European Medicines Agency
Veterinary Medicines and Inspections

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**OVERVIEW OF COMMENTS RECEIVED ON
GUIDELINE ON ENVIRONMENTAL IMPACT ASSESSMENT FOR VETERINARY MEDICINAL
PRODUCTS IN SUPPORT OF VICH GUIDELINES GL6 AND GL 38 – DOC. REF.
EMEA/CVMP/ERA/418282/2005-REV.1 POST PUBLICATION**

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	IFAH-Europe	Belgium
2	Association of Veterinary Consultants (AVC)	United Kingdom

Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW
IFAH-Europe would like to express appreciation for the opportunity to review and submit comments to the *"Revised Guideline on Environmental Impact Assessment for Veterinary Medicinal Products in Support of the VICH Guidelines GL6 and GL38"*. IFAH-Europe is very pleased with the incorporation of the points discussed and agreed during the Focus Group meeting in January 2008, but also found that a few changes that were not discussed are not merely "of editorial nature", as stated in the cover page of the referred document.

SPECIFIC COMMENTS ON TEXT

SECTION 4: STRUCTURE OF THE ENVIRONMENTAL RISK ASSESSMENT OF VETERINARY MEDICINAL PRODUCTS

Paragraph no.	Comment and Rationale	Outcome
4.1 Data requirements; Page 7; Paragraph 1	<u>IFAH-Europe</u>: *"Relevant data obtained from the open literature should always be included in the documentation."* Standards on data quality have been defined during the Focus Group meeting held on 23 January 2008 (see respective summary EMEA/CVMP/ERA/106566/2008). These standards (acceptance of well performed studies following GLP, even if not following OECD protocols; acceptance of literature data from peer reviewed journals; non-acceptance of summaries of assessments) should apply generally for documents being used for the assessment of the environmental impact. IFAH-Europe suggests adding the following to the sentence: *Relevant data obtained from the open literature should always be included in the documentation if originating from peer reviewed journals and representing valid endpoints.*	The paragraph has been amended by inclusion of a reference to guidance, currently available in the draft reflection paper on the implementation of Directive 2001/82/EC, as amended, in respect to the assessment of environmental risks of veterinary medicinal products (EMEA/CVMP/182112/2006) to be published in the Notice to Applicants, once finalised.
Page 13; Question 17	<u>IFAH-Europe</u>: *"<u>Dairy cattle teat dips or sprays</u> Dairy cattle are usually… spread onto land. The PEC_{soil} resulting from spreading dirty water should be calculated using the following equation:"* The term "PEC_{soil}" should be corrected to "$PEC_{soil\ initial}$". *"<u>Dairy cattle teat dips or sprays</u> Dairy cattle are usually… spread onto land. The $PEC_{soil\ initial}$ resulting*	Agreed. PEC_{soil} will be replaced by $PEC_{soil-initial}$.

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	from spreading dirty water should be calculated using the following equation:"	
Page 14; Question 17	IFAH-Europe: *"In the CVMP guideline on fixed combination products (EMEA/CVMP/83804/2005)… Phase II assessment is not necessary if the applicant can provide a scientific justification as to why the summing of the individual PECsoil values is not appropriate for the particular combination under consideration. If an acceptable justification is provided no further assessment in Phase II is necessary."* Although being placed under the header *"Dairy cattle teat dips or sprays"*, this paragraph addresses specific requirements for fixed combination products. Please add header "*Fixed combination products*" before this paragraph.	Agreed. Heading added.
	Following the discussions at the Focus Group Meeting, examples should be provided when the summing of individual PEC_{soil} values in Phase I is not appropriate for the particular combination. IFAH-Europe suggests including the following examples: • *Different chemical classes and indications (e.g. combination of an antibiotic with an NSAID);* • *Different excretion pattern (e.g. one compound excreted via urine, the second via dung or excretion at different time points;* • *Different fate and behaviour during manure storage;* • *Different fate and behaviour in the environment (e.g. different adsorption/desorption to soil following results of QSAR modelling).*	The text has been amended to provide an example regarding the first bullet point given by IFAH Europe. The three other examples suggested by IFAH Europe were not considered to be valid.
Page 15; Paragraph 2	IFAH-Europe: *"At this point it is important to make use of all available documentation relevant…"* Following the discussions at the Focus Group Meeting (see respective summary EMEA/CVMP/ERA/106566/2008), the use of available data should include literature data from peer reviewed journals, especially when representing valid endpoints.	The paragraph has been amended by inclusion of a reference to guidance, currently available in the draft reflection paper on the implementation of Directive 2001/82/EC, as amended, in respect to the assessment of environmental risks of veterinary medicinal products (EMEA/CVMP/182112/2006) to be published in the Notice to Applicants, once finalised.

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	IFAH-Europe would appreciate the following addition: *"At this point, it is important to make use of all available documentation relevant... Apart from the European Community Directives, studies performed to satisfy the requirements of environmental risk assessment posed by other authorities, and literature data from peer reviewed journals, especially when representing valid endpoints may be used. Specifically, the guidelines and test protocols issued by the European Commission [13] and OECD [14] for testing..."*	
Page 16; 2nd bullet point	IFAH-Europe: Although Switzerland does not represent an EU country, it is listed here. Please delete *Switzerland*: *"Ploughing depth: In some countries manures... In other countries, e.g. Greece, Ireland, ~~Switzerland~~ and UK, it is common practice to distribute..."*	Agreed. The reference to Switzerland has been deleted.
2.4 Risk Quotient Approach; Page 16; Paragraph 3	IFAH-Europe: Following the discussions at the Focus Group Meeting, examples on justification for not carrying further assessment should be presented. IFAH-Europe would appreciate adding the following: *"The first instance is that of fixed combination products... Unless it can be justified as to why it is not relevant <u>(e.g. based on different mode of action, excretion pattern or fate/behaviour in environment or while manure storage)</u> it may be necessary to carry out further assessment of the risk presented by the combination of actives."*	No change has been made to this section but an example is now given in relation to question 17 (see above).
3.1.3.2 Tier A Terrestrial Effect Studies; Page 20; *Effects on dung organisms*	IFAH-Europe: The newly introduced text refers to the DOTTS homepage for drafts of the guidelines. However, the drafts are not available there. Include correct reference (to OECD website).	Agreed. The DOTTS website will be replaced by the OECD website.

SECTION 4: STRUCTURE OF THE ENVIRONMENTAL RISK ASSESSMENT OF VETERINARY MEDICINAL PRODUCTS		
Paragraph no.	**Comment and Rationale**	**Outcome**
Normalisation	It is still not understood how the use of "normalised" soil data would help in an assessment. There are no precise details on how to do the calculation for normalisation and neither a definition of a "standard soil". The defined soil values of 3.4% organic matter content or 2.0% organic carbon content are arbitrary. It is accepted that various soil types, which are required for OECD Koc and biodegradation studies will have different values for the various soil characteristics. There is no reason to believe that the soil carbon or organic matter content standardization would have any value greater than that of e.g., standardised soils based on pH, % clay, or moisture content. It should also be noted that test soils could be defined by both organic matter and organic content. By introducing "normalisation" for both parameters, a lot of confusion is created, as that could yield two different values for the derived NOEC or $L(E)C_{50}$.

Applying this standard normalisation would also increase disharmony between the EU and the rest of the world, yielding different endpoints and consequently different assessments. The VICH GL38 refers to the OECD test guidelines as the basis for testing. In OECD test guidelines a range for soil parameters are defined (the same will be true for dung if respective guidelines are available in future), and the compliance with those results in a valid test result. The approach of "Normalisation" therefore not only contradicts with the OECD test guidelines, but also with VICH GL38. Additionally, a soil with an organic carbon content of 2% being defined as a "standard soil" is considered unacceptable for the conduct of terrestrial plant effect study following OECD 208 (acceptable range for organic carbon is 0.5-1.5%).

The European Commission Technical Guidance Document on Risk Assessment (EU TGD, Part II), p 116 section 3.6.2 does briefly mention the option of normalisation for non-ionic compounds, and based on organic matter only (and the new text in the guideline is clearly based on that). Furthermore, it only applies when it can be assumed that the binding behaviour of the non-ionic organic substance is predominantly driven by its $LogK_{ow}$ and that soil organisms are exposed predominantly | This paragraph will be deleted. However, the ERAWP/CVMP considers that further discussion with industry would be useful to develop guidance on this issue. |

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	via pore water. The text in the guideline does not take all this into account and thus imposes normalisation in many instances where this would not be required at all for chemicals, biocides or pesticides. It should be noted that e.g. many veterinary pharmaceuticals are ionised, which can largely influence their binding behaviour (to name only one example). Hence, from a scientific point of view, the whole issue of normalisation as introduced in the text is hard to justify. IFAH-Europe would appreciate complete deletion of this paragraph.	
3.1.4.1 PEC refinement Page 24; Table 6	<u>AVC:</u> We suggest including data for rabbit in Table 6 to provide additional information already present in Table 3. See our proposal in Table 6 below. **Table 6. Default values for use in calculating the PEC$_{soil\ refined}$ following degradation in manure.**	Rabbit data have been included.

Table 6 (within comment cell):

Animal	Number of	Body-	Nitrogen	Storage
Calf	1.8	140	2.5	91
Dairy cow	1	425	15	91
Cattle (0-1	1	200	4.3	91
Cattle (>2	1	450	8.8	91
Weaner pig	6.9	12.5	0.33	53
Fattening	3	65	1.9	91
Sow (with	1	240	6.5	91

Paragraph no.	Comment and Rationale	Outcome
	<table><tr><td>Broiler</td><td>9</td><td>1</td><td>0.03</td><td>41</td></tr><tr><td>Laying hen</td><td>1</td><td>1.6</td><td>0.09</td><td>91</td></tr><tr><td>Replacement layer</td><td>2.6</td><td>0.8</td><td>0.06</td><td>91</td></tr><tr><td>Broiler breeder</td><td>1</td><td>1.7</td><td>0.17</td><td>91</td></tr><tr><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Turkey</td><td>2.7</td><td>6.5</td><td>0.23</td><td>91</td></tr><tr><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Duck</td><td>7</td><td>1.6</td><td>0.06</td><td>52</td></tr><tr><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Horse</td><td>1</td><td>400</td><td>8.8</td><td>91</td></tr><tr><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Rabbit</td><td>8</td><td>1.4</td><td>0.044</td><td>46</td></tr></table> * When the number of cycles is 4 or less, the storage time is set equal to 3 months based on data from reference 11.	
3.1.4.1 PEC refinement Page 24; Table 6	IFAH-Europe: There is no data for rabbits. Data for rabbits should be included.	Rabbit data have been included.
3.2 Criteria for Tier B testing; Page 25; Equations 15-18	IFAH-Europe: The EU TGD (Technical Guidance Document on Risk Assessment in support of the Commission Directive 93/67/EEC on risk assessment for new notified substances), the Commission Regulation (EC) 1488/94 on risk assessment for existing substances, and Directive 98/8/EC of the European Parliament and of the Council on the placing on the market of biocidal products do not foresee the conversion from wet weight to dry weight. Consequently Equation 17 should be deleted and Equation 15 corrected as follows: $$PNEC_{sediment} = \frac{K_{sed\_water}}{RHO_{sed}} \times PNEC_{surface\ water} \times 1000$$	The ERAWP/CVMP sees no reason to change the equations as the final result will be the same. Furthermore, this issue was not discussed at the focus group meeting (see summary of the meeting at EMEA/CVMP/ERA/106566/2008) and consequently no change will be made.

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	If the conversion from wet weight to dry weight will remain a requirement, Equation 17 should be deleted and the legend to the calculations be adopted as follows: $CONV_{sed}$ = Conversion factor for sediment concentrations ww to dwt [2.6 $kg_{wwt}.kg_{dwt}^{-1}$] In this case, it should be explained under which conditions the $PEC_{sediment}$ has to be expressed as wet weight, leading to the omission of $CONV_{sed}$ (first paragraph, page 26). Please correct Equation 15 and delete Equation 17 respectively as follows: $$PNEC_{sediment} = \frac{K_{sed\_water}}{RHO_{sed}} \times PNEC_{surface\ water} \times 1000 \times \cancel{CONV_{sed}}$$ $$\cancel{CONV_{sed} = \frac{RHO_{sed}}{Fsolid_{sed} \times RHO_{sed}}}$$ Please correct the legend as follows: $CONV_{sed}$ = Conversion factor for sediment concentrations ww to dwt [2.6 $kg_{wwt}.kg_{dwt}^{-1}$]	
3.2 Criteria for Tier B testing; Page 26; Paragraph 3	<u>IFAH-Europe</u>: *"The organic carbon content… For the risk characterization it is recommended to normalise the PNEC to the organic carbon content used in the calculation of the PEC in sediment."* The 'normalisation' approach is not acceptable (please see comments above). Additionally, in order to be in line with OECD guideline 218, the organic carbon content used in calculation of $PEC_{sediment}$, which is 5%, should be reduced to 2%. Delete paragraph.	If bioavailability of a compound is related to sorption to organic matter it is logical to normalise the PNEC accordingly. However, the relevant sentence (i.e. the last sentence of the paragraph) will be deleted as this was not discussed at the focus group meeting in January. The rest of the paragraph simply states facts and was carried over from the approved version of the guideline and so will not be deleted.

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5.2.3 Calculation and comparison of PEC $_{water}$; Step 1; Page 38; Equation 35	AVC: Calculation of PEC $_{surfacewater}$ As a first estimate of PEC $_{surfacewater}$, it can be assumed that one part run-off water will be diluted by two parts receiving water. Hence, to determine the concentration in surfacewater (PEC $_{surfacewater}$) the concentration in porewater (PEC $_{porewater}$) has to be divided by 3. $$PEC_{surfacewater} = \frac{\left(\dfrac{PEC_{soil\ initial} \times RHO_{soil}}{K_{soil-water} \times 1000}\right)}{3}$$ where: PEC $_{surfacewaterr}$ = Predicted Environmental Concentration in surfacewater [µg.l^{-1}] PEC $_{soil\ initial}$ = PEC $_{soil\ initial}$ is the PEC $_{soil}$ calculated based on a mixing depth of 5 cm [µg.kg^{-1}] In the first version of the Guideline, PECsurfacewater was considered as equal to PECporewater/**10** with reference to PEC $_{soil}$ calculated based on a mixing depth of **20 cm**. In the revised version (-corr, 2007), PECsurfacewater was considered as equal to PECporewater/**3** with reference to PEC $_{soil}$ calculated based on a mixing depth of **20** cm. The PECsurfacewater values were therefore 3.33 times lower than with the initial version. In this new revised version (2008), PECsurfacewater is now considered as equal to PECgroundwater/**3** with reference to PEC $_{soil}$ calculated based on a mixing depth of **5** cm. As a consequence, PECsurfacewater (the parameter used as a basis for Risk Quotients) is about 1/10th the values calculated in the initial version and 1/4th the values determined using the algorithm proposed in the version dated Sept. 2007. Some substances initially considered as safe may now be considered as	It is acknowledged that this was not discussed at the focus group meeting and consequently the text in the guidance EMEA/CVMP/ERA/418282/2005-corr (4 September 2007) has been retained. However the ERAWP/CVMP would like to state that the proposed screening method to calculate PEC surface water from the concentration in (interstitial) pore water should not be seen as a change in methodology but as a further clarification of the parameters to be used to avoid misinterpretation. It is recognised that based on the former text the pore water concentration could be based on 20 cm instead of the 5 cm used to calculate the initial concentration in soil. The proposed method for calculating PEC $_{surfacewater}$ was taken from the Note for Guidance where it is assumed that interstitial porewater containing veterinary medicinal products (VMP) not adsorbed to soil could run off due to rain and be diluted by a factor of 3 in receiving surface water. Here, as well, the concentration in interstitial porewater is calculated from the PEC $_{soil\ initial}$ that is used for the risk assessment. Therefore it seems logical to base the concentration of VMP in interstitial porewater susceptible to run off from soil on the depth in which the VMP is mixed. For grassland the mixing zone is assumed to be not more than 5 cm. The use of 5 cm in the screening method could be further justified by the fact that for more sorptive compounds the concentrations in surface water predicted by FOCUS are higher than the screening method when 20 cm is used instead of 5 cm. The CVMP considers that this is an issue for further discussion.

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	presenting a risk for the aquatic environment when used in intensively reared animals. A scientific rationale for using the new equation proposed in the revised version of the Guideline should be provided as it is not clear why a additional safety factor of approximately 10 has been added for the calculation of PEC$_{surfacewater}$ since the initial version. This additional safety factor may be a limiting factor for several widely used veterinary medicinal products, thus limiting further the availability of medicines, unless this limitation is based on an unequivocal scientific rationale which is not described in the proposed revised version.	
5.2.3 Calculation and comparison of the PEC water; Page 38; Equation 35	IFAH-Europe: The reason for the change from a 20 cm soil depth to a 5 cm soil depth is not clear. In the draft EMEA/CVMP/ERA/418282/2005, a 20 cm soil depth and a factor 10 was proposed. In the May version of this guideline, the factor 10 was replaced by a factor of 3. One year later, the soil depth is changed? This sequence of (largely unexplained) changes in a very short time frame does raise questions regarding credibility. All it does is prompt applicants to the use of the FOCUS models even sooner, which in a majority of cases produce lower PECs compared even with the current screening calculation (20 cm depth). Delete change from 20 cm to 5 cm: *PECsoil initial = PECsoil initial is the PECsoil calculated based on a mixing depth of 5̶20 cm [⌈g.kg-1]*	See response to AVC comment above
5.2.3 Calculation and comparison of the PEC water; Page 38; Last paragraph	IFAH-Europe: *"Concentrations in sediment can be determined by the concentrations in water and the sediment-water partitioning coefficient, using the following equations:"* The header *"Calculation of the PECsediment"* is missing before the paragraph. Please add the header "*Calculation of the PECsediment*" before the paragraph.	Agreed. The header will be added.
5.2.3 Calculation and	IFAH-Europe: PEC$_{surfacewater}$ used in the equation is actually the initial introduction concentration in surface water. If a Kd value is large, the	No change made. See comments above with regards to equation 15.

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comparison of the PEC water; Page 39; Equation 36	concentration in the surface water would be significantly reduced after partitioning into the sediment. The PEC$_{sediment}$ should be calculated using the significantly reduced concentration when the partition equilibrium between water and sediment is reached, not the initial introduction concentration. Otherwise, it would be a significant overestimation on the concentration for the sediment. The EU TGD does not foresee the conversion from wet weight to dry weight. Consequently Equation 36 should be deleted and Equation 15 corrected as follows: $$PEC_{sediment} = \frac{K_{sed\_water}}{RHO_{sed}} \times PEC_{surface\,water} \times 1000$$ If the conversion from wet weight to dry weight will remain a requirement, the legend to the calculations should be adopted as follows: $CONV_{sed} = $ *Conversion factor for sediment concentrations ww to dwt* $[2.6\ kg_{wwt}.kg_{dwt}^{-1}]$ In this case, it should be explained under which conditions the PEC$_{sediment}$ has to be expressed as wet weight, leading to the omission of CONV$_{sed}$. Please delete Equation 36 and change Equation 15 as suggested above.	
6.2.4.2.1 Direct excretion of active substances into surface waters by pasture animals	IFAH-Europe: This chapter includes advice on how to refine PEC$_{surfacewater}$ (starting at page 47, including Equations 44-47). Together with the refinement advice provided in chapter 6.2.4.2.3. (Equation 49), this information should be provided in a separate chapter, e.g. entitled "Refinement of PEC$_{surfacewater}$". Create a separate chapter entitled "Refinement of PEC$_{surfacewater}$".	No change made. The layout of the guideline tries to conform to the layout of the VICH guideline.
Last sentence of same section; Page 48	*"If the toxicity data is expressed on a sediment dry weight base the PECsediment has to be converted accordingly, using Equation 17."* If Equation 17 is to be deleted, this sentence should be adapted accordingly.	No change made. See previous comments relating to equation 17.

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Paragraph no.	Comment and Rationale	Outcome
	IFAH-Europe suggests the following change: *If the toxicity data is expressed on sediment dry weight base the PECsediment has to be converted accordingly, ~~using Equation 17 (multiplication by default factor 2.6)~~.*	

APPENDIX I: APPLICATION OF FOCUS MODELS

Paragraph no.	Comment and Rationale	Outcome
Groundwater	<u>IFAH-Europe</u>: The PEARL input parameters should be included to be in line with descriptions in Chapter 5.2.3. The value used for Depth (m), under *Absolute applications* is given as, *"soil depth used to calculate PECsoil"*. This phrase has been changed from the earlier version: *Depth (m): → default 20 cm (realistic worst case)*. In other words, the depth could be something less than the 20 cm value used in the earlier version, which would always result in a higher $PEC_{surfacewater}$. Please insert the following: <u>1. Scenario:</u> *Location: → pick one <u>(Okehampton as worst case)</u>*	The words "pick one" will be replaced by "Okehampton".
	<u>5. Substance:</u> *Freundlich sorption* K_{OM}: *→ enter value ($K_{OM} = K_{OC}$ / 1.724; <u>use average K_{OC}</u>)* *Transformation* *Half-life (d): → enter value (<u>use average DT_{50}</u>)*	No change made. However, it should be emphasized that if the recommendation in OECD 106 to investigate 5 different soils is followed, the average K_{oc} of the 5 soil types is used in the risk assessment (refer to section on running FOCUS on p44 of the TGD).
	<u>6. Application</u>	No change made as this was not discussed at the focus group meeting.

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	~~*Application rate*~~ <u>*Dosage*</u> *[kg.ha^{-1}] =* $$\frac{PEC_{soil}\,[\mu g.kg^{-1}]\times depth_{soil}\,[m]\times bulk\ density\,[kg.m^{-3}]}{100000}$$ *(Equation 50)* *Absolute applications* *Date:* → *enter date of application (pre-emergence)* <u>*(03 October)*</u> *Depth (m):* → ~~soil depth used to calculate PECsoil~~ <u>*default 20 cm*</u>	No change made as this was not discussed at the focus group meeting. No change made. In the view of the ERAWP/CVMP the soil depth used should be equal to that used to calculate PEC$_{soil-initial}$
Surface water	<u>IFAH-Europe</u>: The PEARL input parameters should be included to be in line with descriptions in Chapter 5.2.3. Please insert the following: *Sorption* *Enter either K_{OM} or K_{OC} (use average value), the other value will be calculated internally.*	No change made here as this is addressed elsewhere