



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 March 2010
EMA/CVMP/SWP/662388/2009
Committee for medicinal products for veterinary use (CVMP)

Overview of comments received on revised 'Guideline on user safety for pharmaceutical veterinary medicinal products' (EMA/CVMP/543/03-Rev.1-CONSULTATION)

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



1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	<p>IFAH-Europe considers that the revision of the User Safety Guidance has been well done and provides for a valuable improvement. It accomplished the intent of providing clearer guidance and advice on the procedures for user safety risk assessments, laying out strategy and reasonable approaches, without being overly prescriptive. The revision provides clarification to sections that were a bit hazy before. The presentation outline of the User Safety Assessment makes more sense and will provide a better "story". Overall, we believe that this version addressed the majority of concerns previously identified by IFAH-Europe.</p> <p>It would still be helpful to include a general template for the user safety assessment which can be amended according to the special characteristics of the product concerned. Also very helpful, would be the inclusion of a worked example of a full user safety assessment in the appendix, rather than single sections of assessments for different veterinary medicinal products.</p>	<p>The positive comments from IFAH are welcomed and it is hoped that this will provide for improved understanding of what a User Risk Assessment is.</p> <p>A template has been added in an annex. The examples provided have been revised and are presented as full user risk assessments and use the template provided.</p>

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
80	1	<p><i>"An appraisal of the inherent toxicity and any other harmful effects such as flammability, of the active substance and the formulation is made."</i></p> <p>Comments: It would be helpful to add what precisely means "any other harmful effects", by clearly stating "physico-chemical effects" (as supposed by the term flammability).</p> <p>Proposed change: <i>"An appraisal of the inherent toxicity and any other harmful <u>physico-chemical</u> effects such as flammability of the active substance and the formulation is made."</i></p>	<p>Accepted</p> <p>In the context of the guideline "any other harmful effects" refers to physico-chemical effects, which include: flammability, dustiness (particle size) fumes/volatility.</p> <p>The proposed revision is accepted with additional text as follows:</p> <p>"An appraisal of the inherent toxicity and any other harmful physico-chemical effects such as flammability, dustiness, and volatility of the active substance and the formulation is made."</p>
111	1	<p><i>"... if the active substance has been used in human medicine, then data relating to observations in humans and adverse reaction data should be available and submitted in the dossier."</i></p> <p>Comments: This statement should make clearer that public available data may also be used.</p> <p>Proposed change: <i>"... if the active substance has been used in human medicine, then <u>available</u> data relating to observations in humans and adverse reaction data should be available and submitted in the dossier."</i></p>	<p>Accepted.</p>
115	1	<p><i>"If the evaluation results in conclusion that the VMP may have potential to cause adverse effects in users, then further investigation is required"</i></p> <p>Comments: A potential to cause adverse effects depends on dose and exposure and in fact, would then</p>	<p>Partly accepted.</p> <p>Explanation of "further investigation" has been requested and with respect to the proposed amendment, it is clear that additional explanation and clarification is required:</p> <p>"further investigation" means that if the conclusions from the</p>

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		<p>be subject of discussion/evaluation in the risk characterisation. Nevertheless, it is not clear what is meant by 'further investigation'.</p> <p>Proposed change: <i>If the evaluation results in conclusions that the VMP may have potential to cause adverse effects in users, then further investigation is required its consequences should be evaluated under <u>paragraph 5.3.1 Risk characterisation</u>.</i></p>	<p>evaluation indicate that there may be a potential to cause adverse effects, this must be further investigated to assess what the potential hazard is and what the risk might be.</p> <p>Further literature searches would usually be sufficient but there may be occasions when further studies may be required to establish the exact hazard and the risk.</p> <p>The additional information on the hazard and risk can be used in a further evaluation and benefit-risk assessment to establish if the balance is favourable and the hazard/risk acceptable.</p> <p>The following amended text will replace the current text:</p> <p>"If the evaluation results in a conclusion that the VMP may have potential to cause adverse effects in users, then these effects must be more thoroughly investigated to establish the potential of the risk. Additional literature searches would usually be expected to provide adequate data, but in some cases additional studies may be required. The results of this further work should be included in a re-evaluation and an assessment of the overall benefit-risk balance for the product."</p>
136	1	<p>Comments: IFAH-Europe has concerns on the use of safety data from Target Animal Safety studies for the toxicity studies, and the caveat that the unique physiology of some species makes the data not very applicable to human risk assessment.</p>	<p>Not accepted.</p> <p>The comment is noted, however the majority of toxicity data are derived from animal studies and are extrapolated to humans. The reference to target species data has been included as it may provide useful information on parenteral toxicity: the main aim is to use as much of the data in the</p>

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			dossier as possible, to create a "toxicity profile" of the active substance(s) and formulation, on which to base the user risk assessment.
201	1	<p>"An estimate of the possibility of a situation occurring..."</p> <p>Comments: This point is quite subjective: "an estimate" could be qualitative (low, moderate, high) or quantitative. The inclusion of an example on "estimate" would be helpful as this point is not detailed in the Appendix.</p> <p>Proposed change: Please provide an example.</p>	<p>Not accepted.</p> <p>The comment is noted, however an example has been given in the preceding paragraph (lines 198-200).</p> <p>Additional examples can be provided such as comparing the use of a product on a single animal, estimated as low exposure, with a herd treatment, estimated as high exposure.</p> <p>Amendments will be made to the text.</p>
337-344	1	<p>Comments: Some of the examples on warning statements appear extreme. Serious adverse effects with penicillins/cephalosporins could be a problem with powders for example, but does not seem to make sense for tablets or capsules.</p>	<p>Not accepted.</p> <p>The comment is noted, however for a person with a penicillin allergy, handling tablets is sufficient to cause an allergic reaction. Standard warnings for allergic reactions have been agreed by all member states and these warnings are considered necessary for people with such allergies.</p>
384	1	<p>Comments: Not all the definitions in this list (eg. application phase, user, controlled drugs...) are taken from NTA Vol 8 or from the IPCS/WHO (2001), as indicated in the footnote. Furthermore, it would be helpful to use a terminology in line with the one used in the benefit-risk assessment guidance. Even if the scopes are different, this would allow for better consistency. Finally, it seems relevant to add definition of <i>risk</i> and <i>hazard</i>.</p> <p>Proposed change: Please correct the footnote accordingly; align definitions of <i>risk</i> and <i>hazard</i></p>	<p>Accepted.</p> <p>References will be added to clearly identify the source of the definitions.</p> <p>The comment on definitions is accepted and the definitions as agreed for the Benefit-Risk GL will be used: current definitions will be amended accordingly and the definitions for risk and hazard will be added.</p>

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		<p>according to the guideline on benefit-risk assessment; and add the proposed <i>exposure</i> definition, which is a combination of the current and the B/R guidelines:</p> <p><i><u>Risk: The probability of an adverse effect and the severity of that effect, consequential to (a) hazard(s)</u></i></p> <p><i><u>Hazard: A biological, chemical or physical agent or situation having the potential to cause an adverse effect.</u></i></p> <p><i><u>Exposure: The concentration or amount of an agent that reaches the user, in a specific frequency for a defined duration. Contact takes place at an exposure point or exposure surface over an exposure interval.</u></i></p> <p><i><u>For inhalation and ingestion routes, exposure is expressed as a function of exposure concentration; for the dermal route, exposure is expressed as a function of exposure loading.</u></i></p>	
516	1	<p><u>Comment:</u> In the example of quantitative risk characterisation, the product name 'carprofen' is still cited.</p> <p>Proposed change: Please omit the name of the product.</p>	<p>Accepted.</p> <p>The reference to carprofen (which is the active substance rather the name of the product) will be amended to "active substance"</p>