8 December 2016
EMA/CVMP/SWP/523387/2016
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on safety and residue data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market' (EMA/CVMP/SWP/66781/2005–Rev.1)

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

Stakeholder no.	Name of organisation or individual
1	Asociación Estatal Empresarial de Medicamentos para la Salud Animal (ADIPREM)
2	Association of Veterinary Consultants (AVC)
3	Domes Pharma
4	German Environment Agency
5	Federation of Veterinarians of Europe (FVE)
6	European Group for Generic Veterinary Products (EGGVP)
7	European Coalition to End Animal Experiments (ECEAE)

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	We agree with the improvements in Table 2 of the data requirements of waste and safety of Part 3 regarding the minimum data set for minor species (third column of the table).	No action required.
1	When MRLs have been established for major and can be extrapolated to minor species, we support the current proposal. We consider appropriate Part 3 of the dossier, except for: the part 3.A.4.4 (Studies on metabolites, impurities and other substances formulation), Part 3.A.5 (User Safety) and Part (3.A.6 Ecotoxicity).	No action required. Refers to section 7 of the MUMS GL. These are all non-negotiable requirements. Applicants may be able to provide less data, with justification, but the sections must be addressed.
1	Ecotoxicity: It would be considered treating minor species (or some of them) similar to pets, for the ones that it is not a requirement, justifying that the impact is much lower because there are fewer animals treated.	An ERA is likely to finish at Phase I for perceived minor uses (Question 5 of the Phase I decision tree). However, as stipulated in guidance (CVMP/ERA/418282/2005), justification that the product is used in a way which satisfies one of the criteria listed in this guidance should be provided. A Phase II ERA for minor species is not required in the case where an ERA is available for a major species provided that certain conditions are met (for conditions, see Questions and Answers – Implementation of CVMP Guideline on environmental impact assessment for veterinary medicinal poducts in support of the VICH Guidelines GL6 (Phase I) and GL38 (Phase II) \(EMA/CVMP/ERA/172074/2008. Rev.5).
1	In the request of residue data in the case of a VMP that has already been authorized for major species and is administered at the same dose in a minor species, the extrapolation of the withdrawal period already authorized for most species should be accepted in minor species.	See 7.2.1.1 – already allowed.

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	In case you want to reduce a withdrawal period, a new simplified study should be sufficient.	The option to reduce the WP (compared to the major species) hasn't been discussed in the GL. IN these cases a new residues study in line with GLs should be provided.
1	If the VMP already approved for major species is administered to minor species in a greater dose to those already authorized for major species, the study of residues in the target tissue must be considered sufficient.	Depends on whether the 'target tissue' is the same in all species. This will only be known if we have MRLs set for > 1 species.
2	AVC is very pleased to have the opportunity to comment on this new GL. Yes, it is a follow up of all the efforts already made by EMA and more specifically CVMP on this topic.	No action required.
5	FVE welcomes the draft guideline on safety and residue data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market updated. As this consultation is about safety and residue data requirements, for FVE it is difficult to comment in depth as this is more an industry and regulatory matter. From a veterinary practitioner perspective, we experience a lack of medicines availability to treat diseases in MUMS routinely. Practitioners in these cases need to be creative and find other ways or medicinal products to end the suffering of the animals and to try to treat them. Often they have to resort to off-label use. In a recent survey done, we got feedback that 44% of the practitioners said they have to use off-label medicinal products in 1-10% of their prescriptions, 25% indicated that more than 10% of their prescriptions were off-label, 30% less than 1% and 1% more than half of their prescriptions. So a balance needs to be made about which data requirements are really necessary, knowing if nothing is available, totally untested products will be used for these clinical indications/species. The foremost reason why industry does not develop products for	No action required

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	MUMS is because they see no chance for a return on investment. While reducing data requirements can help a bit, in most cases this alone will not solve the situation. We believe the only way forward is for a closer collaboration between regulators, the sectors concerned, the industry and research institutes. Examples of how such an approach can work can be seen e.g. in the US with the AMDUCA system but also in Norway in the aquaculture sector. Only through such a collaborative approach with commitment from all sides and support given to get all the necessary data requirements, more authorised products can come on the market for MUMS. In respect to the definitions we believe that all sheep and all fish should be classified as minor species. In respect of the extrapolations under point 6.2.1 we welcome the extrapolation to groups of animals e.g. from Salmonidae to all fin fish. We also suggest to give more emphasis to statements for in vitro testing for comparative metabolism or for toxicity itself (indicating in the text the 3R' guiding principles for more ethical use of animals in toxicity testing: Replacement, Reduction and Refinement) and highlight also the history of use of some compounds in MUMS.	The CVMP does not currently support this view This is currently allowed. No change required. VICH GL47 on laboratory animal comparative metabolism studies already allows use of in vitro data for comparative metabolism. History of use useful but not pivotal.
6	EGGVP appreciates the opportunity to comment on this draft guideline and welcomes the revision of the MUMS / limited market guidelines. By definition, veterinary medicines intended for MUMS / limited market are of less interest for Industry. The current guidelines are very demanding in terms of studies workload and requirements, making the return of investment very lengthy. This problem is reinforced by EGGVP members' experiences.	No action required.
6	The newly proposed guidelines are positive in the sense that they provide clarification and some extra information. However, no	The substances and products still need to be demonstrated to be safe for users, environments and consumers.

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	substantial changes - in terms of data requirements and costs/workload for industry - are being brought in the proposal, and the efforts to fulfil the provisions remain too high. EGGVP regrets that the reviewed guidelines are a missing opportunity to bring more incentives for industry for the further development of VMPs for MUMS/limited markets. Therefore, it is not expected that the newly proposed guidelines will help improving to the current situation / concerns in the EU about the lack of authorised veterinary medicinal products for minor uses and for minor species.	
6	EGGVP particularly welcomes: • changes in table 2 and table 3, so that the option of using MRL EPMAR is more expressed (but this option was already stated in the text in the current guideline) • safety and residue data requirements in Part III.A: we agree with the improvements set in table 2 concerning minimum dataset for minor food-producing species.	No action required.
6	EGGVP proposes that, regarding residue data requirements for VMPs already authorized for major species and administered at: • the same dose/pattern in a minor species: the extrapolation of the already authorized withdrawal period for major species to minor species should be accepted, as it is allowed the extrapolation of the MRL's within classes of animals. • a higher dose/pattern in a minor species: residue study in limiting tissue should be considered enough.	Refers to section 7.2.1.1 This is allowed, within relevant groups (ruminants, poultry, etc.). The Commission is working on an implementing regulation that allows extensive extrapolation between minor/major species. However, having a 1:1 extrapolation of withdrawal periods from e.g. chickens to goats, without data, is not considered to be scientifically valid. Refers to Section 7.2.1.2 Acceptable as long as appropriately justified by the applicant.
6	The title of this guideline refers to data requirements for VMPs intended for minor use or minor species (MUMS) and limited markets. The three terms are well described in the draft GL:	The title of the guideline follows on from the MUMS/Limited market policy and applies also to parallel quality, efficacy and immunological guidelines. It is acknowledged that, in

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	- Definition of minor use - Definition of minor species - Definition of limited market However, the guideline seems to be intended for VMPs for minor species only.	relation to safety testing, it is only the minor species aspect that is relevant.
7	The ECEAE welcomes an update to this guideline, which now includes opportunities to reduce data requirements for veterinary medicines intended for MUMS/limited market, which in turn could result in the reduction of animal tests. However, nowhere in the guideline does it explicitly state that these changes come with the added benefit of saving animals. In Europe there is now a legal obligation to use alternatives to animal tests if available (i.e. Directive 2010/63) and to take the principles of the 3Rs into consideration – both of which should be clearly mentioned in the guideline so as to further encourage their implementation. We urge the CVMP to reference legislation relating to the protection of animals used for scientific purposes, and to incorporate the principles of the 3Rs into the revised guideline where appropriate in the interests of animal welfare.	Text relating to the 3Rs has now been added in the executive summary and the introduction.
7	The wording of the table and sections in the guideline appears to create three possible scenarios related to minor species- where there is no MRL in any **other** food-producing species, where there is an MRL for a **major** food producing species and where there is an MRL for another **minor** food producing species. Is this what was intended? If so, would it be possible to provide a clearer justification for the three categories? According to the guideline, data requirements may be reduced in cases where MRLs have already been established for '**other** species' (lines 288-289). Similarly, according to Article 5 of Regulation (EC) No 470/2009, entitled 'extrapolation', the EMA 'will consider using	There is some confusion here over the SAFETY requirements (i.e. the setting of the ADI) versus the RESIDUES requirements (i.e. the setting of the MRLs). For Safety requirements, data are required if no ADI has been set yet, but no data are required if an ADI has been set already. Only two categories, not three. In lines 288-289, it is the Safety requirements. An implementing regulation is being produced by the Commission to deal with extrapolation (minor to major as

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	MRLs established for a pharmacologically active substance in a particular foodstuff for another foodstuff derived from the same species, or MRLs established for a pharmacologically active substance in one or more species for **other** species'. It is therefore not clear what the justification is for including the last two scenarios (i.e. separate requirements for where there is an MRL for a **major** food producing species and where there is an MRL for another **minor** food producing species) when both the guideline and the legal text suggest that data requirements may be reduced if an active substance has already been tested in **another** species – with no distinction between major and minor species.	well as major to minor, and the commodities). The MUMS guideline will be reviewed once the implementing regulation is in force.
7	The ordering of the sections and the titles of the Tables are causing us some confusion and, as mentioned above, the requirements for these three scenarios is not clear: Table 1. is entitled "Data requirements for safety testing for establishment of MRLs for minor food- producing species (when there are no MRLs established in a **major** food-producing species)." But the table falls under section 5. MRL Applications for minor species with no MRL established for **other** species – General requirements. Section 6 relates to "MRL Applications for minor species where MRLs have been established for **other** species – General requirements" But is not clear if this is where the MRLs are from major or minor species. "Section 7. Marketing authorisation applications for food producing minor species – General requirements" discusses the requirements if there is MRLs in only minor species and refers to Table 2 which is entitled "Data requirements for safety testing for a marketing authorisation for minor food- producing species (where MRLs are established for the active ingredient in a **minor** food-producing species)"	The titles of the tables have been amended as follows: Table 1 Data requirements for safety testing for establishment of MRLs for minor food-producing species (where no toxicological evaluation has taken place yet) Table 2 Data requirements for safety testing for a marketing authorisation for minor food-producing species (where the ADI has been established or was not considered necessary)

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	A description of Table 2 in line 552 says: “Table 2 Data Requirements for Safety Testing for a Marketing Authorisation for Minor Food- Producing Species (where MRLs are established for the active ingredient in a **major/minor** food-producing species)” Presently, going on the titles of Table 1 and 2, a product with an MRL from a minor species would need to satisfy the requirements of both tables. We suspect Table 1 refers to where there is no MRL in any species and Table 2 refers to where there is an MRL in only a minor species. And we suspect that Section 6 refers to where data is available from a major species and can be extrapolated with no specific additional data requirements (warranting a table). Is it possible to list the three scenarios more explicitly and/or ensure that the titles of the sections match the Tables and that clarity is given as to whether Table 1. should refer to **any other** species or **major** species?	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
62-73, Executive summary	7	**Comment**: We suggest that, as well as highlighting the main benefit of reducing regulatory requirements for veterinary medicines intended for MUMS/limited market (i.e. 'to stimulate the development of new veterinary medicines'), the positive implication of this on animal savings should be mentioned in the executive summary. This would also be an appropriate place to reference the 3Rs principles and highlight the legal obligation to conduct animal tests only as a last resort. **Proposed change**: Add: "This guideline also presents several 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".	Accepted.
63, 94	5	**Proposed change**: Change to 'In order to stimulate the ***research, development and innovation (R+D+I)*** of new veterinary medicines…'	Accepted.
After 81 and before 82	2	**Comment**: A Task Force on availability of veterinary medicines was initiated in 2007 by HMAv; EMEA, Commission and different stakeholders participated actively in this Task Force. A reference to this report should be added. **Proposed change**: Add a sentence : Already in 2006-	Not accepted. The value of adding this to a technical guidance document is not seen.

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		2007,a Task Force on availability of veterinary medicines was initiated in by HMAv; EMEA , Commission and different stakeholders participated actively in this Task Force.* which made already a lot of short-term, medium-term and long-term recommendations . *Report of Task Force on availability of veterinary medicines , 2007 http://www.hma.eu/veterinarymedicines.html	
After 87 and before 88	2	**Comment**: Add a reference to a key document for applicants: Regulation (EC) No 2049/2005 concerning micro, small and medium-sized enterprises (SMEs) which foresees the adoption of specific provisions allowing a reduction of fees, deferring the payment of fees, and providing administrative assistance for SME registered applicants. **Proposed change**: Add a line with "As a lot of potential applicants for veterinary medicines intended for MUMS are SME's, the Regulation (EC) No 2049/2005 concerning micro, small and medium-sized enterprises (SMEs) which foresees the adoption of specific provisions allowing a reduction of fees, deferring the payment of fees, and providing administrative assistance for SME registered applicants may motivate SME's".	Not accepted. Fees are outside the scope of this guideline, which focuses on data requirements for MUMS products.
112, 113 Also 123, 124, 127, 204, 213, 389	5	**Comment**: Clarify sort of products. **Proposed change**: *'or if a product concerns an active substance belonging to a well-known class of **pharmacologically active** substances. However, for products containing entirely*	Partly accepted. The title of the guideline has been amended to specify that it relates to pharmaceutical VMPs (rather than to immunologicals).

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		*new **pharmacologically** active substances, novel therapy products…'*	
115-119	2	**Comment**: AVC does not support this sentence "addressing a specific risk when the MUMS product concerns antibiotics and/or vaccines containing GMO's and so requesting "adequate data to justify…". In fact also MUMS products will be based in the near future on new technologies and as long as safety is guaranteed, as for any new technology, nothing specific in addition should be foreseen. New ways to develop antibiotics which do not induce resistance will hopefully be developed in the near future and may provide relevant aid to treat diseases in MUMS also. **Proposed change**: Withdraw this sentence "Similarly, for products presenting a specific risk if the product is classified as MUMS/limited market."	Not accepted Adequate data would still be expected.
130-131	2	**Comment**: Scientific advice is free of charge in some cases for MUMS products if requested by SME's. This facility should be added in relation to scientific advice. It was not helpful that financial incentives are only granted for food producing animals. This is especially true in the case of antimicrobials for pets, as there certainly is a public interest. The same is true in cases of any zoonotic claim made in pet products. This should be added, if not already done **Proposed change**: add a phrase: "In case the applicant is a SME and under some conditions, a free scientific advice can be requested as foreseen in Regulation (EC) No 2049/2005". "In some cases financial incentives should also be	Not accepted. This scope of this guideline does not include financial considerations.

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		granted for dogs and cats, especially in the case when veterinary medicines are of public interest, eg antimicrobials"	
142	3	**Comment**: "The data requirements for a major species for a marketing authorisation application for a limited market." No section in the table of contents states this possibility. No details on this option is developed in the draft guideline. Could you provide us more detailed information on this option?	Accepted. The title of the guideline follows on from the MUMS/Limited market policy and applies also to parallel quality, efficacy and immunological guidelines. It is acknowledged that, in relation to safety testing, it is only the minor species aspect that is relevant. The quoted sentence has been deleted.
146-167	7	**Comment**: We suggest that the 'definitions' section be expanded in order to clarify the meaning of some of the other terms used extensively throughout the guideline e.g. MRL, ADI, SR, EPMAR. **Proposed change**: Include definitions for MRL, ADI, SR and EPMAR.	Partly accepted. These have been expanded upon within the text (at the first use in the document, other than the contents page).
153, 156	5	**Comment**: We believe all sheep and all fish should be classified as minor species. **Proposed change**: Delete sheep and Salmon.	Not accepted A redefintion of major and minor species is not within the scope of the current work.
153	6	**Comment**: EGGVP proposes "sheep (meat animals)" to be classified as minor species. **Proposed change**: ~~sheep (meat animals);~~	Not accepted. See above.
168-192, Legal basis	7	**Comment**: Reference to Directive 2010/63/EC should be included in the 'legal basis' section. **Proposed change**: Add: "This document should be read in conjunction with Directive 2010/63/EC (regarding the protection of animals used for experimental and other scientific purposes).	Accepted. Relevant text has been included in the introduction.
202, 516	5	**Comment**: 5.1.1. Establishment of the ADI	Partly accepted.

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		Proposed change: Add list of abbreviations at the end or explain them in the text.	These have been expanded upon within the text (at the first use in the document, other than the contents page).
208-209 377	5	**Comment**: Suggest to specify the pharmocodynamic effects. **Proposed change**: '*Pharmacological data for a minor species must provide sufficient information for an assessment of the pharmacodynamic effects* ***(i.e., primary and secondary pharmacodynamic studies)*** *in order to establish whether a pharmacological ADI is required.* *Also need changing on line 377.*	Not accepted. The setting of a pharmacological ADI is addressed in the CVMP GL on the approach to establish a pharmacological ADI (EMA/CVMP/SWP/355689/2006), which does not use the terms primary and secondary pharmacodynamics.
212-215	5	**Proposed change**: '*However, an abbreviated dataset not including pharmacodynamic studies may be considered, depending on the substance under consideration, but the absence of data must be ~~satisfactorily~~* ***scientifically*** *justified with a summary of anticipated pharmacodynamic effects*.'	Accepted.
229-230	5	**Comment**: Clarification. **Proposed change**: '*Possible exemptions are substances where there is evidence that the only residues of concern are known and can be determined by* ***validated*** *analytical methods'.*	Accepted.
236-237 239	5	**Comment**: Clarification. **Proposed change**: '*i. available absorption, distribution, metabolism and excretion (ADME) data (e.g. in laboratory* ***animal*** *species) that may be extrapolated to the minor species*.' 239 – '*in laboratory animals or other target* ***animal*** *species,'*	Not accepted. Not considered to provide additional clarity.

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242-243	5	**Comment**: Clarification. **Proposed change**: '*• the metabolism of such medicines is well known and comparable* ***across all species****,* *• structural differences between the novel compound and other substances of the same class of drugs are not indicative for a significantly different metabolism* ***reactions****,*'	Partly accepted. The first proposal is agreed, but also expanded to include the concept of the metabolism being comparable within the same chemical class, as this is what the paragraph is about. The second proposal is not agreed, as it does not add to the clarity of the document.
246	5	**Comment**: Clarification. **Proposed change**: '*there is no indication of* ***metabolite(s) or degradation products*** *of specific concern,*'	Accepted.
251	5	**Comment**: Clarification. **Proposed change**: '*resulting from the proposed MRLs* ***values for target tissues'***.	Not accepted. Not considered to provide additional clarity.
Chapter 5 MRL not yet established 5.2.1 Total residue studies 252-255	2	**Comment**: In case an MRL is not already established (eg no use in a major species) and as well summarised in Table 1, even the minimum dataset can be too expensive for a MUMS product. AVC appreciates that two exemptions from the general rule on the need for radiolabelled studies to establish a MRL exist for products for fish and for bees. As CVMP is extrapolating MRLs in certain cases, there should also be a way that in case of MUMS products the applicant can ask the CVMP for a free service with reduced data set, at least, where it is an extrapolation only.	Noted. However, the current guideline is focused on technical requirements. Financial considerations are not within its scope.
262	5	**Comment**: Clarification. **Proposed change**: '*The method should be validated*	Partly accepted.

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273, 284		*in respect to the "limit of quantification"* ***(LOQ)*** *and, at least, for accuracy and precision at the level of the MRL and half the MRL* ***values****".* *We suggest to also change 'MRL' to 'MRL* ***values'****.*	'(LOQ)' has been added, but the addition of 'values' has not as it is not considered to provide additional clarity.
274	6	**Comment**: EGGVP proposes to include more explanation and one possible example. **Proposed change**: **"Example: The administration of the veterinary medicine could be done in autumn or early winter before manifestation of the illness and collect the honey for residues testing in spring or early summer."**	Not accepted. It was not considered to be appropriate to include this sentence in the document. These variables would be decided at the time of MA application/assessment. The text already includes the sentence 'Residue studies covering a reasonable range of commercial treatment conditions are needed….'
5.3 Establishment of MRLs for honey 284	2	**Comment**: Of particular interest is the sub chapter 5.3 Establishment of MRL's for honey. AVC can confirm that "assessment of residues in honey is more complex than in mammalian species". But the conclusion that *the "only feasible withdrawal period in honey is a "zero" withdrawal period*" is very extreme: under some conditions applying a VMP in bees can happen just before the bees are producing honey or at the end of the producing honey period.as long as no residues are detected. **Proposed change**: add a sentence at the end of 284:" Therefore it should be considered also in some cases to apply a VMP before the end of the honey production period or just before the winter period."	Not accepted. The point is covered in the preceding paragraph.
288-300	6	**Comment**: Sections 6.1 and 6.1.1 seem to handle the same subject and therefore cause confusion.	Accepted. Section 6.1 has been updated to clarify.
289-290	5	**Comment**: Clarification.	Not accepted

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		Proposed change: '*The outcome of the evaluation could result in the establishment of the* ***toxicological, pharmacological or microbiologica****l ADI and subsequently MRL* ***values****.*'	Not considered to provide additional clarity. Note that paragraph 6.1 has been updated (see previous comment)
6. MRL applications for minor species where MRL's have been established for other species 315-317	2	**Comment**: AVC noted that in such cases, in general, no additional data are required and also here it is not considered necessary that a fully validated analytical method is provided". AVC would like to stress that the "food basket" used for consumption calculation and which comprise 0,500kg of meat or 0,300kg of fish plus 1500kg milk plus 0,100 kg eggs, foresees also 20 g of honey. AVC would suggest that, as already foreseen in the note of guidance of the risk analysis approach for residues of VMPs in food of animal origin (EMEA/CVMP/187/00-FINAL), there is not always the need to take in account the maximum theoretical intake. For example for honey, in case the theoretical intake exceeds slightly the value of the calculated ADI if the amount of MRL fixed for honey is incorporated in the" food basket", AVC suggests, based on the small amount of honey, that the calculated theoretical amount composed of the other major animal species does not include the amount coming from the 20g honey, in case it is just exceeding this theoretical value. **Proposed change**: add a sentence after line 317: In this document on which CVMP is working to revise the principles on extrapolation of MRLs, the principle of the theoretical amount calculated food basket takes in account also a certain level of honey. In case the	Not accepted. The current approach to setting the MRLs includes consideration of the need to leave a portion of the ADI unused, so that further commodities (e.g. eggs, milk, honey) can have MRLs set at a later date, if necessary. It is not acceptable in this approach to have a theoretical maximum daily intake (TMDI) that is > the ADI. The 20 g value for honey in the food basket is also possibly an underestimate of consumption, as other frameworks consider 50 g to be more accurate.

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		added amount found in 20g honey is exceeding slightly the ADI, a risk analysis approach should not jeopardise the MA for a VMP for bees".	
315-317	5	**Comment**: Extrapolation of MRL's new approach **Proposed change**: Just to remind changing this to the new document when ready.	Accepted. An implementing regulation is being produced by the Commission to deal with extrapolation (minor to major as well as major to minor, and the commodities). The MUMS guideline will be reviewed once the implementing regulation is in force.
315-317	6	**Comment**: Guideline states at certain points that during 2016 new information/point of view will be provided/published, this seems a bit strange strategy for a new guideline and EGGVP would suggest that all is published at one point in time and in one single document (preferably this guideline) in 2016. **Proposed change**: delete paragraph.	Partly accepted. The CVMP agreed that the MUMS guidelines should be published by the end of this year. This is not really a new guideline anyway, but an update. It can be updated again, when further guidance has been published.
330	5	**Comment**: We welcome the extrapolation table and wonder if we could go further. To allow extrapolation from one finfish to all other finfish. **Proposed change**: Change Salmonidae to all finfish.	Not accepted. The current guidance does not allow minor species to minor species extrapolation. This may be amended when further guidance on extrapolation becomes available.
7 MA for food producing minor species 350	2	AVC welcomes the tabulated minimum datasets compiled in Table 2	Accepted.
369 373 391	5	**Comment**: Clarification that peer-reviewed scientific publications can be used. **Proposed change**: *'Article 13a refers to applications*	Partly accepted. Article 13a states 'appropriate scientific literature', so the GL

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526		*made on the basis of "well-established use" and permits the submission of* ***peer-reviewed*** *published* ~~*scientific*~~ *literature in place of study data*.' Also needs changing in Line 373, 391, 526, …	has been updated to reflect this.
377-380	5	**Comment**: Clarification. **Proposed change**: '*…and a summary of the pharmacokinetics* ***data*** *to include absorption, distribution, metabolism and excretion (ADME). The pharmacokinetics* ***parameters*** *of the* ***pharmacologically*** *active substance following oral exposure to residues will have been considered as part of the MRL application and cross reference* ***from peer-reviewed*** *published* ~~***scientific***~~ ***literature*** *can be made to the EMA/CVMP MRL SR/EPMAR*.'	Partly accepted. Text updated as follows: '…and a summary of the pharmacokinetics **data** to include absorption, distribution, metabolism and excretion (ADME). The pharmacokinetics of the active substance following oral exposure to residues will have been considered as part of the MRL application and cross reference can be made to the EMA/CVMP MRL SR/EPMAR'.
7.1.6 Environmental safety 405-412	2	**Comment**: AVC does not see the need for an ERA for minor species. This is based on the principle that it is a very limited use versus the major species. The examples given from line 405 till 412 are based on available date for major species. But AVC proposes to extend this exemption to all VMPs for minor species. **Proposed change**: Take out the lines 405 till 412 included.	Not accepted. An ERA is mandatory for all new applications irrespective of the underlying legal basis and regardless of its use in a major or in a minor species. However, a Phase II ERA for minor species is not required in the case where an ERA is available for a major species provided that certain conditions are met (for conditions, see QA guideline on EIA for VMPs. EMA/CVMP/ERA/172074/2008 Rev.5).
7.1.6. Environmental safety 405-410	4	**Comment**: For the sake of harmonisation, it is recommended to adjust the wording in terms of environmental safety requirements to the provisions given in the Q & A document „Questions and answers. Implementation of CVMP Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH Guidelines GL6 (Phase I) and	Accepted.

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		GL38 (Phase II)" (EMEA/CVMP/ERA/172074/2008 Rev. 5, 14 July 2016). The respective para can be found on page 1, 'Question 4 of VICH GL 6', item 2 (see proposed change below). Furthermore, it might be helpful to keep footnote[1] from the current document on safety requirements for MUMs. **Proposed change**: Taken from the Q & A document, page 1, 'Question 4 of VICH GL 6', item 2: "An ERA for minor species is not required in the case where an ERA is available for a major species, provided that: 1) the minor species is reared under similar conditions as the major species and the primary environmental release of the VMP used for minor and major species is to the same environmental compartment, e.g. soil or water[1]; 2) the exposure to the same environmental compartment from the use of the VMP in the minor species is not higher than from the use in the major species 3) any risks identified in the major species are also considered in the environmental risk assessment for the minor species 4) the ERA of the major species belongs to the same applicant." [1] If a VMP for major species, for example, is approved for stabled husbandry with manure as the primary environmental entry point, the same VMP used for minor species in aquaculture need to undertake an ERA.	
7.2 Residue data requirements	2	**Comment**: AVC welcomes the Table 4 and the 5 examples given as exemptions. AVC is waiting also for the expected draft guidance of VICH on residue studies in aquatic species and honey.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
7.2.1.5 Withdrawal periods for compounds with a "no MRL required" entry	2	**Comment**: AVC welcomes this paragraph as this happens relatively often for VMP for minor species.	Accepted.
417	5	**Comment**: Clarification. **Proposed change**: '*… and dosing regimen* ***(highest dose and longest duration).***'	Accepted.
447	5	**Comment**: Clarification. **Proposed change**: '*Setting of a withdrawal period in the minor species based on overall pharmacokinetic parameters (e.g., plasma* ***terminal*** *elimination half-live* ***calculated from clearance and volume of distribution****) could be an option'.*	Partly accepted. Included 'terminal elimination half-life', but not considered necessary to include how to calculate it.
528-530	5	**Comment**: Clarification. **Proposed change**: *'…and a summary of the pharmacokinetics* ***profile*** *to include absorption, distribution, metabolism and excretion (ADME). Absence of studies in laboratory animals must be* ***scientifically*** *justified*.'	Accepted.
562	5	**Comment**: Clarification in point 4.2 Neurotoxicity. **Proposed change**: *'Signs of neurotoxicity after acute or subchronic administration of new.* ***pharmacologically active*** *compounds in laboratory or target animals may require more detailed studies.* *• Required if substance belongs to: organophosphates,*	Partly accepted. The added comma is appropriate, but addition of 'pharmacologically active' is not considered to provide additional clarity. (Note that the title of the guideline now includes the word 'pharmaceutical').

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		pyrethroids, carbamates, avermectins'.	
568-569	3	**Comment**: The name of the table 3 is "**Data requirements for safety testing for a marketing authorisation for non-food-producing species**" but the third column states "**Minimum dataset for minor food-producing species**". What does this table give requirements for non-food producing species or minor food-producing species?	Accepted: It should be 'Minimum dataset for non-food-producing species'.
568	5	**Comment***: Table 3; should the last column also cover non-food producing species?* **Proposed change***: However, the system has **serious** limitations as **resistance is difficult to recognised** in the field and …*	Not accepted. The proposed change not understood.
370-373 and 564-566	6	**Comment**: In the tables there are changes and these do not always reflect what is mentioned in the text. For instance in table 2 "major" is deleted, but in the text on section 7.1.2. "major or minor" are still mentioned as an option. **Proposed change**: Title table 2: "Data requirements for safety testing for a marketing authorisation for minor food-producing species (where MRLs are established for the active ingredient in a **major or** minor food-producing species)".	Partly accepted. The title of table 2 has been amended to: 'Data requirements for safety testing for a marketing authorisation for minor food producing species (where the ADI has already been established or was not considered necessary').
566	6	**Comment**: EGGVP supports the current proposal when MRLs have been established for any target species and/or can be extrapolated from major/minor species to minor species. **Proposal:** full Part III.A of the dossier except Part III.A.4.4 (Studies on metabolites, impurities, other	Partly accepted. It is already the case that the MRL summary report can be used in Parts 3A2-4. Part 3A5 is a user risk assessment, which has an agreed structure based on established guidance. The data from the summary report can be used to feed into

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		substances and formulation), Part III.A.5 (User safety) and Part III.A.6 (Ecotoxicity) could be replaced by information provided in the "MRL summary reports" adopted by CVMP.	the hazard assessment. There are no data in the MRL summary report that would be appropriate to replace the ERA.
572-573	6	**Comment**: Table 4, first row / fourth column: **Proposed change**: **"**No specific conditions for minor species. **≥1 animal in total, 1 time point can be accepted."**	Not accepted. One animal at one timepoint does not provide enough data to to ensure consumer safety.
572-573	6	**Comment**: Table 4, second row / fourth column: **Proposed change**: "No specific conditions for minor species. **≥1 animal in total, 1 time point can be accepted."**	Not accepted. See previous comment.
572-573	6	**Comment**: Table 4, third row / fourth column: This section refers to egg, not milk. **Proposed change**: (correction) "No specific conditions for minor **egg** ~~milk~~-producing species."	Accepted.