European Medicines Agency
Veterinary Medicines and Inspections

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OVERVIEW OF COMMENTS RECEIVED ON

DRAFT GUIDELINE EFFICACY AND TARGET ANIMAL SAFETY 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	Country
1	Association of Veterinary Consultants (AVC)	EU
2	Federation of European Aquaculture Producers (FEAP)	EU
3	IFAH Europe	EU
4		

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW

AVC

- Welcomes the draft Guidelines
- Lack of clear and consistent definition in the EU for "minor species" is still of concern
- Authorities should provide free pre-submission scientific advice for MUMS applications
- Any decision by the EMEA/CVMP on the validity of "minor use" for a particular product should also be binding for national authorities

FEAP (Federation of European Aquaculture Producers)

- Welcomes the draft Guidelines
- FEAP's main concern refers to the definition of MUMS, and the subsequent list of animal species included: 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. 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.

IFAH Europe

- Welcomes the draft Guidelines
- A strict interpretation of these guidelines will not lead to any reduction of the required data package
- Guidelines do not offer enough guarantee that data requirements will be sufficiently reduced, industry might not take the risk to develop MUMS products just based on these guidelines.
- Pre-development discussion is needed for all countries to agree on MUMS status of intended products and free scientific advice is essential for MUMS, irrespective of procedure to be followed and target species (food producing animal or pets).

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
1.INTRODUCTION (4th paragraph) *"In this context, data requirements …"*	**IFAH Europe** The impact of the substance/product type on the data requirement should be specified; otherwise this sentence fragment should be revised to avoid uncertainty on product-dependent data requirements.	Agreed. The text has been revised to clarify that data requirements would be influenced by the known safety and/or efficacy profile of an active or a related substance.
2.SCOPE	**IFAH Europe** The two first bullet points should be combined.	Agreed.
2.1 Definitions	**FEAP** Salmonids should be excluded from a major species list. If salmon (Salmo salar) is to be considered as a major species, the other salmonid species should be seen as minor species. **IFAH Europe** Minor species are defined by default, as not being a major species. Definition of 'Minor Use' is necessarily vague (as was discussed in our 2003 comments to the first MUMS Policy paper), but perhaps the meaning of *'occur infrequently'* and *'limited geographical area'* should be further explained. In the absence of general principles, and the need for *'case-by-case'* consideration, a procedure for an applicant to apply for a ruling on an application for a 'MUMS designation' for the potential product should be established.	The definitions for minor species and that for minor use are given in the CVMP Position Paper Regarding Availability of Products for Minor Uses and Minor Species (MUMS) (EMEA/CVMP/477/03) which is not under consideration in this guideline. The definitions for minor species and that for minor use are given in the CVMP Position Paper Regarding Availability of Products for Minor Uses and Minor Species (MUMS) (EMEA/CVMP/477/03) which is not under consideration in this guideline.

[1] Where applicable

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
3. LEGAL BASIS	**IFAH Europe** The content of Annex I is currently under revision. When the new version is published this guideline should be reviewed to include new opportunities for reduced data requirements for MUMS.	Point noted. In Annex I, there is only one specific reference to reduced data requirements. Annex I, Introduction, Paragraph 10: 'In cases of application for marketing authorisation for VMPs indicated for animal species and indications representing smaller market sectors, a more flexible approach may be applicable. In such cases, relevant scientific guidelines and/or scientific advice should be taken into account.' Apart from this reference, there is no specific direction in what may be accepted as a minimum data package for demonstration of efficacy.
4. GENERAL REQUIREMENTS FOR APPLICATIONS FOR MINOR USES OR MINOR SPECIES	**IFAH Europe** The description given in this paragraph is not presented in an 'easy to read' version. It should be considered to put this information into a table - as it is done in the QUALITY and SAFETY & RESIDUE guidelines. This way differences in requirements for MUMS would become clearer.	Disagreed. The EWP considered this issue and agreed that there would be no advantage to presenting the information in a table format.
	Extrapolation is possible where pharmacology of test product is comparable in both species. Does that mean we have to conduct pharmacology studies in both species? Please clarify.	Disagreed. The guideline actually states 'Extrapolation of data … <u>is most appropriate</u> where the test product is authorised for the same or a similar indication in the major species, and where the pharmacology (both in terms of pharmacodynamics and pharmacokinetics) of the test product <u>is likely to be comparable</u> in both species.' This outlines the circumstances in which extrapolation is most appropriate. The preceding sentence advises that interspecies extrapolation will be accepted whenever scientifically justified. No further clarification is considered necessary.
	Data to characterise mechanism of action: It should be clarified whether this information has to be obtained in the major species and extrapolated to the minor species or to be generated for both species. The latter interpretation would require too much investment for a minor species.	Disagreed. Interspecies extrapolation will be accepted whenever scientifically justified. Therefore, if justified, data to characterize the mechanism of action in the target species may not be necessary. No further clarification is considered necessary.

[2] Where applicable

GUIDELINE SECTION TITLE		
Line no.[3] + paragraph no.	**Comment and Rationale**	**Outcome**
Bullet points: ***"Generally, the following information will be required:…":***	**IFAH Europe , AVC** Safety and efficacy requirements in this section appear to be similar to those for a major species. .	Disagreed. Before a product authorisation can be granted, the competent authority must have certain basic information relating to the safety and efficacy profile of the product. This basic information includes: information to characterise the mechanism of action and known pharmacological effects of the active substance; data to support the recommended treatment regimen; data to characterise tolerance; and, data to support efficacy. However, for MUMS products, it is accepted that the quantity, quality and source of data to meet those fundamental requirements should be less onerous on applicant companies. No amendment is required.
Last bullet point: **"*Data to demonstrate the efficacy...*"**	**IFAH Europe** Replace "demonstrate" with "support", to be consistent with two paragraphs above "Data to support the recommended treatment dose..". "Demonstrate" implies that statistical significance of the primary efficacy variable has to be demonstrated. This might not always be possible (e.g. rare diseases, limited areas of disease incidence).	Agreed. The proposed amendment can be accepted. The concerns of IFAH were addressed later in this section in the guideline: 'The Applicant should test for treatment differences using appropriate statistical methodology. It should be possible in all cases to demonstrate a benefit of treatment (either relative to a control or, where appropriate, relative to pre-treatment data) that is statistically significant. However, the practical limitations of data collection for an infrequently occurring disease will be taken into consideration.'

[3] Where applicable

GUIDELINE SECTION TITLE		
Line no.[4] + paragraph no.	**Comment and Rationale**	**Outcome**
	AVC In generating data to support a MUMS claim it must be born in mind that by the very nature of the product, clinical cases may be relatively rare in a particular species, and will almost certainly be rare where the product has a minor use. This means that the conventional methods of collecting clinical case data from a limited number of investigators will not be possible. AVC welcomes the fact that this is recognised by relaxing GCP requirements. However the paucity of clinical data means that in the demonstration of efficacy and field safety **much more emphasis** should be placed on data in published literature, and on extrapolation of clinical effect from the major species data where this is applicable. AVC believes that the focus should be more on field safety data accompanied by limited specific efficacy data as with immunological products.	Disagreed. The concerns of AVC with respect to collecting clinical case data are addressed later in this section in the guideline: 'The Applicant should test for treatment differences using appropriate statistical methodology. It should be possible in all cases to demonstrate a benefit of treatment (either relative to a control or, where appropriate, relative to pre-treatment data) that is statistically significant. However, the practical limitations of data collection for an infrequently occurring disease will be taken into consideration.' In addition, the guideline acknowledges that published literature may be used to support an efficacy claim and that interspecies extrapolation of data will be accepted whenever scientifically justified. No specific amendment to the guideline is required.
Section commencing with "Where new studies are conducted…."	**AVC** It is unlikely that the specified conditions can be met, especially the requirement for using appropriate statistical methodology. It is likely that this will be frustrated by the inability to recruit a sufficient number of animals, especially in individual practices. Furthermore there is the problem of the availability of comparator products and so the need to include untreated control animals in a study. This will severely inhibit owners allowing their animals to be used for study purposes. It is clear that the Efficacy Working Party recognise that these problems exist by the incorporation of paragraph 7 – please see comments below.	Disagreed. The concerns of AVC are noted, but it is the opinion of EWP that these concerns have been addressed: '*The Applicant should test for treatment differences using appropriate statistical methodology. It should be possible in all cases to demonstrate a benefit of treatment (either relative to a control or, where appropriate, relative to pre-treatment data) that is statistically significant. However, the practical limitations of data collection for an infrequently occurring disease will be taken into consideration.*'

[4] Where applicable

GUIDELINE SECTION TITLE		
Line no.[5] + paragraph no.	**Comment and Rationale**	**Outcome**
1st bullet	**IFAH Europe** Does it mean carried out according to GCP? What is the difference between *"principles of GCP"* and GCP? For MUMS non-GCP historical data, if done to a reasonable standard, should be taken into account.	Yes, studies should be conducted in accordance with GCP. In the preceding paragraph, it is clearly stated that 'existing studies may not satisfy current Good Clinical Practice (GCP) requirements. Such studies may be considered acceptable if the design is appropriate to the stated objective of the study'.
3rd bullet	**IFAH Europe** The Applicant should test for treatment differences..." "*Differences*" should be replaced with "effects". The demonstration of non-inferiority to a positive control cannot be considered because of the large number of animals required in these studies and the associated costs. In many instances, controlled studies are not even possible because of practical limitations.	Agree. Disagree. Where the Applicant is proposing to conduct new studies, they should aim to demonstrate a statistically significant treatment effect. The guidance does acknowledge that in certain circumstances there may be practical limitations, but apart from acknowledging this fact and indicating that the authorities will be mindful of it when evaluating applications, additional, more specific guidance cannot be provided. No further amendment to the guideline is proposed in respect of this point.
"…practical limitations of data collection for an infrequently occurring disease will be taken into consideration..."	**IFAH Europe** Does not provide sufficient guidance to estimate time and costs to generate sufficient data.	Disagree. Where the Applicant is proposing to conduct new studies, they should aim to demonstrate a statistically significant treatment effect. The guidance does acknowledge that in certain circumstances there may be practical limitations, but apart from acknowledging this fact and indicating that the authorities will be mindful of it when evaluating applications, additional, more specific guidance cannot be provided. No amendment to the guideline is proposed in respect of this point.

[5] Where applicable

GUIDELINE SECTION TITLE		
Line no.[6] + paragraph no.	**Comment and Rationale**	**Outcome**
5. SPECIFIC REQUIREMENTS FOR PRODUCTS FOR MINOR SPECIES" **5.1 Pre-clinical studies**	**IFAH Europe** Rationale for selection of the dose: preclinical data should not be required at all in the minor species, provided extrapolation of data from a major species is "scientifically justified". For unit dose forms (ex: intra-mammary product, implants…), if the product is already licensed in a major species, no dose confirmation study in the minor species should be required. If in the minor species, the dose recommended may represent an overdose, it is then agreed that in this case, the applicant should show that this has no impact on safety in the minor species.	Disagreed. The concerns of IFAH are not clear. The guideline clearly states that 'interspecies extrapolation of pre-clinical data to support applications for minor species will be accepted whenever scientifically justifiable'. The guideline goes on to state that 'The proposed treatment regimen may be justified using: specific dose determination studies, and/or pharmacokinetic and pharmacodynamic (e.g. MIC) data, and/or literature data/results of pilot studies/clinical experience reports, and/or *extrapolation from another species for which the product is authorised'*. No amendment to the guidance is required.
2nd paragraph **"*A rationale for the selected dose, dose range and duration of therapy...*"**	**IFAH Europe** Should be changed to "A rationale for the selected dose **or** dose range and duration of therapy..." Only in this way the mentioning of both dose and dose range makes sense.	Agreed. The sentence has been amended to read: 'A rationale for the selected treatment regimen and duration of therapy …….'
5.2 Target animal safety studies ***"related species"***	**IFAH Europe** Further explanation or examples are needed. When can species be considered as "related", especially rabbits and horse (see general comments)?	Agreed. The definition of the term 'related species' is unclear and has therefore been replaced (throughout the text) with the term 'another species'.
"This info may include literature reports,…."	**IFAH Europe** add "and data from toxicity studies in lab animals."	Agreed.
"wide margin of safety"	**IFAH Europe** A more explicit definition of "wide" is needed. The dose selection as proposed in the draft VICH TAS GL would at best result in a margin of safety of 5-fold. In all cases the design should be adapted to the therapeutic index of the molecule (ex: possibility to test only 2x the dose, limited number of animals, only a few end-points examined….	Disagreed. It is not considered necessary to define the term 'wide margin of safety'.

[6] Where applicable

GUIDELINE SECTION TITLE		
Line no.[7] + paragraph no.	**Comment and Rationale**	**Outcome**
" field study data demonstrating satisfactory tolerance in the target species etc , may be considered adequate"	**IFAH Europe** The guideline states that if a test product is approved, and has a wide safety margin, *" field study data demonstrating satisfactory tolerance in the target species etc, may be considered adequate"*. Does this mean that a specific field study is required in the intended species, or will this data be derived form Pharmacovigilance data following off label use? If it means from specific field studies, how does this match in with the section on clinical trials where it states that field studies may not be required. The requirements of the guideline should be made consistent.	The concerns of IFAH are not clear. It would appear that this sentence has been read in isolation without giving consideration to the context. The sentence highlighted by IFAH begins with the wording 'For example, ….'. The sentence preceding that highlighted by IFAH states: 'This information may include literature reports, pharmacovigilance data and information derived from efficacy studies'. Clearly, if a product is authorised in another MS/territory, consideration would be given to the pharmacovigilance profile of that product. As stated in other parts of the guidance document, in principle, the findings of a field study should be provided. However, it is acknowledged that adequate efficacy data from other sources may obviate the need for a field study.
	IFAH Europe Some EU member states may not grant authorisation for conducting field studies with MUMS, considering the limited safety data that may be available. It will add constraints to the evaluation of the products	Not within the scope of this guideline.
Last two paragraphs of chapter 5.2. **First paragraph, 1st sentence** "*In many cases …*"	**IFAH Europe** Which cases? Cases where no data are available?	Agreed. In order to clarify, it is proposed to amend the beginning of that paragraph as follows: 'Where no/limited data on the safety profile of the active substance in the target species are available, a basic controlled study ….'.
	Would peer-reviewed published case reports be allowed as reports published for non-food animals often do not include controls?	Clearly relevant information from the literature will be considered. However, the quality of data available will dictate what, if any, additional data should be provided.

[7] Where applicable

GUIDELINE SECTION TITLE		
Line no.[8] + paragraph no.	**Comment and Rationale**	**Outcome**
Second paragraph "…to establish the safety of veterinary medicinal products intended for … breeding animals relevant data are necessary. Otherwise, a label restriction to non-breeding animals will be required."	**IFAH Europe** In order to make veterinary medicinal products available to minor species where the species are breeding animals it should be considered if extrapolation of safety data from other species could be made. If data from major species are available, no studies in minor species should be required. If reproduction data from major species are not available one rodent and one non-rodent species *(see also Safety/residue GL-draft for MUMS)* should be sufficient. Insert "Where safety in breeding animals of the major species is demonstrated, additional safety data in breeding animals of the minor species might not be necessary." This is consistent with general safety requirements within the scope of the guideline (see p. 5, section 5.2, 2nd paragraph).	Agreed. The text has been amended accordingly: 'Where safety in breeding animals of another species is demonstrated, additional safety data in breeding animals of the target species might not be necessary. However, in the absence of adequate data, a restriction on use in breeding animals (e.g. use in accordance with the risk/benefit assessment of a veterinary surgeon) may be required.'
5.3 Clinical studies	**IFAH Europe** The requirements for minor species seem to be nearly as onerous as for a major species (dose titration, dose confirmation, field studies). Minor species by definition implies relatively few in number and therefore a minor use of product for any one condition. On this basis the efficacy requirement should be the same as for minor claims in major species. The need for appropriately statistically powered field studies does not seem to be a reasonable requirement.	Disagree. Where the Applicant is proposing to conduct new studies, they should aim to demonstrate a statistically significant treatment effect. The guidance does acknowledge that in certain circumstances there may be practical limitations, but apart from acknowledging this fact and indicating that the authorities will be mindful of it when evaluating applications, additional, more specific guidance cannot be provided.
	Dose titration/confirmation should not be specifically requested. A dose rationale should be sufficient. This could be based on published literature. In general, only confirmation of the efficacy in the minor species should be requested, using experimental infection or a model on the target species if available or alternatively a field clinical trial	The concerns expressed by IFAH are not clear. While ideally one would wish to see some sort of dose finding/dose confirmation studies, these are not specifically required. E.g., in section 5.1, it is stated "*The proposed treatment regimen may be justified using: specific dose determination studies, and/or pharmacokinetic and pharmacodynamic (e.g. MIC) data, and/or literature data/results of pilot studies/clinical experience reports, and/or extrapolation from a related major species for which the product is authorised*'.

[8] Where applicable

GUIDELINE SECTION TITLE		
Line no.[8] + paragraph no.	**Comment and Rationale**	**Outcome**
2nd paragraph, 3rd line **-"*However, if a GCP field study has been provided...*".**	**IFAH Europe** Delete "GCP" to be consistent with p.5, section 4, 3rd paragraph "*It is recognised that existing studies may not satisfy current Good Clinical Practice (GCP) requirements*."	Agreed. Accept proposal to delete GCP.
3rd paragraph **Post authorisation trials**	**IFAH Europe** After marketing authorization, pharmacovigilance data addressing lack of efficacy and adverse reactions are sent to the authorities. Therefore, after approval, no additional data should be submitted to support field efficacy and safety. Lack of efficacy, tolerability, operator or environmental safety, should all be monitored adequately by the modern pharmacovigilance system.	Agreed. The sentence beginning 'However, in such cases, it may be a condition of the product authorisation….' has been deleted.
6. SPECIFIC REQUIREMENTS FOR PRODUCTS FOR MINOR USES	**AVC** The generation of field data for minor uses may be more difficult than that for minor species due to low incidence and the problem of identifying acceptable comparator products.	See comments above.
Last paragraph	**IFAH Europe, AVC** The requirement that target safety data should be generated in diseased animals is outside the scope of existing CVMP guideline and will inhibit the development of products for minor use, particularly as such a requirement will be in addition to the data generated for existing products that already have a marketing authorisation in that particular species. Why an exception for MUMS when all other drugs are tested on healthy animals including those used in the treatment of endocrine disorders? Undertaking safety studies in diseased animals will be practically impossible.	Disagreed. This was a misunderstanding. For certain product types, specific tolerance studies conducted in healthy animals may not be relevant to the proposed indication and in such cases, field efficacy data could be used to support the requirement for tolerance data.

GUIDELINE SECTION TITLE		
Line no.[9] + paragraph no.	**Comment and Rationale**	**Outcome**
"*In such cases, tolerance should be investigated in field studies*."	**IFAH Europe** Modify to *"In such cases, tolerance should be investigated **within the scope of field studies on efficacy**"*. The reason is that in field studies that involve privately owned animals, it is impossible to administer overdoses or prolonged treatments. Informed animal owners will reject this. Thus the only way to assess target animal safety in field studies is to closely monitor putative adverse drug reactions in the study animals during a field study testing efficacy.	Agreed.
7. APPROVAL OF VETERINARY MEDICINAL PRODUCTS IN EXCEPTIONAL CIRCUMSTANCES	**AVC** It is likely that most potential MUMS products will fall into the "exceptional circumstances" category, more particularly under a). The AVC believes that this approach should in principle be adopted for all MUMS products, but without commitment to generating the additional data required within the current draft guideline. The AVC believes that this can be dealt with in a proportionate manner on a risk/benefit basis. Any minor species/minor use will be covered by pharmacovigilance as for any other authorised product. Most products for major species / major uses are also used off-label from the very beginning and are therefore within the pharmacovigilance system. Post-authorisation problems that arise in the field relating to safety and efficacy will be detected through the pharmacovigilance procedures in place within the EU.	Not within the scope of this guideline.
p.7, section 7, 2nd paragraph from below	**IFAH Europe** "...under the circumstances detailed in paragraph 8.1..." The guideline does not have a paragraph 8.1.	Agreed

[9] Where applicable