European Medicines Agency
Veterinary Medicines and Inspections

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OVERVIEW OF COMMENTS RECEIVED ON

DRAFT GUIDELINE SAFETY AND RESIDUE DATA REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS INTENDED FOR MINOR USES OR MINOR SPECIES

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Region/Country
1	Fédération Européenne des Emballeurs et Distributeurs de Miel (FEEDM)	EU
2	The Food Standards Agency (FSA)	United Kingdom
3	Federation of European Aquaculture Producers (FEAP)	EU
4	IFAH-Europe	EU
5	AVC	EU

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Table 2:Discussion of comments

GENERAL COMMENTS – OVERVIEW

Fédération Européenne des Emballeurs et Distributeurs de Miel (FEEDM) :

The benefit of bees to agriculture is estimated to be seven to ten times the value of any honey produced, depending on the crop. They are also important in ameliorating the loss of biodiversity. Beekeeping is an excellent occupation for sustainable livelihoods in rural areas, particularly in developing economies. Thus it is important to protect wild and feral bees as far as possible and to encourage beekeeping.

Bees suffer from a number of diseases and infestations. Some, such as virus diseases, are incurable. Others, such as American Foulbrood, can be controlled by good husbandry, although this may be too time consuming for commercial beekeepers. Some, such as the *Varroa* mite can be controlled by a programme of medicines and husbandry (Integrated Pest Management, IPM).

The EU is only about 50% self-sufficient in honey, relying on imports from China, Argentina, Mexico and other countries, over forty in total having been placed on the EU list permitted under the arrangements detailed in Council Directive 96/23. The presence of chloramphenicol in Chinese honey and nitrofurans in Argentinian honey indicated that controls over usage are not as complete as one would wish. Honey produced in the EU has been found to contain residues of drugs such as streptomycin and sulphonamides for which there are MRLs in other species but not for honey.

The economic incentive to a beekeeper to use drugs, if he can afford them, will be strong if he sees his livelihood at risk from failing colonies. This incentive does not necessarily disappear in advanced economies. The approval for tylosin in the USA is instructive. The approved use will be only for treatment but it is difficult to see how prophylactic use will be avoided. In other countries veterinarians and pharmacists may rely economically on drug sales and have or choose to exercise little control over their use.

Bulk honey in international trade is shipped in 20 tonne container loads. Average production per hive can be as low as ten or fifteen kilos per year, so a large number of beekeepers may be involved in the production of a container load. Now that limits of detection are in the low parts per billion range, contaminated honey from one or a few beekeepers can bring the residue in 20 tonnes above the limit of detection.

The honey industry must pay attention to consumer perceptions and wishes to offer a product that is truly natural and pure. It is therefore strongly opposed to the presence of residues in honey. However, the nature of beekeeping and the long supply chain means this is not always possible for the reasons provided in the previous paragraph.

EU policy that the drug manufacturer will provide and pay for the development of all the data for drug approval is understandable, as the cost would otherwise fall on the taxpayer. Treatments for bees are a good example of the need to find an alternative solution for MUMS.

These are issues in honey production which need to be addressed realistically by the CVMP when finding a way forward.

GENERAL COMMENTS - OVERVIEW

IFAH-Europe:

IFAH-Europe appreciates the efforts to provide guidance on the safety and residue data requirements for veterinary medicinal products intended for MUMS.

Although several goals are identified in the draft guideline, currently it does not provide full clarification on what will be required. Taking existing guidelines into account, CVMP has elaborated a guideline that attempts to cover necessary safety aspects as well as the fact that products of this category should be developed as economically as possible. Unfortunately, in several areas no real reduction of data requirements can be identified, especially in the areas of analytical method development or data requirements for residue analysis/elaboration of withdrawal periods.

The interpretation of the present paper will lead to the conclusion that it will still not be possible to develop veterinary indications falling under this definition.

The wording in several paragraphs has perhaps been deliberately kept open-ended. While flexibility is generally welcomed, could the CVMP to consider the possibilities for adopting a more precise approach where possible, even if this means committing to certain data reductions for MUMS.

Overall attempts made in the guideline (GL) with respect to the reduction of requirements, and attempts to include more flexibility in the interpretation of the existing GLs, are recognized and welcomed. The present GL shows indeed some reduction in the requirements of safety data sets for MUMS. But IFAH-Europe still has the concern that based on the remaining Safety requirements a change in medicines availability cannot be expected. The investments specifically for the safety package are still substantial.

The section dealing with safety is seen to be more stringent than its US counterpart and only few reductions when compared to the major species. The section dealing with residues on the other hand was thought to be confusing with a lot of cross-referencing in the document that did not make sense.
Analytical methods are mentioned throughout the document in vague terms but no clear guidance was given as to what was actually required.

A major concern with this document is that the CVMP still has far too rigorous requirements in the areas of withdrawal period determinations, analytical method validation and injection site residue assessment.

In the following specific comments are provided for further consideration.

GENERAL COMMENTS - OVERVIEW

AVC

The AVC welcomes the production of these draft Guidelines by the CVMP as a considered and useful attempt to encourage and support the development of new veterinary medicinal products (VMPs) or use of existing VMPs for minor species and/or minor uses. The AVC would like to congratulate CVMP and EMEA on this initiative, whilst noting that the drafts fall short of what AVC believes is necessary for adequate encouragement and realisation of the intentions.

There is still no clear or consistent legislative definition in the EU for "minor species". The AVC would urge that this issue is resolved in order to clarify the areas of application of the guidelines as it seems anomalous that there are guidelines for groups of animals for which there is no definition, except by default or reference to legislation concerning other purposes, such as MRLs.

The AVC notes that certain data are allowed to be submitted after authorisation. This concept is to be applauded as it will reduce the initial investment required by applicants to generate the data for the dossier. This is particularly important where application is made for a "minor use" and a change in pharmaceutical presentation is necessary. As a "minor use" is difficult to define and will be decided on a case by case basis, there will be regulatory uncertainty, which in normal circumstances would deter application. It is hoped that free pre-submission advice will cover this topic so that development decisions can be made by potential applicants.

Under these circumstances it is desirable that any decision by the EMEA/CVMP, on the validity of "minor use" for a particular product will be binding on national authorities in order to avoid regulatory uncertainty, and there is no clear mechanism for this to take place.

AVC's opinion is that the document does not give adequate opportunity for many new drugs to be registered for MUMS, as the regulatory requirements remain very strict and are not in fact any less onerous than the current situation. The requirements for a new substance are in fact almost the same as for a major species, with only minor differences:

- apparently fewer requirements for acute toxicity - but we note that this is a relatively minor investment even for a major species
- one 90-day study for MUMS instead of two for major species
- no chronic toxicity study is required, but in any case according to Volume 8 of the Rules, there is no explicit requirement for such studies, for non-genotoxic substances used in major species.

Comments from the Food Standards Agency (FSA) and the Federation of European Aquaculture Producers (FEAP) are addressed in the below *"Specific comments on text"*

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Paragraph.	**Comment and Rationale**	**Outcome**
Fédération Européenne des Emballeurs et Distributeurs de Miel (FEEDM) :		
4.1	The generalisation in the first paragraph is unlikely to apply to honey. Only 20 grams is included in the food basket used for calculating ADIs. The highest average consumption in the EU is 1.5kg/annum (in Germany) or just over 4 grams per day, so there is already a five-fold safety margin.	1.1 See comment below at 1.7.
4.1.1	The industry does not wish to pursue MRLs for veterinary medicines which do not have MRLs established in other species, except in the case (see comments on 4.4) that an antibiotic has been found which depletes rapidly in honey and for which other criteria such as efficacy can be shown).	1.2 Not necessary
4.2.1.	The industry welcomes the fact that radiolabelled studies are not required to assess an MRL in honey.	1.3 Not necessary
4.4	The industry welcomes the fact that the CVMP regards honey as a special case where the product is mainly derived from plants and has a composition only marginally altered by the bees, which mainly remove water and add enzymes. The industry recognises that antibiotics so far found in honey are reasonably stable in that matrix. As the total number of antibiotics is around 1500, it is possible that some antibiotics disappear from honey quite quickly.	1.4 Not necessary

Paragraph.	Comment and Rationale	Outcome
	Conclusion (from the Fédération Européenne des Emballeurs et Distributeurs de Miel) Improving beekeeper training and changing the attitudes of beekeepers to disease in the EU and major exporting countries is likely to be a very slow process. Significant progress has been made in ensuring Annex IV substances are no longer used. However, it is inevitable that as enforcement agencies take action against consignments containing low residues of safe drugs which already have relatively high MRLs in other animal products, beekeepers may simply shift to another antibiotic, for which authorities do not analyse, rather than comply with the legal requirements. Environmental contamination by antibiotics may be picked up by bees, which find mammalian urine an easy source of minerals. The industry appreciates that conclusive proof of such transfer may be difficult but it is a consideration that should not be ignored. The recent paper by Grote et al[1] demonstrates persistence of certain residues in a way that would enable access by bees. Traces of streptomycin have been found in honey from the miombo forest, Zambia. The writer of this note visited the area and found the local population far too poor to afford medicines for bees. They find the suggestion extremely amusing. In addition, the local sub-species of bee does not suffer any diseases that would justify drug use. Two mechanisms can be postulated. The bees collect a great deal of water to cool the hives, providing a concentration mechanism for any streptomycin from Streptomycetes growing in local water sources. Secondly, streptomycin may be excreted in the urine of people treated for tuberculosis. Streptomycin is used as a treatment for fireblight when pome fruits are in flower and bees will be visiting. Some pome fruit growers have beehives placed in orchards to improve pollination. Thus insistence on zero residues in honey is potentially damaging to both areas of the agricultural industry. The industry wishes to develop and maintain a much more active dialogue with the CVMP and DG SANCO. We wish to develop dialogue on two possible ways of moving forward.	

Paragraph	Comment and Rationale	Outcome
	1.Regulation (EC) No. 396/2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC has an Article 18 which states that [the animal product] shall not contain any pesticide residue exceeding 0.01 mg/kg for those products for which no specific MRL is set out… In other words, 10 ppb has been set as an effective limit below which residues can be ignored. Since antibiotics are less toxic than pesticides it should be possible to put forward a good argument that antibiotics in Annexes I or III of Regulation 2377/90 for other animal species may be in honey at any level below 10 ppb.	1.5 See comment below at 1.7.
	1. We also believe arguments can be developed to justify the use of extrapolation to honey.	1.6 See comment below at 1.7.

Paragraph	Comment and Rationale	Outcome
	It will be most helpful if the CVMP can indicate how formal dialogue with FEEDM can be established. **Reference** Grote, M., Vockel, A., Schwarze, D., Mehlich, A and Freitag, M. 'Fate of Antibiotics in Food Chain and Environment Originating from Pig Fattening (Part 1)', Fresenius Environmental Bulletin, **13,** No. 11b, 2004, pp1216-1224.	1.7 The 20 g (0.3 g/kg bw/60 kg person) value appears to be a highly protective value in relation to average honey intake and the average population. Reported upper percentile values for preferential eaters may, however, be significantly higher than this value. The GEMS food data base, for instance, reports a value of 51 g (0.86 g/kg bw) for the highest 97.5 percentile consumption in the general population and 2.26 g/kg bw in children (http://www.who.int/foodsafety/chem/en/acute_hazard_db1.pdf). An occasional high intake above the 20 g may be an issue for consideration with compounds where the most sensitive effect/NOEL underlying the ADI calculation was observed following acute exposure. The intake from a 10 ppb residue concentration proposed by the FEEDM (as mentioned in (EC) No. 396/2005) in 20 g honey (0.2 µg/day) is probably negligible compared to the ADI for most antibiotics or pesticides/antiparasitics used in veterinary medicines. However, this sort of uniform lower exposure limit appears to apply to carry-over and unintentional contamination of honey as a result of treatment of plants and fruits. While recognizing the issue of the environmental contamination of honey and taking notice of possible advantages of a 10 ppb default value for residues of environmental contamination the CVMP considered that this issue is outside its remit and should be addressed by competent authorities within the EU. Veterinary medicinal products are intended for direct treatment of bees or bee hives and residues may far exceed the 10 ppb value under conditions of bee keeping practice. Therefore, in case a 10 ppb default value for residues is used, there should be a minimum of residue studies demonstrating that residues in honey stay reasonably below this value under conditions of bee keeping practice. Residue limits leading to large numbers of positive residue findings in practice would be unacceptable. In any case, whatever limit is proposed, the total intake of residues from the food basket should be in compliance with the ADI.

Paragraph	Comment and Rationale	Outcome
The Food Standards Agency (FSA)		
	No guidance is given on how to test the safety of minor use products. Although the title of the draft Guideline indicates that the document will cover products intended for minor uses or minor species, there is little coverage of products intended for minor uses. The scope of the document (Section 2) covers only products for minor species. Minor use products are mentioned only briefly under Section 2.1 Definitions.	2.1 The CVMP considered that the minor use of a product will be considered on a case-by-case basis taking into account argumentation put forward by an applicant to support the minor use of a product. Reference CVMP Position Paper regarding the availability of products for Minor Uses and Minor Species (MUMS), EMEA/CVMP/477/03-FINAL.
	The suggested reductions in the safety tests required for products to be used on minor food-producing species for which no MRLs have been set (Table 1) do not seem to be justified. The potential exposure of individual consumers to residues from products used in minor species is no less than that resulting from use of products used only in major species. It is likely that some consumers will eat as much produce from a minor species (eg. turkey) as others might eat from a major species (eg. chicken). Therefore, when no MRLs have been set, the tests that have been agreed as being necessary for testing the consumer safety of products used in major species should also be required for testing products that are used in minor food species.	2.2 The CVMP agrees in principle with the comment made and the proposed reduction in data requirements in Table 1 (i.e. data for MRL s) has been amended.

Paragraph	Comment and Rationale	Outcome
	There is a suggestion in the draft Guideline that temporary ADIs could be set, using additional safety factors to compensate for studies omitted from the database. There is however no suggestion of the magnitude of the additional factors needed, so it is not possible for us to tell whether this would give reasonable assurance of consumer safety. Although it is generally accepted that safety factors can be used to compensate for variation (irreducible uncertainty) in the risk evaluation, such factors are not usually used to compensate for uncertainty that could be removed by performing the appropriate toxicological studies. We consider that it would be best to avoid the use of safety factors to compensate for missing studies. However, if it is decided that safety factors are to be used in this way, the magnitude of the safety factors should be sufficiently large to more than adequately cover any high toxicity that might reasonably be anticipated in the missing studies. How does CVMP intend to decide on the values of the safety factors to be used?	2.3 The CVMP supports the comment that uncertainty factors are not usually used to compensate for absent data. The definition for the uncertainty (safety) factor was deliberately left open to allow its determination case by case, based on the individual substance and uncertainties in the abbreviated data set under consideration. It should be noted that there is guidance for the use of default Uncertainty (Safety) Factors in Volume 8 (see also comments at 4.2).
	Throughout the document there is reference to VICH Guidelines. Would it be more correct to refer to the current EU Guidelines?	2.4 VICH guidelines are endorsed by the CVMP. The text has been modified where relevant to make reference to CVMP/VICH guidelines.
Section 2.1, para 1, 2nd sentence:	Mention is made of the CVMP using "global numbers across Europe". Were the numbers global or European?	2.5 The CVMP referred to "global European" numbers i.e. all of Europe.
Section 4.1, para 1, sentence 1:	We suggest that this sentence should begin "Food derived from minor species usually constitutes a small proportion of the diet…" in place of "A minor species usually constitutes a marginal component of the diet…". Apart from this minor point, we endorse the opinion expressed in this sentence and we agree that consumer safety must not be compromised by any reduction in the requirement for safety testing minor use or minor species products.	2.6 Editorial changes have been included.

Paragraph	Comment and Rationale	Outcome
Section 4.1, para 2, sentence 1:	The text rightly states that standard safety data requirements relating to any effects that might occur after a single exposure (eg. developmental toxicity, mutagenicity) cannot be reduced for minor species. It is therefore unclear why acute toxicity studies are not required for minor species (whilst they are required for major species). In addition it is not clear why effects that would only be seen after repeated exposures have been excluded from the list of studies to be performed on drugs for minor species. This is particularly confusing as it has already been stated in the Guideline that one cannot assume that consumer exposure to minor species drugs will be any lower or less frequent than to major species drugs.	2.7 Acute toxicity studies are not required for major species in accordance with Volume 8. Effects after repeated dosing will be taken into account as well but some reduction of repeated dose toxicity testing can be granted on a case by case basis, if scientifically justified (see also discussion below)
Section 4.1, para 2, Final sentence:	The reduced requirement for repeated dose testing that is described here does not seem justified. If adequate safety testing of products used in major species requires 90-day studies in two species plus a chronic toxicity test, what is the justification for using only a 90-day study in a single species. As described in the first paragraph of Section 4.1, some populations of consumers might eat considerable amounts of foods derived from minor species. Why should we require fewer safety tests to protect the safety of consumers of minor species when their potential for exposure to the drug could be similar to that of consumers of major species?	2.8 The CVMP agrees that the full data requirements for repeat dose toxicity are met for minor species. However a justification can be submitted to reduce the data requirements for the repeat dose studies, including chronic studies: this will be considered on a case-by-case basis taking into consideration the species and the pharmacological/toxicological profile and applicants should seek scientific advice from the CVMP in these cases.
Section 4.1.1, para 2, line 1:	We suggest a minor addition to make the wording flow more easily: "It is proposed that**,** based on **an** abbreviated data set and…"	2.9 Editorial changes have been included.
Section 4.1.1, para 2, sentence 1:	Any temporary ADI that is set should be time-limited. There should be a deadline set for the provision of the outstanding data that would allow the setting of a full ADI. If all of the outstanding data are not provided by the deadline, there should be a withdrawal of the temporary ADI and any provisional MRLs set on the basis of the temporary ADI.	2.10 A temporary ADI can be determined for a minor species and MRLs can be established. A temporary ADI would remain until a final ADI would be determined e.g. when an application for a major species was made.

Paragraph	Comment and Rationale	Outcome
Section 4.1.1, footnote:	It is suggested that the uncertainty factor should be sufficiently high to give a temporary ADI that is at least as high as the ADI would be if the missing data were available. This seems to pre-judge the result of a study that has yet to be performed. We find it hard to envisage how this advice could be reliably followed without imposing draconian safety factors to compensate for the increased uncertainty about the value of the ADI.	2.11 The principle is supported by the CVMP. It should be noted that there is guidance for the use of default Uncertainty (Safety) Factors in Volume 8.
Section 4.1.2, sentence 1:	The wording of this sentence is a little clumsy.	2.12 Editorial changes have been included.
Section 4.1.2, para 2, final sentence:	It is not clear whether an abbreviated data set (excluding pharmacodynamics) may be considered, depending on the substance under consideration, for drugs used in any species or whether the abbreviated data set will only be considered if the drug is to be used only in minor species. We consider that such an exemption should be based on the type of drug and not on whether the target species is a major or minor species.	2.13 The abbreviated dataset for pharmacology is based on the substance and not whether it is a major or minor species.
Section 4.1.3, sentence 2:	We suggest the following rewording: "VICH Guidelines should be followed with regard to the **choice** of the studies performed and **the** toxicological tests should be performed **in accordance with** the relevant OECD **methodological** guideline or other **internationally** recognised **methodological** guidelines."	2.14 Editorial changes have been included.
Section 4.2.1, para 3:	This one-sentence paragraph with a series of bullet points is ungrammatical. It might be better to merge this paragraph with the preceding one-sentence paragraph, linking the two sentences with the word "if".	2.15 Editorial changes have been included.
Section 4.2.1, para 3, bullet points:	Do all of the criteria set out in the bullet points need to be met before it is acceptable to extrapolate ADME data to minor species, or does only one of the criteria need to be met? This needs to be made clear.	2.16 These are examples of the data that would be acceptable.

Paragraph	Comment and Rationale	Outcome
Section 4.2.1, para 3, bullet point 2:	It is not clear what is meant by "uniform" metabolism.	2.17 "Uniform" means comparable metabolism. Editorial changes have been included.
Section 5.1.2, sentence 1:	This sentence should be worded more clearly in plain English.	2.18 Editorial changes have been included.
Section 5.1.3:	The purpose of the laboratory animal pharmacokinetics studies is to indicate how the test material is handled by the test animals used in the toxicological studies and also to give an idea of how the drug is handled in humans. Studies performed in some target species (eg. ruminants, fish, bees) might not be appropriate for this purpose and extrapolation of the results to laboratory animals and humans might be misleading.	2.19 For pharmacological data, cross reference can be made to Part IV.
Section 5.1.4, para 1:	It is not clear what substance should be tested. We propose the following rewording: "Toxicological data are required on all pharmacologically-active ingredients of veterinary medicines for an assessment of adverse effects. The dataset must be sufficient to establish this. Any pharmacologically inactive ingredients of the medicine should be known to be safe or else similarly tested."	2.20 The CVMP does not agree to this rewording because it is not in accordance with the Directive 2001/82/EC as amended.
Section 5.1.4, para 2:	It should be made clear that it is the formulated product that should be tested for user safety. However, in some cases data on individual ingredients might be accepted *in lieu*. It might be better to move this paragraph, dealing with user safety, to Section 5.1.5 User Safety Assessment.	2.21 The CVMP does not agree to this paragraph.
Section 5.1.5,	Proposal for a new sentence: We suggest that the following could usefully be inserted after the third sentence: "However, it should be recognised that the amount or frequency of worker exposure to medicines used on minor species will not necessarily be any less than with major species medicines."	2.22 This is already stated in the User Safety Guideline which applies to all Marketing Authorisations and which is referred to in this paragraph.

Paragraph	Comment and Rationale	Outcome
Section 6.1.5,	Proposal for a new sentence: We suggest that the following could usefully be inserted after the third sentence: "However, it should be recognised that the amount or frequency of worker exposure to medicines used on minor species will not necessarily be any less than with major species medicines."	2.23 Same comment as above
Table 1:	We do not believe that there is adequate justification for the proposed reductions in toxicological testing of minor species medicines for which MRLs have not been set. Therefore, we suggest that the term "Same criteria apply" should be stated in the third column at lines 2.1, 2.2, 3.1, 3.2, 3.4 and 3.4 as well as at the lines were this statement is already made.	2.24 It is not appropriate to add "Same criteria apply" because: Line 2.1: the data requirements should be considered on a case by case basis and applicants should have the opportunity to provide a reduced data package which they must justify. Line 2.2: this is the same data requirements but the guideline allows for cross reference to residues dossier when appropriate. Line 3.1: see earlier comment "Acute toxicity studies are not required for major species in accordance with Volume 8" Line 3.2: the SWP has proposed an amendment to this section – see earlier comments . Line 3.4: already states "Same criteria apply"
Table 1, footnote 3:	We would not describe single-generation reproduction studies as having "no scientific significance". However, we agree that two-generation studies should be provided for the assessment of veterinary medicines.	2.25 This comment is supported and the text has been amended as follows:"The 2-generation study replaces the 1-generation study on the grounds that often the 1-generation study has ~~no~~ insufficient scientific significance".
Table 2:	It is not clear to us why the third column requests the provision of reports of toxicological, pharmacological and microbiological studies for minor species products for which MRLs have been set for major species. Surely the CVMP will already have seen and assessed the safety data for such substances. Could not the CVMP refer to its own Summary Reports (plus request reports of any new studies that have appeared in the interim) rather than request the submission of all of the data listed in the third column?	2.26 The data requirements are for a veterinary medicinal product, therefore there may be studies on the product/formulation. The applicant can submit the CVMP MRL Summary Report for the active ingredient as part of the dossier and to justify the absence of study data.

Paragraph	Comment and Rationale	Outcome
Table 3:	In this table that deals with non-food-producing species, we suggest that the statement "*Not required for topical use if negligible systemic absorption*" be deleted from the third column at the line for 3.6 Carcinogenicity. When there is poor topical absorption of a drug given to a pet, the opportunity of human exposure is maximised. The drug stays on the skin (or in the fur/feathers) so that anyone handling the pet will also become exposed. There is nothing to suggest that the exposure of the owner will be any less for a minor species than when a major species is treated, so we see no reason to have different safety testing requirements depending on whether a major or a minor species is treated.	2.27 This exemption is in the legislation in Directive 2001/82/EC as amended by 2004/28/EC in Annex I part 3, Chapter 1, 3.7

Paragraph	Comment and Rationale	Outcome
Federation of European Aquaculture Producers (FEAP):		
	The FEAP, the Federation of European Aquaculture Producers, is thankful to the EMEA and its CVMP for the interest and attention shown on the availability of veterinary medicinal products for minor uses or minor species. The FEAP welcomes the Guidelines that were published on 13th April 2005 and open for public consultation until 31st October 2005. Such Guidelines are intended to be of major use to the pharmaceutical industry involved in the licensing activity of veterinary medicinal products for MUMS. Nonetheless, it is both FEAP's interest and aim to provide its opinions on several of the points within these Guidelines. Firstly, FEAP's main concern refers to the definition of MUMS, and the subsequent list of animal species included: with reference to the AVC document, dated December 2003, FEAP maintains consistently that salmonids should not be included as a single group of animals, since they are not, neither at a zoological level nor at a zootechnical level. This is because the salmonid family contains different species that possess their own individual characteristics that are recognised by different farming techniques. To group all salmonids together means that this position does not take account of the individual species and the individual needs. FEAP has made the point that, if this position is to be the case, all fish could just as easily be grouped as Teleosts. In addition, one should remember that the low commercial value of some species of the salmonid family, such as freshwater rainbow trout, does not justify or support the decision to use numbers or weight (tons) alone for categorising the whole group as a major species. Finally, in the position paper EMEA/CVMP/477/03/FINAL, a footnote indicates " It is recognised that marketing authorisations covering several salmonid species in the data requirements for the second and further species would depend e.g. on the indication and on the route of administration, and should be decided on a case-by-case basis". The FEAP welcomed these comments but believes that this position will only be of help after that one product has been registered, based on the requirements for a	3.1 The comments raise questions on the definition of "MUMS" and in particular "minor species" and the consideration of Salmon as a minor species. The CVMP will consider separately these comments, and will address the definition of Salmon outside the considerations for this guideline.

	major species • FEAP therefore asks that salmonids be excluded from a major species list or otherwise; • If salmon (Salmo salar) is to be considered as a major species, the other salmonid species should be seen as minor species.	
	Secondly, when presenting these Guidelines to the public, the publication of Guidelines on immunological products was anticipated for July 2005. To date, such Guidelines have yet to be published. • FEAP underlines the importance of immunological veterinary products to the professional fish farming sector; • Guidelines that helping their licensing requirements are urgently needed. Finally, adopting a more general approach and although FEAP cannot judge the more technical aspects of the Guidelines, as the representative organisation of fish producer organisations throughout Europe, it believes that these are a step in the right direction for the acknowledgement of the importance of the MUMS issue. Taken together, the breeding and the farming of minor species is an important reality with European livestock production. Nevertheless, these production activities must be provided with the conditions to be able to work correctly, while respecting animal health and food safety. The FEAP judges that the availability of veterinary medicinal products as a *conditio sine qua non* for to attain these goals.	

Paragraph	Comment and Rationale	Outcome
IFAH-Europe:		
Introduction	Although "minor uses" is part of the headlines and the definition (2.1), the guideline is really not specific at all about "minor uses", although these are always mentioned along with minor species. Specifically in the scope, minor uses are not included. We would be grateful if the GL could include more explanation about minor uses in the introduction. In the introduction on Page 3, paragraphs 2 and 3 should be deleted, as they are not helpful at all for a general understanding of the topic.	
Ad 2.1. Definitions / Minor uses	The considerations on a case-by-case basis being mentioned in a definition part are by necessity quite vague. However, more guidance would be useful and appreciated by industry.	4.1 See earlier, above, comment at 2.1.
Ad 4.1.1 Establishment of the ADI and MRL in a minor food producing species – Tabulated abbreviated **datasets**	Paragraph 2 states: "*a temporary ADI can be determined which in turn is the basis of the provisional MRLs…*" Our interpretation of this wording is that only temporary ADIs and provisional MRLs can be set for MUMS if there are no MRLs in major species. We see no need to refer to temporary ADIs and provisional MRLs. For a minor species application an ADI and MRLs should be elaborated based on the best information available. If new information is provided at a later date, the ADI and MRLs can be revised. Also the extra safety factor (SF) proposal is a concern as such a value is absolutely open, and thus the whole procedure. IFAH-Europe recommends that this extra SF should be of a minimal nature (e.g. 2-fold) as the reduction of the required data package is limited. We would also appreciate a rewording of the footnote. An ADI, based on a larger data set, should possibly be higher than the one estimated from smaller data packages including a safety (uncertainty) factor. Uncertainty means 'not enough information' and, assuming the required data package for a major food producing species is sufficient, no further uncertainty is present. A possibly conclusion would result in another ADI (higher **or** lower then the first one).	4.2 Setting of the final ADI would require all data according to Volume 8. The ADI is not a species specific value, but refers to properties of the substance used, and a final ADI value can only be set based on complete information for all relevant hazards endpoints. The definition for the uncertainty (safety) factor was deliberately left open to allow its determination case by case, based on the individual substance and uncertainties in the abbreviated data set under consideration. The final ADI can become higher once complete information is available, but it should not become lower. This is why selection of the uncertainty factor is a critical step for setting the temporary ADI. The uncertainty factor should be conservative enough to ensure that potential uncertainties are sufficiently compensated. For this reason a uniform default value (e.g 2) for the uncertainty factor was not considered appropriate.

Paragraph	Comment and Rationale	Outcome
Ad 4.1.2: Pharmacological data	Details of pharmacodynamic studies in laboratory animals are required. This goes beyond the 2001/82/EC requirements. Such data have only to be submitted when they are available. The first paragraph seems to contain contradictory elements. What kind of anticipated pharmaco-dynamic effects might be meant (if no data do exist, especially, if new chemical classes will come under evaluation). The statement in the next paragraph: "*These are fundamental data that are required for selection of appropriate species for toxicity studies and the establishment of an ADI...*" is an overstatement and could be left out. Furthermore, to assume human data, when no food producing major species is yet involved, seems to be unrealistic.	4.3 This is inaccurate. Annex I of 2001/82/EC clearly states the requirement for these data. Annex I " … pharmacological studies may also assist in the understanding of toxicological phenomena. Moreover, where a medicinal product produces pharmacological effects in the absence of a toxic response, or at doses lower than those required to elicit toxicity, these pharmacological effects shall be taken into account during the evaluation of the safety of the medicinal product. Therefore the safety documentation shall always be preceded by details of pharmacological investigations undertaken in laboratory animals and all relevant information observed during clinical studies in the target animal."
Ad 4.1.3: Toxicological data	As VICH relies on OECD already, IFAH-Europe proposes the following rewording: "Toxicological data are required according to the VICH guidelines. Any deviation should be adequately justified."	4.4 Not accepted. The current wording is more informative and gives clarification for the data requirement. The proposed rewording is not accepted.
Ad 4.2.1: Total residue studies	As section 4 refers to minor species only, what about development for a novel compound intended for ***minor uses***?	4.5 see earlier comment on minor use at 2.1.
	This section makes the statement that total residue (radiolabelled) studies are normally indispensable for most VMPs and then lists three possible exceptions when it may not be required for minor species. May we suggest that this first statement is modified to read: "Total residue studies will not normally be required for a minor species. It is suggested that the Sponsor seek scientific advice and review the available literature and study-specific information with the CVMP with respect to the need for radiolabeled studies on a case-by-case basis."	4.6 CVMP agrees to amend this paragraph by deleting "are indispensable" and replace with "will normally be required". Leave the examples for possible exceptions in the guidelines (may be useful in drafting the advice).

Paragraph	Comment and Rationale	Outcome
	Furthermore, it is stated that these studies are indispensable for most veterinary substances to identify the residue of concern in the minor species and to establish the ratio marker to total residues, if necessary. However the EMEA GL on injection Site Residues (page5/11) states that radiometric studies are normally not necessary for known substances with known composition of the residues. This fact should be also reflected the new MUMS safety data guideline in order to avoid discrepancies in the requirements.	4.7 The cited passages in the EMEA GL on "Injection Site Residues" (page 5/11) refer to known (generic) compounds, for which useful information is already available for the substance/formulation under consideration and in the species concerned. The MUMS GL refers to new substances for which an MRL is established for the first time in a specific species and residue data have not been assessed before.
Ad 4.2.2: Marker Residue Studies	This section indicates that a full residue study for minor species is required to set the MRL but this is then contradictory to elements in 4.3.1 where a limited depletion study is mentioned.	4.8 There is a difference between the two statements: paragraph 4.2.2 refers to compounds which have been developed for a minor species and for which there is no MRL in the major species. In this case a marker residue study should be available to demonstrate depletion of residues below the MRL. Paragraph 4.3.1 refers to the extrapolation of an MRL from a major to a minor species. In this case a reduced data package on the residue depletion may be sufficient because the metabolism and residue depletion profile is already known in a (evolutionary related) major species.
Ad 4.2.3: Regulatory analytical methods	Clarification is needed as the wording is rather weak and partly inconsistent: • 'a reduced validation of the proposed regulatory analytical method ***could*** be acceptable.' We believe this is an area where more commitment to accept reduced data could and should be made. For example, requiring data on the limit of detection is not essential and as such it should not a mandatory part of the data package. • Testing at MRL level 'and' half the MRL is mentioned, while on page 10 (5.2.1.4 second paragraph) an 'or' is written. • Also, "… storage stability data should be supplied." versus section 5.2.1.4 stating "… should be supplied when samples are stored prior to analysis".	4.9 Agreed, the limit of detection is normally not the most important parameter in the method validation, but this parameter could nevertheless be very useful in assessing the inherent detection/quantification capability of a method (LOD and LOD/LOQ ratio information may also be useful for reference laboratories when developing multi-substance methods). Apart from that, determination of the limit of detection is not specifically difficult, not specifically time or material consuming (an analysis of blank control samples has to be performed anyway) and is usually not expensive. The other statements now read: MRL level 'and' half the MRL. Storage stability should be supplied for the routine analytical method in any case (it may be expected that samples are frequently stored prior to analysis). For the methods used in residue studies information on storage stability will necessary on a case by case, depending on whether and how long samples/under what conditions samples have been stored prior to analysis.

Paragraph	Comment and Rationale	Outcome
Ad 4.3.1: Extrapolation of MRLs from major to minor species	The text under this paragraph is rather complicated. The "validation of the analytical methods", "presence of marker residue", and "requirement for a depletion study" are mixed in one paragraph. **Proposal**: delete the first sentence on page 7 *"...confirming a similar exposure situation of the consumer in relation to these species*". In our view the food basket for TMDI calculation is independent from species, so this will be irrelevant for MRL setting. There is no definition of a "limited depletion study". And more clarity is required as to what is meant by the statement "*When extrapolating the MRL to a minor species it is considered not necessary to provide a fully validated study*." More clarity and commitment (see above under 4.2.3: Regulatory analytical methods) would help to show how method validation differs from the full validation. Some preamble is needed before paragraphs i) to iv) in this section. Under ii) and iii) on page 7, the statement "as outlined above" in the last sentence is unclear. Section (iv) can be deleted as the important elements are already explained in the 2nd paragraph of 4.3.1.	4.10 The majority of the text in this paragraph is taken from, or is similar wording to that, in the current CVMP Note for Guidance that it refers to (EMEA/CVMP/187/00 – FINAL), therefore no amendments have been made so that guidance is consistent.
Ad 4.4	This section illustrates a fundamental problem with setting all MRLs. It is not understood why the MRL should be influenced by typical residue concentrations instead of being set on safety data (ADI).	4.11 An MRL is not a purely theoretical value - solely influenced by the ADI and independent from the residues actually present in practice. MRLs normally serve as a means of control if veterinary medicinal products have been used according to label instructions and they form the basis for setting practicable withdrawal periods. Therefore, it is necessary to check - prior to setting of the MRL - if the residues which occur in practice, are MRL compliant under normal conditions of use of the veterinary product. This can only be seen in residue depletion studies ("reality check of the MRL"). If residues do not become lower than the proposed MRL within a reasonable withdrawal period, then the MRL may be increased (if the size of the ADI allows it) or, otherwise, a practicable MRL cannot be set .

Paragraph	Comment and Rationale	Outcome
	It is agreed that special requirements exist for honey, but the statement that "zero" withdrawal is the only practical period is questionable. Because honey is stored for long periods of time prior to marketing, or is continually produced in the hive over an extended period, a withdrawal period based on time from treatment should not be excluded.	4.12 The arguments concerning a "zero" withdrawal period in honey as the only feasible and practicable withdrawal period are still considered valid.
5. Marketing authorisation applications for food producing species – General requirements Ad 5.1.4: Toxicological data	**Proposal**: This paragraph should be shortened by stating: "application of user safety guideline (EMEA/CVMP/543/03-Final)". User safety is mentioned twice here and in detail under 5.1.5., and therefore could be covered by one single paragraph.	4.13 The CVMP does not agree with this proposal because this section (5.1.4) refers to "Part III.A.3 Toxicology" of the dossier and presents the toxicology study data (or published literature) for the active ingredient, whereas the following section (5.1.5) refers to Part III.A.5 User Safety which uses the toxicology data to make a user risk assessment.
Ad 5.2.1	Table 1 refers to setting MRLs not withdrawal times (this would be at present table 4).	4.14 This is an oversight and editorial changes have been included. Table 1 has been amended to read "Table 4"
Ad 5.2.1.1	This section is a good example where means should be sought to tighten vague wording, such as: "it could be considered to follow an approach...", "should be possible", ..."could be considered". Unfortunately this type of guidance is not helpful when preparing a development plan and the text should be more precise. If new data on injection site residues are required (which is considered unreasonable for identical product and extrapolation of cattle/sheep to other ruminants, from chicken to other avian species etc.) and if the data have to be elaborated according to the latest injection site residue guideline, then it will be very expensive (and will therefore become an issue of drug availability). Thus, for identical products, there should be no need to re-evaluate injection site residues. It is stated that current guidelines for withdrawal period elaboration do not differ between major and minor species. There should be a major distinction here. This is an opportunity to substantially reduce the requirements.	4.15 It is the CVMP firm believe that the behaviour and depletion of drugs at injection sites or other local sites (e.g. dermal application) can not be predicted to a degree that interspecies extrapolation would be possible without a minimum set of data.

Paragraph	Comment and Rationale	Outcome
Ad 5.2.1.2:	In order to create a useful guidance it is necessary to explain the extent to which an abbreviated set of data will be acceptable (see also point 5.2.1.4).	4.16 Given that differences in species, formulations, dosing regimens, routes of administration etc. can be quite numerous and variable, it was not possible to provide more specific guidance. Here, the guideline can only provide examples and a general outline of points to be considered. It is suggested that the applicant, on a case by case basis, seeks scientific advice with the CVMP or the national authority on the optimal approach to be taken, based on available literature and other compound-specific information.
Ad 5.2.1.2 Products with Different Formulations	3rd paragraph: "*In case of dermal application … local residues…need to be investigated*" – does not seem to be practical. This may include a high variability in application sites and the likelihood of not being accepted by authorities due to "wrong tissues investigated" is high. In Table 3 (Data Requirements for safety Testing For a Marketing Authorisation for NonFood-Producing Species) several data sets can be omitted if the veterinary medicinal product is intended for topical use in case of negligible systematic absorption. Clarification should be provided if this exemption can be extended to orally administered products which show negligible systematic absorption.	4.17 See comment at 4.15
Ad 5.2.2	Last sentence of this chapter in the position paper should possibly read "… according to the rules under 5.2 above"?	4.18 Agreed

Paragraph	Comment and Rationale	Outcome
6. Marketing authorisation applications for non-food producing species – General requirements Ad 6.1	Text under 6.1 and 6.1.1 is practically identical. Please delete the preamble under 6.1.	4.19 The CVMP does not agree with this comment; and considers it is important to provide detailed information.
	The use of MRL summary reports is well understood for a "Bibliographic application". Consequently the long preamble in section 6.1.2 can be deleted so that the text of the paragraph can be reduced to the last sentence ("*MRL summary reports can be submitted*…).	4.20 The CVMP does not agree with this comment – the use of MRL summary reports is new with the new pharmaceutical legislation and the guideline offers an explanation for this change.
	The requirement for pharmacological data under paragraph 6.1.3 in laboratory animals again goes beyond the 2001/82/EC Directive.	4.21 This is inaccurate. Annex I of 2001/82/EC clearly states the requirement for these data. (see also comment at 4.3 above)
	In section 6.1.4 (Toxicological data) it would be sufficient to mention that the toxicological data required to cover user safety are specified in the corresponding guideline. Data on fertility and reproduction effects should not be singled out here as particularly important. The risk of reproduction toxicity after accidental injection would not be covered by a reproduction study according to the 2001/82/EC Directive if the product is for non-food producing species and not intended for breeding animals. The user safety is specifically addressed under 6.1.5, where the text is more than sufficient.	4.22 Similar to CVMP comment 4.13: The CVMP does not agree with this comment because section 6.1.4 refers to "Part III.A.3 Toxicology" of the dossier and the toxicology study data (or published references) for the active ingredient, whereas the following section 6.1.5, refers to Part III.A.5 User Safety which uses the toxicology data to make a user risk assessment.
Tables Ad Table 1	There is no reference to Ecotoxicity in table 1, although Ecotoxicity is included in Tables 2 and 3.	4.23 Ecotoxicity is not a requirement for MRL applications and is therefore not included in Table 1.
	Generally, one should refer to VICH GLs under standard data requirements. While it seems very generous that single dose toxicity studies are not required, the well-known fact is that these data will be available from manufacturing and transport safety. Under "Repeat dose toxicity" the reference to species selection and pharmacokinetic data should be deleted. In this section the meaning of "appropriate" (pharmacokinetic data) is not understood.	4.24 The single dose requirements are the same as those in the current requirements in Volume 8 and therefore there are no changes proposed. The CVMP proposes a change to the draft guideline (see earlier comments at 2.8) in that the full data requirements for repeat dose toxicity are met for minor species. The Repeat dose toxicity data will not be reduced and this text has been deleted.

Paragraph	Comment and Rationale	Outcome
	The same lack of understanding is with "Cross-refer to any other acute toxicity studies (e.g. user safety studies)". Furthermore, is OECD 425 (preferred in the US) not acceptable?	4.25 This comment refers to the current wording in Volume 8 which refers to other acute toxicity studies that may have been performed to obtain information on other aspects, such as operator safety. If such data exists (published literature or study data) it should be referred to in the dossier. OECD 425 is not listed because this is not given in the VICH Guidelines. Applicants have the opportunity to submit alternative protocols with a justification for the deviation from the VICH guidance. No further comment from CVMP.
Page 15 point 3.5:	There has been a mix-up of the guidelines between point ii) and iii). Apart from this mix-up, the package under I) – iii) is listed according to Volume 8, but VICH 23 requests an *in vivo* study already in the standard battery. (There are differences between the authorities on these points, but the VICH decided to go this way – also to be in line with ICH).	4.26 Same comment a above.
Section 4.3.1.	Assuming section 4.3.1. (gut-flora evaluation) will remain, then provision for even further reduction of toxicology requirements should be permitted when it is clear that the microbiological ADI will be determining. This is especially needed for a MUMS product.	4.27 The CVMP does not agree with this comment, however applicants can submit justifications for the omission of data.
Section 4.3.2	Section 4.3.2 should not need to be considered for a minor species. The food processing issues are not related to human food safety. This would also apply to Table 2, section 4.3.	4.28 The CVMP does not agree with this comment, however applicants can submit justifications for the omission of data.
Ad Table 2:	Some text appears less accurate than expected in a guideline: e.g. "Study in 1 species at 90 days and this may be replaced by a target animal study". OR: What does "Modified tests" mean?	4.29 The text in 3.2 for "Repeat dose toxicity" has been amended (see earlier comments) so the mentioned text has been deleted. However, "Modified tests" refers to studies that may not follow standard protocols.
Ad Table 3:	Again, "pharmacological studies in laboratory animals" is not a standard data requirement. "No abbreviated data set" does this have the same meaning as "same criteria apply"? More consistent language should be used.	4.30 This is innacurate. Annex I clearly states the requirement for these data. The terms do mean the same and editorial changes have been made to use consistent terminology.

Paragraph	Comment and Rationale	Outcome
Ad Tables 4 and 5:	Important instructions are given in Tables 4 and 5. These are not mentioned in the Table of contents nor are they in the text of the guideline elsewhere. This should be reconsidered.	4.31 The Table of Contents have been updated The tables 4 & 5 display current data requirements for residues studies and analytical methods and are for reference only. Requirements for minor species will be superseded by the provisions of this guideline, once adopted.
	The requirements for the withdrawal period (WDP) for a minor species are too high. An appropriate WDP can be proposed based on data from *ca* 4 animals if the marker is detected at or near the MRL. The reference to statistics in this section should be deleted. There is no need for a statistical WDP for a MUMS product. The idea of performing a milk residue with 19 cows for a MUMS product is not realistic. Our impression is that the focus on the purpose of the guideline is completely lost here.	4.32 See comment above.
Table 4:	Reference under "meat/withdrawal periods" should read footnote 3 (not4). Table5: is reference under minor species to footnote 3 correct?	4.33 Editorial changes have been included. The correct reference is "footnote 2" Editorial change have been included. Reference has been made to Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species (EMEA/CVMP/153a/97).
Table 5	This table needs to be clarified. What is the purpose of third column?	4.34 This is the current requirement for the residues depletion studies conducted for the application.
	The analytical method requirements need to be further reduced for MUMS. In one occasion (6 replicates at 2 concentrations) validation of accuracy and precision should be all that is required. LOD should be deleted; LOQ may be deleted based on what two concentrations are chosen for the validation. Stability data are required only to the extent necessary to validate the residue data in a specific study.	4.35 See comment above at 4.31.
	Page 21 of draft guideline: reference to 610/01 should read "Points to consider regarding efficacy requirements for minor …" (also cited wrong in the running text before in the position paper).	4.36 Editorial changes have been included.

Paragraph	Comment and Rationale	Outcome
Association of Veterinary Consultants (AVC)		
4.1.2. Pharmacolo-gical data	"… 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 justified with a summary of anticipated pharmacodynamic effects." This sentence is vague and practically inapplicable. It would be difficult for an applicant to anticipate pharmacodynamic effects without any data, so we recommend that CVMP clarify how it expects applicants to address this (e.g. by expert report, by including published data from other members of the same structural family, or other means).	5.1 As this would be applied on a case-by-case basis, more specific guidance cannot be given. Requests for scientific advice can be submitted in case of doubts.
4.2.1. Total residue studies	Radiolabelled studies could be conducted on a case-by-case basis, e.g. when: "Available absorption, distribution, metabolism and excretion (ADME) data (e.g. in laboratory species) may be extrapolated to the minor species." The conditions for extrapolation should be described. Again we question on what basis extrapolation can be possible from species to species without some data on the fate of total drug?	5.2 It is not fully clear what the comment is suggesting. Section 4.2.1 is dealing with requirements for "total residue studies" in case of novel compounds intended for minor species. It is clearly stated in this section that total residue studies will normally be required (and that there is normally little basis for extrapolation). However, this section also gives some hints and examples as to the conditions under which radiolabelled study could be dispensed with on a case by case basis. This is not to be considered as an exhaustive discussion of all situations that may arise. Each exception will have to be specially justified.

Paragraph	Comment and Rationale	Outcome
4.2.3. Regulatory analytical methods	"However, a reduced validation of the proposed regulatory analytical method could be acceptable. The method should be validated in respect to the "limit of detection" and the "limit of quantification" and, at least, for accuracy and precision at the level of the MRL and half the MRL" There is no justification for the limit of detection to be determined by the applicant for MUMS (or for major species, for that matter): 1) The LOD is irrelevant for substances to be analysed at a defined level (i.e. with an MRL). It is only of importance for banned substances or unauthorised substances, outside the scope of the Guideline on MUMS. 2) Furthermore, a LOD determination is only relevant to the samples and equipment used at the time the tests are performed. If the work is repeated in a different laboratory, with different reagents, different animal sources, different equipment, etc, then a different result could be obtained. 3) There is little agreement on how it should be determined. These guidelines require 20 samples. To serve the real objective of a LOD, this means samples should be taken from 20 animals, and in fact 20 animals from different breeds, kept under different husbandry conditions, from different member states. Is it really ethical to demand 20 samples from animals, i.e. about the number already sacrificed for a residue depletion study, for a result that is instrument-based and irrelevant for a residue depletion study?	5.3 Some general discussion on the relevance of the LOD and clarification regarding the requirements for precision and accuracy is already contained in previous comments (see discussion of IFAH's comments on "Regulatory analytical methods"; Ad 4.2.3)
	The proposal for precision and accuracy (1/2x MRL ***and*** 1x MRL levels) should be consistent with other parts of the guideline, e.g. 5.2.1.2. (".. accuracy and precision at one concentration level only – i.e. at the level of MRL") and 5.2.1.4. (…" accuracy and precision at the level of interest only – e.g. at the level of MRL or half of the MRL" …). AVC has used approximate actual costs as experienced by their clients, to perform the following analysis, comparing the basic cost of a registration file (Safety/Residues only) for major species with that proposed by the current draft guidelines for minor species (*table included, not reproduced here*) It may thus be stated that the cost of the Safety/Residue file is reduced by only 15% for a MUMS application when compared with an application for a major species. In AVC's view and experience, this will be insufficient to be considered as a significant improvement to address the problem of lack of veterinary medicines for MUMS.	The last paragraph of Section 5.2.1.2 has been brought in line with the statement under 5.2.1.4. "For residue studies in the minor species an abbreviated validation of the analytical method could be acceptable. It could be sufficient to validate the method for accuracy and precision at two concentration levels only – i.e. at the level of the MRL and one half the MRL. Under 5.2.1.4 (second paragraph) it reads now "at the level of the MRL and half the MRL" for consistency.

Paragraph	Comment and Rationale	Outcome
4.3. Extrapolation of MRLs	No additional consideration of special nature of MUMS - similar to existing guideline (EMEA/CVMP/187/00-Final).	5.4 The text in this paragraph is a summary of the provisions of the current CVMP Note for Guidance that it refers to (EMEA/CVMP/187/00 – FINAL), therefore no amendments nor additional considerations have been made.
5.2 Residue data requirements	Several parts of this chapter are vague, e.g.: "In case of the same veterinary medicinal product with the same MRL in the major/minor species, it *could be considered* to follow an approach similar to the approach for extrapolation of MRLs, i.e. no specific or no residue depletion studies required in the minor species. In accordance with the approach accepted for extrapolation of MRLs, an extrapolation of withdrawal periods *should be possible* from cattle/sheep to other ruminants, from chicken other avian species, from *Salmonidae* to other fin fish etc." "The analytical method used in a residue depletion study must be validated *to some extent*; otherwise the study itself would not be valid. If the analytical method had been used for the residue studies in a major species, then applicants *might send* an abbreviated set of data." "For the purpose of residue studies in a minor species, an abbreviated validation of the analytical methods *could be acceptable*. *It could be sufficient* to validate the method for accuracy and precision at the level of interest only, e.g., at the level of the MRL or half the MRL if the aim of a study is to demonstrate that residues are below this level …" "Residue studies according to guidelines *are normally required* for veterinary medicinal products for a minor species where previously no similar product was authorised for a major species." Our opinion is that the industry can work only with more precise guidelines.	5.5 The wording in several paragraphs has been purposely kept open for reasons of increased flexibility. But, nevertheless, it should not been overlooked that the guidelines offer some interesting and very concrete options to significantly reduce data requirements for residue studies (e.g., simple extrapolation of residue data between major/minor species is possible under certain conditions, largely reduced validation requirements, possibilities to omit residue data based on reasoned scientific justification instead of conducting standard studies). Another reason for not adopting a more precise and straightforward approach in some parts of the guidelines (e.g., extrapolation between non-identical products, route-to-route extrapolation, necessity for radiolabelled studies etc) is that, up to date, there is very limited scientific data and experience in applying interspecies extrapolation of residue data in the field of "food safety" (e.g., withdrawal periods). Therefore it seems prudent to adopt a case-by-case approach in order to select and design the most appropriate method for specific problems in each individual situation. In relation to non-standard cases, it is suggested that applicants seek scientific advice with the CVMP or the national authority on the optimal approach to be taken, based on available literature and other compound-specific information. On basis of ongoing scientific discussions and practical experience it might be possible in the future to have further extensions or amendments to the guideline.

Paragraph	Comment and Rationale	Outcome
Tables 4 and 5	The wording "No specific conditions" in Tables 4 and 5 is not clear. Does this mean that the same requirements as for major species/major uses would apply to minor species or that no specific requirements have yet been defined for minor species? We suggest that there should be more precise explanation of what is meant	5.6 The tables 4 and 5 display current data requirements for residues studies and analytical methods and are for reference only. Requirements for minor species will be superseded by the provisions of this guideline, once adopted.