18 February 2021
EMA/CVMP/57188/2020
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on "Revised guideline on safety and residue data requirements for pharmaceutical veterinary medicinal products intended for minor use or minor species (MUMS)/limited market" EMA/CVMP/SWP/66781/2005–Rev.2

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

Stakeholder no.	Name of organisation or individual
1	AnimalhealthEurope
2	Association of Veterinary Consultants (AVC)
3	EGGVP – European Group for Generic Veterinary Products
4	Federation of Veterinarians of Europe (FVE) & Federation of European Companion Animal Veterinary Associations (FECAVA)

Some comments have become obsolete: the new guideline now includes provisions from Regulation (EU) 2019/6 and its scope is limited to marketing authorisations. Considerations on MRLs for minor species are the subject to a separate guideline.

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	AnimalhealthEurope welcomes the opportunity to comment on this draft revised guideline. It has been noted that in e.g. in Table 1 (starting at line 574) Cross-references to VICH guidelines have been newly inserted (e.g. in line with A3 toxicological studies) or cross-references to OECD guidelines have been replaced by cross-references to VICH guidelines. (e.g. 90 day study). The stakeholder assumes that this will not imply increased data requirements (neither for the standard data requirements, nor for the Minimum dataset for minor food-producing species.) The stakeholder would welcome a clarification statement on this in the section on Executive Summary or 1. Introduction.	This table has been removed from the guideline.
1	It has been noted that terminology was revised e.g. in Table 2 (starting at line 576) for line '4.3 Microbial studies' the term 'anti-microbial' was replaced by 'antibacterial'. On the other side in the New VMP Regulation 2019/6 in Article 4 (12) (definitions) the term 'antimicrobial' is defined, whereas 'antibacterial' is not. The stakeholder would welcome a clarification statement on terminology alignment in the section on Executive Summary or 1. Introduction.	This table has been removed from the guideline.
2	We thank EMA to allow AVC providing some comments on this revised Guideline. As detailed below, and after careful study of the revised Guideline, AVC concludes that this revised Guideline does not provide any significant incentive to develop new products compared to the previous situation. It should be	

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	recalled here that developers need long-term visibility to be able to engage in new projects and that the few proposed waivers (most, if not all, of which are already known) are often still too imprecise to allow the expected predictability. It is therefore concluded by AVC that this guideline is unlikely to stimulate the research, development and innovation of new veterinary medicines intended for minor uses or minor species (MUMS)/limited market AVC welcomes nevertheless EMA's intention to provide opportunities to waive animal testing requirements for veterinary medicines intended for MUMS/limited market, which is in line with the recent implementation of Directive 2010/63/EC (regarding the protection of animals used for experimental and other scientific purposes) and the 3Rs principles of replacement, reduction and refinement. These updated criteria should enable applicants to provide the minimum required data to increase the availability of medicines for both major and minor species, by allowing the CVMP to set MRLs for additional animal species and commodities. In theory this revised guideline aims to stimulate the research, development and innovation of new veterinary medicines intended for minor uses or minor species (MUMS)/limited market with the intention to reduce data requirements where possible for products classified as MUMS/limited market while still providing assurance of appropriate quality, safety and efficacy and complying with the legislation in place and leading to an overall positive benefit-risk balance for the product.	

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	A careful examination led AVC to consider that the only potential waivers cannot be considered as a significant reduction of the requirements: see below: 1 – Establishment of MRLs for minor food-producing species The only possible case where a minimum data set may be accepted is represented by "Pharmacodynamics", but this is only "on a case by case basis" (in the absence of human data). For all other studies (PK, toxicology), a similar list of studies as for major species is required. This cannot be considered as a significant reduction of the requirements; moreover, predictability is difficult for a developer, since this is done on a case-by-case. 2 – Marketing authorisation for minor food producing species (where an ADI has been established) All studies (pharmacodynamics, PK, toxicology): similar list as for major species. This does not reflect any reduction of the requirements 3 – Marketing authorisation for minor non-food-producing species All studies (pharmacodynamics, PK, toxicology): similar list as for major species, except for "other toxicological studies" (immunotoxicity, etc.), unless relevant effects in repeat dose studies have been observed. This cannot be considered as a	<u>To point 1:</u> For a new active substance, no more reduction of data is possible, as an ADI is not determined for a minor species but is valid for the substance as such. Therefore, reduction is only possible for known substances (where reference can be made to the ADI) and in relation to the residue part of the dossier. As there are many possibilities and differences (e.g. depending on the substance), it is not possible to give more detailed advice in a guideline. However, companies are invited to ask for a scientific advice to define the case-by-case requirements. <u>To point 2</u> The requirements cannot be reduced, as the status "minor species" should not have an impact on the level of protection of the user or the consumer. <u>To point 3</u> See Point 2 (same answer regarding the protection of the user)

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	significant reduction of the requirements, which do not significantly differ from those applying to major species. 4 – Residue studies It is stated in the guideline that extrapolations are part of the evaluation in the first species, i.e. no submission of stand-alone applications for the extrapolation of MRLs is possible. A significant clarification is needed by applicants to describe which regulatory actions are needed to have an extension of MRL from a major to corresponding minor species. Applicants need indeed transparency in regulatory procedures to ensure the predictability required for any significant investment. 4.1 Establishment of MRLs Meat: limited number of animals/time points possible Milk: no limitation for number of samples/time points, but extrapolations possible in case of MRLs in a major species Egg: no limitation for number of samples/time points, but extrapolations possible in case of MRLs in a major species Honey: 6 colonies per site/4 sites It is clear from reading this table that only limited waivers are possible (to perform a limited residue study in meat would anyhow require preliminary tests to be performed to predict when residues will likely fall below MRLs), except in case of extrapolation from a major species.	 To point 4 In accordance to Commission Regulation (EU) 2017/880, EMA considers possible extrapolations as part of an MRL evaluation and no standalone submission for an extrapolation is possible. However, it is possible for applicants to include in an MRL-application supporting data for another species to give EMA the possibility to extrapolate to another species within this procedure. A new section will be included in the MRL guideline regarding extensions. To point 4.1 In order to ensure consumer safety, no further reductions are possible. The considerations on MRLs will be the subject to a separate document.

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	4.2 - Establishment of withdrawal periods Meat: no limitation for number of samples/time points, but extrapolations possible in case of WT established in a major species Milk: no limitation for number of samples/time points, but extrapolations possible in case of WT established in a major species Egg: no limitation for number of samples/time points, but extrapolations possible in case of WT established in a major species Honey: 6 colonies per site/4 sites No waivers are possible except in case of extrapolation from a major species. 5 – Analytical methods The requirements are identical as for major species (VICH GL49), with a few exceptions (e.g. precision at two levels) that do not represent a significantly lower workload. In conclusion, the proposed guidance should be considered as a very useful comprehensive review of the existing regulations and guidance documents in relation to safety and residues of MUMS VMPs. However, it is AVC's opinion that, in view of the complexity of the task, a more extensive reflection should be performed as soon as possible with all interested parties (including AVC who would be an active partner) instead of considering the proposed guidance as directly useful for	<u>To point 4.2</u> Surrogate approaches have been mentioned in the guideline, while ensuring consumer safety. The table to which the comment refers to has been removed from the guideline. <u>To point 5</u> In order to ensure consumer safety, no further reductions are possible.

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	developers in the industry to meet the initial targets (namely increasing the availability of medicines for minor species). In the past, EMA organised meetings with the industry to collect opinion from all sides (academics, including the European College of Veterinary Pharmacology and Toxicology, regulators, regulated, consumers, other concerned bodies), for finalising guidance documents in the fields of e.g. ecotoxicology, bioequivalence, PK/PD models. Such an action would clearly be beneficial here for all parties and AVC would be grateful if it could be undertaken before the proposed guidance is considered by EMA to be final.	A focus group meeting is intended to take place for the finalisation of the limited market guidelines.
3	Many thanks to the CVMP/SWP for the revision of the safety MUMS guideline, which is welcome. EGGVP would only make recommendation – so as to facilitate readiness and make the document more useful for the user/applicant – to include: - the list of minor species either in section 3 or as in appendix. - an example regarding extrapolating MRL from Major to minor species in chapter 6.2.1.	The term "minor species" is defined as every species not mentioned as "major species", therefore no specific list exists. Regarding marketing authorisations, the new Regulation (EU) 2019/6 does not mention the term "minor species", instead the term "limited market" is defined, this new terminology will be considered in a revised version of the guideline. In accordance to Commission Regulation (EU) 2017/880, EMA considers possible extrapolations as part of an MRL evaluation and no standalone submission for an extrapolation is possible. However, it is possible for applicants to include in an MRL-application supporting data for another species to give EMA the possibility to extrapolate to another species within this procedure. The principles and criteria for extrapolation are addressed in the above-mentioned Regulation.

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4	FVE welcomes this guideline intended to reduce data requirements for products classified as MUMS/limited market while still providing assurance of appropriate quality, safety and efficacy and leading to an overall positive benefit-risk balance for the products. We strongly support the intention behind this revised guideline, to stimulate the research, development and innovation of new veterinary medicines intended for minor uses or minor species (MUMS). The development of new veterinary medicines for minor species would be a positive outcome for animal health and animal welfare. There is a lack of licensed medicinal products across a range of minor species or for minor indications including for farm animals (e.g. goats and camelids) and most small and exotic pets. This has significant impact on the health and welfare of these animals. One area where there could be a stronger evidence base would be to ascertain dose rates that are both effective and safe. At present, there is a greater emphasis on finding a safe dose rather than the most effective dose. This can mean that the dose rates can be too low to be effective. This can lead to practitioners being encouraged to under dose e.g. for analgesia, which is a welfare issue. An improved evidence base could provide dose rates that are simultaneously effective and safe. We also specifically welcome the opportunity to waive animal testing requirements and introduce the extrapolation criteria to be considered by the CVMP when assessing applications for MRLs. This follows the 3-R principles. It is generally accepted	This GL specifically addresses safety. A separate Limited Markets GL addresses efficacy issues.

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	that animal testing should be reduced, refined or replaced as far as it is practicably possible. FVE recommends that some of the alternatives, which are already used as screening studies, metabolism studies and mechanistic investigations to animal experiments (in vitro) are recommended in the document. There are also a wide variety of in vitro models, which are used as screening studies, metabolism studies and mechanistic investigations among other applications that could be included in this EMA documents. In addition, silico models are not included, while they are accepted by other European agencies like ECHA to predict toxicity based on QSAR. We strongly suggest to make this revised guideline a part of a wider joined-up initiative around increasing availability. The factors that lead to the development of new veterinary medicines for any species or disease depends on many factors, and regulatory oversight is only one of them. Therefore, we very strongly support initiatives like the HMA/EMA task force on availability and the FishMedPlus Coalition.	VICH GL47 on laboratory animal comparative metabolism studies already allows use of in vitro data for comparative metabolism. There is currently consensus (e.g. ECHA information) that (Q)SARs cannot be used to address complex toxicological properties. However, for some limited endpoints QSAR may be used.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
119	4	**Comment:** **Proposed change (if any):** … stimulate the development **and innovation** of new veterinary medicines…	Agreed
139	1	**Comment:** alignment with MRL statement *(… an MRL has been established for **another** species …)* **Proposed change:** … *may be scope for data reductions if a product has already been authorised for a ~~major~~ **another** species*,	This text has been removed from the guideline.
140/141	1	**Comment:** please ad definitions in section 3 and clarify that this refers to substances used either in veterinary or human medicines. **Proposed change:** Definition for 'entirely new active substances' Definition for 'substance belonging to a well-known class of substances'	This text has been removed from the guideline. 1.
147	4	**Comment:** **Proposed change (if any):** … vaccine **containing GMOs** will need to be established…	This text has been removed from the guideline. As vaccines are not within the scope of this guideline, there is no reference to vaccine anymore.
152	4	**Comment:** **Proposed change (if any):** …has been authorised **by the European Union or other regulatory bodies (e.g. FDA, Canada, etc.)** in a related major species…	This text has been removed from the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
152/153	1	**Comment:** To ensure consistency **Proposed change:** whether or not the product is/has been authorised in a related ~~major~~ species for the same or a similar route of administration	This text has been removed from the guideline.
153-156	4	**Comment:** Please introduce some examples of systemic **and/or special toxicity studies based on the experience of EMA.** **Proposed change (if any):**	This text has been removed from the guideline.
154/155	1	**Comment:** To ensure consistency **Proposed change:** a similar route of administration in ~~a major~~ **another** species, information relating to use	This text has been removed from the guideline.
158	4	**Comment**: Please clarify what does 'comprehensive toxicity information' means. Proposed change (if any):	This text has been removed from the guideline.
236	4	**Comment**: Nothing is indicated about microbiological active substances. Proposed change (if any): …(i.e. pharmacology**,** ~~**and**~~ toxicology **and microbiology**)…	This text has been removed from the guideline.
237-238	4	**Comment**: Proposed change (if any):	Not agreed, as "value" (=limit) is already included in the term MRL (Maximum residue limit). Moreover the outcome of the procedure to establish MRL can be "no

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		…of an MRL **value,** where…	MRL required". However this text has been removed from the guideline.
239	4	**Comment**: Please what '*broadly the same*' means. Proposed change (if any):	This means that there are only a few waivers possible, which can be seen in the tables. No amendments necessary.
241-248	4	**Comment**: Nothing is indicated about microbiological active substances, which should also been considered and added. Proposed change (if any):	The requirements are in general the same as for other substances, therefore no special chapter is needed.
249-251	4	**Comment**: **Proposed change (if any):** …in laboratory animals **by the intended route of adminstration**, and if available, human data should be submitted for the assessment of the fate of the **acrive** substance. These are fundamental data that are required for selection of appropriate **laboratory animal** species for toxicity studies and the establishment of an ADI and MRLs.	Partially agreed. As the chapter is for MRL-Applications, the studies in laboratory animals should be by the oral route.
228-257	4	**Comment**: Please include also safety data requirements for microbiological data. **Proposed change (if any):**	The requirements are in general the same as for other substances, therefore no special chapter is needed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
262	4	**Comment**: **Proposed change (if any):** …total residues **(MR/TR)**, if necessary…	We prefer the term **(MR:TR)**, which will be included in the guideline
265	4	**Comment**: **Proposed change (if any):** …radiolabelled **residue** study…	Agreed
265-267	4	**Comment**: Please elaborate into sources for substitute data, e.g. can in vitro studies be used to get substitute data? **Proposed change (if any):**	This is a case-by-case decision and therefore no specific examples are useful.
269-270	4	**Comment:** **Proposed change (if any):** …laboratory **animal** species)…	Agreed
274-278	4	**Comment:** **Proposed change (if any):** • such ~~medicines~~ **active substances** are not or are hardly metabolised, • the metabolism of such ~~medicines~~ **active substances** is well known and comparable (within the chemical class 275 and across species), • structural differences between the novel compound and other **active** substances of the same class 277 of drugs are not indicative for a significantly different metabolism,	Agreed

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
280	4	**Comment:** **Proposed change (if any):** … metabolite**(**s**)**…	Agreed
284-285	4	**Comment:** **Proposed change (if any):** … total residues**(MR/TR)**, which can be used, for the calculation of the intake of residues 284 resulting from the proposed MRLs **values**…	We prefer the term **(MR:TR)**, which is now included in the guideline Regarding the term "value" (=limit), it is not agreed to include this as it is already included in the term MRL (Maximum residue limit).
390	4	**Comment:** Please clarify: does the term 'observed effects' mean 'adverse effects'? **Proposed change (if any):**	The term means **any** effect, as already written in the text. No amendments necessary
412-413	4	**Comment:** **Proposed change (if any):** … of human exposure **(i.e. acute or chronic)** to the **final veterinary medicinal** product…	Agreed
450	4	**Comment:** Please justify the 'uncertainty factor of 1.5'. Is it due to the difference of metabolism between species or are there other reasons? **Proposed change (if any):**	The safety factor is used to compensate for uncertainties in the extrapolation and based on experience from authorisation procedures.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
454	4	**Comment:** **Proposed change (if any):** … dosing regimen/**different** routes of administration…	This title has been removed from the guideline.
455	4	**Comment:** **Proposed change (if any):** …pharmaceutical **form** composition…	The wording is changed to "differences in ~~**the pharmaceutical composition**~~ **formulation or conditions of use** …"
493	4	**Comment:** **Proposed change (if any):** …, ~~elimination~~ **depletion** of residues…	Here elimination is meant, therefore no change was necessary. However, this text has been removed from the guideline.
499-500	4	**Comment:** Please include some examples. **Proposed change (if any):**	This is a case-by-case decision and therefore no specific examples are useful.
501	4	**Comment:** **Proposed change (if any):** …necessitate residue **depletion** studies…	Agreed. However, this text has been removed from the guideline.
505	4	**Comment:** **Proposed change (if any):** …based on **residue** depletion…	Agreed. However, this text has been removed from the guideline.

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td>510</td><td>4</td><td>Comment:
TDI value is for contaminants and other foreign chemicals not used internationally.

Proposed change (if any):
…Tolerable Dietary Intake for contaminants and other foreign chemicals)…</td><td>Agreed. However, this text has been removed from the guideline.</td></tr>
<tr><td>548</td><td>4</td><td>Comment:

Proposed change (if any):
… associated with the route of administration…</td><td>Agreed. However, this text has been removed from the guideline.</td></tr>
<tr><td>558</td><td>4</td><td>Comment:

Proposed change (if any):
…critical effects (end points) found in…</td><td>Not acceptable. All relevant effects as well as all endpoints should be discussed (i.e. if no teratogenicity was observed, this should be presented)</td></tr>
<tr><td>575</td><td>4</td><td>Comment:

Proposed change (if any):
<table><tr><td>4.4 Observations in Humans</td><td>Observed effects in human therapy medicinal products.
All relevant epidemiological, pharmacological, toxicological, microbiological and clinical data to be provided.</td><td>Same criteria apply.</td></tr></table></td><td>Agreed. However, this table has been removed from the guideline.</td></tr>
</table>

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td>577</td><td>4</td><td>Comment:

Proposed change (if any):
<table>
<tr><td>3.1 Single dose toxicity</td><td>• Data relevant to the assessment of possible adverse effects of accidental administration to humans
• To reduce animal numbers, alternative validated protocols and internationally recognised protocols will be accepted</td><td>Same criteria apply.</td></tr>
<tr><td>…</td><td>…</td><td>…</td></tr>
<tr><td>3.6 Carcinogenicity</td><td>2-year carcinogenicity study in rats required if:
i. active substances(s) have close chemical analogy with known carcinogens (referred to as 'Structural Alerts'),
…</td><td>Same criteria apply.</td></tr>
<tr><td>…</td><td>…</td><td>….</td></tr>
<tr><td>4.3 Microbiological studies</td><td>Required for antibacterial compounds.

Investigate risk to human intestinal flora and risk of</td><td>Same criteria apply.</td></tr>
</table></td><td>Not agreed. This sentence comes from Directive 2001/82/EC which does not mention the word “adverse”. All effects in humans are potentially considered. However, this table has been removed from the guideline.

Agreed. However, this table has been removed from the guideline.</td></tr>
</table>

Line no.	Stakeholder no.	Comment and rationale; proposed changes			Outcome
			antimicrobial resistance development. Investigate if **antimicrobial** residues can affect processes in ~~industrial~~ foodstuffs **industrial** processes.		Agreed. However, this table has been removed from the guideline.
		4.4 Studies on metabolite**(**s**)**, **impurity/**impurities**, degradation products**, other substances and formulation	Appropriate studies to assess the toxicity of metabolite**(**s**)**, **impurity/**impurities**, degradation products**, other substances and formulation	Same criteria apply.	Agreed. However, this table has been removed from the guideline.
577	4	**Comment:** 4.1 Special studies	Special studies including specific target organ toxicity (e.g. immunotoxicity, endocrine function tests, liver and renal function tests, effects on enzymes, neurotoxicity, sensitisation, skin and eye irritation, inhalation toxicity, **mechanistic**	Same criteria apply	Partially agreed, relay toxicity studies are not considered necessary. However, this table has been removed from the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<table><tr><td></td><td>**studies**, **relay toxicity studies**, etc. as appropriate).</td><td></td></tr></table> The alternative methods must be considered in this document according to "3R approach", e.g. "mechanistic studies" could be performed in in vitro cells. "Relay toxicity studies" are related to the toxicological effects of residues, so perhaps should be moved to another cell. **Proposed change (if any):**	Surrogate approaches such as in-vitro, in-silico or extrapolation of existing data are addressed in the guideline.
579	**4**	**Comment:** **Proposed change (if any):** <table><tr><td>3.1 Single dose toxicity</td><td>• Data relevant to the assessment of possible **adverse** effects of accidental administration to humans …</td><td>Same criteria apply.</td></tr><tr><td>3.2 Repeat dose toxicity</td><td>Study in 1 species and this may be replaced by an equivalent study in the target species. Tests may be modified (with **scientifically based** justification) for new combinations of known substances. See VICH GL31.</td><td>Same criteria apply.</td></tr><tr><td>…</td><td>..</td><td>..</td></tr></table>	Not agreed. This sentence comes from Directive 2001/82/EC which does not mention the word "adverse". All effects in humans are potentially considered. However, this table has been removed from the guideline. Partially agreed. However, this table has been removed from the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes			Outcome
		3.6 Carcinogenicity	Long term carcinogenicity study required if: i. active has a close chemical analogy with known carcinogens (referred to as 'Structural Alerts'), or, ii. positive mutagenicity tests, or, iii. suspect **clinical** signs during toxicity testing. Studies designed in accordance with current state of scientific knowledge. See VICH GL28.	Same criteria apply.	3.6. Not agreed. Suspect signs are likely to be non-clinical and may be seen at pathology. However, this table has been removed from the guideline.
		…	…	…	
		4.4 Studies on metabolite**(**s**)**, **impurity/**impurities**, degradation products**, other substances and formulation	Appropriate studies to assess the toxicity of metabolite**(**s**)**, **impurity/**impurities**, degradation products**, other substances and formulation.	Same criteria apply.	4.4 Agreed. However, this table has been removed from the guideline.

<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></td><td></td></tr>
<tr><td>579</td><td>4</td><td>Comment:
<table><tr><td>4.1 Special studies</td><td>Special studies including specific target organ toxicity (e.g. immunotoxicity, endocrine function tests, liver and renal function tests, effects on enzymes, neurotoxicity, sensitisation, skin and eye irritation, inhalation toxicity, mechanistic studies, relay toxicity studies, etc. as appropriate).</td><td>Data not required unless relevant effects in repeat dose studies have been observed.</td></tr></table>The alternative methods must be considered in this document according to "3R approach", e.g. “mechanistic studies” could be performed in in vitro cells.
“Relay toxicity studies” are related to the toxicological effects of residues, so perhaps should be moved to another cell.

Proposed change (if any):</td><td>Relay toxicity studies are not considered necessary. However, this table has been removed from the guideline.</td></tr>
<tr><td></td><td>4</td><td>Comment:

Proposed change (if any):
Please use the terms “veterinary medicinal product” or “VMP” instead of “product” as well as “pharmacologically active substance” instead of “compound” throughout the whole document.</td><td>Agreed</td></tr>
</table>