic lactones in Haemonchus contortus. Int. J. Parasitol. 29, 1101-1111.
Sargison ND, Bartram DJ, Wilson DJ, 2012. Use of a long acting injectable formulation of moxidectin to control the periparturient rise in faecal Teladorsagia circumcincta egg output of ewes. Vet. Parasitol. 189, 274-283.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
233	5.	**Comment:** Hazard is not the right wording in this framework. **Proposed change:** Please delete “hazard and”.	Accepted.
241	4.	The recommendation that products should be administered at the correct dose for the recommended treatment period in order to reduce the risk for the environment implies that there is a common misuse of products, otherwise this statement has no meaning. Is this really the case and if so it would be useful to discuss this as well.	Noted. It is correct that this specific statement is more relevant to the issue of resistance development (generally recognised as an important factor to limit resistance development); however, it is to be seen as one of a number of general recommendations that are aimed at reducing reliance on medicinal treatments. No change in text necessary.
241	5.	**Comment:** This bullet point implies misuse of the product in practice. However, each product is authorised under the presumption that it will be used in accordance with the SPC. Hence, this point seems needless. **Proposed change:** Please consider deletion or clarify.	See comment above.
243	4.	**Comment:** ‘toxicological concern’ The subject of the paper is PBT, why address separately substances of toxicological concern? Moreover, restricted classes of toxicity are covered in the T criterion. **Proposed change:** remove: (toxicological concern and potential PBTs)	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
244	4.	**Comment:** 'primarily' This indicates that potential PBT/vPvB substances are also used in other areas of aquaculture than sea lice treatment. Even if these are probably (because of the 'primarily') less in number, please include these uses as this is highly relevant. **Proposed change:** list other areas of concern	Not accepted. The focus of this part of the reflection is on VMPs used to treat sea lice. The purpose is to provide some context to the consideration of PBT: it was thought useful to reflect on the benefits of such products, the conditions of use (in general terms), the route of entry of the active substance into the environment and whether or not any RMMs or restrictions on use could be usefully applied to reduce emissions of individual products in the event that the active substance is classified as PBT. This reflection feeds into other aspects of the RP, including: seeing the direct and indirect (combating resistance emergence) benefits of products and consideration of options to

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			reduce emissions to the environment. While it is accepted that VMPs are used in aquaculture for other purposes, it is considered unnecessary to expand on this part of the RP.
245-250	1.	**Comment:** Lice infestation, and other diseases, on farms can also lead to reduced appetite in the fish and increased wastage. This not only impacts production but can lead to organic enrichment and impacts in the environments around the farm. The slower growth of the fish can also reduce the time available for fallowing the sites between growth cycles. This means that there is less potential to reduce the background infection pressure and break the infection cycle for both the farmed and wild fish, in situations where there might be such a relationship. It also reduces the time for impacted sediments beneath the farms to be recolonised and recover. **Proposed change:** Please recognise that the inability to use appropriate medicines to control disease can have wider impacts.	Not accepted. The focus of this part of the reflection is on VMPs used to treat sea lice. The purpose is simply to provide some context to the consideration of PBT (see comment above). Further elaboration of this point as proposed by the stakeholder comment is considered unnecessary.
245-246	3.	**Comment:** It would be relevant to add that sea lice infestations represent not only a welfare issue, they also make fish more susceptible to other infections with possible severe ill-health and mortality. **Proposed change:** Untreated sea lice infestations represent a considerable welfare problem **putting fish at greater risk of infections which may cause suffering and death and** have the potential to cause significant economic losses.	Partially accepted. The sentence has been amended to read: "….associated with reduced production, increased susceptibility to other infections, reduced marketability……".
245-246	5.	**Comment:** The potential economic losses should not be mentioned in this paper.	Not accepted. It is a fact

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Please delete "and have the potential to cause significant economic losses".	that economic losses are a consequence of sea lice infestation and this will be a primary consideration of producers of farmed fish.
245	5.	**Comment:** It should read 'animal welfare' instead of 'welfare' **Proposed change:** Please add 'animal'	Accepted with minor amendment. The text reads"….fish welfare…"
255	5.	**Comment:** The use of VMPs in aquaculture might also cause unwanted effects to the consumers. **Proposed change:** "…there are potential unwanted environmental effects **as well as** hazards for occupational (user) **and consumers** related to the use of VMPs."	Noted. The sentence "However, there are potential……." is unnecessary and has been deleted. Consequently, the proposed change will be unnecessary.
263-264	3.	**Comment:** In the table following line 264, reference is made to authorised treatments in fish via bath or medicated feed administration routes and that environmental exposure would vary when treatment location is either hatcheries or at sea. To our knowledge, no currently approved sea lice medicines would be used in the hatcheries. Treating fish in the hatchery against sea lice would be preventative treatment as sea lice would not be present in the fresh water phase. With the relatively short acting medicines currently available, it makes little sense to treat the fish at a stage where sea lice are not present. It is however, possible to foresee that preventative treatment of fish could be useful if long-acting medicines are made available. In such case the active substance would need to be absorbed into fish and remain in the fish through the efficacy period at sea. It would	Not accepted. The text and table reflect the current situation (as acknowledged in the comment).

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		then be expected that excretion from fish would also occur when fish are treated in hatcheries. **Proposed change:** The route of administration of ~~authorised~~ **sea lice** treatments in fish **could be** ~~is either~~ via immersion bath, ~~or~~ medicated feed **or by injection**. In the table, add "Excretion from treated fish" if fish are treated against sea lice in hatcheries. Add administration route by injection to the table.	
277-278	1.	**Comment:** We believe it should be clarified that "susceptibility of the sea lice to the chosen treatment" is subject to both the mode of action of the substance on relevant sea lice development stages and the prevalent resistance situation[12,13]. Many management thresholds have been set to reduce the perceived risk to wild fish as opposed to farm stock. This can result in more frequent treatments than the prescribing veterinarian would consider necessary based on his professional expertise and may drive the development of resistance to the limited number of treatments available. **Proposed change:** Please clarify and consider implications of excess use of products to assuage concerns which are still under discussion.	Partially accepted. The text in line 277-278 can be clarified as requested. However, the proposal to "clarify and consider implications of excess use of products to usage concerns" is unclear. In the RP, there is a focus on appropriate use and minimising reliance on medicinal treatments (which would be expected to reduce

[12] Aaen et al. A screening of medicinal compounds for their effect on egg strings and nauplii of the salmon louse *Lepeophtheirus salmonis* (Krøyer). Journal of Fish Diseases (2016) doi: 10.111/jfd. 12462

[13] Helgesen & Horsberg. Single-dose field bioassay for sensitivity testing in sea lice, Lepeophtheirus salmonis: development of a rapid diagnostic tool (2013) Journal of Fish Diseases 36, 261-272

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			both resistance emergence and the environmental impact).
276-278	3.	**Comment:** It is appreciated that this bullet point is intended to ensure that sea lice treatments are only performed when absolutely required and to ensure such treatment is as efficacious as possible. However, as other authority agencies will sanction sea lice levels above certain thresholds, farming practice would be to keep sea lice levels as low as possible and especially lower than thresholds at which legal action could be expected. In Norway, farmers are also observing the benefit of keeping levels low to avoid large reservoirs of sea lice building up in their farms. Furthermore, for some active substances it may be important to treat the fish before the level of adult sea lice reach an unacceptable level. Maximum legal thresholds are normally linked with a certain number of adult female lice – a stage which is not controlled by all available treatment alternatives against sea lice. **Proposed change:** Use of medicinal treatments should be targeted based on the monitoring of lice infestation **and the mode of action of the medicinal product to be used.**~~and triggered when the levels of lice on fish exceed management thresholds~~. Efforts should be taken to ensure susceptibility of the sea lice to the chosen treatment.	Partially accepted.
279-281	1.	**Comment:** This suggests that prophylactic treatment with PBT molecules is considered inappropriate, e.g. treatment in the hatchery for protection against sea lice after transfer to an open marine environment. One of the main advantages of treatment in hatcheries is reduced environmental exposure to chemotherapeutants. Hatchery water can be filtered and discharged following both in-feed, injection and immersion treatments in hatcheries, unlike treatment in open water. In addition, food loss and wastage, and contaminated	Partially accepted. While no such products are currently available, it is accepted that there may be interest in the development of such products for the reasons stated by the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		excreta from treated fish can be more easily controlled and discarded. Smolts are highly susceptible to sea lice and infectious diseases following introduction to sea pens[14,15,16]. Pretreatment against sea lice not only controls lice infestation but reduces physical damage to fish caused by lice, which makes them more vulnerable to infection[17, 18]. Some products with long duration of action could be administered in hatcheries, resulting in fewer treatments at sea and reduced environmental exposure with a positive impact on environmental safety[19]. Treatments of smaller fish in hatcheries also require lower treatment volumes, resulting in less use of product. This is particularly relevant in regions that have a history of high seasonal sea lice counts where sea treatments are frequent and necessary. Lastly, reduced handling of fish in the sea phase in general will improve fish welfare and reduce the risk of both handling damages and other infections[20]. **Proposed change:** Please delete the bullet point, as it isn't appropriate in this situation.	stakeholder. Therefore, it is accepted that the RP should not rule out the possibility that such products may be developed/authorised where an improved safety profile (in particular, the potential to significantly reduce environmental emissions) is documented.

[14] *Skilbrei O. T. et. al.* Impact of early salmon louse, *Lepeophtheirus salmonis*, infestation and differences in survival and marine growth of sea-ranched Atlantic salmon, *Salmo salar* L., smolts 1997–2009. J of Fish Dis. 36(4), 2013, pp. 249-260.

[15] *Jarungsriapisit et al.* Atlantic salmon post-smolts challenged two or nine weeks after seawater-transfer show differences in their susceptibility to salmonid alphavirus subtype 3. Virology J. 13(66), 2016.

[16] Fast M. D. et. al. The effects of *Lepeophtheirus salmonis* infections on the stress response and immunological status of Atlantic salmon. Fish & Shellfish Immun. 21 (3), 2016,pp. 228-241.

[17] Nolan D. T. *et. al.* Infection with low numbers of the sea louse Lepeophtheirus salmonis induces stress-related effects in postsmolt Atlantic salmon. Can J Fisheries & Aquatic Sciences. 56 (6), 1999, pp. 947-959.

[18] Mardones F. O. *et. al.* Epidemiologic investigation of the re-emergence of infectious salmon anemia virus in Chile. Dis Aquat Org. 84, 2009, pp. 105-114.

[19] Perret et. al. WO 2011/157733 A2. Filed on 15 June 2011.

[20] Carey J. B. and McCormick S. D.Atlantic salmon smolts are more responsive to an acute handling and confinement stress than parr. Aquaculture. 168, 1998, pp. 237-253

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
279-281	3.	**Comment:** On the basis of currently approved medicines to treat sea lice, it would not be useful to treat on a preventative basis. However, it seems ill-advised to block the opportunity for long-acting products which could reduce the number of required acute treatments during a production cycle. Avoiding frequent treatments could be beneficial to the environment and reduce development of resistance towards existing active substances. Furthermore, treatments of small fish before transfer to sea could also reduce the total amount of active substance needed for treatment and thus reduce the discharged amounts to the environment. **Proposed change:** Given the general principle to use medicinal treatments only when needed, the administration of treatments prior to transfer to sea and exposure to the parasite (essentially on a preventative basis) is considered ~~in~~appropriate **only when fish are transferred to areas where sea lice are abundant**.	Partially accepted. Text to be amended so that the possibility of preventative use is not totally excluded. See comment above.
282-292	1.	**Comment:** This is already advised on data labels, SPCs and in literature from the pharmaceutical companies and producers organisations. As presented here it appears to suggest this is not common practice and ignores the fact that farming companies will always strive to reduce the medication costs. **Proposed change:** If this text is to remain, please amend it to reflect the fact that this is already common practice.	Accepted.
282	4.	See comment 241 *(Stakeholder No. 4)*	See previous comment.
282	5.	Please see comment above for line 241 *(Stakeholder No. 5)*	See previous comment.
288	4.	The second measure on the administration of in-feed treatment is not easy to link to the reduction of the quantity of active substance use. Please add further explanation.	Not accepted. It is correct that this specific statement is more relevant to the issue

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			of resistance development (generally recognised as an important factor to limit resistance development); however, it is to be seen as one of a number of general recommendations that are aimed at reducing reliance on medicinal treatments.
291	4.	Editorial: please revise the bullet point as follows: reduce the size of the net-cage to **the** minimum possible **size** ……	Accepted.
294-296	1.	**Comment:** There is surely a need to assess whether theoretical hazards actually translate into environmental impacts as can be determined in field studies and monitoring under commercial use. This would be at very least required to establish whether the proposed elimination of an existing PBT or vPvB substance is truly warranted and to inform future decisions. **Proposed change:** Please amend this title to reflect these options.	Not accepted. The title reflects the need for a strategic approach to the assessment of risks posed by PBT substances. Amendment of the title to reflect this specific comment is not considered necessary. Further, it should be noted that, in the case of PBTs, it may not be prudent to wait for documented evidence of environmental impact before addressing the issue of PBTs in VMPs. Further, in section

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			3.1, it is suggested that in situations where VMPs containing PBT substances are authorised/maintained, consideration can be given to specific monitoring for environmental impact.
294-389	3.	**Comment:** In section 3.1, reference is made to PBT substances. It is understood that when "PBT status" is used this also covers vPvB substances. However, in cases where PBT substances are specified, are vPvB substances excluded? **Proposed change:** Add **/vPvB** where appropriate.	Accepted. The text has been revised accordingly.
294	4.	**Comment:** vPvB is missing If this paper is only about PBT substances, please also refer to how vPvB substances should be managed. According to the CVMP PBT guideline: “vPvB substances are resistant to environmental degradation and consequently they have been known to persist in the environment, transport long distances, bioaccumulate in human and in animal tissue, and bioconcentrate. Thus, 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.”.	Accepted. The text has been revised accordingly.
297-301	1.	**Comment:** The section is misleading, and could suggest that no Community regulatory action is possible in such a situation; however referral procedures can be initiated. Indeed, such a procedure is currently ongoing for the concerned substance moxidectin.	Partially accepted. It should be noted that the moxidectin referral procedure was not initiated until Nov 2015. At

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: **As noted in Section 2.1.2. above, recently, a Community Referral under Article 35 of Directive 2001/82/EC, was initiated to examine all veterinary medicinal products containing moxidectin to be administered to cattle, sheep and horses** ~~a marketing authorisation for a generic VMP containing one of the substances identified as PBT was refused by Member State national competent authorities~~ **based on concerns regarding the risk for the environment due to PBT properties**~~. However, it is acknowledged that products containing the same substance are authorised in the Community.~~	that time, the RP was at an advanced stage of drafting. However, it is accepted that specific mention of the ongoing moxidectin referral can be included. The RP has been updated in section 2.1.2. and includes information on the ongoing referral (up to the time of writing, April 2017).
301-307	1.	**Comment:** Earlier in the text, it is mentioned that some 20 substances are potentially implicated. That is a fraction of the veterinary medicine portfolio and as such actually supports a case-by-case approach, rather than to have all substances used in any veterinary product go for a full PBT-assessment – most of them unnecessarily. **Proposed change:** Please provide adequate justification including a legal basis for such an approach.	Not accepted. The constraints of the existing legislation are clearly outlined in section 3.2 of the reflection paper. This serves as a robust justification for recommending additional legal tools. Further justification is considered unnecessary.
310-311	1.	**Comment:** The principle of threshold of exposure as set by Phase I evaluation, and as done in the REACH regulation, should remain. Hence, to be able to evaluate if the exposure threshold is reached, the PBT evaluation should not be disconnected from the evaluation of a product.	Not accepted. The specific point raised is addressed in section 3.1, bullet 3. The intention would be to follow

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: 1. There is a need to determine the PBT status of substances used in VMPs **when Phase I evaluation concludes that a Phase II is required**	the approach outlined in section 1.2 of the CVMP PBT Guideline: *"As the Phase I assessment does not require any specific environmental data the PBT screening can only be conducted as part of the Phase II assessment. However, ……."*
310-311	2.	**Comment:** We agree that there is a need to determine the PBT status of new substances and existing substances used in VMPs. We believe that the determination of vPvB status should also be considered (see also general comment above) **Proposed change:** There is a need to determine the PBT status **and the vPvB status** of substances used in VMPs (both new substances and existing substances).	Not accepted. One of the possible outcomes of determining PBT status is that the substance is categorised as vPvB and further clarification is not considered necessary.
310-389	4.	**Comment:** Please refer to the methods as described in the CVMP PBT guideline in this chapter.	Accepted.
312-318	1.	**Comment:** The correct legislation to compare with is the human pharmaceutical legislation. For pharmaceuticals, a two-step approach is followed. The first step is an estimation of environmental exposure. Especially in veterinary medicine, markets are small and fragmented due to the variety of target species and exposure might be very low. This approach is also followed under REACH: *no CSA and PBT-assessment are required for substances imported or manufactured in the EU at less than 10 tonnes per year*; this appears to be the threshold for no concern. The manufacturing volume defined in REACH is considered to be an indicator for the extent of environmental exposure expected	Not accepted. For human medicines, a PBT assessment is always performed in Phase I of the ERA if the log Kow is ≥ 4.5 irrespective of any exposure considerations. Exposure considerations differ

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		following the use of the chemicals. **Proposed change:** please add the following: **the assessment should start with an exposure assessment through Phase I. If the Phase I evaluation concludes that a Phase II is required, an environmental risk assessment including determination of the PBT-status will follow.**	considerably between human and veterinary medicinal products. In the RP generally, and in the lines in question specifically, the purpose of the reference to pesticides and biocides is to outline the approach to PBT assessment for these other chemical substances.
312-318	2.	**Comment:** The reference to environmental risk assessment in BPR and PPP legislation is incomplete and thus not correct. **Proposed change:** Under other legislative frameworks (e.g. BPR and PPP), the environmental risk assessment follows a two-phase approach. First there is an evaluation of the intrinsic properties of the active substance, which includes the determination of PBT **and vPvB** status. If a substance is identified as PBT or vPvB ("cut-off candidate") either the substance is excluded from further use or the applicant can apply for derogations. **Based on this evaluation a decision on approval or non-approval of the substance is carried out.** If the substance approval is confirmed. The following product authorisation includes an environmental risk assessment of the product that contains the PBT/vPvB substance. Risk mitigation measures are laid down either/and on substance or product level. Any consideration of the hazards related to PBT/vPvB substances in VMPs should follow the same basic approach: that is, the PBT/vPvB status of the substance should be determined before conducting/considering a product-specific assessment of the risk to the	Accepted. Text has been reworded based on the proposal.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		environment.	
312	4.	**Comment:** the processes in the BPR and PPP frameworks are not correctly addressed. See comments on line 90-91, 93-94, and 124-125. **Proposed change:** See above cited comments *(310-389 Stakeholder No. 4)*	Partially accepted. Text has been reworded based on the proposal.
312-317	5.	**Comment:** The environmental risk assessment of PPP follows a two-step process. First a **substance-specific** assessment (PBT, vPvB, POP) as well as a **risk assessment** for the active substance takes place at EU level. As a next step a further risk assessment on product level will be performed. **Proposed change:** Please revise the text accordingly. E.g. 'First the active substance has to be permitted on EU level. This implies the evaluation of the intrinsic properties of the active substance, including the determination of the PBT status, as well as a risk assessment of all intended uses for the active substance. This is followed by an environmental risk assessment at product level.	Partially accepted. Text has been reworded based on the proposal.
312-318	5.	**Comment:** The ERA for VMPs already follows a two-phase approach. However, this is different to that for PPP and BPR as for VMPs in Phase I according to VICH GL 6, the decision is made whether a Phase II assessment is necessary based on the decision tree and not on intrinsic properties of the active substance. Nevertheless, the decision tree could be amended to take account of potential PBT properties. **Proposed change:** Please consider amendment/revision of this paragraph accordingly	Noted. However, the text has not been modified, as what is meant here is not a 2-Phased ERA, but a 2- phased assessment procedure, i. e. determination of PBT status on a substance level independent of product authorization procedures.
319	5.	**Comment:** to avoid confusion of guidelines, the respective guidelines should be fully	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		quoted. It should read 'VICH GL 38' **Proposed change:** Please add '38'	
319-323	1.	**Comment:** Products (not substances) may stop in Phase I because the exposure of the environment to the active ingredient is not of concern – comparative with the 10 tonnes limit in REACH. **Proposed change:** please delete the last sentence.	Partially accepted. The text of this paragraph has been reworded to clearly indicate that no PBT assessment, other than in exceptional circumstances, would be required for substances included in products that do not enter Phase II assessment.
319-323	2.	**Comment:** According to the VICH GL, a PBT assessment is not required for all active substances used in veterinary medicinal products. Current requirements are that a PBT assessment is performed for all substances that enter Phase II and have a log K ow > 4. Consideration needs to be given to whether or not a PBT assessment should be required for (any) substances that would normally stop in Phase I of the VICH GL. We strongly support that a PBT/vPvB assessment is performed for all substances. **Proposed change:** We propose to change the VICH GL accordingly.	Not accepted. As stated above, the intention would be to follow the approach outlined in section 1.2 of the CVMP PBT Guideline: "*As the Phase I assessment does not require any specific environmental data the PBT screening can only be conducted as part of the Phase II assessment. However, …….*"

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
321	5.	**Comment:** According to VICH GL 38, the trigger value is a logKow ≥4 and not >4. **Proposed change:** Please replace 'log Kow >4' by log Kow ≥4	Accepted.
321-323	5.	**Comment:** Our proposal: Analogous to human pharmaceuticals for all substances in Phase I with a log Kow ≥ 4.5 a PBT assessment should be required. **Proposed change:** Please add a corresponding paragraph.	Not accepted. For human medicines, a PBT assessment is always performed in Phase I if the log Kow is ≥ 4.5 irrespective of any exposure considerations. For products that enter Phase II, Tier A provides data on persistence, long-term toxicity and if log Kow ≥ 3 on bioconcentration in fish. Therefore, the factual trigger for PBT assessment in Phase II is a log Kow ≥ 3. In case of veterinary medicines the log Kow for performing a BCF study in Phase II is log Kow ≥ 4. The approach suggested in the CVMP PBT GL is consistent within the VICH framework, although it is acknowledged that this

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			differs from the approach for human medicines. To be consistent with human medicines, an action limit of ≥ 4.5 would have to be accompanied by a change in the VICH GL to require Phase II BCF studies in case log Kow ≥ 3. Notwithstanding the differences in triggers for PBT assessment, the PBT classification criteria are the same for both human and veterinary medicinal products; therefore, a substance that is identified as PBT when used as human medicines would also be classified as PBT when used as a veterinary medicine.
323	5.	See comment at line 319 *(Stakeholder No. 5)*. Here it should read 'VICH GL 6' **Proposed change:** Please add '6'	Noted. This paragraph has been redrafted as per other comments. The change proposed is not applicable

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			any longer.
324-326	1.	**Comment:** This bullet point seems to suggest that when a substance is PBT/vPvB, further risk assessment for the product will not be done and marketing authorisation for the product will be refused. This is in conflict with VICH, the TGD, the PBT-guideline and the whole legal principle of benefit-risk assessment. That is a purely HAZARD-based decision which can be considered unethical from a medical perspective. As indicated above, a formal RISK assessment is possible for a PRODUCT, since risk takes exposure into account, and that is determined by the product characteristics. **Proposed change:** please delete this bullet point.	Not accepted. The CVMP would suggest that the interpretation of this bullet as presented in the comment is a misreading of the text. What is stated in this bullet is that, unlike under other frameworks, there will be no specific proposals for dealing with substances that meet 2 of the 3 criteria.
327-328	1.	**Comment:** Evaluation should start with exposure in Phase I **Proposed change:** 5. For new substances (not previously used in VMPs) **that go through Phase II evaluation**, an assessment of PBT status should be conducted ~~prior to, or~~ at the time of~~,~~ the initial application for marketing authorisation.	Comment partially accepted. The substances requiring PBT assessment is now detailed in bullet 3 of this section. The text in bullet 5 has been amended to clarify that the PBT assessment be conducted at the time of initial application for MA.
327-328	2.	**Comment:** In order to secure environment from PBT/vPvB substances and to secure coherence to other legislative frameworks (e.g. BPR and PPP) the evaluation of the intrinsic properties of the active substance including the determination of PBT/vPvB status, followed by **a** decision on approval or non-approval of the substance should be performed	Not accepted. The comment suggests that the proposal is to have a formal 'substance approval'

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		prior to the environmental risk assessment at the product level. **Proposed change:** For new substances (not previously used in VMPs), an assessment of PBT **/ vPvB** status should be conducted prior to~~, or at the time of~~, the initial application for marketing authorisation.	based on PBT status. That is not the proposal. What is being proposed is, simply, to determine the PBT status of substances used in VMPs and, for confirmed PBT substances, to determine the conditions under which products containing those substances can be authorised. Under this proposal, PBT status could be determined at the time of initial application.
327-328	5.	**Comment:** Actually, this is already foreseen in the revised guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 AND GL 38, p49 in reference to REACH. Maybe it is necessary to make it clearer.	Not accepted. The CVMP GL in support of GL 6 and GL 38 does not include guidance on the approach to PBT assessment. A reference to the CVMP PBT guideline has now been included in this section of the reflection paper, under bullet point 1.
329-333	1.	**Comment:** There is no such requirement from a legal point of view. **Proposed change:** please delete this bullet point.	Not accepted. What is outlined in section 3.1 of the RP is what the AHEG

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			considers is needed to comprehensively address the PBT issue. Section 3.2 clearly outlines the constraints of the existing legislation.
329-332	2.	**Comment:** We welcome that an initial screening for substances of concern (potential PBT substances and vPvB substances) and the compiling of a formal PBT/vPvB substances list. In order to make this happen, a timetable is to be fixed. **Proposed change:** For existing substances, an initial screening for substances of concern (potential PBT substances**, vPvB substances**) is required. For all existing substances identified in the screening process, a definitive determination of PBT**/vPvB** status will be required (in effect, a formal list of PBT**/vPvB** substances should be generated). The screening process (including categories of substances to be screened) needs to be documented. **A binding timeframe for the screening and the definitive determination of PBT status is to be set. A public access to the formal list of PBT/vPvB substances must be secured.**	Partially accepted. The reference to vPvB is accepted. However, regarding a timetable and in order to make this happen, the priority is to get the legal tools to appropriately address the PBT issue. Once the tools are in place/known, a timetable for the work can be established.
334-338	1.	**Comment:** When comparing the frameworks, it is obvious that there is no coordinated or harmonised approach: neither for the criteria used to decide on PBT-status nor for the way such substances are dealt with. The fact that there are differences between categories of substances that justify different approaches should be recognised. Furthermore, the Commission ultimately decides to authorise a VMP or not based on the recommendation from the relevant Agency (EMA). PBT evaluation is only part of the decision.	Not accepted. This bullet point relates specifically to the approach to PBT classification. While it is accepted that there may be justifiable differences in approaches to authorising

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: please delete this bullet point.	products containing PBT substances depending on their intended use, the approach to PBT classification should be harmonised across the different categories of substances.
338-339	2.	**Comment:** We propose to add the following Paragraph between Point 7. And 8. **Proposed change:** Authorisation for vPvB or PBT substances should generally be denied with very limited derogations as defined under 8.	Not accepted. The text in section 8 is considered sufficiently clear: "*an authorisation should only be granted/maintained if it is shown that emission to the environment can effectively be prevented or if the therapeutic benefits outweigh the risks arising from the use of the substance, and if there are no suitable alternative substances or technologies (that is, there is a clear therapeutic need for the product to improve animal welfare and/or address a*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			public or animal health concern)."
339-343	1.	**Comment:** No company will make the investment to develop a product for the EU that could be classified as PBT and for which the decision on approval relies on a subjective evaluation of therapeutic need at that particular time the application is made. This could prove to be problematic for example for parasite control in the future, in view of increasing anthelmintic resistance. Furthermore, the same issue is discussed in more detail in bullet point 9, making bullet point 8 redundant. In addition, there is a conflict: prevention of environmental exposure versus limited potential or reduced environmental exposure. **Proposed change:** please delete this bullet point.	Not accepted. The PBT status of a substance is only one of a number of factors that will be taken into account when deciding to develop a new active substance. As noted in bullet 8, in situations where the intended use of the substance will be associated with limited emissions or where the product offers a clear therapeutic benefit, then authorisation of products containing this substance could be considered.
339-343	1.	**Comment:** The prevention of emission to the environment goes beyond what is proposed later in the text lines 346-347. **Proposed change:** Please modify point 8 for consistency: 8. For VMPs containing PBT or vPvB substances, an authorisation should only be granted/maintained if it is shown that ~~emission to the environment can effectively be prevented~~ **there is a limited potential for environmental exposure** or if the therapeutic benefits outweigh the risks arising from the use of the substance, and if there	Not accepted. The text is considered to be sufficiently clear.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		are no suitable alternative substances or technologies (that is, there is a clear need for the product to improve animal health and welfare and/or address a public or animal health concern).	
339-343	2.	**Proposed change:** For VMPs containing PBT or vPvB substances, an authorisation should only be granted/maintained if it is shown that emission to the environment can effectively be prevented **which means that the exposure of the environment and non-target organisms under realistic proposed conditions of use is negligible,** or if the therapeutic benefits outweigh the risks arising from the use of the substance, and if there are no suitable alternative substances or technologies (that is, there is a clear therapeutic need for the product to improve animal welfare and/or address a public or animal health concern). **VMPs containing PBT or vPvB substances shall be authorised for a period not exceeding seven years. The product authorisation has to lay down mandatory risk mitigation measures and substitution plans and specific pharmacovigilance requirements are to be defined.**	Not accepted. The conditions that may attach to the authorisation of a VMP containing a PBT substance are already detailed under bullet 11 (lines 345-349) and do not need to be repeated here.
346-347	1.	**Comment:** Note that in reality, it is impossible to synthesise and test all metabolites formed in an animal in case of extensively metabolised substances. Such a requirement again discourages product development. Use of products with an extended duration of protection in controlled environments prior to transfer of fish to sea is the most obvious way to limit environmental exposure yet this is excluded earlier, see lines 279-281. **Proposed change:** delete “non-PBT” and amend to enable treatment under conditions where release can be controlled.	Partially accepted. The point has been re-drafted for clarification and in line with VICH GL 6. In addition, the example has been amended to include treatment under conditions where release can be controlled.

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346-351	5.	**Comment:** This part should be deleted because for PBT or vPvB substances it is excluded that they can be fully metabolized, fully degraded or that it can be demonstrated under field condition that there is no unacceptable risk. A safe concentration for PBTs /vPvBs cannot be established. Thus, exposure should be prevented, not only reduced. **Proposed change:** Please delete point a and b.	Not accepted. Both points should be retained as possibilities. As noted in the previous comment, environmental exposure may be reduced by use of products under conditions where release can be controlled.
348-351	1.	**Comment:** As above it is unrealistic to synthesise and test all metabolites of an extensively degraded substance, which would most likely qualify as a “green” pharmaceutical. **Proposed change:** please delete “non-PBT”	Partially accepted. Bullet 9, paragraphs (a) Section (b) have been re-drafted to clarify this issue. It should be noted that if degradation is to be used as a justification for authorising a VMP containing a PBT, it would have to be shown with data that the products of the degradation process (formed at $\geq$ 10 % of the administered dose) are themselves not PBT substances.
348	4.	**Comment:** Although in theory the example given could be possible, in reality it is very unlikely that a substance that meets the P criterion will degrade extensively in	Not accepted. Point should be retained as a possibility.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		manure/slurry. **Proposed change:** remove point b.	
348	5.	**Comment:** A safe concentration for PBTs /vPvBs cannot be established. Thus, exposure should be prevented, not only reduced. In line 340 it is stated 'if it is shown that 'emission to the environment can effectively be prevented', nothing mentioned about reduction. **Proposed change:** Delete the term "reduce or".	Partially accepted. The term "limited environmental exposure" has been used (instead of the term 'reduce environmental exposure') consistently throughout the document.
350	5.	**Comment:** What is exactly meant by 'extensively degraded in manure/slurry'? As per definition all transformation products and parent <5%, total mineralisation or anything different? It would be useful to specify. It seems unlikely that a PBT substance will be degraded so easily in manure or slurry. **Proposed change:** Please consider amendment.	Accepted. Clarification is now provided in bullets a) and b).
352-365	1.	**Comment:** It should be noted by the environmental and regulatory agencies that developing a veterinary medicinal product for limited use in only a few MSs is usually not feasible from a business point of view; the market for VMPs is simply too small to carry the cost (note that the veterinary pharmaceutical market is just 3-5% of the human pharmaceutical market). It would be interesting to see the criteria for comparison of substances/products; this assessment risks becoming extremely subjective and disproportionate. **Proposed change:** In the context of resistance alone, it would be more appropriate to	Not accepted. As acknowledged in section 4.1 of the RP, in addition to having the necessary legal tools (to address the PBT issue), there would be a clear need to elaborate guidance on an approach to

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		call this “limited availability of effective alternatives.” Limited authorisation in some MSs because of regional differences in availability seems rather unethical; the benefit-risk assessment is either positive or negative.	comparative assessment. The point referred to in the comment already acknowledges that any consideration of effectiveness should take into account the potential for issues such as resistance development.
352	4.	**Comment:** absence of alternatives alone is not a reason to grant authorisation. It needs to be shown that marketing of the product is essential and that effective alternatives are absent (NB the latter may need to be checked against authorisations in other MS, where alternatives could be marketed). This would include alternatives regarding animal husbandry practices.	Noted. ‘Absence of alternatives’ is just one of a number of factors to be considered. This is already acknowledged in the RP.
352-366	5.	**Comment:** In analogy to authorisations under REACH, it is proposed that both c) and d) should be fulfilled at the same time, i.e. absence of alternatives AND benefits outweighing the risks. Effectively, this change excludes applications without alternative, but of low benefit as well as important applications that can be readily addressed by suitable alternatives. Furthermore, it is crucial that emissions are minimized for any use of PBT/vPvB substances. **Proposed change:** c. Absence of effective alternatives AND benefit clearly outweighs the risk. […] Minimization of emissions should be mandatory for any use.	Not accepted. The introductory sentence to bullet 9 acknowledges that the conditions under which PBT substances can be authorised need to be defined. What follows are just examples. No change to the text required at this time.
358	5.	**Comment:** ‘pose a relatively greater user safety risk’. What exactly is meant, the user	Not accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		who will administer the product or the consumer? If consumer is meant: The user safety is established for all substance authorised in food-producing species by setting of the MRL. Furthermore, a risk to the user should be minimised by per se by appropriate warning sentences in the product information. Hence, there should not be a substance with a 'greater user safety risk'. **Proposed change:** Please consider deleting 'and pose a relatively greater user safety risk'	Any reference to 'user safety' in the context of VMP assessment means the person that administers the product to the animal. What is intended with the text as currently written is that any consideration of alternatives should not just focus on the indication/efficacy profile, but also consider the safety profile of the 'alternative'. One would have to be cautious about removing a product from the market because of potential environmental concerns when its absence from the market may result in the increased use of another product for which there are different safety concerns.
365	2.	**Comment:** We very welcome the concept of comparative assessment and the inclusion of alternatives including non-chemical treatments and prophylactic measures. We agree that an approach to such comparative assessment would need to be elaborated. It is to be	Noted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		ensured that the process is carried out in a transparent manner and with public consultation.	
366-372	1.	**Comment:** Agreed; the current weight of the environmental safety and PBT-classification is clearly out of proportion and more balanced criteria and weighing are needed, including projections in the future taking factors such as estimated evolution of anthelmintic resistance into account. A core question here is: how important is an animal's life, its health or its welfare? Decisions driven by hazards alone also risk putting the competitiveness of EU livestock production at stake. And public health, from a food perspective but also in case of direct contact with pets – some of these parasites are zoonotic. Hence, this proposed guidance should be elaborated by a multi-disciplinary team (c.f. One Health) to include people with relevant backgrounds, such as clinical experts, in addition to environmental specialists. Furthermore, this would require consultation of the veterinary medical community. In addition, there appears to be a general acceptance that substances which are designated as vPvB should not be approved. This appears to be justified on the grounds that they might have unknown potential to have as yet unknown adverse effects. This is disputable and may be disproportionate when compared with the benefit. **Proposed change:** please add "**by an expert group consisting of people with appropriate backgrounds to evaluate and weigh elements of public and animal health**" to the last sentence.	Not accepted. It should be noted that any guidance on the benefit risk assessment is elaborated at the level of the CVMP. This Committee can be considered to consist of people with appropriate backgrounds to consider elements relating to public and animal health. Further, any guidance elaborated in this area will be the subject of a public consultation.
367	5.	**Comment:** This was not an official statement by the Commission which was published but a reply to a letter from the VMD. Hence, it might be dangerous to present it like this which implies that this is an official statement by the Commission. **Proposed change:** Please consider revision of the text or even deletion	Not accepted. The letter in question was a formal response from the Commission to a question posed by a NCA. Therefore,

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			it can be seen as an official statement by the Commission.
373-378	1.	**Comment:** What would be the aim and scope of that review? **Proposed change:** Please clarify and add proposed aim and scope.	The proposed aim of the review would be to identify VMPs containing PBT substances for which the conditions for maintaining authorisation are not met. This is clear when points 10, 11 and 12 are read together.
373-378	2.	**Comment:** Proposed change (if any): Once the PBT/vPvB status of a substance has been established, and consideration has been given to the conditions under which PBT/vPvB substances can be authorised as veterinary medicinal products **for a period not exceeding seven years**, a plan to systematically review authorised VMPs containing PBT substances where the use of the product gives rise to an emission scenario(s) of concern should be put in place **within the first two years of the authorisation period**. For existing products, regulatory action on a product level would not be taken until such time as the determination on a substance basis is complete.	Not accepted. Regarding the proposal for a time limit on the authorisation of VMPs containing PBTs, this is addressed in the existing text (bullet 11). The second proposed amendment does not make sense in that the point in question relates to a review of authorised products (some of which may be on the market for less than two years, others will be in the marketplace for considerably

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			longer).
376-378	4.	It is unclear what is meant with the last part of the sentence: " until such time ….. is complete" . Please clarify what is meant here.	Accepted. What is intended is that no action would be taken at a product level (that is, no decision to remove existing products from the market) until such time as the PBT status of all substances (of concern) is known. This is considered an important point because in order to take informed decisions in respect of a specific substance/product, it would be necessary to know the PBT status of other 'alternative' substances.
379-383	2.	**Comment:** We support the consideration that products containing PBT substances are to be authorised/maintained only for a limited period of time and that the marketing authorisation should be subject to specific conditions, e.g. a Risk Management Plan (RMP), specific monitoring and specific pharmacovigilance requirements and mandatory substitution plans. **Proposed change:** Where products containing PBT substances are authorised/maintained, it should be considered if the marketing authorisation should be subject to conditions, e.g. a Risk Management Plan (RMP) with time-limited review (that is, such products would be granted a marketing authorisation for a~~n un~~limited period of	Not accepted. Given that the conditions included in this bullet are presented as examples requiring further consideration, an amendment to the text, as proposed, is not considered necessary.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		validity **not exceeding 7 years),** specific monitoring and specific pharmacovigilance requirements.	
384-389	1.	**Comment:** The concept of phasing out is not recognised in any pharmaceutical legislation, which is the correct comparative legal framework. "Replacement" may be a feasible option from a chemical's point of view; this is not the case for a veterinary medicine requiring at least 10 years of development time. Should this proposed approach become adopted, its negative impact on future development of parasiticides and potentially other therapeutic areas should not be underestimated.	Noted. The concept of 'phase out' has been explained in the RP. While the RP acknowledges the concept of 'replacement'/ 'substitution' as it applies in the areas of PPPs and Biocides, it is not proposed as an option for VMPs. Again, what is being proposed is, simply, to determine the PBT status of substances used in VMPs and, for confirmed PBT substances, to determine the conditions under which products containing those substances can be authorised. For existing products containing PBT substances, if the conditions for maintaining the authorisation (yet to be elaborated, see 304-338) are not met, it is proposed

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			that these products would be removed (phased out). The proposal is that such products be allowed to remain on the market for a defined period of time to allow the 'marketplace' to adjust to the impending loss of the product and to allow the MAH to manage the phasing out from the market and look for an alternative substance/product as a replacement (as in other frameworks).
384-389	2.	**Comment:** We support the setting of a defined phase-out period for existing products containing PBT/vPvB substances and where exclusion provisions are not applicable. This phase-out period shall be concretised e.g. "… a phase-out period of 5 years" and shall be linked to an obligational research for and support of less hazardous alternative (substances/products and treatment methods.	Noted.
390 ff	5.	**Comment** to Chapter 3.2: 'Constraints of existing legislation' Was this part of the order from CVMP? This all makes it more difficult to read and is not helpful for the understanding of the overall aim of the paper. The sentence in chapter 4 regarding the review of legislation is sufficient. It is not clear if the law not already includes the possibility to refuse PBT substances. UBA is of the opinion that there is this	Not accepted. CVMP/HMA considered it useful to develop a strategy to address the PBT issue. The AHEG considered how this work should ideally be

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		possibility! **Proposed change:** Delete line 397-418 and rewrite the text above.	approached and this approach is outlined in section 3.1. However, the AHEG acknowledges that the ideal approach to appropriately addressing the PBT issue cannot be realised with the existing legislation (that is, the appropriate legal tools are not available). Accordingly, section 3.2 is considered necessary in order to fully understand the reflections of the AHEG and the recommendation for legislative change (section 4.1).
396-397	1.	**Comment:** As stated before, there are vast differences between the provisions for chemicals, PPP and biocides; hence no “similar” provisions can be automatically proposed. **Proposed change:** please delete the comment between brackets, or, alternatively, recognise the need to harmonise these approaches first or, alternatively, recognise the fact that there are differences between categories of substances that justify different approaches.	Accepted.
399	1.	**Comment:** Products that stop in Phase I should remain out of scope. **Proposed change:** Determination of PBT status, **as appropriate**, in the context of	Not accepted. The specific sentence referred to is a general consideration. The

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		assessment of new product applications.	proposed amendment is considered an unnecessary refinement of this consideration. Comment on the scope of the PBT assessment is included elsewhere.
400-401	1.	**Comment**: Regulatory action is taken at the time of application for a marketing authorisation. What other regulatory action would be envisaged, and why this list? One aspect has not been considered at all: what about generic versions of an authorised product containing a PBT-substance?	Noted. The 'regulatory action' referred to in the sentence highlighted is the possibility of action which may involve the review of existing (authorised) products (see section 3.1, bullets 10, 11 and 12). The AHEG are of the view that if, for a confirmed PBT substance, the authorisation of a product containing that substance under certain conditions of use is accepted, then there should be no obstacle to authorising a generic where the same conditions of use apply.
402-403	1.	**Comment:** The concept of substitution of a medicine would be so subjective that it can	Not accepted.

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		never be predictable. A product is either approved because there is a need for it and the benefit-risk assessment is positive, or it is not approved. It is well recognised that multiple treatment options are beneficial for any condition in animals or humans. Specifically with parasiticides, rotation of different classes is a key component in the effort to slow down anthelmintic resistance. See e.g. BVA : "The continual use of an anthelmintic on the same animals grazing in the same fields leads to selection for a resistant population of parasites". For other types of VMPs, individual differences in tolerance require the availability of multiple options, as is the case with NSAIDs. Would potential resistance be factored into this? **Proposed change:** please delete this bullet point.	If the general principle of what is proposed in the reflection paper is accepted (developing a strategic/systematic approach to addressing the PBT issue), then the concept of 'comparative assessment' must at least be considered. Regarding the need for multiple treatment options, this is recognised in the RP as originally drafted.
405-411	1.	**Comment:** For (veterinary) pharmaceuticals, the formulation and route of administration are crucial factors determining efficacy and the environmental, consumer, user and target animal safety of a product – not a substance. Therefore, an **MA for a VMP will always need to be product-based**. It is **overly simplistic** to believe that the environmental hazards of an active ingredient should be the only ones to be taken into consideration when deciding on authorisation of a VMP. In the case of VMPs, active ingredients are not just sprayed on a field like e.g. PPP. (V)MPs require a vast amount of studies during their development to ensure their quality, safety and efficacy. **Proposed change:** please consider all aspects of a VMP and recognise that an authorisation (on scientific grounds alone) will have to be product based.	Not accepted. CVMP accepts that a decision to authorise will be based on a consideration of all data in the dossier. Overall, a decision to authorise or maintain a MA for a VMP containing a PBT will be taken on the basis of an overall B/R assessment. This point was adequately captured in the text as originally drafted (299-338).

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405-409	2.	**Comment:** In other legislative frameworks (e.g., BPR and PPP) PBT and vPvB properties have been recognised as criteria for exclusion from authorisation. Under the existing veterinary medicines legislation it is not possible to refuse a MA on the basis of PBT or vPvB status alone according to the reflection paper. For the environment it makes no difference whether it is being contaminated by a PBT/vPvB substance from a PPP or a VMP. We strongly suggest ensuring that the current revision of the European veterinary medical product regulation includes such provision or that at least it secures that a process that denies authorisation of such products in the future is established. (cf. http://www.pan-germany.org/download/veterinary_pharmaceuticals/Enhanced_Protection_of_Environment_from_Veterinary_Medicinal_Products.pdf S. 4)	Noted.
405	4.	**Comment:** It is possible to do an assessment of PBT status on a case-by-case basis… This should be rephrased. It is not the PBT status that is to be assessed, rather a PBT assessment – of the substance under consideration- should be performed **Proposed change:** It is possible to perform a PBT/vPvB assessment on a case-by-case basis…	Accepted.
405	4.	**Comment:** in the current situation, for a PBT assessment to be carried out, this would need that the PBT assessment in itself may require new data to be requested. It is our practical experience that the general ERA dossiers in most cases do not contain all data necessary to conclude on the PBT status. In particular, long term toxicity data on three trophic levels are generally absent and the same holds for data on bioconcentration. This is explained from the point that the current CVMP guidance prompts for a *screening* for PBT/vPvB substances, rather than a full assessment. This situation also applies to new product applications.	Noted. The PBT assessment should be conducted in accordance with relevant VICH/CVMP guidance. The RP has been revised to include a statement to the effect that the CVMP guideline is the appropriate reference for such an

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			assessment. It is assumed that this will address the concern raised. For most (potential) PBT/vPvB substances the Tier A ERA triggers Tier B ecotoxicity testing of the relevant model species and VICH GL 38 also requires the submission of a BCF test according to OECD 305. If a Tier B test is needed for PBT assessment which would not be triggered by the results of the risk assessment, it is considered possible to require submission of this test as any other higher tier test which is needed for an informed benefit/risk assessment.
405-406	5.	**Comment:** Not only the application for a new product allows for a PBT assessment but also applications for extension or major variation of a product where PBT was not assessed in the initial application. For extensions and major type II variations an ERA is required which would include a respective PBT assessment.	Accepted. It should be noted that in accordance with current guidance, an ERA would only be required where there is expected to

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Please consider amendment	be a change in pattern of use that will result in increased environmental exposure.
409-411	2.	**Comment:** The current assessment of an application for a marketing authorisation for VMPs is product based, and not substance-based. We strongly suggest that in the current revision of the European veterinary medical product regulation the introduction of a substance based monograph system is regulated. (for more information please see http://www.pan-germany.org/download/veterinary_pharmaceuticals/tierarznei-EN-160321-web.pdf p 2/3)	Noted. However, the current RP relates to PBT substances only and, to address this specific issue, “a substance based monograph system’ is not required.
409-411	4.	**Comment:** assessment is product based, not substance based. This is true, but it does not mean that a decision cannot be taken based on substance properties or hazard related to the substance contained in that product. The decision would still be product based. This sentence (409-411) does not relate or add to the argument. **Proposed change:** delete sentence.	Not accepted. The sentence in question is useful in that it emphasises the point that the overall assessment and decision to authorise is product based.
412-114	2.	**Comment:** The reflection paper states that currently there is no legal basis for establishing a list of PBT/vPvB-substances and that any list generated would not be formally binding in the sense of a legally binding act. We strongly suggest ensuring that in the current revision of the European veterinary medical product regulation the legal bases for stablishing such a list is secured.	Noted.
415-418	1.	**Comment:** Any comparative assessment would have to be product based. We are dealing with medicinal products and quite a few aspects need to be considered as already briefly identified in lines 352-365. Potential alternatives may not have the same efficacy or spectrum of activity, safety for the target animal, user, or consumer. In quite a few cases,	Not accepted. If the general principle of what is proposed in the reflection paper is accepted (developing a

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		individual animals may display a greater sensitivity to side effects of a certain product (not substance) compared to others, hence the availability of alternatives is needed. In the frame of resistance development, having treatment choices and being able to rotate with products of different classes is indispensable for veterinarians. **Proposed change:** please delete this bullet point; comparative assessment is not ethical from a medical point of view. If the benefit-risk assessment is positive, a product is approved, and otherwise it is not.	strategic/systematic approach to addressing the PBT issue), then the concept of 'comparative assessment' must at least be considered.
415-418	2.	**Comment:** The reflection paper states that the existing legislation does not allow for a concept of "comparative assessment". The European veterinary medical product regulation (currently under revision) should be changed accordingly to ensure that in the future comparative assessment is part of the authorisation process of VMPs.	Noted.
419-420	1.	**Comment:** The rationale as presented fails to justify the compelling need for specific legal tools. PBT-classification would be stated in the (E)PAR and product literature. If there are only 20 substances of potential concern, why the compelling need for a legally binding list? What purpose would such a list serve? For scientific reasons stated before, MA needs to be product based given the importance of formulation and route of administration and from non-environmental perspectives of safety and efficacy. **Proposed change:** please either justify the need for new legislation, or delete this sentence.	Not accepted. The limitations of the existing legislation when it comes to comprehensively addressing the PBT issue are clearly laid out in section 3.2. The need for specific legal tools to appropriately address the issue have been justified.
422-423	1.	**Comment:** This statement is incorrect. In the case that the risk posed by the product containing a substance that has the PBT-hazard status outweighs the benefit, the MA can be refused. Unless the intention is to be able to refuse authorisation of a product based on the PBT-hazard of its active ingredient by default, without any proper risk assessment. **Proposed change:** please be clear about the intentions; if CVMP wants to be legally able	Partially accepted. What is being proposed is, simply, to determine the PBT status of substances used in VMPs and, for confirmed PBT

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		to refuse MAs based on the PBT-hazard without any risk assessment then please clearly state this at the beginning of this document in a section on the objectives of the reflection paper.	substances, to determine the conditions under which products containing those substances can be authorised. For existing products, if the conditions for maintaining the authorisation (yet to be elaborated, see 304-338) are not met, it is proposed that these products would be removed (phased out) from the market (350-356). However, it is acknowledged that the purpose/objective of the RP is not clearly stated at the beginning of the document. The document has been revised so that the objective is clear from the outset.
424	4.	**Comment:** the path to perform PBT assessments for each new product authorisation would impose considerable burden on industry submitting applications for marketing authorisation with the same API (comparable to the current situation with ERAs for generics) and unnecessary duplication of data. Since PBT properties are substance based and do not change due to the use of the product	Noted. The proposal is that PBT characterisation should be done at a substance level, not product level, and same

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		(in contrast to risk assessment), all products with the same substance should in principle arrive at the same PBT conclusions. Some insight is needed on how to proceed with other products containing the same substance. It would be useful to reflect on this aspect as well.	substance assessments should not need to be conducted for subsequent marketing applications. However, it is acknowledged that this approach is not possible under the current legislation, given that applicants have to submit data for all endpoints required.
428-441	1.	**Comment:** It is assumed that these two paragraphs refer to the current situation with moxidectin. If it is the intention to refuse all PBT-substances and to act on the hazard without a proper risk assessment, then the reason why this is formulated as a problem statement is clear. Whilst consistency in decisions and the decision making process is ultimately the desired outcome, the ability to modify or identify new mitigational measures (delivery systems, use pattern, engineering controls etc.) still needs to be taken into consideration in a product by product risk based approach. **Proposed change:** same as for lines 422-423	See answer to comments to lines 422-423.
434-441	1.	**Comment:** Please clarify your proposed alternative to this situation, and how you see the benefit-risk comparison. **Proposed change:** please add a clarification.	Not accepted. The intention of this paragraph is simply to highlight the fact that an Article 35 referral may not be the ideal mechanism for

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			appropriately addressing concerns raised in respect of PBT specifically. As stated, a decision on any such referral will have to be taken in isolation (without making comparisons with other products). In this specific case, the RP does not offer an 'alternative'.
434	5.	**Comment:** In terms of PBT this is rather a hazard than an 'unacceptable risk to the environment'. **Proposed change:** Please consider revision of the paragraph accordingly	Not accepted. On this occasion, reference to 'risk' is considered appropriate because any decision to refer will be taken on the basis of a 'risk to the environment' that is considered unacceptable and outweighs the claimed benefits of the product.
444-448	1.	**Comment: Line 444:** Agreed. Exposure is a key factor in the assessment. Not just exposure in general, but overall fate and behaviour in the environment are important. The B and T criteria directly relate to surface water. However, potential PBT-substances often bind very strongly to soil, such that exposure of the aquatic compartment might be negligible. Potential bioaccumulation in terrestrial species may be more pertinent etc. Lines 445-448: As indicated before, the assumption that an applicant by default would be	Partially accepted. The text has been amended to provide some clarification of the examples given. The intention here is to provide some examples of

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		able to synthesise and subsequently test all metabolites formed in the animal is ignoring reality. Not only are there technical limitations to such an approach, it is also unlikely that any VMP could bear this burden from a financial point of view. Lines 445-448 again repeat what has been stated elsewhere in the paper. **Proposed change:** please delete lines 445-448	considerations when reflecting on extent of environmental exposure. The inclusion of these specific examples does not prevent an applicant from providing other arguments in support of a claim that there is limited potential for environmental exposure.
447	5.	**Comment:** 'environmental exposure is limited'. This is in contrast to what is written in line 340 i.e. 'if it is shown that 'emission to the environment can effectively be prevented'. So what is meant by 'limited environmental exposure'? Prevented exposure?	Noted. See previous comment on the appropriate terminology.
452-456	5.	**Comment:** '…to limit the potential for significant exposure'. What is meant by 'significant exposure' if exposure should be prevented in general	Noted. The term 'significant' has been deleted.
462	3.	**Comment:** Here again 'reduced emission where actually emission should be effectively prevented. This is contradictory. **Proposed change:** Please consider revision	See previous comment on the appropriate terminology.
462	5.	**Comment:** Here again 'reduced emission where actually emission should be effectively prevented. This is contradictory. **Proposed change:** Please consider revision	See previous comment on the appropriate terminology.
467-472	1.	**Comment:** The major factor for dosing precision is a correct estimation or determination	Noted. It is accepted that

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		of the animal's body weight; topical pour-on products can be administered as correctly as injectables.	topical pour-on products can be administered precisely; however, systemic availability is typically lower for pour-on products compared to injectables (based on current authorised products) with the result that the required treatment dose (and therefore potential environmental exposure) is higher. No change to text required.
473-475	1.	**Comment:** This is not necessarily true and far too general. The purpose is also to interrupt the life cycle of the parasites to reduce the infestation pressure. In case that short-acting products are used, multiple treatments will be required, resulting in equal or higher environmental exposure. **Proposed change:** please delete the text between brackets, or expand based on scientific references.	Not accepted. While long acting products (persistent efficacy) may limit the number of treatments, there are growing concerns that persistent efficacy may be a significant factor in resistance emergence (refs. provided above). As reflected in the RP, what is needed is a more sustainable approach to parasite control (more judicious use of

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			products), not longer-acting products.
476-481	1.	**Comment:** This is already the case, cfr. the guideline on fixed combination products.	Noted. The combination guideline requires that the combination is appropriately justified (offers an advantage over the individual mono-substance products). The text in the RP goes further and suggests that any combination that includes a PBT substance should also satisfy an otherwise unmet need.
482	4.	**Comment:** see comment to line 348 (*Stakeholder No. 4*)	See previous answers to respective comment.
484	5.	Please see comment at line 462 (*Stakeholder No. 5*) **Proposed change:** Please consider revision	See previous answers to respective comment.
490-492	2.	**Comment:** The Reflection Paper suggests that in addition to highlighting potential environmental effects, steps should be taken to promote, via product information, a sustainable approach to parasite control. We agree that steps to promote a sustainable approach to parasite control are needed but we think that promoting such via product information is by far not enough. Sustainable parasite control needs reference examples, education, training and independent advice.	Noted. This point is captured in section 4.2 'Other general recommendations', first bullet. No change to the text of the RP required.
496-501	1.	**Comment:** These are not specifically options to reduce emissions, but conditions to	Accepted.

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		authorise and as such do not belong in this bullet list. **Proposed change:** please delete lines 496-501.	Text revised so that the bullets in question are not included as part of this specific bullet list.
496-498	2.	**Comment:** When talking about the "overall benefit risk balance" it is important to stick to the "overall therapeutic benefit" and not to a however defined "socio-economic/quantitative benefit". When vPvB and PBT Substances enter the environment there is reason to fear that they cause a long-lasting environmental burden. This is why we dismiss the monetary Risk-Benefit-Assessment for vPvb/PBT substances as a decision tool: To come up with relevant results a monetary risk-benefit-assessment has not only to calculate the economic advantages of the use of PBT/vPvB substances but it also has to calculate the monetary benefit of not-using PBT/vPvB substances for the protection of our natural resources and the ecosystems. In our view this is impossible to calculate and therefore socio-economic/quantitative risk-benefit-assessments are not feasible.	Noted. This bullet point has been deleted in the final RP.
502-526	1.	**Comments:** IFAH-Europe places a very high value on the scientific credibility of the CVMP and would wish to see that reputation closely guarded. We urge the CVMP to remain entirely science-based (which has been the case to-date). We are concerned that the present paper makes a number of assumptions, statements and proposals without any scientific reference, on which these policy recommendations are based, while placing undue emphasis on references to the regulatory frameworks for other but crucially different sectors. We also believe that the paper omits consideration of the vast dataset generated in support of VMPs and a proper consideration of a medical need.	Noted. However, the CVMP does not accept that this RP undermines the scientific credibility of the Committee. While it is acknowledged that the RP contains a number of "assumptions, statements and recommendations" without specific scientific reference, these are typically general in nature and all are considered

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			reasonable “assumptions, statements and recommendations” based on experience in the regulation of VMPs. The CVMP does not accept that there is undue emphasis on other regulatory frameworks. The CVMP is of the opinion that considerations with respect to product authorisation should be tailored for VMPs specifically. That is, the fact that a substance is ‘not allowed’ under another legal framework should not necessarily influence any decision to authorise as a VMP. Contrary to what is stated in the final sentence of the comment, the CVMP is of the view that the RP gives much emphasis to the need for an

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			adequate range of authorised VMPs and that MAs for VMPs containing PBT substances should be granted/maintained where there is a clear therapeutic need for the product in question.
507	1.	**Comment:** what would be the purpose of the list? As an alert to potential developers? As an automatic ban? **Proposed Change:** please state the purpose of the list.	Accepted. This has been clarified. The intention of the 'list' is simply to know what is PBT and what is not. Once the PBT status is known, informed decisions can be taken in respect of product authorisation. See comments above. It is accepted that information on the PBT status of a substance will also allow potential applicants to take informed decisions with respect to product development.
512	4.	**Comment:** any legislative changes should preferably be aligned with existing legal frameworks dealing with PBT/vPvB substances, specifically REACH. Please add the notion	Not accepted. In section 3.1, bullet 7, the need for a

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		to strive for a horizontal approach over different pieces of EU chemicals legislation. In that respect it might also be useful to reflect on the possibility that the active substance in a VMP could also authorised or banned under other legal frameworks **Proposed change:** additional bullet • Align with and refer to PBT/vPvB assessment under existing pieces of EU chemicals legislation, i.c. REACH.	harmonised approach to PBT assessment across all legislative frameworks is recognised. However, alignment with other frameworks is not something that would need to be specified in the legal text. Further, while the principle of a harmonised approach to PBT assessment is accepted, CVMP is of the opinion that considerations with respect to product authorisation should be tailored for VMPs specifically. That is, the fact that a substance is 'not allowed' under another legal framework should not necessarily influence any decision to authorise as a VMP.
515-518	2.	**Comment:** The Reflection paper states (see chapter 4) that it is recognised that in view of the complexity of the matter and the need for extensive consultations for agreement on the procedure to consider PBT substances in veterinary medicinal products, it might be	Noted. The RP does not propose specific legal text but

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		appropriate at this stage to propose a general provision in the current text requiring subsequent legislation on this particular issue. We strongly call for the inclusion of such legal provision into the ongoing revised veterinary pharmaceutical legislation.	suggests that "*Amendments to the proposal [for a veterinary regulation] can now be made by the European Parliament or Member States*." No change to text of the RP is necessary.
523-526	2.	**Comment:** In addition to having the necessary legal tools, there is a need to elaborate guidance on: • The approach to comparative assessment. • Approaches to reducing emissions. • How the issue of PBT/vPvB should be viewed in the overall context of the benefit risk assessment. • Surveillance of the effects of risk mitigation measures	Noted.
523	4.	**Comment:** PBT/vPvB assessment is highly specific and requires detailed technical guidance at the various aspects. Existing guidance is under continuous development within the REACH framework (mainly R.11 and endpoint specific guidance R.7), but also e.g. in FOCUS (degradation kinetics). Access/reference to in-depth technical guidance should be taken care of. It is highly important and should preferably be mentioned here. Please specify also the CVMP PBT guideline and include dynamic references to REACH criteria and methods (as was done in the CVMP PBT guideline), to ensure that the VMP guidelines do not need to be changed when the REACH guidelines change.	Partially accepted. The bullet list in question relates to areas where future guidance is likely to be required. For PBT assessment guidance is available in the form of the CVMP guideline. A clear reference to the

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		Proposed change: additional bullet • The technical and scientific aspects of PBT assessment. Please refer to the CVMP PBT guideline [REF] for specific guidance. As advanced guidance is continuously being developed under REACH (a.o. R.7, R.11) and FOCUS, accurate prescription of using specific guidance documentation should be taken care of.	CVMP PBT guideline has been included in the RP.
524	1.	**Comment:** for reasons previously explained, we believe comparative assessments are not within the scope of reasons to refuse a MA, and would undermine the principle of access to a range of treatment options so that the veterinarian can issue a prescription tailored to the specific individual clinical circumstances, taking into account all the properties of individual products.	Noted. See previous comments. No change in text of RP required.
525	5.	Please see comment at line 462 (*Stakeholder No. 5*) **Proposed change:** Please consider revision	Noted. See previous comment on the appropriate terminology.
528	1.	**Comment:** please note there are several spelling mistakes in this line. **Proposed Change:** To ensure informed use of authorised v~~a~~**e**terinary medic**i**nal products	Accepted.
528-530	1.	**Comment:** This statement is rather serious as it implies lack of professional knowledge and irresponsible use by veterinarians and farmers, but no justification on which information this conclusion is based. In that respect, it might be useful to review the following guidelines, issued by the British Veterinary Association: BVA. Other professional associations have similar initiatives. **Proposed change:** Please revise this statement to reflect the training and education already given to professionals in this area. Ideally, since this is a RP on PBT in general, this paragraph should be considered out of place and deleted.	Partially accepted. In relation to the first point, the CVMP does not accept that the statement implies lack of professional knowledge. Rather, it is an acknowledgement that the thinking in respect of appropriate parasite control

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			is evolving and that it no longer simply a case of 'treat all, often'. For the reasons outlined previously, the general recommendation will be retained. However, the text has been amended to acknowledge initiatives in the area.
528-530	2.	**Proposed change:** To ensure informed use of authorised veterinary medicinal products, **independent** training of vets and farm professionals on judicious use of antiparasitics agents, and the risks associated with inappropriate use, **is to be secured** ~~may be appropriate~~.	Not accepted. The text as originally proposed is a general recommendation and is not under the direct responsibility/authority of the regulatory authorities. Therefore, it can remain as a 'may' recommendation, rather than an obligation.
531-536	1.	**Comment and proposed change:** As this is a RP on PBT in general, this paragraph is out of context and should be deleted. What is presented here has been published elsewhere, initially by the Integrated Sea Lice Management group in Scotland and by other bodies in other salmon farming countries. It is worrying that while this bullet point appears to welcome an integrated approach, the use of PBT substances is precluded by statements earlier in the document.	Not accepted. For the reasons outlined previously, the general recommendation will be retained. The CVMP does not agree that "*the use of PBT substances is precluded by statements earlier in the*

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			document".
531-536	2.	**Comment:** We agree that there is a need for increased research into non-chemical approaches to parasite control to reduce reliance on medicinal treatments and to face growing problems with resistance.	Noted.
537-538		**Comment:** Please provide a definition of "low risk to the environment". Or is this meant to be "hazard"? Some PBT-substances can pose a low risk to the aquatic environment due to their behaviour. **Proposed change:** Please clarify whether it should be hazard or risk, and provide a definition of "low".	Accepted. The text has been revised accordingly. "low risk to the environment" is to be interpreted as meaning having the potential for limited environmental impact.
539-549	1.	**Comment:** Does this paragraph belong here, or in a separate document after the proposed Workshop on medicines in aquaculture? This is already required and done in a number of countries. However, it has been suggested that in some cases the models employed to determine what can be used and how monitoring is undertaken have not been appropriately validated.	Noted. Regarding the location of the paragraph, it is appropriately situated in the RP (that is, under the heading "Other general recommendations").
539-552	5.	**Comment**: The use of PBT/vPvB substances in the aquatic compartment results in considerable emissions of PBT/vPvB substances to water. This is not acceptable given the damage that can be caused by PBT/vPvB substances. Therefore, PBT/ vPvB substances should not be approved for that use. Alternative methods of pest control should be applied for aquacultures. Another option might be the restricted use in closed facilities with controlled disposal of the aquatic waste matrix via incineration if this is technically feasible. Open water treatment should not be allowed. **Proposed change:** The use of PBT/vPvB substances in the aquatic compartment results	Not accepted. A decision to authorise will be based on a consideration of all data in the dossier. Overall, a decision to authorise or maintain a MA for a VMP containing a PBT will be taken on the basis of an overall B/R assessment. This

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		in considerable emissions of PBT/vPvB substances to water. This is not acceptable given the damage that can be caused by PBT/vPvB substances. Therefore, PBT/ vPvB substances should not be approved for that use. Alternative methods of pest control should be applied for aquacultures.	point is adequately captured in existing text (304-338).
543-544	5.	**Comment:** There are no acceptable environmental concentration thresholds for PBT/vPvB substances. Minimization of emissions using best available techniques is crucial for the application of PBT/vPvB substances. **Proposed change:** Further, it is acknowledged that there is no significant acceptable environmental concentration threshold for PBT and vPvB substances.	Not accepted. While the RP acknowledges that there are significant challenges associated with the setting of thresholds for PBT substances, the primary point of this bullet is that use of VMPs containing PBT substances in aquaculture should be the subject of monitoring. No change in text considered necessary.
550-552	1.	**Comment:** The quantity of active substance is determined by the animal's body weight and the effective dose. To ensure accurate dosing, body weights should be estimated correctly. Also see e.g. Defra: inaccurate or no weighing of animals leading to underdosing is cited as a cause of anthelmintic resistance as well. Much effort goes into formulation development and dosing accuracy; this information is an integral part of a product's dossier.	Noted. However, the intention of this text is promote research/product development into more effective/efficient methods of product delivery (for example, to improve systemic availability, thereby allowing for a reduction in

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			total dose of active administered). The text has been clarified to reflect this.
553-556	1.	**Comment:** Does this belong here, or as a point in a separate document after the proposed Workshop on medicines in aquaculture? **Proposed change:** Please delete this paragraph.	Not accepted. The paragraph is appropriately situated in the RP (that is, under the heading “Other general recommendations”). Positive developments in this area would be expected to reduce emissions of VMPs into the environment.
553-556	5.	**Comment:** If no alternatives are available the only acceptable option might be the restricted use in closed facilities with controlled disposal of the aquatic waste matrix via incineration and complete removal of the active substance. Open water treatment should not be allowed. **Proposed change:** please consider revision.	Not accepted. Circumstances may require ‘open water treatment’. In such cases the risk to the environment has to be balanced against the consequences of not treating.

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