19 April 2018
EMA/CVMP/SWP/30675/2017
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on user safety of topically administered veterinary medicinal products' (EMA/ CVMP/SWP/721059/2014)

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

Stakeholder no.	Name of organisation or individual
1	Federation of Veterinarians of Europe (FVE)
2	IFAH-Europe

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1. General comments – overview

Stakeholder no.	General comment	Outcome
1.	FVE welcomes the CMVP initiative to establish a Guideline on user safety of topically administered veterinary medicinal products. Public health safety is very important and therefore respective considerations should be taken and appropriate safety guidelines should be included in the leaflet. FVE would like to draw the attention to the fact that the guideline seems to focus on products for companion animals. However similar products are used in production animals as well. It should be clear in the title and text of the document what the intention is. FVE supports that any requirements proposed in this guideline follow the 3Rs principles, value non-animal approaches where possible and does not impose unnecessary administrative burden to marketing authorisation of those products. An overall comment has to do with wording. We would suggest that a note is included in the document to ensure that the term - 'product' refers to 'veterinary medicinal product' - 'active substance' refers to 'pharmacologically active substance' - 'residues' refers to 'residues of the pharmacologically active substance and/or degradation products'	The focus has been clarified in the guideline (see 2. Scope). The focus is on topical products for companion animals that remain on the surface of the animal's body. The guideline was introduced in order to harmonise the assessment of user safety of topically administered VMPs, especially spot ons and flea collars. However, the principles of this guideline, for example in relation to the (pre-)application phase, may also be applicable to VMPs for food producing animals or other topical VMPs that do not remain on the surface of the animal's body. A sentence with respect to take account of 3R principles has been added (see 4. Principles of the assessment). A note to explain the terms had been added (see 2. Scope).
2.	IFAH-Europe welcomes the opportunity to comment on this draft	Noted.

Stakeholder no.	General comment	Outcome
	revised guideline. We appreciate the efforts by CVMP to bring more clarity to this topic; particularly as a lot of open points have still been identified in the user safety guideline several revisions. Development of user safety assessment has a long history with a lot of criticism in that time frame. This is generally a well-reasoned guidance document that is consistent with the state of the science for estimating risk from topically administered veterinary medicinal products. The worked example is particularly helpful in illustrating the application of the various factors and outcomes. Unfortunately the draft guidance still suffers from a lack of a good balance between detailed guidance and allowing necessary flexibility. Even if it is written that such details are 'recommendations' (see e.g. wipe test line 386ff) there is a tendency at assessment to insist that all these recommendations are fulfilled.	This is a guideline, like all other guidelines. So these are recommendations in order to improve and harmonise the assessment of user safety of topically administered VMPs. Applicants may deviate from the recommendations if they can justify. Noted
2.	**SCOPE** Additional clarity needs to be given to the scope of this guideline and where it applicable to companion animals (small animals) and/or livestock. There are several paragraphs that seem to concern only topical products for companion animals (e.g. 558-560, 507-514) and others for which it is not clear especially at the beginning of the document. **4.2. ESTABLISHING TOXICOLOGICAL REFERENCE VALUVES (TRVS) FOR ALL SCENARIOS** This chapter details with how to perform a toxicological risk	The focus has been clarified in the guideline (see 2. Scope). The focus is on topical products for companion animals that may remain on the surface of the animal's body. The guideline was introduced in order to harmonise the assessment of user safety of topically administered VMPs, especially spot ons and flea collars. However, the principles of this guideline, for example in relation to the (pre-)application phase, may also be applicable to VMPs for food producing animals or other topical VMPs that do not remain on the surface of the animal's body. Much of the information is similar to that in the current user safety guideline but it is here for completeness and to

Stakeholder no.	General comment	Outcome
	assessment. Information between lines 100 and 150 (table included) are applicable for all VMPs, whatever their route of administration. This section should be included in the general EMA Guideline on URA (EMA/CVMP/543/03-rev.1) **4.5 MARGIN OF EXPOSURE** The words used to define acute, repeated, short-term, sub-acute, chronic, long-term…exposures should be the same in all chapters in order to ensure coherence. This should be harmonised between "Exposure" and "Study" and the duration of each type should be set (e.g. 1 month, <3 months, 3-6 months etc.)	provide extra clarity. We are currently not updating the user safety guideline. Definitions are provided in the definition section. Consistency of terminology has been applied throughout the document. As the posology of the different products vary, the appropriate toxicity study to be used for deriving a TRV will vary. No recommendations are therefore made for the study duration. Case by case approach. For clarity the following terms are now used for exposure: **Short-term exposure:** Contact with a substance that occurs once or repeatedly for only a short time. In the context of this guideline, short-term exposure covers from the time of treatment until the time point at which the highest exposure occurs. This is likely to be up to 12 hours but could be later. **Long-term exposure:** Contact with a substance that occurs over a longer period. In the context of this guideline, long-term exposure covers the period of claimed efficacy.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
4-5	1.	Comment: Clarify what the animal species this guideline is focused on, i.e. only on companion animals or in animals in general. Proposed change (if any):	Agreed. See general comments.
55	2.	Comment: A definition of topical products would be welcomed. This guideline should not be applicable to topical products applied to the eyes and this should be mentioned. It should be specified that we are talking about products applied topically through the skin intended of local and/or systemic actions. Proposed change (if any): **Topically administered products are either solid (e.g. collars, powders) or liquid products (e.g. pour-on, spot-on, sprays, aerosol, and shampoo) administered through or on the skin in order to induce local actions and/or systemic actions, products with systemic action are commonly named transdermal products.**	See general comment.
55	2.	Comment: The scope should mention that the GL is not to be used retrospectively. Proposed change (if any): **The guideline on user safety of topically administered veterinary medicinal products is only applicable to new veterinary medicinal products to be administered topically.**	This guideline is not intended to be applied retrospectively (i.e., to products marketed prior to adoption of this guideline). However, some types of post-approval changes warrant a reassessment of user safety. See revised guideline 2. Scope.
55	2.	Comment: A definition of “user” is needed, since in chapters 4 and 4.1, the generic term “user” is used with no more details.	This guideline should be used in conjunction with the GL on User safety for pharmaceutical VMP.

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		Proposed change (if any): **The term user refers to the non-professional adult handler responsible of the product administration (i.e. owners) and also to the other household members (e.g. children).**	The term 'user' has been defined in that GL.
61	2.	Comment: Additional text for clarity Proposed change (if any): Into contact with the **treated** animals	Agreed. However the 'scope' section has been revised and the referred sentence has been moved to section 1. Introduction.
68-69	2.	Comment: A definition of topical products which fall under this guideline should be revised. While spot-ons, collars, pour-ons and topical powders are topically applied pharmaceutical forms, "transdermal products" describes the pharmacokinetic properties and any of the listed pharmaceutical forms can contain an API which is absorbed via the skin. Additionally shampoos, bathing products and topical aerosols are absent If the list is intended only to provide examples and not be exhaustive the text should make this clear. One possibility may be to have a definition of each category of topical products like in the EPA SOP, 2012. Proposed change (if any): Please modify the text for clarity; see also the comment to line 55.	Referred lines have been deleted. See 2. 'Scope' for the focus of this guideline.
92 – 93	1.	Comment: Please precise whether 'toxicity of the VMP' refers to pharmacologically active substance and/or degradation products. Proposed change (if any):	Neither. VMP refers to the whole formulation, active substance(s) including excipients and/or impurities if present. This has been further enlightened in section 4.2 Establishing

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Toxicological Reference Values (TRVs) for all scenarios.
99-150	2.	Comment: §. 4.2. Establishing toxicological reference values (TRVs) for all scenarios This chapter is not exclusive to topical VMPs. To leave this chapter in the Guideline on user safety of topical administered VMPs may lead to errors from applicants and discrepancies. This is common for all VMPs, whatever the type and route of administration, thus it should be included in the initial guideline for all VMPs (EMA/CVMP/543/03-rev1.) While reading this section, questions are raised if the mentioned studies concerned more the product or the active ingredients having in mind that toxicity studies on local effects should be done on final formulation. Whereas if toxicity studies on systemic effects are available on the relevant (active) ingredient(s) of the formulation, toxicity of the formulation can be deduced. (cf. EMA/CVMP/543/03-rev1.) Proposed change (if any): Withdraw this paragraph and revise EMA/CVMP/543/03-rev1	Reference has been made to the guideline for all VMPs. Much of the information is similar to that in the current user safety guideline but it is here for completeness and to provide extra clarity. We are currently not updating the user safety guideline. The first principles for hazard identification and characterization is made clear in the first lines of this section: "*The first step of the user safety assessment corresponds to the hazard identification and characterization of each active substance(s) and excipients and/or final product formulation as per the CVMP 'Guideline on user safety for pharmaceutical veterinary medicinal products', in order to derive TRVs with respect to the identified exposure scenarios.*"
99 ff.	2.	Comment:	LD50s are definitely not

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Chapter 4.2 (TRVs): It is not very logical on how to finally assess acute scenarios if LD50 values are not appropriate but NO(A)ELs from acute studies should be taken. Current toxicological guidelines will no longer recommend (at least in several Member States) such acute testing. And secondly the recommendation to a benchmark dose is not clarified with regard to that process. Proposed change (if any): Please clarify	appropriate as the parameters investigated in these studies are very limited. The guideline does state '*…based on acute NO(A)ELs or, if not available, on sub-acute or sub-chronic NO(A)ELs, the latter representing in general a worst case approach…*" The sentence concerning BMD has been replaced from which it is clear that BMDs can be derived in most cases when quantitative dose-response analysis is allowed.
100-101	2.	Comment: Depending on the exposure scenario, user exposure may be related only to the active ingredient(s) or to the final product with all active/inactive ingredients. Therefore, depending on the scenarios of exposure, studies on the active substance(s) or on the final product are relevant for risk assessment. Proposed change (if any): The first step of the user safety (…) characterization of each active substance(s) **and/or final product** in order to define TRVs with respect to the identified exposure scenarios	Hazard identification should be performed for all the ingredients in a product. Although most of the time studies with the active substance(s) are provided, studies using the final product formulation (in particular for new combinations) may also be included. Interaction (if using data from single actives) should be addressed as per the combination guideline. Sentences have been amended.
107-108	2.	Comment:	Agreed, but no need to repeat

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		The need for performing new studies should be carefully evaluated in the light of the three Rs. The possibility of extrapolating values from different exposure routes should be stated here as outlined in lines 140-141. Proposed change (if any): The need for any additional studies depends on the exposure and any identified gaps in the dataset. **In the absence of a TRV for a specific route of exposure, for example, dermal, the use of a TRV defined from an oral study can be considered using route to route extrapolation with adequate absorption factors.**	what was already written in line 140-141. Instead at the end of the former line 108 it is added: '*…if extrapolation from route to route is not possible'*.
107-108	2.	Comment: If new tests have to be performed, a tiered approach (chemical grouping, read-across, in silico tests, in vitro tests and in the last in vivo tests) should be followed to avoid unnecessary testing on vertebrates with respect to 3Rs principles. The new study should be done on the best test item i.e. (active) ingredient or product/final formulation.	Noted. A sentence with respect to take account of 3R principles has been added (see 4. Principles of the assessment)
110	1.	Comment: 'Reputable publishing source' needs to be clear. Clarification should be included, for example, manuscripts published in referee journals. Proposed change (if any):	Studies should be from scientific literature and published by a reputable source and preferably peer-reviewed. The full texts of cited studies should be provided. For well-known active substances information from summary reports, e.g. MRL Summary Reports, may be available and are considered acceptable. Scientific monographs may be submitted, however, the data on which the TRVs are based must be reported in sufficient detail to allow the

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			CVMP to satisfy itself that the TRVs have been correctly set. Extra clarification has been included in the guideline. See 4.2 Establishing Toxicological Reference Values (TRVs) for all scenarios.
110	2.	Comment: The meaning of “reputable” is open to considerable interpretation. Whilst we appreciate the flexibility given on sources some examples would be helpful. Proposed change (if any): The studies used to define TRVs should be carried out in accordance with VICH/OECD guidelines and current methodology or may be from a reputable published source (**e.g. peer reviewed scientific journal**).	Agreed. Studies should be from scientific literature and published by a reputable source and preferably peer-reviewed. The full texts of cited studies should be provided. For well-known active substances information from summary reports, e.g. MRL Summary Reports, may be available and are considered acceptable. Scientific monographs may be submitted, however, the data on which the TRVs are based must be reported in sufficient detail to allow the CVMP to satisfy itself that the TRVs have been correctly set. Extra clarification has been included in the guideline. See 4.2 Establishing Toxicological Reference Values (TRVs) for all

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			scenarios.
110-112	2.	Comment: The different types of exposure should be coherent within the guidance. Definition where there is the following notions: -Acute exposure / short-term exposure -Exposure of intermediate duration -Chronic exposure / long-term exposure There is no notion of sub-chronic exposure in the chapter definition. Is it equivalent to exposure of intermediate duration? Proposed change (if any): These studies should provide sufficient data for the assessment of the toxicity of the active substance for acute (**short-term**), sub-chronic (**intermediate duration**) and chronic exposure (**long-term**) scenarios (…)	For clarity the following terms are now used for exposure: **Short-term exposure:** Contact with a substance that occurs once or repeatedly for only a short time. In the context of this guideline, short-term exposure covers from the time of treatment until the time point at which the highest exposure occurs. This is likely to be up to 12 hours but could be later. **Long-term exposure:** Contact with a substance that occurs over a longer period. In the context of this guideline, long-term exposure covers the period of claimed efficacy. Consistency of terminology has been applied throughout the document.
115-116	2.	Comment: In the acute/accidental risk assessment the default values to be used is acute data. The use of sub-acute, sub-chronic or chronic data can be used if acute NOAEL is not available Proposed change (if any): "The acute/accidental risk assessment should be based on acute NO(A)EL **or if not available, to be based on sub-acute, sub-chronic or chronic NO(A)ELs, representing a worst case approach**"	Sentence has been amended into: '*The risk assessment of short-term exposure should be based on acute NO(A)ELs or, if not available, on sub-acute or sub-chronic NO(A)ELs, the latter representing in general a worst case approach. In addition, the TRV may be based on information*

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			from long-term studies if, in such studies, acute effects have been observed on the first day(s) of dosing. For the risk assessment of long-term exposure, the use of a sub-chronic NO(A)EL or chronic TRV can be considered acceptable.'
117-119	2.	Comment: The proposed guideline states that human data will not be accepted if the dose used is the therapeutic dose. However, there may be cases where the expected exposure of the user is covered by the therapeutic exposure of humans. In these cases it should be scientifically justified to use such human data generated with therapeutic doses. Proposed change (if any): "…Available human data can also be considered if these studies are relevant from a scientific point of view ~~(i.e. not using therapeutic doses)~~…"	The point the SWP was trying to make was that frequently applicant's try to make the point that exposure to human therapeutic doses produces very minor effects so risk is ok. However, in the case of HMP, risks are acceptable because of a positive risk-benefit balance. The sentence has been deleted, however, further clarification has been provided in the guideline.
117-119	2.	Comment: The draft guideline states that the acceptance of human data presents an ethical issue which the competent authorities undertaking the user safety assessment will need to consider. However, any recent study performed in humans needs to be approved by an ethics committee or the data would be from old bibliographic information. Therefore if such a human study has been approved by the responsible ethics committee, it is outside the scope of the competent authorities to judge whether or not such a study is ethically acceptable. The key point of	The part referring to ethical acceptance has been changed into: '*Available human data can also be considered if these studies are relevant from a scientific point of view (i.e. not using therapeutic*

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		human data is to have sufficient information on their reliability, on the confounding factors, real doses of exposure etc. to assess their adequacy to define correctly a TRV. Proposed change (if any): "…Available human data can also be considered if these studies are relevant from a scientific point of view ~~(i.e. not using therapeutic doses), although the ethical acceptance of these human data is an issue that the competent authorities undertaking the user safety assessment will need to consider~~…."	*doses) and are considered ethically acceptable' Available human data can also be considered for derivation of TRVs if these studies are relevant from a scientific point of view and, if generated experimentally, the applicant can confirm that the studies were accepted as ethically acceptable*[1]*.* in accordance with the declaration of Helsinki.
121-123	2.	Comment: It I unclear if the term "degradation" product also includes "impurities" in general? The safety qualification of degradation products and impurities, either in active substance or the final product, are managed by specific "Quality" guidelines. It should be mentioned that such guidelines are applicable since they propose specific methodology for the safety qualification. (VICH GL10, VICH GL11 etc.) The toxicological relevance of such assessment should be based on the Quality Guidelines and on the scientific knowledge available at the time of Dossier Application. Impurity def.: any component of the drug substance that is not the chemical entity defined as the drug substance. (VICH GL10) Degradation def.: any impurity resulting from a chemical change in the drug substance brought about manufacturing and/or storage of the VMP by the effect of light, temperature etc. (VICH GL11) Proposed change (if any): The sentence should be clarified and completed.	Impurities include degradation products. However, as the safety of degradation products and impurities is managed by the quality guidelines (notably VICH GL10 and VICH GL11) no further is made.

[1] If data are provided from studies conducted in humans it should be confirmed that the study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

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124-125	2.	Comment: What is covered by the term 'substance(s) of concern'? In beginning of the chapter, studies are related to active substance(s) Proposed change (if any): Please clarify	The beginning of the chapter has been revised into: '*… active substance(s) and excipients and/or final product formulation…*'.
135	1.	Comment: Proposed change (if any): …for all relevant ***toxicological end-points (***critical effects***)***, and…	Agreed.
135	2.	Proposed change (if any): In every cases, TRVs are applicable for all relevant critical effects, and are specific to a substance **or a final product**, duration of exposure	Disagreed. The TRV is for a substance, whether or not used in a formulation. It may also be related to an excipient.
139	2.	Proposed change (if any): In the context of the risk assessment, these values should be compared to exposure levels of the active substance(s) **or final product** that correspond to (…)	As above.
143	1.	Comment: Proposed change (if any): … the most ***critical*** sensitive effect…	Agreed.
147	2.	Comment: Latter in the document, no guidance is given on inhalatory risk assessment. Proposed change (if any): For topical spray, **aerosol** and powders, inhalation exposure should be considered.	Section 4.3.1 now states: *'For some products, e.g. sprays, aerosols, powders, exposure by inhalation may be relevant and needs to be taken into consideration. No guidance is provided on assessment of risks*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			via the inhalation route of exposure, *which should be addressed on a case by case basis.'*.
147	2.	Comment: This table should have : - a title (e.g. Relationship between exposure scenarios and relevant toxicological studies and endpoints) - names for column (e.g. Scenarios / Human exposure / Relevant toxicity studies and TRVs) Proposed change (if any):For clarity please add: For clarity please add: **The best toxicological study and TRV is to be selected considering the route of exposure (oral, dermal etc.), the frequency of exposure (single or repeated exposure i.e. acute,) and the component(s) concerned (i.e. product or (active) ingredient(s))** **Depending on the exposure frequency (e.g. single, repeated), the best toxicological study having similar treatment duration (e.g. acute, sub-chronic, long-term etc.) should be considered for the establishment of the TRV (NOAEL, ARfD…). To consider a study with frequency of treatment higher than user's exposure represents a worst case approach.** **In the absence of dermal toxicity study, TRV could be based on route-to-route extrapolation principle i.e. other route toxicity studies corrected by absorption rates ratio.** **Depending on the exposure, studies on the final formulation or on the (active) ingredient(s) are relevant. Nevertheless, studies on the (active) ingredient(s) are acceptable to deduce the potential effects of the final formulation.**	Column headings for the table are not considered essential. The table is self-explanatory. The proposed text is covered in the existing text. Where necessary, the text has been extended for clarity.
Lines 149, 465,	1.	Comment:	Has been changed into NO(A)EL.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
488, 721		Refer always to '**NOEL /** NOAEL'. Proposed change (if any):	
149 C – 149 D	2.	Comment: An exposure time represents a daily contact therefore a 24-hour exposure duration. Therefore a chronic exposure scenario is beyond 24 hours. However in some cases a shorter exposure may be justified based on easily dislodged residues, for example. Proposed change (if any): Post ~~12~~**24**-hour	For clarity the following terms are now used for exposure: **Short-term exposure:** Contact with a substance that occurs once or repeatedly for only a short time. In the context of this guideline, short-term exposure covers from the time of treatment until the time point at which the highest exposure occurs. This is likely to be up to 12 hours but could be later. **Long-term exposure:** Contact with a substance that occurs over a longer period. In the context of this guideline, long-term exposure covers the average exposure during the period of claimed efficacy, including the first 24 hours.
150-166	2.	Comment: The paragraph on the Use of Dermal penetration enhancers is t unclear. In the lack of dermal TRV with the active, oral TRV with the active could be used. "However, in instances when the dermal absorption is greater than an oral absorption, use of an oral TRV would not be acceptable." Does this sentence concerns dermal absorption of the active alone or within the	The sentence has been deleted and the section rewritten for clarity. The following sentence has been included:

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		final formulation? An example would be helpful? If absorption rates are available in each route (oral and dermal) in order to do a route-to-route extrapolation the dermal TRV estimated from the oral TRV may be applicable. In the lack of adequate TRV either due to difference on the route of administration or on the component tested versus the exposure scenario, internal dose/exposure could be derived using adequate information on absorption rate. This will allow the comparison of TRV and user exposure overcoming the routes and considering formulation effects. In such a case and if adequate information is available, internal/systemic exposures and TRV could be compared even if the dermal absorption is greater than the oral one.	*'If no data on bioavailability are available, the TRV from an oral study might be used as a surrogate, assuming that in general a TRV from a dermal study will not be lower than a TRV from an oral study'*
153-166	1.	Comment: Replace where 'final formulation' by the following Proposed change (if any): …final ***drug/product*** formulation…	Agreed. Has been changed in the guideline into 'final product formulation'.
155	1.	Comment: Proposed change (if any): … producing the ***adverse*** effects observed…	For clarity this section has been rewritten. Referred line has been deleted.
162	1.	Comment: Proposed change (if any): … comparing the absorption ***rate and extension*** of the formulation …	This section has been rewritten.
165	2.	Comment: Taking into account a 100% dermal absorption represents a worst case situation. Proposed change (if any): In absence of formulation …., **worst case** dermal	This section has been rewritten

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>absorption is assumed to 100%.</td><td></td></tr>
<tr><td>166</td><td>2.</td><td>Comment:
An exposure time represents a daily contact therefore a 24-hour exposure duration. Therefore a chronic exposure scenario is beyond 24 hours.

Proposed change (if any): (beyond ~~12~~ <u>24 hours</u>)</td><td>See comments to line 149C – 149D</td></tr>
<tr><td>167</td><td>2.</td><td>Comment:
Exposure scenarios
It is not clear why this chapter begins with considerations of oral exposures.
A simple way would be to define exposure phases
- pre-application phase
- application phase
- post-application acute phase
- post-application chronic phase
then concerned users (adult/child), the potential routes of exposures and the components concerned (whole product / final formulation, residues of product, inactive ingredients, actives…)
A table would allow a better understanding since several scenarios are possible.

Proposed change (if any):For example:
This summary table is not exhaustive but represents main scenarios of exposure to address.
HTM: hand-to-mouth (indirect ingestion) – HTE: hand-to-eye (indirect ocular exposure)
<table>
<tr><th>Phases</th><th>User</th><th>Details</th><th>Routes of exposure</th><th>Component of exposure</th><th>Frequency of exposure</th></tr>
<tr><td>Pre-</td><td>Adult</td><td>Product</td><td>Skin</td><td>Final</td><td>Accidental</td></tr>
</table></td><td>Section has been rewritten. A table has been included.</td></tr>
</table>

Line no.	Stakeholder no.	Comment and rationale; proposed changes						Outcome
		application		handling Accidental exposure Splashes	Eye / HTE HTM	formulation	Acute/once	
			Child	Product accidental access Accidental exposure Splashes	Skin Eye / HTE Oral / HTM	Final formulation	Accidental Acute/once	
		Application	Adult	Product application Accidental exposure Splashes	Skin Eye / HTE HTM	Final formulation	Accidental Acute/once	
			Child	Not relevant since the product is to be administered by an adult.				
		Post-application Acute Phase (first 24h)	Adult Child	Handling/stroking of treated animal Normal skin exposure and other indirect exposures	Skin HTE HTM	Final formulation	Normal use / Repeated	
		Post-application Chronic Phase	Adult Child	Handling/stroking of treated animal Normal skin exposure and	Skin HTE HTM	Residues	Normal use / Repeated	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(post 24h) | | other indirect exposures | | |	
179	1.	Comment: Proposed change (if any): …ocular irritancy ***and/ or corrosivity*** of the product…	Agreed.
179	2.	Comment: Skin exposure and skin irritancy/sensitisation should also be mentioned.	Agreed. See section 4.3.1.
182	1.	Comment: Proposed change (if any): … stroking the ***animal ~~pet.~~***	Agreed. 'Pet' has been changed into 'animal' in the guideline.
185-192	2.	Comment: It is not clear why the spot on solution is the only formulation that does not mention the dermal route of exposure.	Section has been rewritten. The particular product types have been omitted.
186-187	2.	Proposed change (if any): A spot-on solution provided in a pipette may be regarded as a child-resistant packaging **or not. A child-resistant packaging could be claimed** only if it has demonstrated to be in accordance with the European Standard EN14375.	Sentence has been replaced to section 4.6 risk mitigation measures.
195	2.	Comment: To add that the exposure of children may be accidentally; case of acute risk Proposed change (if any): "it is possible that children would become exposed **accidentally** dermally and even orally"	Section has been rewritten. The particular product types have been omitted.
196-197	2.	Comment: The unpalatability of other formulations besides shampoos seems likely. Has any consideration been given to requiring a palatability assessment, or at least making it an option if MOE are not adequate?	Section has been rewritten. The particular product types have been omitted. There is guidance for testing

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			palatability. (EMA/CVMP/EWP/206024/2011) However, this is for the target animal. And it is stated in this GL: 'Palatability of a VMP in one species may not be extrapolated to another species'. So far known, there are no palatability studies performed in human.
197	2.	Comment: Direct ingestion of a shampoo by a child is considered unlikely and low due to taste of the shampoo. Proposed change (if any): **Thus there is no significant direct oral child exposure by ingestion for shampoo.**	Section has been rewritten. The particular product types have been omitted. In general, as a default, it is assumed that 10% of the product can be ingested. However, a maximum of 5 ml (swallow volume) is now included for liquids.
200	2.	Comment: Children scenarios in connection with collar handling where it is mentioned that swallowing of cut-offs may have a remarkable impact. This scenario as described here leaves a lot of uncertainty how to really assess the situation. Larger cut-offs cannot be swallowed by children.	Section has been rewritten. The particular product types have been omitted. In general, as a default, it is assumed that 10% of the product can be ingested. However, a maximum of 2 cm is

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			now included for collars. An example for RMM has been added to section 4.6.
203	2.	Comment: Direct ingestion of part of a collar by a child is considered unlikely and low due to bitter taste of the collar and physical difficulties. Proposed change (if any): **Thus there is no significant direct oral exposure of a child regarding collar through chewing part of it**.	See above.
205	2.	Comment: Pour-on: The main risks concern the pre-application and application phases. Proposed change (if any): Accidental dermal exposure for the person administering the product as well as **accidental** dermal and oral exposure to children (pre-application and application phases) should be considered.	Section has been rewritten. The particular product types have been omitted. The focus of this guideline is topically applied VMPs for companion animals.
207	2.	Comment: This short paragraph gives contradictory advise how to proceed. On the one hand farm animal products should not come into direct contact with children. On the other hand accidental dermal exposure should be considered. But good guidance is not given. How to generally judge 'rare cases' in an assessment. Would that scenario lead to a wipe testing in farm animals? Proposed change (if any): This should be only handled in a risk mitigation chapter.	See above.
210	2.	Comment: Aerosol also needs to be covered. Proposed change (if any): **Powder/Spray/Aerosol**	Agreed. Section has been rewritten, including aerosols.
212	2.	Comment:	Section has been rewritten. The

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		Please add the exposure phase Proposed change (if any): For powder/spray formulations, the main risk of exposure is … the generation of dust/vapour and inhalation **during application phase**"	particular product types have been omitted.
213	2.	Proposed change (if any): Adult as well as children may also be exposed dermally when handling animals that have been treated with a topical powder**/spray/aerosol**	Section has been rewritten. The particular product types have been omitted.
224	2.	Comment: In line 147, it is indicated that inhalation exposure should be considered, but there is no specific chapter on this exposure that may occur mainly during the acute phases. Could it be indicated that no guidance is defined in this guideline for Inhalatory risk assessment regarding specific topical products.	Section has been rewritten. It is added that '*No guidance is provided on assessment of risk via the inhalation route of exposure*, *which should be addressed on a case by case basis.*'
224	2.	Comment: 4.3.1. Risk assessment for acute dermal and oral exposure scenarios and corresponding exposure levels after contact with the product As a general comment, it should be reminded that "*following paragraphs focuses on the most sensitive population i.e. children when both adult and children could be exposed*" If this is not the case, adult exposure should also be detailed in section "Pre-application Phase"	Agreed. It has also been added that: '*Additional calculations for adults are therefore not necessary, except when the substance may pose a risk for specific populations, e.g. pregnant women or women of childbearing age. Then, in addition to exposure during application, the post-application exposure i.e. stroking a treated animal should also be considered for this population*'.
229	2.	Comment:	Agreed.

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		If a packaging is not child-resistant packaging (CRP) according to EN 14375 or other CRP standards, it does not mean that the product is easily accessible. Several packaging methods allow a container strong and difficult to open especially for a child. Proposed change (if any): (…) or if the product is ~~easily~~ accessible by a child (i.e. if the product is not in a child-resistant packaging)	However, if a child-resistant closure is warranted it should be demonstrated in accordance with the European Standard EN14375 for non-reclosable packaging or EN8317 for reclosable packaging. See section 4.6. Risk Mitigation Measures.
235	2.	Comment: Application phase - There is no consideration of accidental eye splashes or indirect hand-to-eye contacts with contaminated hands.	Section has been rewritten. In section 4.3.1. the following is now stated: '*Direct ocular exposure and hand-to-eye contact after dermal exposure is also possible and the ocular irritancy/corrosion of the product should be addressed. Exposure via eye contact is not considered to result in significant systemic exposure levels and/or subsequent adverse systemic effect'.*
245	2.	Comment: When the user exposure is estimated in term of percentages of the packaging size or product type, this is expressed in final formulation or product and not in active substance. The exposure in term of active substance is dependant of the product composition in active substance. For the acute exposures during pre/post-application phases, since oral exposure is considered as the worst case, there is no estimation of the direct dermal exposure for children. Therefore there is no need to compare the dermal exposure to the dermal toxicity.	The section has been updated to clarify.

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		Proposed change (if any): **For child exposure**, direct oral exposure **to the product (i.e. final formulation)** will be a maximum (…)	
245	2.	Comment: Previous chapters indicate that for a shampoo, most of the product would be spat out as the shampoo is likely to be unpalatable (line 196). Therefore, the quantity ingested by a child is not proportional to the size of the shampoo packaging but to a fixed volume linked to the child mouth anatomy and the unpalatability of a shampoo since most of the volume present in the mouth will spat out. The estimated exposure for a shampoo is therefore more a default volume. Proposed change (if any): Direct oral exposure (…) 10% of a collar or ~~10%~~ **xx ml** of shampoo	In general, as a default, it is assumed that 10% of the product can be ingested. However, a maximum of 5 ml (swallow volume) is now included for liquids, including shampoo.
245-246	2.	Comment: In contrast with collar (hard consistency) and spot-on (low volume), the value of 10% for shampoos seems unrealistically high, this should be determined based on total volume present in the package size.	See above.
247	2.	Comment: This sentence concerns the application phase and an adult? Proposed change (if any): **For adult exposure**, direct dermal exposure **to the product (i.e. final formulation)** (…) **(for scenario B)**	The section has been updated for clarity.
250-254	2.	Comment: Indirect oral exposure (…) This paragraph is unclear. For children (scenarios A and C) no dermal exposure has been estimated since it was focused on the oral exposure worst case. If this paragraph is also applicable for adult indirect oral exposure it should be mentioned and the notion of collar/shampoo/spot-on “contents” should not be done. For the adult the exposure is estimated based on the administered dose and	The section has been updated for clarity. It is agreed that exposure is estimated based on the administered dose and not content of the product.

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		not the product content. A simple sentence indicating that indirect oral exposure represents 10% of the dermal exposure of the product/final formulation is sufficient. As previously mentioned, the exposure estimates concern the product and final formulation, not the active ingredient. Proposed change (if any): **Indirect oral exposure represents 10 % of the dermal exposure.**	
255	2.	Comment: Formula following Line 255: AR (amount administered) and FA (available fraction): Guidance on the use of for example, leachable studies (with artificial saliva) in order to get more realistic figures, would be appreciated. Proposed change (if any): Please list acceptable study types to evaluate or replace default values.	A sentence that '*The default values may be modified if justified by the provision of adequate information, e.g., from studies on leaching of collars.'* is added. This will be on a case by case basis.
257	2.	Comment: The acronym AR corresponds more to Application Rate. For children, the exposure is a percentage of a VMP unit (i.e. highest pipette) whereas for adult the exposure is a percentage of the therapeutic dosage which is different depending on the product type. Therefore the point of departure "AR" may not be systematically the same.	Agreed. AR has been changed into Application Rate. In this guideline it is described in the definition as '*For children this is the amount (of substance of concern) present in the product. For adults it is the amount (of substance of concern) applied to animal in the largest collar, largest pipette or largest shampoo dose applied to the animal).* For children and adults it will be the same if i.e. the largest pipette

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			is the therapeutic dose. However, for e.g. shampoo not the total content may be used during application, therefore the AR will be the dose applied to the animal.
259	1.	Comment: Proposed change (if any): … Fraction available ***or bioavailable*** for exposure…	Disagreed. It is the fraction of the amount administered that is available for exposure (not including bioavailability).
259	2.	Proposed change (if any): FA = fraction available for exposure by the relevant route **and scenario**	Agreed.
263	2.	Comment: Indicate the references use to choose the bodyweights, as this is done after.	Reference has been added.
276 and 278	2.	Comment: An exposure time represents a daily contact therefore a 24-hour exposure duration. Therefore a chronic exposure scenario is beyond 24 hours. Proposed change (if any): the first ~~12~~ **24** hours	See previous comments.
281	2.	Comment: 4.3.2.1.Dermal exposure of children after contact with the treated animal. Clarification on the residues concerned is required. Proposed change (if any): **The residues, to which a child may be exposed after the topical treatment of an animal, are mainly residues of active ingredients.**	Agreed. Though, during the acute exposure phase (short-term exposure) also residues of excipients should be taken into account.
316	2.	Proposed change (if any): Generally the pipette size, **collar size or therapeutic dosage** used to treat a medium size animal.	Sentence has been deleted.
317	2.	Comment:	The recommended application rate

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		The application rate is in relation with the treated animal body weight range and the pipette size allowing delivery of the highest dose of active substance. Proposed change (if any): AR = Application Rate, the amount of active substance applied to the animal (mg). ~~Generally the pipette size used to treat a medium sized animal (10 to 20 kg for a dog or <6 kg for a cat) should be used~~ **The pipette size used to treat the animal should correspond to the pipette allowing to deliver the highest active substance to surface area.**	that gives highest active dose to surface area ratio should be used. Sentence has been amended.
318-319	2.	Comment: F_{AR} On how many studies, species and on which type of product (spot-on, collar…liquid, solid), default F_{AR} have been set?	Defaults have been established based on experience with the assessment of wipe tests in general, mostly spot-on's. For chronic exposure the US EPA value of 2% is adopted. It is acknowledged that the defaults are worst case, however can be used as a first tier. Refinements can be made by performing wipe test with the product.
323	1.	Comment: Proposed change (if any): … (10 to 20 kg ***of bodyweight***) and	Referred line has been deleted. A table is now included in the guideline stating the bodyweights and surface areas of small-, medium- and large-sized animals.
323-324	2.	Comment: The surface area of a small cat is not indicated. As well as body weight of medium cats.	A table with all bodyweights and surface areas for cats as well as dogs has been included.

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		Proposed change (if any): (…) and 2500 cm2 for a cat **(3 to 6 kg or < 6 kg)** (small dog surface (…); **small cat surface area is 1500 cm^2** and large cat surface area is 4000 cm^2)	
340-341	2.	Comment: It is not entirely clear how the mentioned surface area is put together. Whereas 270 cm^2 belongs to the surface are of both hands of a child it is not specified what is behind 1790 cm^2.	1790 cm2 is the surface area of the unprotected body parts of a child, considered to be both hands, both arms and head including neck of a 2 to <3 year old child (see section 4.3.3.1) Sentence has been extended to clarify.
358	2.	Comment: the value to use by default for HTM is not clear there seems to be a value missing: should it be 20 per day, or 20 x 24h = 480 per day? The HTM contacts per hour (=20) were extrapolated to HTM per day (=20). This implies that there is only 1 hour of contact per day. Proposed change (if any): The default (HMT contact per day) is extrapolated to **XXX** contact per day	The default of 20 contacts per hours is extrapolated to 20 per day as the mouthed area is assumed to be fully loaded every time HTM contact occurs. Sentence has been extended to clarify.
374	2.	Comment: 4.3.2.3. Combined exposure by different routes This paragraph refers to the general EMA Guideline on URA (EMA/CVMP/543/03-rev.1). Guidance on this assessment would be welcome.	Noted. The example of combined exposure is already provided in the Annex.
375-376	2.	Comment: Is human oral/dermal absorption is assumed to be the same as for laboratory animals (as shown in the worked example) and what happens in cases where it is unknown or different?	Human data are preferred; however in general data in laboratory animals are available/generated. Studies in laboratory species are acceptable

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			for oral absorption data. For dermal absorption studies in laboratory animals are in general considered worst case. If it is unknown 100% dermal absorption is assumed. See also section 4.2. Establishing TRVs for all scenarios
377 ff.	2.	Comment: Chapter 4.4: Wipe test As already mentioned in the general statement this chapter is extremely detailed although it is stated that there are 'a number of recommendations'. This implies to the reader that there is clearly not much room for alternatives, e.g. sampling time points, number, location and order of stroking's. And it should be possible to assess the individual results and not categorically use the 'single highest value found'. Proposed change (if any): Please condense this long paragraph	The purpose of inclusion of this section on wipe test methodology was to ensure adequate study data across different applications are provided. The variation in tests was mainly concerning the number of wipes, time points and how it was done. As there is currently no guideline on this topic, it was decided to give more detailed information on how to perform such a test. The applicant may use an alternative design if justified to be as adequate as currently recommended. Some amendments are made.
381-382	2.	Comment: The sentence is applicable to all type of topical products	Disagreed. In the case of a collar, the user may touch the animal's

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		Proposed change (if any): (…) when the active substance is present on ~~a collar being worn or is present on~~ the animal's skin or fur.	skin including the collar. Sentence has been amended into '*when the active substance is present on the animal's skin or fur (including to touch the collar when stroking)'.*
391	2.	Comment: The element tested in a wipe could be the product or the substance (active for example), thus a generic wording is proposed. Proposed change (if any): ~~Test substance~~ **Test Item**	Agreed. In addition, '*The wipe test should be conducted using the final product formulation administered/applied to the test animals as recommended in the proposed SPC'*, has been added.
392	2.	Comment: wording modified for clarity. Proposed change (if any): This should be adequately described, ~~tested~~ **analysed** and stored.	Sentence has been deleted.
395-400	1.	Comment: Indicate that experimental design should follow 3Rs principles, provisions in EU Directive 2010/63 and other linked recommendations. Proposed change (if any):	A sentence with respect to take account of 3R principles has been added (see 4. Principles of the assessment)
395	2.	Comment: Please add an example Proposed change (if any): (unless required by product information, **e.g. shampoos**)	Agreed. The sentence has been extended "…(unless required according to the proposed conditions of use e.g. for shampoos)."
397	2.	Comment: wording altered to improve clarity.	Test substance has been changed into test item.

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		Proposed change (if any): (…) and have not been exposed to the ~~test substance~~ **test item** for 90 days (…). Animals should not be bathed after application of ~~test material~~ **test item** (…)	
401	2.	Proposed change (if any): The number of animals (at least 8), breed, approximate age, sex, hair length, **body** weight **and length** should be documented.	Partly agreed. 'Body' has been added. The recording of the length is not considered relevant. Default surface areas are included in the guideline which are based on the bodyweights.
402	2.	Comment: Since the duration of the study is dependent on the product indication and claimed duration of efficacy, animals may be housed individually for a long period of time. This is quite difficult for species like cats and this may lead to abnormal behaviour and be unacceptable from an ethical point of view. Therefore, periods of common housing may be required in order to allow social interactions and maintain normal behaviour and welfare. In all cases, these periods have to be reduced to the minimum, and avoided during the critical phase after treatment in order to limit cross-contamination and residues transfer between animals. Proposed change (if any): The animals should be housed in~~dividually~~ **groups as far as possible in order to respect animal welfare. However individual housing must be used during the critical phase after treatment in order to limit cross-contamination and residues transfer between animals.**	Agreed. The animals should be housed in groups as far as possible in order to respect animal welfare. However, individual housing must be used during the critical phase after treatment. The text has been revised.
403	2.	Proposed change (if any): Application of ~~product~~ **Test Item**	Agreed.
404	2.	Comment: Each laboratory has different methods and treats on D0 or on D1; this has no impact on the subsequent sampling time this just a different way of recording. Proposed change (if any): Animals should be treated ~~on day 0~~ in accordance with the product information.	Agreed.

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405	2.	Comment: In order to be coherent with the risk assessment and previous sections on exposure estimation, the animals used in the wipe test should be of medium size (10-20 kg for dogs and 3-6 kg for cats or < 6 kg). In addition, for spot-on product the pipette giving the highest active substance to surface area ratio is generally the lowest pipette indicated to the smallest body weight range. Animals used in wipe test are common laboratory animals and they generally do not correspond to the smallest body weight range recommended for such products. Proposed change (if any): For spot-on products, the pipette ~~that gives the highest active substance to surface area ratio~~ **intended to be used in medium sized animals** should be used.	For spot-on products, the pipette that gives the highest active substance to surface area ratio should be used. The sentence now reads: 'For spot-on products, the dose that gives the highest active substance to surface area ratio should be used as determined for small, medium and large animals when the product is intended for various animal sizes. This dose is to be applied to the test animals, which are in general medium sized animals. To obtain the highest active substance to surface area dose, the test animals should be dosed with the worst case amount (mg/kg) recommended in the SPC. *For example, when in accordance with the proposed conditions of use, a 2ml pipette is recommended for a medium sized animal of 10 to 20 kg bw, the highest active dose to surface area will be 2ml applied to 10kg animals. In case the test animals in the wipe test weigh 20kg a dose*

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			of 4ml would be applied.
406-407	2.	Comment: A requirement that “animals should have weights in the lower 10% weight range specified in the product information” may be difficult to comply with. Proposed change (if any): We would suggest using the maximum recommended dose.	See above
411-412	2.	Comment: An exposure time represents a daily contact therefore a 24-hour exposure duration. Therefore a chronic exposure scenario is beyond 24 hours. Proposed change (if any): beyond ~~12~~ **24 hours**	Disagreed. See previous comments.
416-418	2.	Comment: Sampling time points should be defined also on the pharmacokinetics knowledge on the final product and/or the active ingredient.	Sentence has been added.
416 to 418	2.	Comment: In contradiction with lines 384-385 “at the time of writing there does not appear to be any “standard” wipe test protocol”. Because of this, listing precise timepoints does not appear appropriate. Proposed change (if any): Sampling time points should be prior to treatment and ~~at 1, 4, 12 hours, 1, 2, 4, 7, 14, 21, and 28 days~~ **then selected to appropriately describe the dislodgeable residue profile over at least** the claimed duration of efficacy **or the recommended minimum treatment interval**.	Sentence has been amended. It is important that the suggested time points remain especially early time points to allow an acceptable RMM to be made. However, if justified other time points can be selected. This is a guideline like all other guidelines. It is not prescriptive, if adequately justified alternatives can be used.
420	2.	Comment: Does this exclude the use of an artificial mannequin hand? And should we consider a child sized human hand rather than an adult to determine the Fraction of Application Rate?	The use of a human hand is recommended as it mimics practice situation. However, the

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			use of a mannequin hand is acceptable. By performing a wipe test the total fraction of the application rate that is available as transferable residue is measured. The actual exposure calculation takes into account the size of a child's hand.
435-436	2.	Comment: Plastic gloves are not systematically analysed. The sentence should be written to allow to dosage in the cotton glove **and/or** plastic glove.	Changed into '*… cotton and impermeable gloves…*'.
438	1.	Comment: Proposed change (if any): … of residues (***i.e.*** parent ***pharmacologically active substance*** and/or relevant degradation products)	Has been changed into….. (i.e. active substances and/or substance of concern)
438	2.	Proposed change (if any): Analysis of residues (**active substance** ~~parent~~ and/or relevant degradation products)	Changed into .. *'Analyses of residues (i.e. active substance(s) and/or substance of concern)…'*
439	2.	Proposed change (if any): The amount of residues on the whole cotton **and/or plastic** gloves (…)	Changed into *…cotton and impermeable gloves….*
442	2.	Comment: Wording altered for consistency with earlier comments. Proposed change (if any): The amount (mg) of ~~active substance~~ **test item** applied to each animal should be recorded as well as the amount of residue dislodged (collected **on the plastic and or cotton** gloves) at each time point as well as animal **body** weight, breed, **body length** and hair type.	Sentence has been amended. It is not considered necessary to change active substance into test item and to record the body length.
401, 444	1.	Comment:	The sex and age of test animals in

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		Proposed change (if any): …weight, ***sex,*** breed and hair type…	the wipe test is not considered relevant information.
449-451	2.	Comment: Using the results of a single animal at a single time point gives tremendous influence to one data point. Perhaps use of a statistical upper bound or upper confidence limit would make better use of the data from all animals and reduce the potential influence of a single "outlier". However, we recommend not utilising statistical estimates that exceed the highest measured value.	Only 8 animals are included in the wipe test. In practice situation, even higher residues may be expected. To reflect the variability in data and cover that only a limited number of animals are included in the wipe test, the upper tolerance limit should be calculated, based on the highest residue values of all individual animals (for the acute exposure scenario) or the TWA (for the chronic exposure scenario). The text has been amended including a definition for Upper tolerance limit.
460	2.	Comment: 4.5 Margin of exposure This section is applicable to all VMPs and should be set in the general EMA Guideline on URA (EMA/CVMP/543/03-rev.1) Proposed change (if any): Please delete this section and refer to the general guidance.	This section is now identical to the parallel section in the general EMA guideline on user risk assessment of pharmaceutical veterinary medicinal products
469	1.	Comment:	Disagreed. Could be looking for a NOEL or

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		Proposed change (if any): … of ***adverse*** effect;	NOAEL. However, this section is now identical to the parallel section in the general EMA guideline on user risk assessment of pharmaceutical veterinary medicinal products
489	1.	Comment: Refer to 'LOEL/LOAEL' and provide explanation of the abbreviation in the definition section include the definition of LOEL and LOAL Proposed change (if any):	Agreed. However, this section is now identical to the parallel section in the general EMA guideline on user risk assessment of pharmaceutical veterinary medicinal products
491	1.	Comment: Proposed change (if any): … the severity of the ***adverse*** effect…	Agreed. However, this section is now identical to the parallel section in the general EMA guideline on user risk assessment of pharmaceutical veterinary medicinal products
493	1.	Comment: Proposed change (if any): … Severe ***adverse*** effects…	Agreed. However, this section is now identical to the parallel section in the general EMA guideline on user risk assessment of pharmaceutical veterinary medicinal products
497-498	2.	Comment: This paragraph mentions correction factors relating to route-to-route extrapolation. Are there some examples for inter/intra-species variability factors?	The default uncertainty factor is recognised to be 100 (10 for interspecies and 10 for

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			intraspecies). The applicant may use other uncertainty factors if adequately justified as pointed out in section 4.5. However, this section is now identical to the parallel section in the general EMA guideline on user risk assessment of pharmaceutical veterinary medicinal products
500-501	2.	Comment: It is good to recognize that expert judgment is involved. However, even for data derived from a wipe test, the methods proposed for exposure estimation have not been systematically evaluated (validated). Thus the practitioner should be aware that where biomonitoring was used to estimate adult and/or children's exposure, the proposed methods overestimated measured values by 10 to 100 fold (Driver, J.H., Ross, J.H., Holden, L.R., Selim, S., Sharp, J.K, Carlson, D. and Nouvel, L. (2015). Cyphenothrin Flea and Tick Squeeze-on for Dogs: Evaluation of Potential Health Risks Based on the Results of Observational Biological Monitoring. J. Toxicol. Environ. Health A. Health A. 78:1105-1121).	Noted, that expert judgement is involved. With respect to the provided literature: In this study only one substance is tested, with a very short half-life (2.5-4h). For substances with a longer half-life the internal exposure levels may be much higher. Moreover, in the article it is said that: 'The mean measured values in children were 13-fold lower than those estimated using the US EPA current SOP for pet products (assuming 5% dermal absorption), although the maximum absorbed dosage of one child on one day

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			was equivalent to the default valued derived from the SOPs.' So the US EPA value appears to be reasonable worst case. However, this section is now identical to the parallel section in the general EMA guideline on user risk assessment of pharmaceutical veterinary medicinal products
520	2.	Comment: Harmonisation with line number 187 Proposed change (if any): in accordance with **European Standard EN14375**	Sentence has been amended. A packaging can be claimed as child-resistant packaging, only if it has been demonstrated to be so in accordance with the European Standard EN14375 for non-reclosable packaging or EN8317 for reclosable packaging.
532 to 534	2.	Comment: A mitigation measure related to potential contact of the eye with the product should be suggested as well.	These are just examples. Sentence has been extended.
537	2.	Comment: Like gloves, safety glasses are commonly accessible for non-professional users (i.e. housework glasses)	Safety glasses are not expected to be commonly accessible for the non-professional user. However, glasses should only be recommended if the product is very irritant or corrosive. This appears not relevant for topical applied products as focussed on in current guideline.

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542	2.	Comment: Medical product waste: This is to note that exposure to medical product waste, leads to levels of exposure far below the pre-application and application phases, since part of the product has been used during application.	Noted. Though, post-application the product may more easily be left unattended or may not be disposed properly.
556 and 562-563 and 731	2.	Proposed change (if any): Replace "~~to sleep with the owner~~" with "**to sleep in the same bed as the owner**"	Disagree as it might not be in bed.
571	2.	Comment: As in other risk assessments it is unclear how to demonstrate that the proposed risk mitigation measures are feasible.	*'demonstrate'* has been changed into '*justify'*.
581 - 620	1.	Comment: Include definition of (LOEL/LOAEL) Proposed change (if any):	Agreed. Abbreviation has been added.
595	2.	Proposed change (if any): Exposure: contact with a substance by swallowing, breathing, **and/or through** the skin or eyes. Exposure may be short-term (acute exposure), of intermediate duration, or long-term (chronic exposure)	In the definition '*touching*' has been changed into '*contacting*'. Exposure in the context of this guideline may be short-term (once or for a short time), or long-term (repeated exposure for a longer period).
599	2.	Comment: An exposure time represents a daily contact therefore a 24-hour exposure duration. Therefore a chronic exposure scenario is beyond 24 hours. Proposed change (if any): This is likely to be up to ~~12~~ **24 hours**.	See previous comments.
601	2.	Comment: An exposure time represents a daily contact therefore a 24-hour exposure duration. Therefore a chronic exposure scenario is beyond 24 hours. Proposed change (if any): the chronic exposure covers a period of time beyond ~~12~~ **24 hours**	As above.

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616-617	2.	Comment: Deriving a TWA by "setting measurements below LOQ to LOQ" is not good practice. Perhaps for a single time point, this would not result in overly large overestimates, but for multiple time points, especially if extrapolating over several weeks; such a practice can be deceiving.	The definition has been adapted to clarify. It now reads: 'dislodgeable amount per individual animal averaged over the time until claimed length of efficacy or until two subsequent measurements are below LOQ, with setting measurements below LOQ to half LOQ".
646	1.	Comment: Proposed change (if any): … oral absorption ***(bioavailability)*** of the active ***pharmacologically active*** substance…	Changed into ….'Data indicate oral absorption (bioavailability) of the active substance to be 80% and dermal absorption to be 1% (using an aqueous solution)'
691-694	2.	Comment: IFAH-Europe wonders why a correction for oral bioavailability was made for post application oral exposures, but not pre-application, and at application oral exposures.	Corrections for bioavailability are made when no corresponding NOAEL/study using the same exposure route is available. For the pre-application phase, the oral (external) exposure of a child is compared to an oral (external) NOAEL. For the application phase, The oral (external) exposure of an adult is compared to an oral (external NOAEL). For dermal exposure, the external

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			dose level is compared to an oral NOAEL corrected for oral and dermal bioavailability (as no dermal NOAEL/study is available) For the calculation of combined exposure (dermal+oral), an internal dose level is calculated taking into account bioavailabity and compared to an internal NOAEL.