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4 Reflection paper on the authorisation of veterinary 5 medicinal products containing (potential) persistent, 6 bioaccumulative and toxic (PBT) or very persistent and 7 very bioaccumulative (vPvB) substances

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Reflection paper on the authorisation of veterinary medicinal products containing (potential) persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances

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1. Background

Persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances are associated with specific concerns because of their persistence, their ability to accumulate in the environment and in living organisms and their toxicity. Due to the combination of these intrinsic properties and possible redistribution across environmental compartments, PBT/vPvB substances can give rise to toxic effects after a longer time and over a greater spatial scale than substances without these properties. The effects of persistence/bioaccumulation are unpredictable in the long-term. 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. In the case of vPvB substances, even if no toxicity is demonstrated in laboratory testing, there is a concern that long-term effects may be possible since high but unpredictable levels may be reached in animals at the top of the food chain or the environment over extended time periods[1]. The criteria for the identification of PBT/vPvB substances are detailed in Annex I.

Chronic exposure and long term, cumulative adverse effects may lead to uncertainty when calculating the predicted environmental concentration (PEC) via established exposure models, and/or establishing the predicted no effect level (PNEC) from standard laboratory tests. As it is difficult to predict fate/environmental concentrations and the effects of PBT/vPvB substances in the environment, a conventional quantitative risk assessment is not an appropriate approach to determining the impact on the environment for such substances. It is considered necessary to conduct a hazard based PBT/vPvB assessment which focuses on intrinsic properties of substances only (See "*Guideline on the assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicinal products* (EMA/CVMP/ERA/52740/2012)).

2. Introduction

2.1. Assessment of PBT status

Under different European legislation relating to the regulation of chemical substances, it is recognised that substances that are either PBT or vPvB must be considered hazardous for the environment due to their potential for eliciting long-term adverse effects. However, while the goal of identifying and preventing exposure of humans and the environment to PBT and vPvB substances is shared among different EU regulatory frameworks, the mandatory measures imposed for a substance identified as a PBT or vPvB vary between the different regulatory frameworks.

2.1.1. Approach to PBT assessment for industrial chemicals or substances included in biocides and pesticides

Chemicals (REACH): The criteria for the identification of PBT/vPvB substances are given in Annex XIII of Regulation (EC) 1997/2007. The REACH Regulation pays specific attention to the PBT/vPvB substances, with the aim to 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. A PBT/vPvB assessment must be conducted for all substances for which a chemical

[1] ECHA (2014). Guidance on information requirements and chemical safety assessment-Chapter R.11: PBT/vPvB assessment (available at: http://echa.europa.eu/documents/10162/13632/information_requirements_r11_en.pdf)

safety assessment (CSA) is required under REACH. When substances fulfil the PBT/vPvB criteria as specified in Annex XIII of REACH, these substances are listed as substances of very high concern (SVHCs) in accordance with Article 59 of the Regulation. A substance identified as a PBT/vPvB immediately triggers the obligation of registrants to recognise this status in their registration dossiers and in their supply chain communication, and implement the necessary measures for minimising the release and exposure in the whole supply chain and lifecycle. PBT/vPvB substances will eventually be included into Annex XIV to the REACH Regulation (the Authorisation List). The aim of the authorisation requirement is to make sure at the Community level that the risks arising from the uses of PBT/vPvB substances are properly controlled and that these substances are progressively replaced with suitable alternative substances or technologies. Alternatively, if more suitable, restrictions under Title VIII of REACH may be developed (Restriction List), with the aim to limit or prohibit specific uses of PBT/vPvB substances.

Plant protection products (PPP): Regulation (EC) No 1107/2009 concerns the placing of plant protection products on the market. For all substances intended to be used in PPPs, the environmental risk assessment (ERA) follows a two-step process. The first step relates to the assessment of the properties of the active substance (for inclusion in an EU list of active substances approved for use in PPPs), which includes an assessment with regard to the PBT criteria[2]. When a substance is identified as a PBT it will not be approved as an active substance, hence it cannot enter the second step which is centred on a risk assessment of any products containing the authorised active substance. That is, 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'. The regulatory consequence of this classification is that the substance will be approved for seven years instead of 10 years, and that any product containing the substance will be authorised for a shorter period of time. In addition, prior to authorisation of a product containing a candidate for substitution, comparative assessment by the competent authority is required. The aim is to gradually replace products containing candidates for substitution by methods and products of lesser concern, while minimising the economic impact and practical disadvantages for agriculture (SANCO/11507/2013 rev. 12, 2014).

Biocides: The Biocidal Products Regulation (BPR, Regulation (EU) 528/2012) concerns the placing on the market and use of biocidal products. For all substances intended to be used in biocidal products, the assessment of the risk to the environment follows a two-step process. The first step relates to the assessment of the properties of the active substance (for inclusion in an EU list of active substances approved for use in biocides), which includes an assessment with regard to the PBT criteria[3]. The second step is centred on an assessment of the product containing the authorised active substance. An active substance will not be authorised if it meets the criteria for being PBT or vPvB triggering a prohibition of the active substance and all biocidal products containing this substance. However, in accordance with the BPR, derogations exist which allow for the authorisation of products containing PBT/vPvB substances if certain conditions are met (for example, where it can be demonstrated that there will be negligible risk to the environment or where it can be argued that refusal to authorise the product will have a disproportionate negative impact on society). When this is the case, then the approval of the substance will be granted for a maximum of five years, the biocidal products are subject to a comparative assessment before granting an authorisation, and the biocidal products can be authorised only in Member States where the conditions for derogation are met. Also, and as it is the case for PPP, the substitution of active substances which meet two out of three PBT criteria is encouraged. The approval of these active substances is for a maximum period of seven years, and

[2] The criteria for the identification of PBT/vPvB substances are given in Annex II to Reg. 1107/2009
[3] The criteria for the identification of PBT/vPvB substances are given in Annex XIII of REACH.

biocidal products containing these have to be subject to a comparative assessment before granting an authorisation (CA-March14-Doc.5.4).

In conclusion, for industrial chemicals, biocides and plant protection products, there is a clear legal basis requiring assessment of PBT properties for regulated substances. For PPP and biocides, there is a two phase approach to determining the risk to the environment. First, there is an evaluation of the intrinsic properties of the active substance, which includes a determination on the PBT status of the substance. This is followed by an environmental risk assessment at the product level, if applicable.

2.1.2. Assessment of the risk to the environment under the veterinary medicinal products legislation

According to Directive 2001/82/EC, as amended, an environmental risk assessment is mandatory for all new applications, independent of the application procedure (central or national marketing authorisation) and underlying legal basis ("full", "generic" etc.). The environmental risk assessment is an evaluation of the possible fate, exposure and effects of the product in the environmental compartments of concern. For VMPs, the risk assessment is structured around the risk quotient (RQ) approach as described in the VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) guideline (GL) 38 on environmental impact assessment for veterinary medicinal products - Phase II (CVMP/VICH/790/03-FINAL) (CVMP/VICH 2005). The RQ is defined as the ratio between the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC), with a potential risk identified when the RQ>1 (i.e., PEC>PNEC). The properties of the PBT/vPvB substances lead to an increased uncertainty in the estimation of risk when applying quantitative risk assessment (i.e. RQ). For these substances a safe concentration in the environment cannot be established with sufficient reliability. Therefore, this approach is not applicable for these substances and a separate hazard based PBT/vPvB assessment is required, which focuses on intrinsic properties of substances (see EMA/CVMP/ERA/52740/2012: Assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicinal products).

As noted above, for VMPs, the assessment of a risk to the environment is conducted at the time of assessment of an application for marketing authorisation (at the product level). Unlike the situation for industrial chemicals, biocides and plant protection products, the relevant veterinary legislation does not specify that an assessment of PBT properties for regulated substances is required, nor does it specify restrictions that may apply to PBT/vPvB substances or VMPs containing PBT/vPvB substances. That said, the need for a PBT/vPvB screening for veterinary medicinal products (VMPs) is specified in the current CVMP guideline on 'Environmental impact assessment for veterinary 46 medicinal products in support of the VICH guidelines GL6 and GL38' (EMEA/CVMP/ERA/418282/2005-Rev.1).

A preliminary screening of active substances used (or intended to be used) in veterinary medicinal products (VMPs) identified up to 20 candidate substances which are potentially PBT (for the purposes of this exercise, potential PBT substances are defined as those with log K_{ow} (octanol/water partition coefficient) higher than 4.0). For the majority of these substances, the necessary data to make a definitive determination of PBT status is currently not available. However, in the context of an assessment of an application for marketing authorisation submitted via the 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.

It should also be noted that log K_{ow} values are not available for all substances used in veterinary medicines; therefore, the number of potential PBT substances may be somewhat higher than the number of candidates identified at this time.

Almost all potential PBT substances identified to date are parasiticides, the majority of which are authorised for use in food-producing species and can be considered widely used; therefore, parasiticides are the focus of this report. However, the possibility that substances from other therapeutic classes may fulfil the criteria for PBT/vPvB cannot be excluded.

At this time, products containing potential PBT substances authorised in the EU are all authorised via decentralised routes (that is, in accordance with national, mutual recognition or decentralised procedures).

2.2. Use of parasiticides in veterinary medicine

2.2.1. Products used for terrestrial animals

To date, substances that have been categorised as PBTs or potential PBTs are used mainly in veterinary medicinal products (VMPs) for the treatment of (a wide range of) parasites (both internal and external) in all major food-producing animal species. It is expected that they are used extensively throughout Europe.

Parasite infections in livestock have to be treated as they may have an impact on animal welfare and may cause significant economic losses to farmers due to negative effects on animal performance, productivity and reproductive potential.

Depending on the parasite in question, different measures may be employed for parasite control. For example, control measures for helminth infections in farmed livestock are primarily based on good husbandry and farm management practices (pasture care, stocking density, etc) and the use of authorised medicines. Other control options include vaccination (for the prevention of lungworm in cattle specifically) and selectively breeding animals that are resistant to parasite infection; however, at present, other control options do not eliminate the need to use veterinary medicinal products. Related to the use of VMPs, there are potential adverse environmental effects and occupational (user) hazards. In addition, emerging resistance to authorized parasiticides is a serious concern**.** In particular, resistance to anthelmintics is an increasing problem in sheep, goats and horses worldwide and is an emerging problem in cattle. When resistance develops, it may threaten animal welfare and production due to treatment failure.

Authorised parasite treatments are administered via a number of routes including oral (drench, drinking water, feed, oral paste, tablet), topical (bath treatment, pour-on, ear tag, spot-on, collar, shampoo) or by injection. For VMPs administered to intensively farmed (housed) animals, the active substance enters the wider environment mainly via slurry or manure. Slurry is spread onto land which can result in contamination of soil, ground water (by leaching) and surface water (via ground water or via surface run-off). For products administered to animals at pasture, active substance will be excreted from treated animals with the potential to reach soil, ground water (by leaching) and surface water (via ground water or via surface run-off). In addition, there is the potential for exposure of surface water by direct excretion (cattle) or direct exposure of all compartments by run-off from treated animals (for example, in the case of bath treatments for sheep). Further, with respect to bath treatments specifically, the disposal of waste medicated water represents a significant route of environmental exposure. Regarding entry of a substance into the environment, it should be noted that the hazard posed by PBT substances is not compartment specific. In effect, emissions to all

environmental compartments (e.g. soil, surface water) are of concern since the substances can move between compartments.

The active substances in products used for the treatment of parasitic infections are in general not extensively metabolised in the body of the animals and therefore, typically, a large proportion of the administered dose is excreted into the environment unchanged. However, for products that are extensively metabolised, there is, at present, no/very limited information on the PBT status of these metabolites. Further, for many of the substances of concern, there is no/very limited information on degradation/transformation products in manure (excretion profile, toxicological profile, PBT status, etc.).

Factors that influence the total dose of active substance to be administered include: size of the animal, administration route, intended duration of activity, frequency of treatment, amongst others. With respect to administration route, it is generally assumed that the amount of active substance used for an individual animal treatment and thus the exposure of the environment would be highest for baths and dips, followed by pour-on products and lowest for products administered by injection. While it is generally expected that parenteral administration will allow for more precise dosing and reduce the potential for direct environmental exposure, it is noted that some substances are only available for topical administration (that is, due to the characteristics of the substance, other administration routes are not possible).

General recommendations on appropriate use

For the control of helminth infections, it is recognized that there is a need for a more sustainable approach based on good grazing practices, monitoring of parasite infections and targeted treatments (based on the monitoring of level of infestation). The principal aim is to minimize the potential for resistance development and to minimize treatments. Indeed, from the point of view of resistance development (relating to helminthes specifically), the CVMP has advised that strategies to limit selection for resistance (based on judicious use of anthelmintics) should be practiced (EMEA/CVMP/EWP/170208/2005). Control strategies based on judicious use of antiparasitic agents would thus contribute to reduction of environmental exposure to substances in these VMPs and any related environmental effects.

In order to reduce reliance on medicinal treatments and, as a consequence, to reduce the hazard and risk of associated environmental effects and the potential for development of resistance, the following general recommendations are considered appropriate:

- Medicinal treatments should only be used as part of a parasite control programme. The goal of such a programme should be to minimize the level of parasite infestation and, at the same time, minimize reliance on, and reduce the use of, medicinal treatments.
- Where appropriate, the use of medicinal treatments should be targeted (based on the monitoring of level of infestation).
- Products should be administered at the correct dose for the recommended treatment period.

2.2.2. Products used in aquaculture

The substances of concern (toxicological concern and potential PBTs) which are intended for use in aquaculture are included primarily in VMPs used to treat sea lice infestation of Atlantic salmon.

Untreated sea lice infestations represent a considerable welfare problem and have the potential to cause significant economic losses. In addition, it is believed that large sea lice burdens in farmed salmon negatively impact wild stocks of salmon populations due to increased infection pressure; however, the extent of the impact is a matter of debate. Farm-specific costs of sea lice infestation include those associated with reduced production, reduced marketability due to skin injuries, fallowing and sea lice treatments.

A variety of methods are used to manage sea lice infestation in farmed salmon as part of an integrated pest management system, including good husbandry and management practices, biological control measures, mechanical/technical control measures and, when necessary, authorised medicines. At present, none of the other control options eliminate the need to use VMPs. However, there are potential adverse environmental effects and occupational (user) hazards related to the use of VMPs. In addition, emerging resistance to authorised products is a serious concern and, to reduce selection pressure on resistance development and maintain efficacy, it is necessary to have a number of different authorised products available with different modes of action.

VMPs for the treatment of sea lice infestation are used mostly in NO, UK and IE, with limited use in other EU Member States (MSs). Based on sales data available to the national competent authorities, the use of such products is greatest in NO, followed by UK, then IE and this reflects the size of the salmon farming industry in those Member States.

The route of administration of authorised treatments in fish is either via immersion bath or medicated feed. Therefore, the possible scenarios of environmental exposure are as follows:

Administration route	Treatment location	
	Hatcheries	**At sea**
In-feed	Disposal of manure from hatcheries as fertiliser on land Waste water discharge	Food loss/wastage Excretion from treated fish
Immersion bath	Waste water discharge	Discharge following well boat treatment Discharge following treatment in a sea pen

General recommendations on appropriate use

In order to reduce reliance on medicinal treatments and, as a consequence, to reduce the hazard and risk of associated environmental effects and the potential for development of resistance, the following general treatment recommendations are considered appropriate:

- Medicinal treatments should only be used as part of a comprehensive sea lice control and management strategy designed for a defined geographical area. Area wide management approaches are recommended, as unlike individual 'field to field' approaches, they apply against an entire pest population within a delimited geographical region. The goal of such a strategy is to minimise the level of sea lice infestation and, at the same time, minimise reliance on, and reduce the use of medicinal treatments. The strategy, including the use of medicinal treatments, should be subject to regulatory oversight.

- Use of medicinal treatments should be targeted based on the monitoring of lice infestation 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.
- 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 inappropriate.
- Products should be administered at the correct dose for the recommended treatment period. In addition, the following practical measures may be taken to reduce the quantity of active substance used:
  - In-feed administration:
    - Medicate an appropriate amount of feed to ensure complete and homogenous consumption; and,
    - Administer in-feed treatment in the absence of intercurrent disease (which could lead to a reduced appetite in fish).
  - Immersion bath:
    - Reduce the size of the net-cage to minimum possible without unduly impacting on fish welfare.

3. Discussion

3.1. The need for a strategic approach to the assessment of the risks posed by veterinary medicinal products containing (potential) PBT substances

As noted in Section 2.1.2. above, recently, 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.

Recognising that the decision on the authorisation of the products with active substances identified as (potential) PBT substances lies with the Member State concerned, the CVMP and the Heads of Medicines Agencies considered it useful to develop a strategic approach for marketing authorisations for VMPs containing (potential) PBT substances rather than making case–by-case decisions on any new application. An ad-hoc Expert Group (AHEG) with representatives from the Committee for Medicinal Products for Veterinary use (CVMP), the CVMP Environmental Risk Assessment Working Party (ERAWP) and Member States was set up to develop such a strategy.

The AHEG met on seven occasions between April and December 2015.

The AHEG agreed the following:

1. There is a need to determine the PBT status of substances used in VMPs (both new substances and existing substances).
2. 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 status. This is followed by an environmental

risk assessment at the product level. Any consideration of the hazards related to PBT substances in VMPs should follow the same basic approach: that is, the PBT status of the substance should be determined before conducting/considering a product-specific assessment of the risk to the environment.

3. According to the VICH GL, a PBT assessment is not be 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.

4. The focus should be on PBT/vPvB substances only (that is, all criteria for classification satisfied). The environmental risks posed by other substances (those that do not satisfy all, or any, of P, B, T) will be addressed under the RQ approach to evaluating environmental risk.

5. For new substances (not previously used in VMPs), an assessment of PBT status should be conducted prior to, or at the time of, the initial application for marketing authorisation.

6. For existing substances, an initial screening for substances of concern (potential PBT substances) is required. For all existing substances identified in the screening process, a definitive determination of PBT status will be required (in effect, a formal list of PBT substances should be generated). The screening process (including categories of substances to be screened) needs to be documented.

7. Under other legislative frameworks, a formal decision with respect to PBT status is taken by the European Commission based on recommendations from the relevant Agency. Therefore, any consideration of PBT status by CVMP needs to be in line with the approach to PBTs taken under other frameworks. There needs to be a coordinated/harmonised approach to PBT classification across all legislative frameworks.

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 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).

9. The conditions under which PBT substances can be authorised as VMPs need to be defined. For example:

    a. Limited potential for environmental exposure (for example where the parent compound is extensively metabolised to non-PBT substances).

    b. Effective risk mitigation measures (RMMs) can be applied to reduce or prevent environmental exposure. For example, restrict use to intensively reared (housed) animals where the active substance is extensively degraded in manure/slurry to non-PBT degradation products.

    c. Absence of effective alternatives. There is a need for efficacious VMPs to treat parasite infestations in animals and fish (animal welfare, public health, animal health, socioeconomic considerations). It would be appropriate to consider whether or not this requirement can be met by non-PBT alternatives. Any consideration of alternatives needs to take into account the risk profile of potential alternatives (for example, it should be explored whether it would be justified to propose, as an alternative to a PBT containing product, a substance/product

that may not be PBT, but may be more toxic and pose a relatively greater user safety risk) and their expected effectiveness (also taking into account the potential for issues such as resistance development). It is acknowledged that there will be differences between Member State in terms of authorised products; therefore, any consideration of the availability of alternatives may need to take account of regional differences (that is, provide for the possibility to authorise a product containing a PBT substance in one or more Member States, where a clear need for the product has been identified in that/those Member States). An approach to such comparative assessment would need to be elaborated.

d. Benefit clearly outweighs the risk (including consideration of the implications of a refusal to authorise). The European Commission has recently stated that an application for marketing authorisation cannot be refused solely on the grounds of the active substance being PBT but that, as with other applications for MA, the conclusions of the ERA should be considered as part of the overall benefit/risk balance. More detailed guidance on how to weigh the environmental impact posed by a PBT substance in relation to other factors in the benefit/risk balance should be developed.

10. Once the PBT status of a substance has been established, and consideration has been given to the conditions under which PBT substances can be authorised as veterinary medicinal products, 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. 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.

11. 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 not be granted a marketing authorisation for an unlimited period of validity), specific monitoring and specific pharmacovigilance requirements.

12. For existing products, where the conditions under which VMPs containing PBT substances can be authorised have not been met, consideration needs to be given to allowing a phase-out period. The concept of a “phase-out” is recognised under other legislative frameworks and the aim is to gradually replace products containing substances of concern such as PBTs by methods and products of lesser concern, while minimising the economic impact and disadvantages for animal health.

3.2. Constraints of existing VMP legislation

As noted in section 2.1.2., while the current CVMP guideline on ‘Environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38’ (EMEA/CVMP/ERA/418282/2005-Rev.1) specifies that an environmental risk assessment should include a determination for PBT/vPvB properties, the veterinary medicines legislation does not have any specific legal (binding) provisions relating to the assessment/authorisation of products containing PBT/vPvB substances (that is, legal provisions on PBT/vPvB substances similar to those that apply to industrial chemicals, biocides and plant protection products). In view of this, consideration was given to what can be achieved under existing veterinary medicines legislation, regarding:

- Determination of PBT status in the context of assessment of new product applications.

- The possibility of the establishment of a “formal” list of PBT substances in VMPs knowing that this is being established for the purposes of regulatory action.
- The possibility of “comparative assessment” (possibly leading to refusal to authorise a VMP containing a PBT substance on the basis that a non-PBT alternative is available).

On these specific points, the following conclusions were reached:

- It is possible to do an assessment of PBT status on a case-by-case basis in the context of an application for new product authorisation. However, 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. The impact to the environment one of a number of factors that have to be considered. In accordance with current legislation relating to the regulation of VMPs, the assessment of an application for a marketing authorisation is product based, and not substance-based.
- Regarding the proposal to establish a list of PBT-substances, there is no legal basis for establishing such a list; therefore, any list generated would not be formally binding in the sense of a legally binding act.
- Regarding the concept of “comparative assessment”, the existing legislation does not allow for such an approach. Again, in accordance with current legislation relating to the regulation of VMPs, the decision to authorise, or not, a product is product-specific and is taken on the basis of the overall benefit risk balance.

In view of the above, it is concluded that there is a need for specific legal tools to appropriately address concerns relating to the use of PBT substances in VMPs.

3.3. What can be achieved under existing VMP legislation?

The absence of a clear legal basis limits what can be done to address concerns relating to the use of PBT substances in veterinary medicinal products at this time. However, it is possible to do an assessment of PBT status on a case-by-case basis in the context of an application for a new product authorisation. The decision to authorise, or not, a product is taken on the basis of the overall benefit risk balance and the impact to the environment is one of a number of factors that have to be considered.

While it was accepted that decisions can be taken on a product-specific basis, there is a concern that decisions on individual applications may be disproportionate in the overall context of managing PBT substances (in particular, when the substance in question may be present in marketed products with a valid marketing authorisation). It was noted that the principle reason for establishing the AHEG was to develop a Network strategy for evaluation/consideration of (potential) PBT substances generally and move away from decisions on individual applications.

In the event that an unacceptable risk to the environment (relating to PBT status) is identified in the context of a new product application and this raises questions about the risk to the environment posed by marketed products containing the same active substance, Member States have the option to have the risk relating to all concerned products evaluated in the context of an Article 35 referral. However, it is generally accepted that a referral in accordance with Article 35 may not be the ideal mechanism in that a decision would still be taken for a product (or group of products) in isolation without taking account of the benefits and risks of alternative products (including PBT status which, for many substances, may not be known).

When considering authorising (or maintaining) a VMP containing a PBT substance, thought should be given to:

- The expected extent of environmental exposure when the product is used as recommended. Environmental exposure is expected to be limited for substances included in products used for the treatment of clinical disease in individual animals. In addition, for certain substances, it may be possible for an applicant to demonstrate that environmental exposure is limited where parent compound is extensively metabolised to non-PBT substances.
- The expected benefits. Is the product efficacious and is there a clear therapeutic need that is not met by available VMPs? This consideration should take into account the need for substances from various substance classes to address concerns relating to resistance emergence.
- What measures, if any, can usefully be applied to limit the potential for significant environmental exposure?

The guidance document on ERA in support of the VICH Guidance GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1) and the reflection paper on risk mitigation measures related to the environmental risk assessment of veterinary medicinal products (EMA/CVMP/ERAWP/409328/2010) discusses a number of risk minimisation measures (RMM) that can be employed to reduce environmental exposure to active substances in VMPs e. g. not allowing treated animals access to surface water for a certain number of days. However, none of the RMMs in current use will effectively prevent the release of the PBT substances into the environment. It is therefore necessary to consider other approaches/control measures to reducing emissions of PBT substances. For non-aquaculture products, options to reduce emissions to the environment include:

  - Restricting the conditions of use to individual animal, targeted treatments (for example, for gastrointestinal nematodes, treat only those animals that have a faecal worm egg count above a certain threshold), noting that a number of potential PBT substances are available as premixes, solutions for drinking water and dip baths to facilitate group treatment).
  - Restricting use to certain methods of administration. Where substances are authorised in different pharmaceutical forms for different routes of administration, the amount of active substance required for an individual animal treatment may vary depending on administration route (typically lower for parenteral treatments than for topical treatments). Consideration could be given to authorising only those pharmaceutical forms that are most efficient in terms of active substance delivery and that allow for precise dosing.
  - Limiting the dose and/or number of administrations to the minimum required for effective treatment of ongoing infections (and, as a consequence, discourage the use of high-dose, long-acting formulations).
  - Authorising as single-substance products only (noting that a number of substances of concern are presented in combination with other substances). If marketing authorisations for combination products including PBT substances are to be authorised/maintained, the applicant/MAH should be required to demonstrate that the combination offers a clear therapeutic advantage over the use of individual mono-substance products and that authorisation of the combination would satisfy an otherwise unmet need.
  - Can emissions to the environment be controlled or eliminated following treatment. If, for any substance, there is documented evidence to confirm that parent compound will be degraded in

slurry to non-PBT degradation products, a possible measure to reduce environmental exposure would be to restrict use of the product to the treatment of intensively reared (housed) animals.

- Designation of categories of users. All authorised products containing PBT substances to be supplied subject to veterinary prescription.
- Clearly communicating, via product information, the risks and hazards to the environment (including PBT status) to the prescriber, the user and any other individual with responsibility for instituting a parasite control strategy on a farm. In addition to highlighting potential environmental effects, steps should be taken to promote, via product information, a sustainable approach to parasite control. That is, medicinal treatments should only be used as part of a parasite control programme, the goal of which is to minimize the level of parasite infestation and, at the same time, minimize reliance on, and reduce the use of, medicinal treatments by appropriate monitoring and targeting treatment to those that require it.
- The overall benefit risk balance. Is authorisation (availability) of the product in the interests of animal/public health and do the benefits clearly exceed the risks/hazards (including consideration of the implications of a refusal to authorise)?
- Issuing of the marketing authorisation subject to conditions, e.g. a Risk Management Plan (RMP) with time-limited review whose periods would be determined on a case-by-case basis, specific monitoring and specific pharmacovigilance requirements in the future.

4. Recommendations

4.1. Recommendations for legislative change

There is a need for specific legal tools to appropriately address concerns relating to the use of PBT substances in veterinary medicinal products in order to prevent exposure of humans and the environment to these substances. Ultimately the legislation should:

- Allow for the establishment of a list of PBT substances;
- Consider the possibility of refusing/revoking a marketing authorisation based on the PBT status of the active substance;
- Provide specific conditions under which marketing authorisations could (exceptionally) be granted/maintained for PBT substances;
- Allow transitional arrangements (phase-out).

In view of the ongoing review of the veterinary pharmaceutical legislation, which at present does not address PBT substances, it is considered crucial to ensure adequate legal provisions in the current review. 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 appropriate at this stage to propose a general provision in the current text requiring subsequent legislation on this particular issue.

It is noted that the proposal for the review of the veterinary pharmaceutical legislation was submitted by the European Commission in 2014 to the European Council and the European Parliament and the discussion is well advanced in both institutions. Amendments to the proposal can now be made by either the European Parliament or Member States.

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 should be viewed in the overall context of the benefit risk assessment.

4.2. Other general recommendations

- To ensure informed use of authorised vaterinary medicnal products, training of vets and farm professionals on judicious use of antiparasitic agents, and the risks associated with inappropriate use, may be appropriate.
- There is a need for increased research into non-chemical approaches to parasite control to reduce reliance on medicinal treatments. Non-chemical approaches to sea lice control, for example, include: mechanical lice removal, vaccines and immunostimulants, selective breeding for increased resistance to sea lice infestation, and the use of cleaner fish. While it may be the case that none of these approaches, individually, will treat/prevent severe sea lice infestation, some of these may ultimately become components of a sea lice control and management strategy.
- Consideration should be given to incentivise products of low risk to the environment, in particular for the aquatic compartment.
- Use of PBT substances in the aquatic compartment should be restricted/subject to permit and tightly regulated as part of a pest management strategy. Such use should include a requirement for independent monitoring for substances in the vicinity of, and distant to, treatment sites. It is acknowledged that the setting up of such monitoring systems is likely to be very difficult due to the properties of PBT and vPvB substances. Further, it is acknowledged that there are significant challenges associated with setting acceptable environmental concentration thresholds for PBT and vPvB substances. Other regulatory bodies (such as SEPA and Norwegian Medicines Agency) have some experience in monitoring the release of substances used to treat sea lice into the environment and therefore may be able to provide some input on the approach to such monitoring. The appropriate regulatory body to oversee such a monitoring programme needs further consideration.
- Consideration should be given to the development of treatment delivery methods that are more effective in terms of active substance delivery and that allow for precise dosing (in an effort to limit the quantity of active substance administered to the minimum needed).
- Consideration should be given to the development of new (or enhancement of existing systems) in filtration of treatment water (to remove active substance) for implementation at hatcheries, sea cages and well boats. The effectiveness, practicality and availability to fish farm facilities of any such system would require regulatory consideration.

5. References

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Annex I

The criteria for the identification of PBT/vPvB substances

Annex XIII of Regulation (EC) No 1907/2006 (as amended by Regulation (EC) 253/2011) lays down the criteria for the identification of PBT/vPvB substances and together with the supporting technical guidance are used as a point of reference for the assessment of the PBT/vPvB of a substance/product within different legislative frameworks in the EU (i.e. for industrial chemicals, pesticides or biocides). To ensure a harmonised approach, the CVMP recommends that these criteria together with the methodology in the current REACH guidance on PBT-assessment (Guidance on information requirements and chemical safety assessment Chapter R.11: PBT/vPvB assessment and Chapters R7.a, 7.b, and R7.c on endpoints specific guidance) should be followed for PBT/vPvB assessment of substances used in veterinary medicinal products.

Property	PBT criteria	vPvB criteria
Persistence	A substance fulfils the persistence criterion (P) in any of the following situations: (a) the degradation half-life in marine water is higher than 60 days; (b) the degradation half-life in fresh or estuarine water is higher than 40 days; (c) the degradation half-life in marine sediment is higher than 180 days; (d) the degradation half-life in fresh or estuarine water sediment is higher than 120 days; (e) the degradation half-life in soil is higher than 120 days.	A substance fulfils the "very persistent" criterion (vP) in any of the following situations: (a) the degradation half-life in marine, fresh or estuarine water is higher than 60 days; (b) the degradation half-life in marine, fresh or estuarine water sediment is higher than 180 days; (c) the degradation half in soil is higher than 180 days.
Bioaccumulation	A substance fulfils the bioaccumulation criterion (B) when the bioconcentration factor in aquatic species is higher than 2000.	A substance fulfils the "very bioaccumulative" criterion (vB) when the bioconcentration factor in aquatic species is higher than 5000.
Toxicity	A substance fulfils the toxicity criterion (T) in any of the following situations: (a) the long-term no-observed effect concentration (NOEC) or EC10 for marine or freshwater organisms is less than 0.01 mg/L; (b) substance meets the criteria for classification as carcinogenic (category 1A[4] or 1B[5]), germ cell mutagenic (category 1 or 1B), or toxic for reproduction (category 1A[6], 1B[7] or 2[8]) according to Regulation EC No 1272/2008[9] (c) there is other evidence of chronic toxicity, as identified by the substance meeting the criteria for classification: specific target organ toxicity after repeated exposure (STOT RE category 1 or 2) according to Regulation EC No 1272/2008.	

[4] Substances known to have carcinogenic potential for humans (epidemiological and/or animal data)
[5] Substances presumed to have carcinogenic potential for humans (animal studies)
[6] Known human reproductive toxicant (human evidence)
[7] Presumed human reproductive toxicant (animal studies)
[8] Suspected human reproductive toxicant (some evidence from humans or experimental animals, not sufficiently convincing to place the substance in category 1)
[9] Regulation on classification, labelling and packaging (CLP-Regulation (EC) No 1272/2008)