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Committee for Veterinary Medicinal Products (CVMP)

Questions and answers

Implementation of CVMP Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH Guidelines GL6 (Phase I) and GL38 (Phase II)[1,2]

Phase I (VICH GL 6)

Question 4 of VICH GL6: "Is the veterinary medicinal product (VMP) intended for use in a minor species that is reared and treated similarly to a major species for which an environmental impact assessment (EIA) already exists?"

1. Q Are horses minor species?

A Horses are considered minor species.

2. Q For minor uses/minor species (MUMS), when is an ERA (environmental risk assessment) required and is the ERA always limited to Phase I?

A An ERA for minor species is not required in the case where an ERA is available for a major species, provided that: 1) the minor species is reared under similar conditions as the major species and the primary environmental release of the VMP used for minor and major species is to the same environmental compartment, e.g. soil or water; 2) the exposure to the same environmental compartment from the use of the VMP in the minor species is not higher than from the use in the major species; 3) any risks identified in the major species are also considered in the environmental risk assessment for the minor species; 4) the ERA of the major species belongs to the same applicant.

Question 17 of VICH GL 6: "Is the predicted environmental concentration of the VMP in soil (PEC_{soil}) less than 100 µg/kg?"

1. Q If PEC_{soil} for only one age group of the animals exceeds 100 µg/kg but the others did not, can the manures from different age group of animals be mixed to get the PEC_{soil} value to be less than 100 µg/kg?

[1] This document provides clarification on the mentioned VICH guideline and was prepared following a Focus Group meeting held at the EMEA on 23 January 2008. This document will be regularly updated to provide answers to questions related to the guideline.

[2] Document EMEA/CVMP/ERA/418282/2005-Corr; often called the "Technical Guidance Document" (TGD)

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A Manure from different species or different age groups should not be mixed for the calculations of PEC_{soil} values. If the value of 100 µg/kg in one of the species or age groups is exceeded then the assessment has to proceed to Phase II.

2. Q Are deviations from default values in the Technical Guidance Document (TGD) allowed?

A Deviations from using default values in the TGD can be used if it can be shown that the deviation is based on the actual pattern of use of the product, which is outlined in the SPC. However, there is a strong preference for the standardised approach.

Phase II (VICH GL 38)

1. Q Can studies not according to the OECD guidelines and publicly available data be used for Environmental Risk Assessment (ERA)?

A As indicated in the document 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-CONSULTATION): *"The guidance provided in the Notice to Applicants (NTA) [2] regarding published data applies[3]. Expert judgment will be required to decide on the reliability of the data..... Published data provided must be of a standard to enable an assessment of the risks to the environment which is equivalent to that enabled by specifically generated studies in accordance with agreed guidelines, i.e. they can only be used to substitute studies, if the publication contains a sufficient amount of data and sufficient details on the design and conduct of the study to allow a full and independent assessment."*

2. Q Which Koc value should be used in assessing leaching to groundwater and run off to surface water the mean, minimum or maximum?

A In situations where the adsorption to soil is predominantly influenced by organic carbon the geomean value of the available Koc values can be used, provided that at least five Koc values are available otherwise the lowest value should be used.

In those cases where soil conditions other than organic carbon content will influence adsorption (e.g. the effect of pH on the adsorption of ionisable substances or where adsorption is correlated to clay content), the lowest Koc value should be used in step 1 calculations of the PEC for groundwater and surface water (see section 5.2.3 of the TGD). If, based on the outcome of step 1, a further refinement in step 2 is necessary, the most appropriate adsorption coefficient for the leaching (ground water) and/or run-off and drainage (surface water) scenario(s) selected for step 2 calculations should be used.

3. Q Combination products: do PECs always have to be added?

A PECs have to be added in any case. This also applies to substances with different modes of action because it is not possible to extrapolate from the pharmacological action in the target animal to effects on environmental organisms.

[3] According to the NTA Vol. 6A, Chapter 1, section 5.4, Documentation "published literature implies that the text must be freely available in the public domain and published by a reputable source preferably peer-reviewed. The published information should be presented in sufficient detail so that the quality of the results can be established.

4. Q Is there a need to perform an OECD GL222 study (sub-acute toxicity) in earthworms rather than OECD GL207 (acute toxicity)?

A A sub-acute study is required. However, when low toxicity is anticipated a "limit test" of the OECD 222 could be done, i.e. conducting a reproduction study with a control and one (high) exposure concentration, typically 1000 mg/kg. To increase the validity of the "NOEC value" derived in such a limit test, it is recommended using six replicates in both exposure groups instead of the normal four replicates.

5. Q Which soil depth should be used when calculating the $PEC_{groundwater}$ and $PEC_{surfacewater}$?

A When calculating $PEC_{groundwater}$ the PEC_{soil} based on a 20-cm depth penetration into soil is used. This is based on the fact that when VMPs are ploughed into soil they might reach groundwater faster and is therefore considered a realistic worst case.

6. Q Why is FOCUS the recommended model for determination of PEC values for groundwater and surface water?

A The TGD recommends FOCUS in favour of VetCalc because the FOCUS models have been the subject of much investment and testing and are recognised by regulatory authorities. FOCUS models are being continually re-evaluated and updated. The maintenance and update of VetCalc was not part of the original project remit and any updates are unlikely. VetCalc is mentioned in the TGD guideline, but FOCUS is the preferred option. Results generated using VetCalc may be accepted but it should be recognised that the results may be different compared with FOCUS. As the FOCUS models are continually updated, the most recent version of the model should be used (http://focus.jrc.ec.europa.eu/).

7. Q Can manure degradation be incorporated into FOCUS?

A Manure degradation cannot be incorporated into FOCUS, but refinements can be done manually.

8. Q How do you select the most suitable scenarios to run in the FOCUS models?

A FOCUS is likely to produce different results in different scenarios. In the TGD a proposal is given on which scenarios can be used in a centralised and de-centralised procedure. However, the most appropriate scenarios would have to be determined on a case by case basis.

9. Q How are the results of the nitrogen transformation study (OECD 216) to be interpreted in relation to the footnote given in VICH guideline GL38 under Table 4?

"An assessment factor is not relevant to this end point – when the difference in rates of nitrate formation between the lower treatment (i.e. the maximum PEC) and control is equal to or less than 25% at any sampling time before day 28, the VMP can be evaluated as having no long term influence on nitrogen transformation in soils. If this is not the case, the study should be extended to 100 days at Tier B (see Table 8)."

and to the footnote under Table 8?

"An assessment factor is not relevant to this end point - when the difference in rates of nitrate formation between the lower treatment (i.e., the maximum PEC) and control is equal to or less than 25% at any sampling time before day 100, the VMP can be evaluated as having no long term influence on nitrogen transformation in soils."

A The results of the nitrogen transformation study should be interpreted as follows: If on day 28 of the study the nitrate production rate of the maximum (1X) PEC soil treatment is within ± 25% of the control rate then the study can stop and it can be concluded that the VMP has no long term influence on nitrogen transformation in soils. Deviations between control and maximum (1X) PEC nitrate production rates of >25% at earlier time points is not considered to be critical. If on day 28 the nitrate production rate of the maximum (1X) PEC soil treatment deviates from the control rate by more than 25% then the study should be continued up to a maximum duration of 100 days. If at 100 days (or an earlier time point if sampled) the nitrate production rate of the maximum (1X) PEC soil treatment is within ± 25% of the control rate then the study can stop and it can be concluded that the VMP has no long term influence on nitrogen transformation in soils. If on day 100 the nitrate production rate of the maximum (1X) PEC soil treatment deviates from the control rate by more than 25% then it has to be concluded that the VMP has an adverse effect on nitrogen transformation in soils.

10. Q In the EU a test with "blue-green algae" is required when the active substance is an antimicrobial compound. How should the results of this test be used in the assessment of the risk to algae?

A Firstly it should be noted that the use of the term "blue-green algae" in CVMP and VICH guidelines is referring to the taxonomic group of cyanobacteria (prokaryotes) which are not related to algae (eukaryotes). The implication that cyanobacteria are somehow related to algae is not correct. However, a growth inhibition study on cyanobacteria is required because these organisms are usually more sensitive than algae to compounds with antimicrobial activity. The results of the study are used to assess the risk to microbial populations in fresh water systems and as such are part of the assessment of risk to the lower trophic level of the aquatic compartment. If the RQ value for cyanobacteria is ≥1 this indicates a risk for the aquatic compartment as a whole and not to any particular aquatic species.

11. Q Calculation of the PECsoil requires as input the daily dose of the active substance in mg/kg. In some products the active substance is present in salt form or associated with molecules of water. Should the dose used in the calculation of the PEC_{soil} in Phase I of the ERA be expressed in terms of the base form of the active substance or should the dose be expressed in terms of the active substance plus any salt or water associated with the base?

A The daily dose used in the calculation of the PEC_{soil} in Phase I of the ERA should be expressed as the quantity of the active substance administered to the animal (mg/kg) without any associated counter ions and/or water molecules, i.e. in terms of the base form of the active substance. The calculation of the PEC_{soil} in terms of the base form of the active substance also means that the doses tested in the toxicity tests in Phase II Tier A should be expressed in terms of the base form of the active substance.

12. Q The OECD guideline (OECD 307) on soil biodegradation recommends that four different soils should be tested in the study. In the past, studies have been accepted where only three soils have been tested. How many soils should be tested in the study of biodegradation in soil?

A The VICH guidelines require that OECD guidelines are followed. Therefore, new studies to investigate soil biodegradation should be carried out using four different soils. In a study where four soils have been used then it is acceptable to use the geometric mean DT50 value in the risk assessment.

13. Q The algal growth inhibition test (OECD 201) produces EC_{50} values for both algal growth rate and yield (biomass). The VICH guidelines indicate that the EC_{50} for inhibition of growth rate should be used in the risk assessment. If the EC_{50} for yield (biomass) is lower than the EC_{50} for growth should the EC_{50} for growth still be used in the risk assessment?

A In the risk assessment the EC_{50} determined for effects on algal growth rate should be used.

14. Q If beside toxicity data on fresh water organisms, also data on marine species are available should these be used in the environmental risk assessment for the fresh water compartment?

A To derive a PNEC for algae/plant, invertebrates and fish for fresh water, toxicity datasets of marine and freshwater species are normally combined. As indicated in the technical guidance for deriving environmental quality standards (2011), the current marine risk assessment practice s suggests a reasonable correlation between ecotoxicological responses of freshwater and saltwater biota (i.e. the same datasets can be used interchangeably for freshwater and saltwater effects assessment). Where this is not justified based on the available evidence (i.e. there is a clear difference in the sensitivity of the freshwater and saltwater biota), PNECs must be derived on the basis of distinct datasets for freshwater and marine organisms. This can be done by statistical analysis. If the data are too limited to allow such analysis, a precaution approach should be followed and all data should be combined.

15. Q What assessment factors should be applied when data is available from a targeted ecological risk assessment that has been triggered by the provision in VICH/CVMP Guidelines GL6 (Phase I), stating: *"Some VMPs that might otherwise stop in Phase I may require additional environmental information to address particular concerns associated with their activity and use. These situations are expected to be the exception rather than the rule and some evidence in support of the concern should be available"*.

A In cases where there is scientific reason for requiring a risk assessment of substances with a PEC below the trigger value, it is acceptable to use an assessment factor of 10 with an EC10/NOEC endpoint if it reflects the specific mode of action in a chronic test, e.g. endocrine disrupting substances.

16. Q When is the EC_{10} from chronic ecotoxicity data recommended to be used to derive PNEC values?

A It is recommended to use EC_{10} values over NOEC values when deriving PNEC values. Scientific evidence supports that EC_{10} values give a more robust estimate than NOEC values when used in the risk assessment. This is reflected in the recommendation of OECD in several of their guidelines relevant for VMP. It is therefore highly recommended to design the ecotoxicity study in line with OECD recommendations, with test concentrations aiming to optimise EC_{10} estimations, e.g. a reliable dose-response relationship needs to be generated and the tested concentrations ideally should bracket the EC_{10}[4] .

17. Q In which cases can a PEC time-weighted average (PEC_{twa}) be used?

A According to the CVMP TGD, calculating the PEC_{twa} is a potential Phase II refinement option following the Tier B chronic risk assessment of VMPs for surface water. The PEC_{twa} for surface water calculated with the FOCUS models can be compared to the PNEC derived at the chronic exposure time (time to onset of effects; TOE) causing the effects in the most sensitive species tested, if the following conditions are met:

[4] European Chemicals Agency (ECHA). 2008. Guidance on information requirements and chemical safety assessment Chapter R . 10 : Characterisation of dose [concentration] -response for environment May 2008.)

- The concentrations in the relevant eco-toxicological effect test are kept constant to ensure that an equilibrium (steady state) has been reached.
- The determination of the time to onset of effects (TOE) is possible within the test setup. This TOE determines the chosen time window over which concentrations are averaged. The effect threshold for TOE is the lowest observed significant effect (LOEC). An example where determination of TOE is not possible is the algae growth inhibition tests (OECD 201), where the standard evaluation of cell numbers is performed every 24 hours which encompasses several generation times and therefore recovery of the population cell number in the test system may have occurred.
- The observed toxic effects directly depend on the product of concentration and time. Latency of effects (a delay in determination of effects) resulting from delays in the chain of events between exposure and determination of effects needs to be excluded. Therefore, for endocrine active substances PEC_{twa} is not appropriate because latency is common (e.g., for reduced reproduction). In addition, results are affected by the relatively short exposure of critical developmental stages, e.g. gonad development. The effect endpoint in the chronic test is not based on acute toxicity effects occurring early in the test, e. g. in the first 96 hours.

  For soil, calculating a PEC_{twa} or a PEC actual after a certain time period is not possible because PNECs for soil tests are generally based on nominal concentrations which need to be compared to initial PECs. In addition, in case of ecotoxicity tests in soil, it is difficult to assess if the above mentioned requirements for the use of time-weighted concentrations are met.

  Care should be taken that time-weighted average concentrations can only be compared with toxicity endpoints based on average concentrations during the same time period. So, a time weighted PEC should never be compared with toxicity endpoints based on initial concentrations.

18. Q Which Freundlich adsorption coefficient (n) is to be used in FOCUS models?

A 1) In case a full OECD 106 batch sorption study at multiple concentrations derives reliable 1/n values, the arithmetic mean of the empiric 1/n values should be used in the FOCUS model.

2) In case of a full OECD 106 batch sorption study at multiple concentrations where it is impossible to derive reliable n values, a default 1/n of 0.9 is to be used in any FOCUS modelling. This value takes account of the Applicant's effort to derive empiric data for the relationship between the substance's sorption and concentration.

3) For VMPs, generally a study at multiple concentrations is required. However, if in specific cases only the screening stage experiment of OECD 106, investigating sorption at a single concentration is available, a default 1/n of 1 is to be used in any FOCUS modelling. This more conservative value is needed because of the lack of data on the relationship between the substance's sorption and concentration.

19. Q Which input application parameters should be used when running the FOCUS Surface Water Scenarios Help (SWASH) tool, specifically regarding the application method, the application dates (for all the scenarios), the chemical application method (CAM) and the incorporation depth (for runoff scenarios only)?

A **1) Application method:** "Granular appl." should be selected for all scenarios (scenarios "D" and "R") as indicated in the TGD. Due to a software bug in the model, the application method has to be selected individually for each scenario without using the "copy" button.

2) Application dates: The default dates set by the model should be kept and the predicted

application time (PAT) should not be changed.

3) Chemical application method (CAM): CAM is an input parameter required for running PRZM, which is one of the models contained in SWASH used for modelling runoff ("R" scenarios). PRZM allows modelling with eight different CAMs. For calculating the entry into surface water of a VMP through runoff after the application of manure in soil, CAM 4 (i.e. "Incorporation in soil with uniform profile and user-specified depth") should be used. The choice for CAM 4 can be selected in the separate "Applications" box in the "Application" window and only applies for the "R" scenarios.

4) Incorporation depth: If CAM 4 is selected, PRZM requires the user to specify an incorporation depth which depends on agricultural practice(s). It can be safely assumed that most of the manure will be incorporated to grasslands and arable lands. According to data from Eurostat[5], around 50% of the agricultural surface that could be manured in Europe will not be or only superficially ploughed (i.e. grasslands, conservation tillage and zero tillage lands). Although that percentage varies widely in the different countries of the EU, it is considered appropriate to use an incorporation depth of 5 cm as a realistic worst-case estimate. Although it is acknowledged that the incorporation depth will be higher in arable land subject to conventional tillage, a higher value should not be used.

Annex I to Q & A 19: Summary of all input parameters required for running the FOCUS SWASH tool

1. Substance management ("Create, View and Edit Substances")

Parameter	Value	Comment
"General" tab		
Molar Mass (g/mol)		Enter value
Saturated vapour pressure (Pa)		Enter value
Molar enthalpy of vaporisation (kJ/mol)	95	Default[6]
Solubility in water (mg/l)		Enter value
Molar enthalpy of dissolution (kJ/mol)	27	Default[6]
Reference diffusion coefficient in water (m²/d)	4.3E-5	Default[6]
Reference diffusion coefficient in air (m²/d)	0.43	Default[6]
"Sorption" tab		
Soil		
Option	Kom, pH independent	Enter value
Freundlich sorption exponent (-)	0.9 or 1 or arithmetic mean	Enter value (see Q 18)
Kom (l/kg)	Geometric mean ≥ 5 soils Lowest value < 5 soils or no organic carbon correlation	Enter value (see Q 2)
Surface water		
Kom (l/kg)	Geometric mean ≥ 5 soils Lowest value < 5 soils or no organic carbon correlation	Enter sorption data for soil (see Q 2)
Freundlich sorption exponent (-)	0.9 or 1 or arithmetic mean	Enter value (see Q 18)
Reference concentration (mg/l)	1	Default[6]
Coefficient for linear sorption on	0	Default[6]

[5] Eurostat. Agri-environmental indicator - tillage practices. 2016. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Agri-environmental_indicator_-_tillage_practices#Analysis_at_EU_level. Accessed on 15 February 2022.

[6] Generic guidance for FOCUS surface water scenarios. Version 1.4. May 2015. https://esdac.jrc.ec.europa.eu/public_path/projects_data/focus/sw/docs/Generic%20FOCUS_SWS_vc1.4.pdf. Accessed on 8 March 2022.

Parameter	Value	Comment
macrophytes (l/kg)		
Sediment		
Kom (l/kg)	Geometric mean ≥ 5 soils Lowest value < 5 soils or no organic carbon correlation	Enter sorption data for soil (see Q 2)
Freundlich sorption exponent (-)	0.9 or 1 or arithmetic mean	Enter value (see Q 18)
Reference concentration (mg/l)	1	Default[6]
"Transformation" tab		
Soil aerobic		
Half-life (d)	Geometric mean	Enter value, first order kinetic (SFO) (see Q 12)
Measured at (°C)	20	Default[6]
Walker (-)	0.7	Default[6]
Calibrated value (-)	0.49	Default[6]
Moisture content (%) at which half-life is measured (%)	100	Default[6]
Option for moisture content in transformation study	Relative to field cap	Default[6]
Q10 Factor for effect of temperature on transformation	2.58	Default[6]
pF at which half-life measured	2	Default[6]
Effect of temperature	0.0948	Default[6]
Surface Water		
Half-life (d)	1000 d	Default; enter value if study available (see TGD)
Measured at (°C)	20	Default[6]
Molar activation energy (kJ/mol)	65.4	Default[6]
Sediment		
Half-life (d)	1000 d	Default; Enter value if study available (see TGD)
Measured at (°C)	20	Default[6]
Molar activation energy (kJ/mol)	65.4	Default[6]
"Crop processes" tab		
Wash-off factor	1E-6	Enter value (see TGD)
Canopy progress option	Lumped	Default
Half-life on crop canopy (d)	1000	Enter value (see TGD)
Coefficient for uptake by plant	0	Enter value (see TGD)

2. Project management ("User-defined Wizard")

Parameter	Value	Comment
Select substance		Select substance recorded
Available crops	Winter cereals	Select crop (see TGD)
Select water body types		Select all (see TGD)
Available scenarios		Select all scenarios (see TDG)

3. Application management ("View Projects and Define Applications")

Parameter	Value	Comment
Appl. method	Granular appl.*	For all scenarios (see TGD)
Possible days of application		Use default PAT (see Q 19)
Rate (kg/ha)		Enter value
Chemical application method	CAM 4 (4-incorp soil uniform)	Enter value (see Q 19)
Depth incorporated	5 cm	Enter value (see Q 19)

* The application method has to be selected individually for each scenario without using the "Copy" button.

Annex II to Q &A A 19: Examples of FOCUS SWASH results obtained with representative substances

Example 1: Mock substance

Input parameters:

Parameter	Value
Molar mass (g/mol)	564
Saturated vapour pressure (Pa)	0.0001
Solubility in water (mg/l)	12000
Freundlich sorption exponent (1/n)	0.9
Kom (l/kg)	5.8
Half-life (d) (soil aerobic)	18
Rate (kg/ha)	1.64

Results:

Scenario	Results (µg/l)
D1 ditch	76.02
D1 stream	50.58
D2 ditch	252.6
D2 stream	164.3
D3 ditch	35.07
D4 pond	38.81
D4 stream	23.01
D5 pond	45.78
D5 stream	27.50
D6 ditch	41.43
R1 pond	0.2782
R1 stream	25.84
R3 stream	61.03
R4 stream	0.2696

Example 2: FOCUS surface water "Example_Sub_A" (EXSW1)

Input parameters:

Parameter	Value
Molar mass (g/mol)	Default
Saturated vapour pressure (Pa)	Default
Solubility in water (mg/l)	Default
Freundlich sorption exponent (1/n)	Default
Kom (l/kg)	Default
Half-life (d) (soil aerobic)	Default
Rate (kg/ha)	1.64

Results:

Scenario	Results (µg/l)
D1 ditch	12.89
D1 stream	9.912
D2 ditch	133.9
D2 stream	88.31
D3 ditch	0.4011
D4 pond	0.01945
D4 stream	0.08165
D5 pond	0.6317
D5 stream	2.273
D6 ditch	13.57
R1 pond	0.2284
R1 stream	21.65
R3 stream	43.37
R4 stream	0.08619

Annex III to Q & A 19: Table containing suggested FOCUS SWASH input data for inclusion in an application dossier/assessment report

Parameter	Value
Molar mass (g/mol)	
Saturated vapour pressure (Pa)	
Solubility in water (mg/l)	
Freundlich sorption exponent (1/n)	
Koc/Kom (l/kg)	
Half-life (d) (soil aerobic)	
Half-life (d) (surfacewater)	
Half-life (d) (sediment)	
Wash off	0
Application method	Granular
Rate (kg/ha)	
Chemical application method (PRZM)	4-incorp soil uniform
Depth incorporated for run off scenarios	5 cm
Plant uptake	0
Crop	Winter cereals