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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. 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].

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 concentration (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[1]. It is considered necessary to conduct a hazard based PBT assessment which focuses on intrinsic properties of substances only. The criteria and methods for the identification of PBT/vPvB substances are described in the Committee for Medicinal Products for Veterinary use (CVMP) "*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) (CVMP PBT GL (EMA, 2015)).

Unlike the situation for industrial chemicals, biocides and plant protection products, the veterinary medicines legislation does not have any specific legal provisions relating to the assessment/authorisation of products containing PBT/vPvB substances. However, 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 medicinal products in support of the VICH guidelines GL6 and GL38' (EMEA/CVMP/ERA/418282/2005-Rev.1) and, following adoption of the CVMP PBT GL (EMA, 2015), there has been an increased focus on PBT assessment as part of the environmental risk assessment (ERA). Recognising that any decisions on the authorisation of products with active substances identified as (potential) PBT substances has implications for authorised products containing the same, or related, substances, 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 CVMP, the CVMP Environmental Risk Assessment Working Party and Member States was set up to develop such a strategy. Specifically, the AHEG considered:

- the existing provisions relating to ERA generally, and PBT substances specifically, in the veterinary medicines legislation and legislation relevant to other chemical substances;
- the benefits of parasiticides in veterinary medicine (noting that all potential PBTs identified to date are parasiticides), the conditions of use (in general terms), the route of entry of the active substance into the environment and whether or not any risk mitigation measures (RMMs) or

[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)

restrictions on use could be usefully applied to limit emissions of individual products in the event that the active substance is classified as PBT/vPvB;

- a possible systematic approach to determination of PBT status of substances used in veterinary medicinal products and the conditions under which authorisations for such products should be granted/maintained; and,
- noting the proposed systematic approach, what can be reasonably achieved under the existing legislation and what additional regulatory 'tools', if any, are required to appropriately address concerns regarding the use of PBT/vPvB substances in VMPs.

The considerations and recommendations of the AHEG are detailed in this reflection paper. The purpose of this reflection is to determine the tools that are available or needed to comprehensively address the concerns regarding the use of PBT/vPvB substances in VMPs and, ultimately, reduce the risk to the environment due to the use of such products. However, given the importance of veterinary medicinal products for maintaining public and animal health, it is acknowledged that any proposals for addressing the PBT issue should not adversely impact availability of products where there is a clear therapeutic need.

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): For industrial chemicals, Regulation (EC) No 1907/2006, as amended on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), mandates that a PBT/vPvB assessment must be conducted for all substances for which a chemical safety assessment (CSA) is required. According to Article 14(1) of the REACH Regulation, in general this includes 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. The criteria for the identification of PBT/vPvB substances are given in Annex XIII of the REACH Regulation and, in accordance with Article 59 of the Regulation, those substances fulfilling the PBT/vPvB criteria are listed as substances of very high concern. Registrants/manufacturers of substances identified as a PBT/vPvB are obliged to recognise this status in their registration dossiers and in their supply chain communication. In addition, implementation of measures to minimise the release and exposure of these substances into the environment throughout their supply-chain and lifecycle are required. Further, these substances are replaced with suitable alternative substances or technologies, when technically and economically feasible. 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.

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 risk/hazard of emission of PBT substances into the environment. 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 hazard and risk 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]. The second step is centred on a risk assessment of products containing the approved active substance (that is, this step will only occur if the active substance is approved in step one). When a substance is identified as a PBT it will not be approved as an active substance and seeking a market authorisation for a product containing that active substance is not possible. That is, there are no derogations that will allow for its use in a PPP in any of the EU Member States. 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 or 15 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 is an assessment of hazard and risk of the active substance which includes an assessment with regard to the PBT criteria[3]. Only substances for which safe use can be established are included in an EU list of active substances approved for use in biocides. For biocidal products, a marketing authorisation can only be sought for products containing approved active substances. A risk and hazard assessment of the product is also part of the product authorisation procedure. An active substance will not be approved 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. Further, as in Regulation (EC) 1107/2009, as amended, active substances that meet two out of three PBT criteria are classified as "candidate for substitution". The approval of these active substances is for a maximum period of seven years, and biocidal products containing these have to be subject to a comparative assessment before granting an authorisation (CA-March14-Doc.5.4).

[2] The criteria for the identification of PBT/vPvB substances are given in Annex XIII to Reg. (EC) 1107/2009
[3] The criteria for the identification of PBT/vPvB substances are given in Annex XIII of REACH Reg. (EC) 1907/2006.

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 step approach to determining the risk to the environment. First, there is the process of active substance approval at EU level, during which a full hazard and risk assessment is performed. When applicants apply for a market authorisation, a product specific dossier is submitted (product which contains an EU approved active substance), and again a full risk assessment is performed.

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 ERA is mandatory for all new applications, independent of the application procedure (central or national marketing authorisation) and underlying legal basis ("full", "generic", etc.). While the legal requirement to perform an ERA and provide this with an application for marketing authorisation was included in Directive 92/18/EEC, a comprehensive harmonised ERA in the EU only started when the VICH guidelines on the ERA came into force in 2000 (Phase I) and 2005 (Phase II). The ERA is an evaluation of the possible fate, exposure and effects of the product. 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. 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 CVMP PBT GL (EMA, 2015)).

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 screening for VMPs is specified in 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).

A preliminary screening of active substances used (or intended to be used) in VMPs conducted in 2015 by the CVMP environmental risk assessment working party, using information available to national competent authorities (in the context of applications for marketing authorisation and/or known from PBT assessment activities under other legal frameworks), identified up to 20 candidate substances which are potentially PBT/vPvB (for the purposes of this exercise, potential PBT/vPvB substances are defined as those with log K_{ow} (octanol/water partition coefficient) equal to or higher than 4.0).

All potential PBT substances identified as part of this screening exercise are parasiticides, the majority of which are authorised for use in food-producing species and can be considered widely used. However, it should also be noted that reliable log K_{ow} values are not available for all substances used in veterinary medicines; therefore, the possibility that substances from other therapeutic classes may fulfil the criteria for PBT cannot be excluded and the number of potential PBT substances may be somewhat higher than the number of candidates identified 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).

For the majority of substances used in veterinary medicines identified as potential PBT, the necessary data to perform a full PBT assessment and conclude on PBT status is currently not available. However, in the context of an assessment of applications for marketing authorisation submitted via the decentralised procedure in accordance with Article 13 of Directive 2001/82/EC, as amended (a generic), 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 and refused to grant marketing authorisations for the products concerned on that basis. Arising from this decision, Germany considered that action should be taken at a European level since moxidectin-containing products are authorised in the majority of EU Member States (MSs) and a Community (Article 35) referral procedure for all VMPs containing moxidectin to be administered orally, topically or subcutaneously to cattle, sheep or horses was triggered. The CVMP was asked to determine if moxidectin is a PBT and, if PBT status is confirmed, to provide a recommendation on the appropriate measures to prevent the emission of moxidectin into the environment, conduct an overall benefit risk analysis of the products concerned and conclude on whether the marketing authorisations for the products concerned should be maintained, suspended or revoked. This referral procedure is ongoing currently.

Noting that most potential PBTs identified to date are parasiticides, consideration has been given to the benefits of such products in veterinary medicine, 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 limit emissions of individual products in the event that the active substance is classified as PBT/vPvB. This reflection (presented as Annex I to this document) feeds into other aspects of the reflection paper, including: seeing the direct and indirect (combating resistance emergence) benefits of products, appropriate use (from the perspective of environmental safety and resistance emergence) and consideration of options to limit emissions to the environment.

3. Discussion

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

As noted in Section 2.1.2. above, recently, marketing authorisations for generic VMPs containing moxidectin were refused by MS national competent authorities based on concerns regarding the risk for the environment due to PBT properties. Noting that other products containing the same substance are authorised in the majority of EU MSs, a Community (Article 35) referral procedure for all VMPs containing moxidectin to be administered orally, topically or subcutaneously to cattle, sheep or horses was triggered. This referral procedure is ongoing currently.

Recognising that the decision on the authorisation of products with active substances identified as (potential) PBT substances lies with the MS 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 and MS was set up to develop such a strategy.

The AHEG met on eleven occasions between April 2015 and January 2017.

The AHEG agreed the following:

1. There is a need to determine the PBT status of active substances used in VMPs (both, new active substances and existing active substances). As previously advised, the approach to PBT assessment and the criteria for determining the PBT status of substances used in VMPs are described in the CVMP GL on PBT assessment of veterinary medicines (EMA/CVMP/ERA/52740/2012). In line with the standard approach to an ERA assessment for VMPs, the focus is on the active substance. A specific PBT assessment for excipients is not foreseen in the CVMP PBT GL. However, if an excipient happens to be a known PBT substance, this will have to be discussed/addressed during the authorisation process.

2. Under other legislative frameworks (e.g., BPR and PPP), the ERA follows a two-step approach. First the active substance has to be approved at 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 ERA at the product level. Any consideration of the hazards related to PBT/vPvB substances in VMPs should follow the same basic (phased) approach: that is, the PBT status of the substance should be determined before conducting/considering a product-specific assessment.

3. According to VICH GLs 6 and 38 on how to conduct an ERA for VMPs, and 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), a PBT assessment is not required for all active substances used in VMPs. Current requirements are that a PBT assessment is performed for all substances that enter Phase II and have a log Kow ≥ 4. In line with the CVMP PBT GL, a PBT assessment in Phase I could only be required if there is evidence, or strong indications that an active substance of a product, that would otherwise stop in Phase I, potentially has PBT properties. For example, this could be the case for substances with a valid octanol/water coefficient Kow ≥4 or that have been assessed as PBT/vPvB in other regulatory frameworks. A PBT assessment should not be requested for products for non-food producing species, for products containing natural substances, or if the substance is shown to be extensively metabolised in the animal, as defined in the Phase I decision tree.

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 the 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/vPvB substances) is required. For all existing substances identified in the screening process, a definitive determination of PBT status will be required. 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 the PBT status is taken by the European Commission based on recommendations from the relevant Agency. Therefore, any consideration of the 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 there is limited potential for environmental exposure 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/vPvB substances can be authorised as VMPs need to be defined. For example:

    a. Prevention of, or limited potential for, environmental exposure. For example: use of the product under conditions where release can be controlled; where the parent compound is extensively metabolised (parent and all metabolites ≤ 5% in line with Question 5 of VICH GL 6); or, where the parent compound is metabolised to non-PBT substances. In the latter case, the non-PBT status of the metabolites present at concentrations greater than 10% of the total residue would have to be confirmed by data.

    b. Effective risk mitigation measures (RMMs) can be applied to prevent or limit the potential for environmental exposure. For example, restrict use to intensively reared (housed) animals where the active substance is extensively degraded in manure/slurry, or where the active substance is degraded to non-PBT degradation products and the non-PBT status of degradation products present at concentrations greater than 10% of the applied dose is demonstrated.

    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 MSs 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/vPvB substance in one or more MS, where a clear need for the product has been identified in that/those MS). 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/vPvB but that, as with other applications for marketing authorisations, 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/vPvB 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 VMPs, a plan to systematically review authorised VMPs containing PBT/vPvB substances where the use of the product gives rise to an emission scenario(s) of concern should be put in place. For existing products, the need for

regulatory action would be considered as part of the product review. This can only be successfully implemented when the PBT status of potential 'alternative' substances is known.

11. Where products containing PBT/vPvB 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/vPvB substances can be authorised have not been met, consideration needs to be given to allowing a phase-out period. In this case, 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 marketing authorisation holder to manage the phasing out from the market. The concept of a "phase-out" is recognised under other legislative frameworks.

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 ERA 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. 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/vPvB 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/vPvB substance on the basis that a non-PBT alternative is available).

On these specific points, the following conclusions were reached:

- It is legally possible to require a PBT assessment in the context of an application for new product authorisation. In the context of an application for extension, or major variation of a product, where the PBT status of the active substance was not assessed in the initial application and where there is expected to be a change in pattern of use that will result in increased environmental exposure, a PBT assessment is also required. However, it is not possible to refuse a marketing authorisation 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 is 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.

  The CVMP PBT guideline suggests that authorisations for products containing vPvB substances should not be granted (specifically, it is stated: "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"). However, current veterinary medicines legislation does not include any specific

provisions relating to vPvB substances; therefore, there are no legal grounds for refusing to grant a marketing authorisation for a product only on the basis that it contains a vPvB substance. The AHEG would suggest that the additional hazard considerations posed by these substances should be taken into account when considering the overall B/R assessment.

- 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/vPvB substances in VMPs at this time. However, it is possible to do an assessment of the PBT status on a case-by-case basis in the context of an application for a new product authorisation (or extension/major variation, see above). 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/vPvB 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/vPvB substances generally and move away from decisions on individual applications.

In the event that an unacceptable risk to the environment (relating to the 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, MSs 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 the PBT status which, for many substances, may not be known).

When considering authorising (or maintaining) a VMP containing a PBT/vPvB 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 the parent compound is extensively metabolised/degraded in manure (all metabolites/transformation products

≤ 5%), or metabolised/degraded in manure to non-PBT substances (PBT assessment necessary for all metabolites/transformation products ≥ 10%).

- The expected benefits. Is the product efficacious and is there a clear therapeutic need that is not met by available VMPs? In the case of parasiticides, 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 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 VMPs (EMA/CVMP/ERAWP/409328/2010) advise on a number of RMMs 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, the extent to which the RMMs in current use are effective at limiting the release of PBT/vPvB substances into the environment is open to question. It is therefore necessary to consider other approaches/control measures to reducing emissions of PBT substances. For non-aquaculture products, options to limit the potential for environmental exposure 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 PBT/vPvB substances may be presented in combination with other substances). If marketing authorisations for combination products including PBT/vPvB substances are to be authorised/maintained, the applicant/marketing authorisation holder 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 a parent compound will be extensively degraded in slurry or degraded to non-PBT degradation products, a possible measure to reduce environmental exposure would be to restrict the use of the product to the treatment of intensively reared (housed) animals.
- Designation of categories of users. For example, all authorised products containing PBT/vPvB substances to be supplied subject to veterinary prescription.

- Clearly communicating, via product information, the risks and hazards to the environment (environmental properties, 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 minimise the level of parasite infestation and, at the same time, minimise reliance on, and reduce the use of, medicinal treatments by appropriate monitoring and targeting treatment to those animals that require it.

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/vPvB substances in VMPs in order to limit exposure of humans and the environment to these substances. Ultimately the legislation should:

- Allow for the publication of information on PBT status of substances used in veterinary medicinal products. Knowledge on the PBT status of a substance will allow regulators to take informed decisions in respect of product authorisations and will be beneficial to potential applicants, who could take this information into account with respect to product development.
- 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/vPvB substances;
- Allow transitional arrangements (phase-out).

In view of the ongoing review of the veterinary pharmaceutical legislation, which at present does not address PBT/vPvB substances, it is considered crucial to ensure adequate legal provisions in the current review. Given the complexity of the matter and the need for extensive consultations for agreement on the procedure to consider PBT/vPvB substances in VMPs, it is recognised that 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 will be 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.

4.2. Other general recommendations (relevant to parasiticides)

- To ensure informed use of authorised VMPs, training of veterinarians and farm professionals on judicious use of antiparasitic agents, and the risks associated with inappropriate use, may be

appropriate. On this point, it is noted that professional associations in a number of EU MSs have produced guidance on the appropriate use of anthelmintics in grazing animals.

- 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 that have the potential for low environmental impact, in particular for the aquatic compartment.
- The use of PBT/vPvB 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 the Scottish Environmental Protection Agency and the 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 (for example, to improve systemic availability, thereby allowing for a reduction in total dose of active administered) 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 systems (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.

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Annex I: Use of parasiticides in veterinary medicine

I. A Products used for terrestrial animals

To date, substances that have been categorised as PBTs or potential PBTs are used mainly in 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, reproductive potential and may even result in mortality.

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 VMPs. In addition, emerging resistance to authorised 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 health, 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 metabolised to a great extent in the body of the animals and therefore, typically, a large proportion of the administered dose is excreted unchanged into the environment. However, for products that are 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 limit 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 recognised 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 minimise the potential for resistance development and to minimise treatments. Indeed, from the point of view of resistance development (relating to helminths 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 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 minimise the level of parasite infestation and, at the same time, minimise 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.

I. B Products used in aquaculture

The substances of concern 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 fish welfare problem putting fish at greater risk of infections which may cause suffering and death, 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, increased susceptibility to other infections, 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. 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 infestations are used mostly in Norway, UK and Ireland, with limited use in other EU MS. Based on sales data available to the national competent authorities, the use of such products is greatest in Norway, followed by UK, then Ireland and this reflects the size of the salmon farming industry in those MS.

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 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 are applied 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. Efforts should be taken to ensure susceptibility of the sea lice to the chosen treatment which it is noted, is subject to both the mode of action of the substance on relevant sea lice development stages and the prevalent resistance situation.
- Given the general principle to use medicinal treatments only when needed, the administration of preventative treatments (prior to exposure to the parasite) is questionable and should generally be discouraged. That said, it is accepted that there may be interest in the development of products for use in fish prior to transfer to areas where sea lice are abundant and where an improved safety profile (in particular, the potential to significantly reduce environmental emissions) is documented. It is acknowledged that prophylactic treatment in the hatchery to protect against sea lice infestations which are expected after transfer to an open marine environment may reduce environmental exposure to chemotherapeutic agents (use of lower treatment volumes; water can be filtered and discharged following treatments in hatcheries; food loss/wastage and contaminated excreta from treated fish can be more easily controlled and discarded).

- Products should be administered at the correct dose for the recommended treatment period. In addition, the following practical measures, which are currently employed as recommendations for existing products, 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 the minimum possible size without unduly impacting on fish welfare.