8 March 2012
EMA/CVMP/ERA/737515/2011
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Reflection paper on risk mitigation measures related to the environmental risk assessment of veterinary medicinal products' (EMA/CVMP/ERAWP/409328/2010)

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

Stakeholder no.	Name of organisation or individual
1	IFAH-Europe
2	Federation of Veterinarians of Europe (FVE)
3	EGGVP – European Group for Generic Veterinary Products
4	Association of Veterinary Consultants (AVC)

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	IFAH-Europe appreciates the opportunity to provide feedback to the CVMP/ERAWP Reflection Paper on mitigation measures. It is important for industry to have the option of not performing additional environmental studies by using label restrictions, as specified in VICH GL 38. If the mitigation measure can reduce the risk to an acceptable level or eliminate the risk entirely, performance of additional studies should not be mandatorily required. Sometimes companies have to make deliberate business decisions on proposing mitigation label restrictions instead of performing additional environmental studies. Therefore, the Reflection Paper is welcomed. We noted that the two major explanations for a risk mitigation measure not fulfilling the guideline criteria are: - The animal owner may or may not have control on spreading of manure from the treated animals. - The product usage restriction is in conflict with animal welfare for the need of animal treatment. With these two restrictions, the risk mitigation measure options for terrestrial environmental safety are very limited. Aspects of animal welfare vs. the use of a medicine are in fact not part of the environmental risk assessment and should be taken into consideration in a risk:benefit assessment; it is also not listed in the criteria specified in the TGD. The determination of the adequacy of a mitigation statement in relation to the environmental impact should only address whether or not the mitigation measure protects the environment. We therefore propose that the CVMP ERA Working Party reconsiders the	The ERA WP agrees that for products where Tier B identifies a risk for the environment, risk mitigation measures as specified in VICH GL 38 are an important tool to mitigate that risk. They may eliminate the need to perform higher Tier tests following Tier B. This reflection paper does not aim at replacing benefit:risk assessments or fully addressing the topic of animal welfare. However, the risk mitigation measures need to be in line with agricultural practice. Animal welfare is one point to be taken into account when discussing agricultural practice.

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	statements of concern with respect to animal welfare criteria.	
2	The Veterinary Profession, represented by the Federation of Veterinarians of Europe (FVE) welcomes the initiative of the Committee for Medicinal Products for Veterinary use (CVMP) to review the adequacy/appropriateness of risk mitigation measures included in the current marketing authorisations of veterinary medicinal products. FVE agrees with all the criteria used for the evaluation of the effectiveness of a risk mitigation measure, as well as with the need to consider additional criteria for assuring that measures will be realistic and achievable in the daily practice. Moreover, FVE recognizes that some of the risk mitigation measures currently in use are not fulfilling the guideline criteria (point 4.2) and therefore supports a reconsideration of them. FVE supports this effort and we wish to be kept informed in the future discussions.	
	EGGVP recognizes the growing concern over the impact of veterinary medicinal products on the environment, and supports the steps given by EMA in this direction. Therefore, EGGVP acknowledges the necessity to review the adequacy and effectiveness of the risk mitigation measures which are currently applied. The principal comment from EGGVP on this paper refers to the lack of clear provisions for the measures currently included in marketing authorizations and which might not fulfill the new criteria established. This is quite uncertain in particular for generic applicants willing to get an authorisation for a product whose SPC for the original product includes measures that would not be appropriate after the revision. EGGVP would like to emphasize that the mitigation measures which are currently in force and have been accepted for	The aim of the reflection paper is to improve the use of risk mitigation measures, with overall aim that measures not fulfilling the guideline criteria will not be used for new authorizations. They might only be included as a recommendation for products where the risk for the environment has been taken into account in the benefit:risk assessment and where the benefit has been ranked higher than the risk for the environment. As generics require their own environmental risk assessment the outcome of the risk assessment may differ from the originator product, although it is expected that in most cases the risk identified will be the same. This fact is not

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	the originator should be accepted for the generic applicant as well. Otherwise, it would be objectionable if a generic applicant would want to get an authorisation for the same product and would not be allowed to refer to the same risk mitigation measures. Furthermore, this reflection paper focuses only on the guidelines related to environmental risk assessment and just mentions the general legislation of the EU and Member States. It is important to consider the specific legislation related to farm residues and water courses protection, which has a crucial role in the manure fate and management. The mention to the Good Agricultural Practices (GAP) as defined by the UN FAO should be complemented with the fact that in the UE these practices are actually regulated, and that the aim of this legislation is the environment and the consumer's health protection. Therefore, EGGVP requests to align measures with existing regulations (in Member States and the UE) in the field of GAP, because these regulations already define the scenario of how the farm residues must be treated and the requirements should not be in contradiction, i.e.: - COUNCIL DIRECTIVE of 12 December 1991 concerning the protection of waters against pollution caused by nitrates from agricultural sources (91/676/EEC); - National regulations (i.e. Spanish law 10/1998 of Residues); - Manure Production and Management Plans and Manuring Plans at the farms; - Common Agricultural Policy (CAP) These regulations make themselves a series of risk mitigation measures,	specific to risk mitigation measures, and if eventually divergent risk mitigation measures are recommended, there might be a need for harmonisation of SPCs (e.g. via referrals). Although those references are not specifically mentioned, they have been considered when preparing the reflection paper. In addition, the reflection paper on risk mitigation measures has to be read in conjunction with VICH guideline 6 and 38 and the guideline in support of those VICH guidelines (EMEA/CVMP/ERA/418282-Rev.1). Those guidelines also take into account the relevant EU and national regulations on e. g. the maximum load for nitrogen spreading or the required storage capacity for manure. It is not within the scope of this reflection paper to iterate the provisions already taken into account when calculating exposure of veterinary pharmaceuticals in the environment. For measures already included in the exposure calculation (e. g. Refinement based on degradation in manure according to chapter 3.1.4.1 in the supporting guideline), additional risk mitigation measures are not required. It is also to note that the Directives and regulations mentioned do not address the environmental risk of veterinary pharmaceuticals. It is agreed that the veterinarian is responsible to identify if he/she can comply with the indications in the product's label.

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	hence protecting the watercourses and preventing the soil contamination by regulating the manure disposal. Thus, the present reflection paper should identify all GAP practices and take them into consideration, and not only rely on what is “common” or “rare”. The regional variability should also not be a limit for the validity of a risk mitigation measure, as long as this measure is not clearly violating an already regulated GAP. Finally, EGGVP is of the opinion that it should be the veterinarian’s responsibility, at the time of prescription, to properly identify if he/she can comply with the indications in the veterinary medicinal product’s label.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
142-146	1	*'The farmer may not have the possibility to rotate pasture use'.* **Comment:** The availability of a medicine should not be based on whether or not a small number of potential users have the ability to fully meet all use criteria. The prescription of a medicine has to take into consideration the ability of the user to meet the administration criteria in the same way the weight or age restrictions have to be complied with. Higher tier assessments are of little value, since they will not indicate the repopulation dynamics of dung fauna. Please delete the requirement for these tests. In case a population is negatively affected, it will recover in the following seasons in which the product is not used. Based on life cycles and seasonal activities it is highly unlikely that the complete population will be extinct. Thus non-affected individuals will contribute to the recovery in the following seasons. Additionally, due to high mobility of e.g. beetles and flies, repopulation can reasonably be assumed. Therefore effectiveness of the mitigation is given. **Proposed change:** *"2- Be in line with agricultural practice: ~~Depends~~ Yes*".* *"4- Be possible to demonstrate the effect of the proposed risk mitigation measures by re-evaluating the exposure assessment with the proposed risk mitigation measures included: ~~Depends~~*	Not accepted. It should be possible to easily incorporate risk mitigation measures in agricultural practice to ensure compliance. Measures which a substantial number of farmers are not able to comply with should not be included on the label. As now indicated in the reflection paper, the possibility to e.g. rotate pasture might depend on the production system of each region with more intensive production systems making rotation more difficult, thus resulting in higher concentration of the active principle of the veterinary medicinal product on the soil. It is the applicant's task to submit information showing that veterinarians and farmers can easily follow the risk mitigation measure. Not accepted. It is not the scope of the reflection paper to change the VICH guideline which requires higher tier assessments also for dung fauna. IFAH is welcome to discuss higher tier assessments for dung fauna once ERA WP has published a testing strategy. Not accepted. If the long term effects of the active principle on the environment are of little concern, this should be supported by data showing the impact of the veterinary medicinal product on the environment.

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		Yes".* *"* This might be a suitable mitigation measure; however the farmer's ~~might not have the~~ possibility to rotate pasture will have to be assessed at the time of prescription if mitigation of the risk to pasture fauna ~~or flora~~ is necessary. ~~Data will be needed from higher tier assessment for effects on dung fauna population. The assessment methods of higher tier studies are however still under development."~~* We invite the ERA WP to reconsider the suitability of this proposed risk mitigation measure.	
147-150	1	**Comment**: The comment that the proposed mitigation measure (*Do not treat animals on the same pasture in successive seasons...*) could be in conflict with the health and welfare of the animals under treatment is out of scope and context. It would be an even bigger welfare issue if the treatment was simply not available. If the choices are no product at all or an effective product every other season, certainly the latter is a better option. The determination as to whether the restrictions on use represent a welfare issue should be left to the overall risk:benefit evaluation, where availability of treatment alternatives may be considered. The mitigation statements should only consider the environmental effects. **Proposed change**: Please delete the reference to welfare considerations. We invite the ERA WP to reconsider the suitability of this	As now further clarified on the reflection paper, the potential risk for the environment will be factored into the overall benefit:risk evaluation and the regulatory authority will have to decide if the benefits of the product outweigh the risks (including the potential risk to the environment); during this benefit:risk evaluation the animal health and welfare will also be taken into account.

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		proposed risk mitigation measure.	
151-153	1	**Comment:** Similar measures can also be found on plant protection products sold OTC for use by the general public. This mitigation is no different to any other part of the instructions for use of a medicinal product (e.g. administer x mg/kg on 3 successive days). The risk associated with overdose or extended use in food producing animals also has implications for residues and subsequently human health. The restriction on the frequency of use during a production cycle would seem a perfectly acceptable mitigation, especially as this is already an assumption during the assessment. The use of this mitigation statement only emphasises that this should be adhered to. This is an acceptable mitigation, all outcomes should be yes. It is in line with agricultural practices, in the same way that weight or age restrictions are. The effect of the application of the mitigation can be assessed. **Proposed change***:* Please change outcome of measure 2: *"Be in line with agricultural practice: ~~Depends~~ Yes*".* Please delete reference to animal health/welfare. We invite the ERA WP to reconsider the suitability of this proposed risk mitigation measure.	Not accepted. This measure relates to those target animals such as broiler chickens and weaner pigs where there are a number of animals occupying one stable place in a year. Each of these animals is considered as one 'production cycle'. For some products it may be essential that each production cycle is treated, not to do so would impact on animal welfare. For other products it may be that every 'production cycle' does not have to be treated with the product as some sort of rotation is possible. This is why the condition ""Be in line with agricultural practice" is answered by 'depends'.
173	1	**Comment:** There are extensive restrictions on manure application periods and requirements for storage capacity in many Member States (MSs). These good agricultural practice (GAP) requirements are undoubtedly far more restrictive than	Not accepted. It is agreed that there are restrictions on manure application periods and requirements for storage capacity in the EU and in the Member States. These restrictions are already taken

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		any mitigation applied for a minimum storage period. The requirement for a minimum storage period can be classed as compliant with GAP. Manure degradation data should be accepted in support of a mitigation measure. Typical manure storage periods for which a sufficient number of half-lives of the active substance may occur, resulting in no risk to the environment following application of the manure to land, should be considered to be in line with agricultural practice. If the farmer retains manure to allow sufficient degradation of the active substance, this should be an acceptable mitigation. The rejection of this risk mitigation measure will effectively halt all possible work on manure degradation, as there is no incentive to do any of these expensive and complex studies anymore. **Proposed change:** Please change outcome of measure 2: *"Be in line with agricultural practice: ~~Depends~~ Yes*.* *"*Increasing the storage time used in this procedure ~~is not considered~~ should be in line with agricultural practice as covered by the EU Nitrates Directive."* We invite the ERA WP to reconsider the suitability of this proposed risk mitigation measure.	into account in the exposure calculations according to the guideline (EMEA/CVMP/ERA/418282/2005-Rev.1) and in the options for refinement of the exposure calculations at the end of Tier A. These requirements are also taken into account in the guideline on determining the fate of veterinary medicinal products in manure (EMA/CVMP/ERA/430327/2009). Not accepted.
192-199	1	**Comment:** Most MSs already have a restriction within GAP for the application of farm yard manure (FYM) within certain distances from water courses. To suggest that this mitigation measure is not in accordance with GAP also suggests that the National requirements to protect water courses are non-	Not accepted. The reflection paper does not say that restrictions on the application of farm yard manure within certain distances from water courses are not in accordance with GAP. The 'buffer zone' required to protect surface water from nitrogen

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		compliant with GAP. **Proposed change:** Please change the outcome of measure 2: *"Be in line with agricultural practice: ~~Depends~~ Yes*.* We invite the ERA WP to reconsider the suitability of this proposed risk mitigation measure.	immissions is a fixed value (e.g. 10m in UK). If it was determined in the ERA that the 'buffer zone' required was greater than that required for control of nitrogen, then this would not be in line with GAP. The CVMP/ERAWP is of the opinion that this measure would not then be easily incorporated into agricultural practice and hence the use of 'depends' in the reflection paper. The major concern is that risk mitigation measures should be communicated by the responsible veterinarian to the farmer but if the farmer is not the one who will spread the manure, the manure spreader might not be informed about this risk mitigation measures.
213-220	1	**Comment:** We agree that in some cases further fate and/or effect data may lead to the conclusion that the risk to the environment is acceptable and does not need a mitigation measure. Similarly, if a mitigation measure can reduce the risk to the environment to an acceptable level or eliminate the risk entirely, performance of additional studies (Phase II Tier B) should not be mandatorily required. **Proposed change:** "*However, risk mitigation measures should not be used to replace the requirements for studies of environmental fate and effects as required by VICH Phase II guidelines for Tier A where, in some cases, further fate and/or effect data (Tier B) may lead to the conclusion that the risk to the environment is acceptable without the need for ~~a~~ risk mitigation measures*."	Not accepted. The CVMP follows the principle that tier B testing has to be performed if a risk is identified in tier A and that RMMs are only applied after tier B, this is line with the decision tree presented in VICH guidelines 6 and 38.
64 and footnote 1	1	**Comment:** In line with 'agricultural practice' (line 64) or with good agricultural practices (GAP) (footnote)?	Partly accepted. For the environmental risk assessment it is assumed that good agricultural practice is followed. Any possible non-

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			compliance is not taken into account. The supporting guideline (EMEA/CVMP/ERA/418282/2005-Rev.1) refers to agricultural practice in general. The specific reference to good agricultural practice from UN-FAO has been deleted.
Lines 64-65	3	**Comment:** This reflection paper focuses only on the guidelines related to environmental risk assessment and just mentions the general legislation of the EU and its MS. It is important to consider the specific legislation related to farm residues and water courses protection, which has a crucial role in the manure fate and management. The mention to the GAP as defined by the UN FAO should be complemented with the fact that in the UE these practices are actually regulated, and that the aim of this legislation is the environment and the consumer's health protection. **Proposed change**: Be in line with MS's agricultural regulated practices (when used in food producing species)	Not accepted. See comment on IFAH comment on line 173.
Lines 64 Lines 115-117 Lines 122-124	3	**Commen**t: Line 64: In the case of non-food producing animals, any proposed mitigation measure should also be practical to implement and not in contradiction with other aspects of the SPC. For instance, in line 115 it is mentioned that a collar containing ectoparasiticides is to be removed before the dog enters water bodies; if the SPC requires gloves to prevent contact with the collar, the practicality to implement both measures becomes very low. Similarly, in line 122 it is mentioned that, if the active substance is toxic for aquatic organisms, treated dogs should not be	Accepted. Noted. The reflection paper clearly highlights the considerations for

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		allowed to enter surface water for <x> hours/days. EGGVP wonders how practical/realistic it would be to prevent dogs entering surface water if the mention in the SPC is for large periods (many days or even weeks).	proposing the x period. It is agreed that for products which are released into water for long periods, the measure is less realistic.
Line 142	3	**Comment:** The pasture rotation in successive seasons is reasonable and in line with agricultural practice, but as a special precaution, the farmer must assess his/her ability to fulfil it, and thus decide if this veterinary medicinal product is suitable for his/her livestock farm. In this reflection paper, mitigation measures should be in line with GAP and Member States' regulations, and it is foreseeable that some of them could, in particular cases and particular farms, not be appropriate. These situations won't invalidate the measure: the farmer will have to find a suitable veterinary medicinal product to his/her farm. **Proposed change (if any):** 2- Be in line with agricultural practice: Depends* Yes	We acknowledge the argumentation, but as in all cases it is not possible to rotate, "depends" is the correct term.
Line 172	3	**Comment:** Manure storing at farms is a regulated task in the UE. Depending on the number of animals, the farms must have manure storing tanks to cover a minimum period of time. I.e., according to Spanish Royal Decree 324/2000, the pig manure tanks must have a storage capacity of 3 months, at least, of production. Besides it, if the farm has a contract with a manure manager, this must have the facilities to fulfil those criteria. This means that a minimum period of storage could be identified and, if the DT50 is below that minimum period, this RMM would be feasible.	Not accepted. Manure storage is already taken into account in the refinement of the exposure calculation according to the supporting guideline (EMEA/CVMP/ERA/418282/2005-Rev.1). The storage times listed in table 6 are still considered adequate. For most types of animals it is 3 months. A risk mitigation measure longer than the compulsory storage period is not considered in line with agricultural practise. For the compulsory storage period, a risk mitigation measure is not necessary.

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		Proposed change: 2- Be in line with agricultural practice: No* Depends*	
Lines 166-174	3	**Comment:** A new risk mitigation measure is proposed based on dilution of manure. The measure focuses on manure produced after the treatment with a veterinary medicinal product. This generated amount of manure won't be directly applied to land, but stored for a certain period of time in the manure storage tanks and thus being diluted with non-treated animal manure. In the same way, the manure manager will collect the treated animals manure and dilute it with non-treated manure and/or vegetal wastes to produce compost. This means that, for a certain PEC, after a dilution, it can be reduced to a safer value, where RQ< 1. This dilution can easily be foreseen based on median manure production at the farm or average manure collection of the manager. **Proposed change:** 4.2.1.4 Manure from treated animals must be diluted at <xx%> prior to spreading and incorporating into land to assure a lack of environmental negative effects of <active substance>	Not accepted. Dilution of manure during storage is already taken into account in the exposure calculation (EMEA/CVMP/ERA/418282/2005-Rev.1). The refinement based on degradation in manure already takes into account nitrogen production during storage time (equation 11). An additional dilution is not considered to be in line with agricultural practice. For dilution during the compulsory storage period, a risk mitigation measure is not necessary.
Line 243-249	3	**Comment:** In line with the comments provided in the "general comment" section, what would this mean for generic applicants?	See outcome in the "general comment" section
After line 164, we	4	**Comment:** In the draft guideline, three examples are given to illustrate "MEASURES UNDER THE CONTROL OF THE	Not accepted. The fact that for several types of products and indications

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suggest adding another example.		VETERINARIAN OR ANIMAL OWNER". We suggest adding a fourth example, which is easily applicable by farmers and veterinarians, as shown below: **Proposed change (addition)** 4.2.1.4 <Product> can only be used in the same place for more than <x>% of feedlots included each year to avoid accumulation of <active substance> in soil resulting in a risk for the terrestrial environment and contamination of groundwater with <active substance>. For example, a product would be used in only 2/3 of the feedlots in any given place each year, i.e. 6 broiler chicken feedlots (instead of 9), 4 weaner pigs feedlots instead of 6, 2 fattening pig feedlots instead of 3, etc. We believe that this risk mitigation measure is related to all environmental risk assessment; it mitigates exposure of the VMP to the environment, it is in agreement with agricultural practice and the legislation of the EU and its Member States (alternative treatments may be used) and it is possible to demonstrate the effects of the proposed risk mitigation measures by re-evaluating the exposure assessment with the proposed risk mitigation measures included.	only part of the herd is treated is already taken into account in the exposure assessment according to the supporting guideline (EMEA/CVMP/ERA/418282/2005-Rev.1). For those cases it is not necessary to use a risk mitigation measure. For the other cases, it is not reasonable to assume that if a product is used in a stable only a percentage of the animals are treated unless justified for clinical reasons.