10 September 2015
EMA/CVMP/ERA/74265/2015
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received during the second public consultation on 'Guidance on the assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicine' (EMA/CVMP/ERA/52740/2012)

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

Stakeholder no.	Name of organisation or individual
1	Blue Frog Scientific
2	German Federal Environment Agency, Expert group for PBT assessment of pesticides, biocides, REACH chemicals (Member of ECHA PBT Expert group) and pharmaceuticals
3	National Institute of Public Health and the Environment (RIVM), the Netherlands
4	Pestizid Aktions-Netzwerk e.V. (PAN Germany)
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1. General comments – overview

Comment	Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	1	-	-
2	2	We appreciate the revised version of the Guideline on the assessment of PBT and vPvB substances in veterinary medicinal products which is well structured and clearly arranged. In particular we welcome the amendment of a Part 2 on the assessment of products containing a PBT/vPvB substance and the possible consequences and measures.	Thank you for your comment.
3	3	RIVM appreciates the good work done since the previous version.	Thank you for your comment.
4	4	Considerable amounts of veterinary medicinal products are released into the environment. These include drugs that target parasites, protozoa, worms, and insects, antibiotics that combat pathogenic bacterial, substances for treating infections, and hormone active substances. Before the background of the growing contamination of surface water, soil, and food with residues from veterinary medicinal products PAN Germany sees an urgent need to revise legislation in the field of veterinary pharmaceutical policies to ensure that the environment and human health will be more effectively protected from the adverse effects of veterinary medicinal products. PAN Germany therefore welcomes very much that the high environmental concern of veterinary medical products (VMP) with persistent, bioaccumulative and toxic properties (PBTs) and vPvBs is taken seriously and that there will be a specific guidance on how to perform a PBT/vPvB assessment for VMPs. This meets	Thank you for your comment.

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		PAN Germany's recommendation "Criteria for active ingredients in veterinary medicinal products that are especially hazardous to the environment must be defined, so that authorisation of such products can be denied in future." (see PAN Germany 2012: Veterinary medicinal products and the protection of the environment. http://www.pan-germany.org/download/tierarzneimittel/tierarznei-EN-130207-web.pdf) Due to PBT substance's ability to persist in the environment, to accumulate in organisms and due to their toxicity, PBT properties have been recognised as criteria for exclusion from authorisation in other spheres of legislation (e.g. for pesticides or biocides). In order to protect the environment and the health of todays and future generations this should in general also apply to VMPs and authorisation for vPvB or PBT substances should be denied. (see PAN Germany 2013: Recommendations for Enhanced Protection of the Environment from Adverse Effects of Veterinary Medicinal Products. Position Paper. http://www.pan-germany.org/download/veterinary_pharmaceuticals/Enhanced_Protection_of_Environment_from_Veterinary_Medicinal_Products.pdf). Authorisation of VMPs with PBT substances must only be granted following very narrow derogations, e g. when there are no less harmful alternative products on the market or treatment methods available, when there are no sufficient prophylactic measures, when the expected exposure is "negligible" or when risk mitigation measures dictated by the assessment limit the	Thank you for your comment. This comment is addressed in Part 2 of the guideline.

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		exposure to such, and when the implementation of those mitigation measures and their effectiveness is controlled.	
		PAN Germany recommends that peer reviewed data and results from independent research on the environmental impacts of veterinary medicinal products are to be included in the environmental assessment. We recommend that the risk assessment includes Scientific peer-reviewed open literature, as determined by the Authority, on the active substance and its relevant metabolites dealing with side-effects on health, the environment and non-target species and published within the last 10 years before the date of submission of the dossier and that these data shall be added by the applicant to the dossier and that relevant data added by third parties must also be included.	Peer reviewed data, when available, can be used together with or instead of studies performed for regulatory purposes, as long as they contain sufficient details about the test procedure and results to assess them for reliability and relevance. This includes studies/ data from the literature or reports which have been conducted according to generally valid and/or internationally accepted testing guidelines (and if possible performed according to GLP), or in which all parameters described are closely related/comparable to a guideline method. It is considered to be standard practice that the expert should present a critical evaluation of the study design, performance and results.
		When vPvB and PBT substances enter the environment there is reason to fear that they cause a long-lasting environmental burden. This is why we dismiss the Risk-Benefit-Assessment for vPvB/PBT substances as a decision tool: To come up with relevant results a monetary risk-benefit-assessment had not only to calculate the economic advantages of the use of PBT/vPvB substances but also to calculate the monetary benefit of not-using PBT/vPvB substances for the protection of nature and the environment. In our view this is impossible to calculate and therefore such a risk-benefit-assessment is not feasible.	Thank you for your comment.
		PAN Germany criticises that a marketing authorisation for a veterinary medicinal product is valid for an unlimited period of time and that a regular environmental review of the approval	Thank you for your comment. The proposed recommendation is outside the scope of the guideline and therefore the text has not been modified.

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		decision that secures an environmental assessment based on the current state of scientific knowledge is not in place.	
		PAN Germany recommends that any market authorisation for a VMP that contains PBT substances shall be limited to 7 years and that this time shall be used to invest in the search of alternative VMPs without PBT substances and/or in the search of alternative treatment methods.	Thank you for your comment. The proposed recommendation is outside the scope of the guideline, as it is meant mainly as a technical guidance for applicants for the identification of PBTs. Therefore the text has not been modified.
		PAN Germany recommends a clear exclusion provision for vPvBs without derogations.	Thank you for your comment. In section II of the guideline, paragraph 1 states that 'vPvB substances are resistant to environmental degradation and consequently they have been known to persist in the environment, transport long distances, bioaccumulate in human and in animal tissue, and bioconcentrate. Thus, given the potential significant impacts on human health and the environment it seems unlikely that an authorisation for a vPvB substance in a veterinary medicinal product where the substance will be released to the environment could be granted'. The text has not been modified as it is in line with the proposed suggestion.
		PAN Germany proposes that the Guideline includes a reference to the European Water Framework Directive (Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy) and its specific subsequent directives, especially the Groundwater Directive (Directive 2006/118/EC of the European Parliament and of the Council of 12 December 2006 on the protection of groundwater against pollution and	Thank you for your comment. The guideline is meant as a technical guidance mainly, with guidance to the applicant on considerations for the assessment of PBT substances. The proposed text is outside the scope of this guideline and the environmental impacts of PBTs for aquatic systems are covered in the introduction section.

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		deterioration), the Commission Directive 2014/80/EU amending Annex II of Groundwater Directive 2006/118/EC and the Directive on priority substances in the field of water policy (Directive 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy). They include provisions or actions as the following: • the development of a strategy to reduce pollution of water by pharmaceutical substances • information concerning risks to the functions of groundwater body • information on bioaccumulation potential, persistence or eco-toxicology of groundwater pollutants • establishing a watch list for identifying relevant groundwater pollutants We would like to highlight that recital 20 of the Groundwater Directive refers to groundwater ecosystem and that better criteria for its protection should be provided. We believe that this is also relevant for the PBT-, vP- or vB- work concerning (veterinary) pharmaceuticals as there are already indications for groundwater pollution by pharmaceuticals.	
5	5	The addition of Part 2 which offers guidance on the assessment of	Thank you for your comment.

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		products containing a PBT substance makes this version greatly improved.	
6	6	It should be remembered that exposure as well as the intrinsic properties of a veterinary medicine need to be considered. Over-emphasis seems to be given to the intrinsic properties. Furthermore, the guideline is based on REACH and the exposure of the environment from veterinary medicines is considerably lower than from chemicals.	Thank you for your comment. The main scope of the guideline was to provide guidance on the assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicine, and to address general principles on how VMPs containing a substance that has been identified as PBT should be further assessed, within the context of the environmental risk assessment and benefit-risk assessment of the product concerned. As the PBT assessment is a hazard assessment, the identification of PBT substances should be based on their intrinsic properties and exposure considerations are not relevant for PBT identification. As the REACH guidance documents offer very detailed guidance on PBT assessment and harmonization of these assessments among frameworks is preferred, it is decided here to follow these guidance documents as much as possible. Emission considerations are taken into account in Part II of the Guideline are not based on REACH guidelines. Therefore, the text has not been amended.

2. Specific comments on text

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
7	44	2	**Comment**: PBT or vPvB substances pose a serious concern for the environment. **Proposed change:** Please delete 'can' and add the following sentence: 'Consequently, for PBT/vPvB substances, a "safe" concentration in the environment cannot be established with sufficient reliability'.	Thank you for your comment. The text has been amended as suggested.
8	44	3	**Comment**: Insertion **Proposed change**: Due to the combination of these intrinsic properties and possible redistribution in the environment, they can pose serious concerns for the environment.	Thank you for your comment. The text has been amended accordingly.
9	58	3	**Comment**: The relevant guidance can be cited here. **Proposed change** : Technical guidance is ~~are~~ used as a point of reference (ECHA guidance on IR & CSA, Chapter R11: PBT guidance, v2.0 Nov. 2014)	Thank you for your comment. The references cited in this section refer to the one cited in the 'Environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38'. The text has not been amended.

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10	60	2	**Comment**: The phrase 'and serve as harmonised criteria' could be misunderstood, as the definitive criteria are well-defined, but the boundary conditions are partly not specified in detail. **Proposed change:** 'and serve as harmonised approach'	Thank you for your comment. The text has been amended as suggested.
11	63-64	2	**Comment**: The mentioned guideline documents (Guidance on information requirements and chemical safety assessment. Chapter R.7a-7c, Chapter R.11, ECHA 2012a-d) have been revised in 2014. **Proposed change**: '(ECHA 2014a-d)', please update also the reference list.	Thank you for your comment. The references have been updated
12	64	2	**Comment**: Please add "boundary conditions" **Proposed change**: '...with focus on scientific data/ information, parameters, default values **and boundary conditions** that should be used for the assessment'.	Thank you for your comment. The proposal has been partially accepted and text has been amended including 'test conditions and default values that should be used for the assessment'.
13	64	3	**Comment**: See previous comment; the PBT guidance was updated. **Proposed change**: Please insert correct reference to R11, v2.0.	Thank you for your comment. The relevant references regarding the revised REACH guidance from 2014 have been updated in the guideline.

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14	68-138	1	**Comment:** Please note some of the relevant ECHA guidance (R.7 & R.11) was updated in November 2014 and the text should be updated to reflect this.	Thank you for your comment. The references have been updated, accordingly.
15	76	3	**Comment**: Prediction of fate and effects of PBTs/vPvBs is very difficult (as mentioned later) so we would suggest a minor edit **Proposed change**: It is neither possible to accurately predict	Thank you for your comment. The text has been amended as suggested.
16	115	6	**Comment**: Suggest that this section includes a precise statement which spells out which criteria need to be triggered for an active ingredient to be classified as “PBT” (all 3, 2 out of 3, just B *etc*).	Thank you for your comment. PBT stands for **P**ersistent, **B**ioaccumulative and **T**oxic. The subsections in 1.2 already specify the criteria to be met for a substance to fulfil the P, B and T criteria and therefore be a PBT substance. The text in the introduction has been modified.
17	123	6	**Comment:** Is the use of the word “suspicion” really appropriate for a scientific guideline? Surely, it should be evidence-based.	Thank you for your comment. The word ‘suspicion’ has been changed to ‘indications’. The aim of the word is to indicate that when there are data gaps for a substance for the P, B and T criteria, additional knowledge on the substance or similar substances can be used to trigger a PBT assessment.

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18	124-125	3	**Comment:** The screening phase seems to be facultative, but in other legislative frameworks, it is mandatory. Therefore, we suggest that this step is not facultative but recommended based on ECHA guidance R11.	In contrast to other frameworks, all data necessary to perform a definitive assessment should already be available in the dossier. Thus, it is not necessary to perform a screening phase.
19	125-126	6	**Comment:** “or that has been assessed as PBT/vPvB in other regulatory frameworks”. Why is it acceptable for CVMP to make reference to data and decisions from other regulatory frameworks, yet the Applicant is not permitted to do so?	Thank you for your comment. The text has not been modified. When a substance has been assessed as to have PBT properties in another framework, this indicates that the compound should also be assessed for PBT properties during the VMP authorisation procedure, even if it would otherwise not go into phase II of the assessment (“However-clause”). The PBT assessment should be re-performed within the VMP ERA and is not automatically taken over from the other framework. The CVMP does not make reference to the data used in other frameworks, but merely uses all available information to decide if there is are indications that the substance has PBT properties. Please note that in most EU frameworks the criteria for a substance to be labelled as P, B or T are the same (although the trigger for the PBT screening might differ).

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20	126-127	3	**Comment:** It might be considered to revise the exclusion of PBT assessments. In the light of the concern for PBTs, the focus is on the entire ecosystem, not only humans. The rationale to restrict the PBT assessment to food producing species or 'man made chemicals' seems therefore not consistent with the goals of the PBT assessment.	Thank you for your comment. Currently, and in line with the request for an ERA for VMPs (see Guideline on Environmental impact assessment (EIAs) for veterinary medicinal products (VMPs) – Phase I, VICH GL 6 (CVMP/VICH/592/1998)), a PBT assessment is not needed when the ERA stops at Phase I, and unless there is a trigger based on specific concerns related to their activity and use.
21	126-127	4	**Comment:** The proposal states that "*A PBT/vPvB assessment should not be requested for products for non-food producing species, (…)*". We do not agree with this exclusion. Also non-food producing animals - like horses, dogs and cats – which are treated with VMPs containing PBT/vPvB substances produce contaminated excrements that find their way into the environment. **Proposed change** : "*A PBT/vPvB assessment should not be requested ~~for products for non-food producing species,~~ for products containing natural substances, or if the (…)*"	Thank you for your comment. Please see the answer to the comment above (20).

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22	127	2	**Comment:** Products for non-food producing species should not be generally excluded from PBT/vPvB assessment, as they also pose serious concerns for the environment, if they contain a PBT or vPvB substance. **Proposed change**: Delete 'for products for non-food producing species'	Thanks you for your comment. Please see the answer to the comment 20
23	134-135	4	**Comment:** In our understanding the statement "*As the emission to the environment will be different for VMPs for use in terrestrial animals and those for use in aquaculture, a differentiation is made in the assessment strategy*." Should be deleted here and instead be inserted under 2.1 as it is relevant for the assessment of PBTs rather than for the identification of PBTs.	Thank you for your comment. The text has been left in this section but also referred to it in section 2.1 as proposed.
24	136	2	**Comment:** The screening criteria for P, B and T are not mentioned in the guideline anymore. **Proposed change**: They should be reinserted at suitable position.	Thank you for your comment. The screening criteria as defined in REACH as a first step in the PBT assessment are not relevant for the VMP PBT assessment, since every ERA dossier should in principle already contain the data needed to perform the definitive assessment.

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25	138	3	**Comment:** ECHA guidance is now v 2.0, 2014 (see previous comment)	Thank you for your comment. The references in the text have been amended accordingly.
26	144-145	2	**Comment:** A reference to REACH Annex XIII is missing in the heading **Proposed change:** Please add PBT and vPvB criteria '**according to REACH, Annex XIII of Regulation (EC) 1907/2006** '. Please adapt the reference to Chapter R.11: PBT Assessment. It should refer to the current version 2.0; November 2014'.	Thank you for your comment. The reference to REACH in Table 1 has been included and the reference data updated.
27	145 Table 1	2	**Comment:** Table 1 'PBT and vPvB criteria' has to be adapted to the current version of Table R.11-1 in the new REACH Guidance Chapter R.11: PBT Assessment (11/2014). **Proposed change**: The updated version of Table R.11.-1 'PBT and vPvB criteria according to Section 1 of Annex XIII to REACH' should be inserted.	Thanks for your comments. The table has been updated.

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28	150	2	**Comment:** We think, the wording in general use is 'remote areas'. **Proposed change**: 'Remote areas' instead of 'distant geographical areas'	Thanks for your comments. The text has been updated accordingly.
29	152	6	**Comment:** VICH GL38 DOES NOT require an anaerobic transformation study (only makes reference to OECD 307). Until this point, anaerobic degradation in soil has not been required by for EU registartions.	Thank you for your comment. The GL makes reference to OECD 307 which is the study guideline for 'Aerobic and Anaerobic Transformation in Soil'. The text has been modified to avoid its misinterpretation.
30	161-165	2	**Comment:** According to the revised REACH guidance R.7b: endpoint specific guidance, published in November 2014, new simulation degradation studies should be carried out around neutral pH values and at 12˚C, which is understood as the mean temperature of European surface waters. Accordingly, temperature correction of degradation half-lives from already available study results to 12˚C is recommended.' **Proposed change**: The text passage should be changed respectively.	Thanks for your comments. The text has been updated accordingly.
31	161-163	4	**Comment:** We support that persistence studies should reflect environmental temperatures in Europe. But using	Please refer to answer to comment no. 30. Although in some areas in Europe an average water temperature of 12 degrees may be too high, we have

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			an average temperature in the persistence studies might lead to an underestimation of the persisting properties of substances. The temperature that is used for the persistence studies should reflect a realistic worst-case-scenario. It should be checked if for some northern regions the 12 ° C temperature is not too high.	chosen to follow the REACH guideline here and not use any lower temperatures.
32	161-162	6	**Comment:** OECD 307 stipulates that soil studies are conducted at 20°C. Suggest reference to conducting at 12°C is removed for clarity, and then just reference extrapolation to 12°C using the Arrhenius equation.	Thank you for your comment. The text clearly mentions that the studies should preferably be conducted at 12 °C, given that "persistence studies shall reflect environmental temperatures in Europe and therefore preferably be conducted at 12°C, as this is the temperature which is understood as the mean temperature of European surface waters. According to the REACH PBT/vPvB assessment guideline (ECHA, R.11, 2014d). If studies are conducted at different temperatures, extrapolation of degradation half-lives to 12°C should be considered." The text also mentions that when this is not the case the Arrhenius equation can be used to extrapolate the degradation half-life (e.g. 20°C to 12°C). The text has not been modified.

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33	162	1	**Comment:** Please note that the 12°C temperature correction is referenced in the current ECHA 2014 R.11 guideline, pg 39, which is more accessible than the old superseded TGD. Also ECHA has a different equation for temperature correction, should this be harmonised? EFSA suggest an Ea of 65.4 kJ/mol while ECHA (R.7b,pg 191) suggest 70 kJ/mol.	Thank you for your comment. The text has not been modified, as the ECHA Guidance refers to the use of a rough hydrolysis temperature correction estimate using a 'fixed' activation energy (circa 70) for all hydrolytic reactions and for all substances. However, no additional information is presented and the value of 70 kJ/mol is, as stated, an approximate value. According to EFSA, the selection of substance specific input values should follow recommendations given in FOCUS (2006) and in the generic guidance for Tier 1 FOCUS ground water. A number of EFSA's guidances' (2007, 2012, 2014) indicate that the molar activation energy should be set to 65.4 kJ mol-1 (EFSA, 2007) and should only be changed based on experimental evidence.
34	164-165	3	**Comment**: Recommendations phrased as 'should' can be ignored, depending on the interpretation which differs between countries. **Proposed change**: Different temperatures, extrapolation of degradation half-lives to 12°C ~~should~~ shall be considered.	Thank you for your comment. The text has been amended accordingly.

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35	176-177	1	**Comment:** Regarding the difficult subject of bound residues / non-extractable residues and derivation of DT50 values. The document states that “bound residues should not be confused with degradation”. DG SANCO 2006 (pg 20, 44 footnote, recommended to be consulted in ECHA R.11) defines degradation products as “*All substances resulting from biotic or abiotic transformation reactions of the test substance including CO2, microbial biosynthetates, and products that are in bound residues.*” ECHA R.11, pg 39, guidance also states: “*Another issue to address is whether parent molecules, or their degradation products, via their interaction with sediment or soil organic matter become bound to or entrapped in the organic matrix. The environmental significance of bound residues is related precisely to the extent to which they become indistinguishable from existing organic matter. This is discussed in Sections R.7.9.4 and R.7.9.5 of the Guidance on IR&CSA, Chapter R.7b).*” R.7.9.4, pg 201 states: “*Knowledge of bound*	Thank you for your comment. In line with the draft CVMP reflection paper on poorly extractable and/or non-radiolabelled substances (EMA/CVMP/ERA/349254/2014), the term ‘bound residue’ in the guideline has been replaced by ‘non-extractable residue’. The definitions for bound residues and for non-extractable residues are those defined by ECETOC. Therefore, as indicated in the comment a ‘bound residue’ can be interpreted as a loss (degraded) It is important that an applicant show that all possible extraction techniques have been employed to be able to call a residue ‘bound residue’.

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			residues and incorporation into biomass also needs to be considered and should be seen as a potential removal pathway. The OECD 308 (2002) Guideline advises as follows: "Bound residues represent compounds in soil, plant or animal that persists in the matrix in the form of the parent substance or its metabolite(s) after extractions. The extraction method must not substantially change the compounds themselves or the structure of the matrix… In general, the formation of bound residues reduces the bioaccessibility and the bioavailability significantly (1) [modified from IUPAC 1984 (2)]." Extraction of the sample, often with a suitable organic solvent is generally repeated 3 or 4 times until no further yield is achieved. Typically a range of solvents are used of increasing polarity (e.g. methanol, acetone, acetonitrile and hexane etc.) under ambient conditions. If the entire residual radioactivity cannot be recovered then appropriate solvent may be mixed with weak acids or bases or coupled to ultrasonic extraction. This aims to provide different conditions that may lead to the chemical or metabolite being released back into solution. Finally, the use of strong acids, bases or refluxing could undoubtedly extract the sample more thoroughly but could alter both the compounds of	

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			interest and the matrices. Such severe extraction techniques are rarely if employed in e.g. routine soil or sediment/water testing. The extraction methods and efficiencies as well as analytical methods and detection limits should always be reported. *These considerations should aid in determining the following environmental assessments for classification, PBT/vPvB and potential exposure*." and *"PBT and vPvB assessment:* *When a substance is not fully mineralised, but degraded to more persistent degradation products, the PBT/vPvB properties of these should be evaluated before a final judgement of whether a substance fulfils the persistence criteria. More guidance is given chapter R.11*." The concern is that the draft guideline does not allow the eventuality that formation of bound residues to be considered as a removal process which appears not in complete harmony with the most recent ECHA guidance of November 2014 or FOCUS guidance.	

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36	175	2	**Comment**: The moisture content is also an important parameter, which influences the outcome of degradation studies and the calculated half-lives. **Proposed change:** According to OECD 307 test guideline, the soil moisture content should be adjusted to and maintained at a pF of between 2.0 and 2.5 The soil moisture content is expressed as mass of water per mass of dry soil and should be regularly controlled throughout the test.	Thank you for your comment. When a test is performed according to the OECD307, the moisture content should be as stated in the comment. Therefore, it does not seem to be necessary to repeat specific OECD guideline specifications in this PBT guidance.
37	178-180	6	**Comment:** If four soils have been used to determine DT50 values, the geometric mean should be used in accordance with current guidance given under VICH Phase II & CVMP ERA. There needs to be consistency between our guidance documents, and as soils are varied across the EU, it is considered valid to use the range of experimental DT50 values to establish whether or not an active ingredient is persistent or not (otherwise, there would be no point in testing four soils). Furthermore, the worst case value may have arisen from a non-typical agricultural soil or there may have been reasons for the result (which can be supported from other data or weight of evidence suggests that one is an outlier).	Thank you for your comment. As the PBT assessment is a hazard assessment and not a risk assessment, the use of a geometric mean is not appropriate. In a risk assessment the reasonable worst case scenario is the one that has to be taken in consideration, and therefore the use of a geometric mean for modelling purposes is adequate in such context, since it generally fits on all scenarios. However, for PBT assessments (hazard based assessment) the approach to consider is that all kind of soils need to be protected, and to do so the DT50 value of the worst case scenario is the one to consider in this circumstances (analogue to the lowest of the toxicity values to protect all aquatic species).

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38	179-181	5	**Comment:** REACH Guidance Chapter 7.b (ECHA 2014) states that: In general, a single simulation study may be sufficient provided the environmental media at environmentally realistic conditions selected for study are appropriate. Availability or generation of multiple simulation test data may allow more WoE [Weight of Evidence] based conclusions to be drawn in relation to environmental half-lives for one or more environmental compartments by expert judgement. The precise manner in which expert judgment should be used in a WoE approach to determine an overall environmental half-life is not described in ECHA (2012). However, there is reference earlier in ECHA (2012) to “FOCUS (2006)”. This refers to Boesten et al. (2006) who produced a Guidance Document on estimating persistence and degradation kinetics from environmental fate studies on pesticides in EU registration. Boesten et al. (2006) state the following, which is of relevance to the reporting of degradation from simulation studies: In some circumstances using averages from different experiments is not appropriate. For example, averaging is not recommended when	Thank you for your comment. The text has not been changed. Please refer to comment 37 for additional information. Also, the paper by Boesten *et al.* has been written with a risk assessment in mind.

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			degradation is a strong function of the properties of the experimental media. Examples where averages should not be used include results of: • hydrolysis studies conducted at different pH values • soil degradation studies when degradation is a strong function of soil properties (such as pH for compounds that are partially ionised in the range of normal soil pH) • water-sediment studies when degradation is a strong function of pH or organic matter nature and content • field dissipation studies when degradation is a strong function of climatic conditions (other than what would be accounted for in the normalisation process discussed in Chapter 9), agricultural practice or soil properties (such as pH, soil structure and nature and content of organic matter). Guidance requiring a mean value may be ambiguous, because different values are obtained if the degradation rates (rate constants) are averaged or the corresponding half-lives (or first order DT50 values) are averaged. Averaging degradation rates results in greater weight being placed on the higher (faster) degradation rates while averaging the corresponding	

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			half-lives results in greater weight being placed on the higher half-lives (slower degradation). One approach which results in giving the same result whether degradation rates or half-lives are averaged is to use the geometric mean rather than the arithmetic mean. As an example, consider the average of four half-lives: 10, 20, 30, and 100 days with corresponding rate constants of 0.06931, 0.03466, 0.02311, and 0.00691 days-1. The arithmetic mean of the half-lives is 40 days and the arithmetic mean of the rate constants is 0.0335 days-1, which corresponds to a half-life 20.7 days. The geometric mean of both the half-lives and the rate constants results in a half-life of 27.8 days. The work group recommends that the geometric mean be used when averages of degradation rates are desired. If rates of parent degradation are based on four or more soils and the metabolite degradation is based on three or more soils then using an average is appropriate (a geometric mean is recommended by the kinetics work group). If the degradation rate is based on fewer soils, then the highest value should be used. When degradation rates in a large number of additional soils are	

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			available then the use of a median value may be most appropriate. Before averaging all values must be corrected to a consistent temperature and moisture content. In the report from the FOCUS Surface Water Workgroup the following recommendation is provided: Generally, information on two different water-sediment systems is available in the dossier. It is recommended to calculate the average of these two values and to use this value in the models STEPS 1 and 2 in FOCUS and TOXSWA in FOCUS. Statistical considerations A dataset can be summarised in several different ways, but the most common summaries include measures of central tendency (e.g. the mean, median or mode). Summaries such as the mean and median are important because they provide unbiased measures of location (Sokal and Rohlf 1981). In other words, if an unbiased sample of a variable parameter is taken, then the mean of this sample provides us with the best indication of where the “true” value lies. If, instead of using a mean or other measure of central tendency, we use only the lowest or highest value in our sample then we will	

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			produce a highly biased estimate of where the true value lies. From a regulatory point of view, the use of only the lowest or highest value from a sample of available values has the perverse effect of penalising substance registrants who present more than just the minimum data package. This is one reason why under REACH registrants with more than one set of toxicity data for a single species (e.g. several Daphnia test results) are recommended to summarise these data as a geometric mean, and why registrants with many data from different taxonomic groups are recommended to summarise them as an HC5 from a species sensitivity distribution. **Proposed change:** If ~~The~~ ~~highest~~ degradation half-lives from four or more soils from the OECD 307 test are available, then the geometric mean should be used for the PBT assessment.~~until further guidance on evaluation of simulation test data on biodegradation is provided by REACH.~~	
39	181.	2	**Comment:** According to the new REACH documents (R.11: PBT-Assessment) in case of biphasic transformation kinetics the relevant half-life for the persistence trigger has to be calculated by	Thanks for your comments. The text has not been updated as a reference to REACH is already included.

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			dividing an appropriately estimated DT90 by the factor 3.32. This “rule” is also proposed in the ‘Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration’ (European Commission DG-SANCO, 2006). **Proposed change:** According to REACH documents (Chapter R.11: PBT Assessment, ECHA 2014 d) for comparison to the P criteria only estimates of degradation half-life are appropriate. When the kinetics of transformation are biphasic, non-first order DT50s calculated from these studies must not be compared to these triggers. Where kinetics are biphasic, dividing an appropriately estimated DT90 by 3.32 gives a half-life estimate that can be compared to the P criteria This is relevant for simulation studies in soil, water/sediment and water.	
40	182-200	5	**Comment:** Equivalent guidance on the treatment of degradation half-lives from water-sediment simulation studies is lacking in the section on persistence in the aquatic compartment (Section 1.2.1.2, lines 182-200). Taking into account all the considerations presented above, and in particular the recommendations from the FOCUS	Thank you for your comment. The use of a geometric mean is not appropriate, as the PBT assessment is a hazard assessment and not a risk assessment. The recommendations of the FOCUS workgroup were made for risk assessments. The text has not been changed.

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			Surface Water Workgroup, the following change (addition) is proposed in Section 1.2.1.2: **Proposed change :** If degradation half-lives from two different water-sediment systems are available from the OECD 308 test, then the geometric mean of these two values should be used for PBT assessment.	
41	196	5	**Comment:** It is assumed that extrapolation to 9 °C also applies to marine sediment. **Proposed change:** …marine water and sediment	Thank you for your comment. The proposed change is accepted.
42	201-214	2	**Comment**: Subsection “1.2.2 Bioaccumulation” is fragmentary and does not address specific requirements for the PBT assessment, except for the need to normalise to 5% lipid content. **Proposed change**: Subsection needs revision. In particular, the following points should be included: - Consideration of additionally available bioaccumulation data for species other than fish or other indications for a bioaccumulation potential of a substance. - How to deal with ionisable substances? - No need for further testing if a substance is not	Thank you for your comment. The proposed changes are partly accepted. The term ‘or other aquatic species’ is added to the text. However, as it is not yet fully established how ionisable substances can be assessed, it is considered premature to address this issue in the guideline. Also, it is considered that there is no need for further testing if a substance is not P. However, in the case of VMPs, all necessary data should already be in the dossier for the ‘regular’ ERA assessment, so this remark is not necessary to make.

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			persistent and not toxic.	
43	202-203	4	**Comment**: The "Log K_{ow} is an important screening information for the PBT/vPvB assessment of substances. A log K_{ow} < 3 indicates a low potential for bioaccumulation. The EMA proposal states: *"In accordance with the VICH guidance a log K_{OW} ≥ 4 is used as a criterion for an assessment of bioaccumulation."* We strongly suggest using a *log K_{OW} ≥ 3 as a criterion for an assessment of bioaccumulation.* **Proposed change**: "*In accordance with the VICH guidance a log K OW ≥~~4~~ 3 is used as a criterion for an assessment of bioaccumulation.*"	Thank you for your comment. These values are the ones specified in the VICH GLs 6/38, and therefore modifying these is outside the scope of this guideline.
44	204	2	**Comment**: The term 'molecular mass' is not used in REACH PBT guidance documents. **Proposed change:** According to REACH documents (Chapter R.11: PBT Assessment) 'molecular mass' should be replaced by 'molecular size (average maximum	Thanks for your comments. The proposed text has not been accepted. The original text is the exact text as stated in the VICH guideline.

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			diameter and maximum molecular length), molecular weight'.	
45	207	1	**Comment:** OECD 305 is the recommended species, though this guidance gives provision for both aqueous and dietary exposure, could OECD 315 also be included for substances that are more likely to partition to sediment and as such a model with a sediment reworker would be more representative? This would also be better for an animal welfare position.	Thank you for your comment. 'Other aquatic species' has been added to the text indicating that the study does not need to be conducted necessarily on fish.
46	212	6	**Comment:** "including a correction for growth dilution". Guidance should be presented within this document on how such a correction is applied.	Thank you for your comment. A reference to the OECD 305 guideline is made, and how to conduct this correction is already specified in the most recent OECD 305 guideline (2012). Consequently, it is not considered necessary to be included in this document.
47	219	6	**Comment:** For active ingredients which are poorly soluble, the T criterion might be met purely on the grounds of low solubility (limited by setting a dose range for the study). Some further consideration needs to be given to compounds which are poorly soluble in aqueous medium.	Thank you for your comment. Toxicity study guidelines require that substance solubility is known, thus further information with regard to solubility is not considered within the scope of this guideline. The text has not been changed.

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48	220	2	**Comment**: Algae/cyanobacteria studies belong to the standard tests and should be mentioned. **Proposed change**: 'algae/cyanobacteria', acute *Daphnia* and fish studies)	Thanks for your comments. The text has been updated accordingly.
49	221-223	3	**Comment:** This is true only if the other T criteria mentioned in Annex XIII are not met. If they are met, no further chronic testing is required for confirmation of the T criterion: the substance meets the criteria for classification as carcinogenic (category 1A or 1B), germ cell mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B or 2) according to the CLP Regulation; or there is other evidence of chronic toxicity, as identified by the substance meeting the criteria for classification: STOT RE 1, or STOT RE 2 according to the CLP Regulation.	Thank you for your comment. To clarify this issue, the text has been amended as follow: "A substance fulfils the T criteria if it meets any of the toxicity criterion outlined in Table 1. A substance is considered to potentially meet the criteria for T when an acute E(L)C50 value from a standard (algae/cyanobacteria, acute Daphnia and fish studies) E(L)C50 toxicity test is less than 0.1 mg/l. If any of the acute criteria is met (screening criterion), the substance is referred to definitive T testing and chronic studies are required to confirm that the substance is indeed T (unless the E(L)C50 < 0.01 mg/l. In this case, the substance can directly be concluded to be T because the chronic value is also <0.01 mg/l). Normally, and for welfare considerations, the testing order for conclusion on T based on chronic data is algae/cyanobacteria, then *Daphnia* and then fish. If the T-criterion is fulfilled (Table 1) by the chronic algae/cyanobacteria or Daphnia data, a chronic fish

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				test is not necessary.
50	223-224	2	**Comment:** From our point of view the 'unless clause' should be explained. **Proposed change:** The substance is referred to definitive T testing and chronic studies are required to confirm that the substance s indeed T, 'unless the E(L)C50 is < 0.01 mg/l. In that case, the substance can directly be concluded to be T because the chronic value is also < 0.01 mg/L.'	Thanks for your comments. The text has been modified accordingly.
51	225	2	**Comment:** Please add 'algae/cyanobacteria' because the algae studies belong to the standard tests. **Proposed change**: T based on chronic data is '**algae/ cyanobacteria, then'** Daphnia…	Thanks for your comments. The text has been updated accordingly.
52	226-230	2	**Comment:** Please change the sentence for better understanding. **Proposed change:** 'If further aquatic toxicity studies are necessary to conclude the T criteria, and if there are indications	Thanks for your comments. The text has been updated accordingly.

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			that representative species from one taxonomic group are more sensitive than species from other taxonomic groups, this sensitive group should be chosen for chronic testing.'	
	233	2	**Comment** 'The information to CMR and chronic toxicity for mammals should be also considered for assessment of T criterion.' **Proposed change**: 'This information can also be found in MRL summary report and should be considered for assessment of T criterion."	Thank you for your comment. The text has not been amended as the CMR properties are already considered in Table 1.
53	237-243	2	**Comment:** We appreciate that VMPs containing vPvB substances are excluded from further assessment as it seems unlikely that an authorisation could be granted, given the potential significant impacts on human health and the environment. From our point of view this also applies to VMPs containing PBT substances, as they pose serious concerns for human health the environment too.	Thank you for your comment.
54	237-243	5	**Comment:** The majority of this paragraph is not considered useful. It very much discourages authorising vPvB substances but it does not ban them. vPvBs should be fully included in Part II as the risk	Thank you for your comment. The text has not been changed. Given the physicochemical properties of vPvB, significant impacts on human health and the environment are foreseen for these type of substances. Thus, an authorisation for a vPvB

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			mitigation measures mentioned could enable a positive Benefit:Risk balance also for vPvBs. **Proposed change**: In all of Part 2, include vPvB.	substance in a veterinary medicinal product where the substance will be released to the environment is unlikely to be granted for these type substances.
56	239-241	4	**Comment:** Please add phrase that clarifies the exclusion of vPvB in the decision making process of authorisation. **Proposed change:** "*Thus, given the potential significant impacts on human health and the environment it seems unlikely that an authorisation for a vPvB substance in a veterinary medicinal product where the substance will be released to the environment could be granted.* No authorisation will be granted for a ~~*for a*~~ *vPvB substance in a veterinary medicinal product* ~~*Therefore,*~~ *Part II of this guideline is based on the assessment of VMPs containing PBT substances only, with no reference to vPvBs*."	Thank you for your comment. The text has not been modified. The text already reflects the fact that it is not likely that an authorisation for a vPvB substance in a veterinary medicinal product where the substance will be released to the environment could be granted. The additional proposed sentence would just emphasise the latter with no additional clarifications.
57	243	4	**Comment:** PAN Germany recommends inserting two articles: One article that states clearly the general exclusion of vPvB/PBT- substances in VMPs and another article that gives the relevant details on the decision tree on how to grant derogations from	Thank you for your comments. The proposed changes would need to be reflected in the legal text and this is considered to be outside the scope of this guideline.

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			this general exclusion for PBTs.	
58	255-275	2	**Comment:** In general, the PBT assessment should be independent of emission scenarios and only be based on the intrinsic properties. As mentioned above, it is necessary to conduct a hazard based PBT/vPvB assessment, which focuses on intrinsic properties only. From our perspective emission assessment or risk characterisation for products containing a PBT substance are unlikely to be feasible and to reproduce due to their very high concern for the environment and their long term and cumulative adverse effects. Therefore a general exclusion of vPvB **and** PBT-substances in VMPs should be intended with the option to grant derogations under specified conditions.	Thanks you for your comment. Please refer to the comment above. Indeed, the assessment concerns intrinsic properties and as such, does not include exposure or emission. However, the benefit/risk analysis, or impact assessment, does include emission considerations.
59	267	3	**Comment:** We wonder how often extensive metabolism occurs. For many PBT-like active substances, it can be assumed that a substantial fraction could still be emitted to the environment and additional risk	Thank you for your comment. If part of the PBT substance would be released to the environment, emission would be considered as mentioned in Part II of the guideline. Consequently, the text has not been amended.

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			management measures might need to be considered. In REACH, PBT/vPvB chemicals fall under an emission minimisation obligation. We suggest to do the same for active substances.	
60	274-276	4	**Proposed change**: "*Generally, the risk characterisation for the environment considers predicted and/or actual emissions to estimate the incidence or severity of potential adverse effects likely to occur in environmental compartments.*"	Thank you for your comment. The text has been modified accordingly.
61	278-279	3	**Comment:** This will only be truly the case if there is zero emission. This is however difficult to achieve and for PBT substances, could be very difficult to establish that here is 'no exposure'. **Proposed change:** Text suggestion: We suggest to add after ' not exposed': *this is however very difficult to achieve, and hence emission minimisation is needed.*	Thank you for your comment. It is considered that the text already mentions that in order for the PBT assessment to stop, the environmental compartment should not be exposed. The paragraph already indicates that if that is not the case additional tests and information are needed, including the determination of additional risk mitigation measures. Therefore, the proposed text has not been included.
62	279-280	4	**Comment:** The proposal states "*Therefore, if the release is controlled and the environmental compartment is not exposed, the PBT assessment can stop here.*" We wonder if such "closed systems" that hinders any current and future release of contaminated substance (manure, water, dust etc.) exist. If there are such closed systems the Guideline	Thank you for your comment. The text explains that if environmental exposure cannot be controlled, then additional RMM should be considered to ensure that the substance is not released to the environment. During the ERA the applicant will be responsible to assess the extent of the environmental release of the product containing a PBT.

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			should lay down how and by whom this is controlled.	
63	286-288	3	**Comment:** Because of the difficulties of risk assessment of PBT/vPvBs, what is asked here cannot give any quantitive assessment of risk. Because the PBT/vPvB assessment focuses on a rare group of truly problematic substances, emission minimisation should be the default option in our view (see next remark)	Thank you for your comment. Please see the answer to the comment above.
64	287	2	**Comment:** An environmental impact might be given in most cases. Risk management measures for PBT containing substances are very difficult to control and cannot completely prevent the entry into the environment, where incalculable risks can occur. Therefore PBT containing substances should not be authorised unless a treatment emergency would be the consequence or release into the environment can definitely be excluded.	Thank you for your comment. Please see the answer to the comments above with regards to the RMMs.

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65	291	2	**Comment:** Risk management should minimise the release into the environment and should only be applied if the exposure to the environment will be reduced to a negligible extent by practicable and easily controlled measures.	Thank you for your comment. Please see the answer to the comments above with regards to the RMMs.
66	291-295	4	**Proposed change**: "*PBT substances pose concerns in the environment due to their intrinsic problematic properties. However, in veterinary medicine some pathogens are difficult to treat, and long-lasting, toxic compounds may be necessary to combat the disease for the animal. Therefore, competent authorities should not base their risk management decisions solely on hazard based PBT classification, but explore all available knowledge, especially on alternatives.*"	Thank you for your comment. The text 'as well as alternatives' has been included.
67	295 -297	3	**Comment:** We agree to this and would like it to be mentioned as the a priori principal approach	Thank you for your comment. The text focuses on specifying how emission can be minimised, and therefore modification to the text has not been included.
68	296-300	4	**Comment:** PAN Germany recommends that the Guidelines must make it very clear, that the applicant has first of all to justify he need for the VMP. Before a PBT substances can get an authorisation the	Thank you for your comment. The text has not been modified, because in the legislation for marketing authorisations, the applicant must always document the therapeutic benefit of the product. This benefit is

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			applicant should be obliged to prove that there are no less harmful alternative substances or alternative treatments (e.g. hygiene measures) available or any other measures (e.g. different breeding) that might prevent the need for the medicine in case. **Proposed change**: "*The purpose of risk management is to control and limit the environmental emission as much as possible for PBT substances, for example by limiting certain uses of the product, using different application methods, by setting appropriate risk mitigation measures and by communicating the hazard clearly to the end users. The Applicant must justify the benefits of the products in relation to the risks, and the control of these risks and the benefit of the non-use. The comparative risk assessment includes preventive and non-chemical measures."*	then evaluated against the risks for the animal, humans and the environment.
69	301-304	4	**Comment:** The proposal states: *"Adverse effects on the environment from PBT substances should be prevented through the application of appropriate risk mitigation measures to ensure that any risks from the uses of a substance are adequately controlled, and with a view to progressively substituting these substances with a suitable safer*	Thank you for your comment. The authorisation process (and the length of the validity of a marketing authorisation) is given in the legislation. It comprises an evaluation of the therapeutic benefits of a product against the risks for the animal, humans and the environment. This is a complex assessment and cannot be simplified to a decision tree.

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			substance, where feasible." PAN Germany states that "prevention" and the "progressive substitution of PBT substances" must begin much earlier in the decision process. (see comment to line 296-300). We propose that the different steps that lead to granting or denying authorisation (decision tree) must be clearer. We suppose to write down the exact steps of the decision tree and to add a corresponding graph to visualise them successive decisions steps. The steps are as follows: If the result of 1 (identification) and 2 (assessment) is that the substance is a PBT and that it can enter the environment, than this lead to non-authorisation. If the applicant can prove that there is a need for the substance the next step must clarify in a comparative assessment if there are alternative products or treatments. If yes, the authorisation must be denied. If not, risk mitigation measures must be set and the search for alternative products and/or treatments must be forced (mandatory substitution plans must be established). This also fosters economic and technological innovation. The approval is limited to max. 7 years	

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70	302	3	**Comment:** Because of the difficulties in the assessment, risks may not yet be identified due to the spatial and temporal dynamics of the environmental system. Therefore, also potential risks need to be mentioned. **Proposed change:** “to ensure that any potential risks from the uses”	Thank you for your comment. The text has been modified accordingly.
71	303-304	5	**Comment:** In these lines it says that substances classified as PBT should be substituted with a suitable safer substance. However, older products with the same indication may exist which never went through PBT assessment before they were registered. It would seem appropriate that the overall Benefit:Risk balance of all products should be compared before removing a product which pose less environmental risk than products lacking a PBT assessment. There may also be situations where access to a variety of active substances may be crucial to avoid resistance development and to avoid off-label (increased) dosing to compensate reduced sensitivity.	Thank you for your comment.

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72	311-313	2	**Proposed change:** 'Products containing PBT substances should not be authorised, if the release into the environment for the PBT substance cannot be minimised/ avoided by effective risk mitigation measures or if the proposed measures seem to be not feasible or difficult to control.	Thank you for your comment. Text regarding the non-authorisation of a PBT containing product is already included in Section 2.4 paragraph 2.
73	311-313	4	**Proposed change** : Please add at the end of line 313: Risk mitigation measures should include "Prevention measures".	Thank you for your comment. The proposed text has been considered but not accepted. Risk prevention is the optimal outcome of risk mitigation.
74	314-316	4	**Comment:** *"Targeted sampling / post-marketing monitoring in the environment following treatment in risk management plans could be envisaged to allow measurement of effectiveness of risk mitigation measures. However, experience with this is limited at present."* PAN Germany welcomes that post marketing monitoring is mentioned here. We state that although assessment during the authorisation process is intended to evaluate the efficacy and potential risks of veterinary medical products, knowledge of the actual environmental effects of a specific product at the time it is authorised is incomplete. It is not until the products are in	Thank you for your comment. Your proposal has been partially considered and the text modified, because we would also appreciate further knowledge on this. However, this is only a guideline and it must stay within the current legal frame.

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			actual use, which leads to their release into the environment, that knowledge about possible adverse effects (such as interactions with other substances) and processes (e.g. accumulation) becomes more comprehensive. Observing authorised products through monitoring and linking monitoring results to the authorisation process are therefore of great importance for long-term evaluation of a veterinary medical product – especially when it comes to vPvB and PBT substances. Although pharmacovigilance has been established as a system for identifying and evaluating undesirable effects of veterinary medical products, this system is (in its current design) inadequate for identifying environmental impacts. We therefore recommend to • Introduce an obligatory environmental monitoring for vPvB and PBT substances in veterinary medical products. • Publish the monitoring data in a data base that is freely accessible for further evaluation and use. • Ensure that the monitoring data is taken into account in the pharmacovigilance system • Introduce and obligatory marketing and use statistics with free access of all veterinary	

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			medical products The monitoring data should serve to verify the effectiveness of set mitigation measures and feed-back the results to the authorisation. **Proposed change**: *"Targeted sampling / post-marketing monitoring in the environment following treatment in risk management plans ~~could be envisage d~~are to be conducted to allow measurement of effectiveness of risk mitigation measures. As ~~However,~~ experience with this is limited at present the monitoring measures will contribute to a better understanding and a better availability of data."*	
75	330	6	**Comment:** Data on hazardous transformation products is not currently generated within the scope of the current VICH guidance. Suggest this phrase is removed.	Thank you for your comment. Data on transformation products is generated when conducting certain studies (e.g. OECD 307). The text has not been modified.
76	340-341	3	**Proposed change:** We suggest to add that the substance is persistent in the environment: "The octanol-water partition coefficient (Kow), the degree of persistence (P or vP) and bioconcentration factor (BCF) of the substance should be included in the SPC, if available".	Thank you for your comment. The text has been partially accepted.

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77	340-341	6	**Comment:** Data on Kow and BCF could be proprietary. This needs to be re-phrased and presented in general terms in the SPC e.g. experimental data indicate that “AI” has a high Kow and high BCF.	Thank you for your comment. Endpoint data should be made public according based on an analysis of relevant legislation, including the Treaty of Arhus, the Directive 2003/4/EC, and national legislation. As such, endpoint data are not proprietary, but the study reports are. Reference: M. Montforts and A Keessen. 2007. Public access to environmental information from the registration of (veterinary) Medicines. RIVM Report 601500006. Available online: http://www.rivm.nl/dsresource?objectid=rivmp:15626&type=org&disposition=inline
78	346	6	**Comment:** Whilst the sentiments of this section are supported, there needs to be further guidance for the Applicants presented on benefit-risk considerations. The current information is too vague and open to interpretation.	Thank you for your comment. We acknowledge the wish for more specific guidance but we also want to avoid being too prescriptive and binding.
79	347	4	**Comment**: (in the Benefit-Risk considerations) When vPvB and PBT Substances enter the environment there is reason to fear that they cause a long-lasting environmental burden. This is why we dismiss the Risk-Benefit-Assessment for vPvb/PBT substances as a decision tool: To come up with relevant results a monetary risk-benefit-assessment had not only to calculate the economic advantages of	Thank you for your comment. Please refer to the answer to comment 74. The benefit-risk balance of a VMP is not based on monetary calculation but on the therapeutic potential to combat disease.

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			the use of PBT substances but also to calculate the monetary benefit of not-using PBT substances for the protection of nature and the environment. In our view this is impossible to calculate and therefore such a risk-benefit-assessment is not feasible. (see general statement above)	
80	348-349	2	**Comment:** Please note that in Phase II (Tier B) complete data set is required by the VICH-GL to evaluate the definitive criteria P, B and T, not only for screening.	Thank you for your comment. The sentence has been deleted.
81	350-354	4	**Comment:** "*For a product containing a PBT substance, an authorisation should only be granted if (…) and if there are no suitable alternative substances or technologies*." We recommend to specify "alternative technologies" by adding a list with examples of such technologies.	Thank you for your comment. The text has not been modified as the term technology is broad and can be understood as any application of scientific knowledge or any devices that can be used for the treatment of a veterinary condition.
82	350-362	4	**Comment:** see comment referring to line 347. **Proposed change :** Please add after line 362: (e) the benefit of non-use for current and future generations/society including the value of a protected biodiversity, the reduction of analyse and purification costs for water suppliers, the reduction of monitoring costs, the reduction of	Thank you for your comment. Please see comments above (C. 79 and 68)

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			heath costs for todays and future generation and the reduction of costs that arise from the risks of multi resistant germs and of measures against the outspread of such multi resistant germs.	
83	355 ff.	2	**Comment:** In our opinion, a detailed guidance to perform benefit-risk considerations taking into account the PBT properties of a substance is missing. The prescribed procedure delegates the main part of the benefit-risk considerations to the applicant or other interested parties. Thus, the applicants obtain a wide influence on the outcome of the benefit-risk analyses. This should be critically kept in mind.	Thank you for your comment. We acknowledge that further information might be necessary for applicants and they may wish to seek scientific advice to clarify the options. The final assessment and decision is always done by the competent authorities.
84	363 ff.	2	**Comment:** The proposed conditions for marketing authorisations such as specific pharmacovigilance requirements, targeted sampling or post marketing monitoring need to be specified (e.g. who is responsible for the implementation?, who control and evaluate the measures?).	Thank you for your comment. We acknowledge that the future implementation of conditions will depend on developments, including the new legal proposal for veterinary medicines.