10 May 2011
EMA/CVMP/EWP/324700/2010
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on demonstration of target animal safety and efficacy of veterinary medicinal products intended for use in farmed finfish' (EMEA/CVMP/EWP/459868/2008-CONSULTATION)

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

Stakeholder no.	Name of organisation or individual
1	PHARMAQ AS, Norway
2	Animals (Scientific Procedures) Inspectorate, UK

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment	Outcome
1	Our general comments to the new guideline, is that it seems vague in some places and too detailed in other instances. Furthermore, it could have been organised better.	The general comment regarding the guideline is taken into consideration. The guideline is organised in the same way as the guideline for immunological products intended for use in fish. It is advisable to organise these two guidelines in the same way as long as some companies are developing both immunological products and chemical products. The section on preclinical studies has however been revised, especially the text on pharmacokinetics.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
078-82	2	Comment: The default situation presented is for the use of 2 temperatures optimal and minimum or maximum. The scientific rationale behind this recommendation seems flawed. For PK and residue studies, minimum and maximum may be relevant. For challenge studies, the most relevant temperature (1 only) is probably the temperature at which the fish are thought to be most sensitive to the disease. Thus it is our belief that the temperatures used should be defined by scientific need, and should not include unnecessary tests. We agree with the text at 152-154. Proposed change: "All laboratory studies should be carried out at ~~both the optimal and the maximum or minimum~~ water temperatures selected to optimise the chances of achieving the scientific output of the particular study for the species of fish and the disease. In some cases, e.g. PK and residue studies, this may require studies at more than one temperature. The applicant should justify their choice of ~~maximum or minimum~~ temperature(s) in relation to the species / choice of product / indication~~. Exceptions from carrying out studies at two different temperatures as described here should be justified by the applicant."~~	Partly accepted The text has been edited for clarification and made less specific regarding choice of temperatures when carrying out laboratory studies. The alterations have been done partly to accommodate the fact that in some part of Europe, farmed fish are kept under conditions where the water temperature is quite stable and to enhance flexibility when the optimal temperature of the disease differ significantly from the optimal temperature of the fish species. As a main rule, studies should still be conducted at two different temperatures.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
078-82 and 153	1	Comment: It is stated that 'all' laboratory studies should be carried out at both the optimal and the maximum or minimum water temperatures relevant for the species of fish and the disease. What is meant by optimal water temperature and what are the criteria for defining it for each species? Atlantic salmon for example live fine at a water temperature of 4 °C, whereas this is much lower than the defined interval for Atlantic salmon. Furthermore, it may not be relevant for the aim of the study to test at the optimal temperature for the fish if the optimal temperature for the disease is different. Proposed change: Line 78/79: All laboratory studies should be carried out at water temperatures relevant for the species of fish and the disease.	Partly accepted The text has been edited for clarification and made less specific regarding choice of temperatures when carrying out laboratory studies. The alterations have been done partly to accommodate the fact that in some parts of Europe, farmed fish are kept under conditions where the water temperature is quite stable and to enhance flexibility when the optimal temperature of the disease differ significantly from the optimal temperature of the fish species. As a main rule, studies should still be conducted at two different temperatures.
083	1	Comment: Please see comment to line 78-82/ 153. How is the optimal temperature in the table attached justified? How is the optimal temperature of sea bass of 8-28 °C justified? Anadromous salmonids as Atlantic salmon and Rainbow Trout are, depending on season, kept at sea temperatures varying between 4 and 18°C in norwegian aquaculture. The fish tolerate this temperature range well. The optimal temperature-ranges for each species varies greatly; from three degree intervals up to a twenty degree interval.	Accepted

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		It is acknowledged that using various temperatures in studies may be relevant in studies of pharmacokinetics, however this is covered in lines 170-172. Proposed change: Remove the table with the optimal temperatures in line 83. If it cannot be removed, at least explain the purpose of performing all laboratory studies at the optimal water temperature for the fish if it is not relevant for disease, as well as including the criteria for defining the optimal water temperature for each species included.	
088-90	1	Comment: This issue is regulated by other rules, and will depend on the initial authorization date for the reference product. (Data protection time for fish products are 13 years.) Proposed change: It is proposed either to delete this paragraph or to refer to the relevant rules which define the criteria for abridged applications.	Not accepted. The text has been edited for clarification.
103-104	2	Comment: Coincidental mortality data not following the disease pattern should not be censored – it is not irrelevant. The immune system will be altered by disease and physiology by changes in water quality. It should require significant re-evaluation of the data. It should be reported and account taken to ensure continued	Accepted

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		validity of study, including evaluation of reduced power. Proposed changes: “For clinical studies the applicant should clearly state the onset and the duration of relevant disease outbreaks. This information will allow ~~censoring of irrelevant~~ evaluation of coincidental mortality data, and the potential~~ly~~ threat~~ening~~ to the statistical power of the study. An explanation should be provided showing how the data continues to be valid and fit for purpose”	
115-117	2	Comment: There continues to be evidence in our experience of a failure to be able to identify the correct experimental unit. It would be useful if EMEA provided some assistance as to when it would expect reports to specify the unit as the fish and when the tank, perhaps by examples for specific types of study. Statistical expertise may be required here. See also text at 355-359.	Not accepted It is usually not a problem for the applicant to define the experimental unit in different type of studies. Specific guidance on this matter should not be necessary. However, for each study the applicant should justify the choice of observation unit.
116-117	1	Comment: ”*…statistically significant* and *clinically reliable.”*? We think clinically *relevant* could be a better term in this sentence. Proposed change: The sample sizes should be sufficiently high to allow for the results to be statistically significant and clinically *relevant.*	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
128	1	Comment: What is defined as small number of test subjects? Proposed change: Include an indication of how many fish a small number is.	Not accepted The methods referred to under section 5.1.1 and 5.1.2[1] are only meant as examples and not specific guidance (requirements?) on how an orally administered dose should be calculated. To further specify small and large numbers of fish would not be in line with the intention of the text.
130	1	Comment: "…number of pellets and then calculate the *actual* dose received." If there are more than one fish in the tank, they will normally not eat an identical number of pellets. Proposed change: Replace "actual" with "average".	Accepted
131	1	Comment: What is defined as large number of test subjects? Proposed change: Include an indication of how many fish a large number is.	Not accepted The methods referred to under section 5.1.1 and 5.1.2[2] is only meant as examples and not specific guidance (requirements) on how oral received dose should be calculated. To further specify small and large number of fish would not be in line with the intention of the text.
138, 157 and 165	1	Comment: This section (5.2 Pharmacology) is understood to be the introduction to sections 5.3 Pharmacodynamics and 5.4 Pharmacokinetics. However, they are on the same	Accepted. The pharmacology section has been rewritten and the numbering of the subsections has been edited accordingly.

[1] Numbering refers to the document version that was for consultation.
[2] Numbering refers to the document version that was for consultation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		level. Proposed change: Change sections 5.3 Pharmacodynamics and 5.4 Pharmacokinetics into subsections of section 5.2.	
146-151	1	Comment: This paragraph seems to belong in the section about pharmacokinetics (5.4). Where to measure the concentration of active substance? Proposed change: Line 146: The changes in *blood* concentration of the active substance (...). Line 146-151: To move the paragraph incl. line 146-151 to section headed Pharmacokinetics.	Accepted
158-159	1	Comment: The mode of action of the active ingredient may not be known. Therefore it would be preferable to keep ", if known" at the end of this sentence as in the old guideline. Proposed change: The pharmacodynamic effects, including the mode of action of the active ingredient(s) as the basis for the recommended use of the product, should be described, if known.	Not accepted The formulation of this paragraph is already rather vague, no specific guidance are given. However, it must be expected that some information regarding pharmacodynamics is available for a medicinal compound.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
172-173	2	Comment: Although treatment under fresh water and saline conditions may be different (the status of the fish may be altered as might the chemistry of the product), it is important that the potential for “read across” be considered in order to reduce the number of animals used and the resources of the testing. Such “read-across” is currently being allowed, where scientifically justified, under legislation regulating chemical testing. Also see 188-9. Proposed change: “When the product is intended for fish kept in both seawater and freshwater, consideration should be given as to whether it is scientifically valid to “read-across” the two conditions. Such decisions should be justified. Where it is not appropriate e.g. some pharmacokinetic studies, tests should be carried out in both types of water.”	Partly accepted For the majority of medicinal compounds intended for use in fish, water salinity does affect the pharmacokinetic properties of the compound. As a main rule, studies should be carried out in both sea- and freshwater, if relevant to the proposed use, unless the applicant can document that the pharmacokinetics of the active substance is not affected by salinity.
175-178	2	Comment: Sample numbers should be scientifically valid and not set arbitrarily. In some cases, historical estimates of variability may contribute to determination of required numbers. OECD guidelines for testing chemicals have set minimum numbers at 7 fish. It does not seem likely that 10 minimum can then be justified for pharmaceuticals.	Partly accepted The section has been substantially rewritten(see new section 5.2.1). The recommendations for a minimum of 10 fish has been removed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: The investigator shall justify the chosen number of fish in each group. Account should be taken of variability and expected difference in measures to be taken between test and control. The prevalence of disease after challenge and expected protection rate may be relevant also. ~~Due to the high degree of inter-individual differences observed in fish, samples from several fish per timepoint (at least 10 are recommended) are required for analyses~~. ~~For repeated blood sampling analysis results from at least 4 individuals are required. The investigator shall justify the chosen number of fish samples per time point.~~	
179-182	2	Comment: European legislation on experiments on animals EU Directive 86/609 requires the use of the minimum number of animals to achieve the scientific objective. This text is not in line with this requirement. While it is accepted that sampling animals from a group may cause stress and leaving small numbers may compromise the trial and / or welfare, there does not seem to be a scientific (or welfare need) to use 1000 fish in each group. This may have been drawn up considering field trials which are not usually covered by the quoted legislation, but some further clarity is required if all studies are not to have 1000 animals per group.	Partly accepted The text has been edited for clarification and the importance of stress reducing measures in the trial period, securing valid results, has been elaborated. The reference to a specific number of fish has been removed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
181-182	1	Comment: ”For many species of fish, the group should preferably consist of at least 1000 individuals”. To which species does this apply, and at what fish size? The level of stress caused during collection of fish by use of net from a tank also depends on the size of the tank and the density of fish. The larger the tank, the more difficult it will be to collect the fish by net and stress will increase. In addition, one should also avoid unnecessary use of research animals. Hence, satisfactory reduction of stress can be gained by optimalization of biomass versus tank volume. Proposed change: The sentence is replaced with; “Stress reduction at sampling should be emphasized when biomass and size of the tanks are decided. A net of adequate size should be used in order to reduce collection time”	Partly accepted The text has been edited for clarification and the importance of stress reducing measures in the trial period, securing valid results, has been elaborated. The reference to a specific number of fish has been removed.
189	2	Comment: Similar comment to that above relating to lines 172-173 Proposed changes: “and <u>where read-across is not possible,</u> products must be tested under relevant conditions (fish kept in seawater and/or freshwater).”	Partly accepted For the majority of medicinal compounds intended for use in fish, water salinity does affect the pharmacokinetics of the compound. As a main rule, studies should be carried out in both sea- and fresh water, if relevant to the proposed use, unless the applicant can document that the pharmacokinetics of the active substance is not affected by salinity.
242-245	2	Comment: Palatability issues need to be addressed. This may be at	Partly accepted The concern is addressed, even though the proposed text is

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		line 66-68. Proposed changes: “Fish have a very marked sense of taste and smell. Consequently, where palatability of active product or excipient has been shown to be reduced, studies with in-feed medication ~~should~~ may need to be carried out with the medicated group (using the test product), a placebo group (using the test formulation without active substance) and / or an untreated “feed-alone” group (i.e. 2 forms of control), ~~otherwise~~ in order to differentiate the feed effect ~~cannot be differentiated~~ from the formulation and medication effect. Such designs should be explained and justified.”	not accepted. The part with references to palatability has been implemented in section 4 (General Considerations) and the part dealing with negative control groups has been rewritten.
248-249	2	Comment: Saline would not usually be considered as an appropriate control substance if the vehicle of the product is not itself saline. It is suggested that saline should be replaced by either vehicle or vehicle/ saline. Proposed change: “The applicant should justify their choice of control substance, taking into account that the excipients may have some effects of their own. For studies of other than in-feed medication, the control substance should be either ~~saline~~ vehicle or finished product deprived of the active substance”.	Accepted
253-254	1	Comment: To reduce stress caused by handling of the fish, and for	Accepted

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		practical reasons, it can sometimes be favourable to allocate and/or mark fish groups immediately before or during administration of the test product (depending on method). Proposed change: “The allocation of fish in groups should be done randomly prior to- or in connection with administration of the test product, using an appropriate method.”	
292	2	Comment: OECD guidelines for testing chemicals have a limit of 2000mg/kg, or special designs when used above this level. It seems highly unlikely that data arising from dosing above this level will add to the regulatory package. This limit should be made absolute. Proposed change: “The maximum dose should ~~usually~~ not exceed 2000 mg/kg fish.”	Partly accepted The sentence in question is deleted.
334-346	2	Comment: It is considered that the current text does not address the potential for additional welfare problems in test animals in challenge studies from the advice to use two negative control groups (placebo and untreated) in in-feed trials. This will double the number of animals that are most likely to show adverse effects. The use of two negative control in tolerance studies (section 5.6.2) does not have the same concern as the control groups in these studies are those least likely to show clinical	Partly accepted The concern is addressed, even though the proposed text is not accepted.

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		signs. Proposed change: “Applicants should justify the choice of control group (positive or negative). If a placebo is used, the applicant is directed to the text regarding control product in section 5.6 (Tolerance in the target species). However, where studies have shown no significant difference in food intake between placebo and untreated groups applicants should consider whether there is sufficient justification to include two groups in which animals are at high risk of suffering from, possibly significant, adverse effects.”	
343-345	2	Comment: It is considered that the current text may not sufficiently encourage the application of early endpoints and that rephrasing the text, as suggested below, to make the default that animals should be removed (i.e. changing the emphasis), whilst allowing the same flexibility to not remove them IF it would genuinely disrupt the study would encourage animal welfare to be prioritised. EU legislation on the protection of animals used in scientific studies requires the earliest endpoint possible to achieve the goals of the study. Proposed change: “~~If feasible and without disrupting the value of the data obtained,~~ ~~f~~ Fish should be removed from the trial when showing definitive signs of disease and/or when there has been pathological confirmation of disease in the	Partly accepted. The concern is addressed, even though the proposed text is not accepted (see new section 6, paragraph 7).

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		holding unit rather than waiting for death to occur. Only where the removal of fish showing clinical signs would significantly disrupt the value of the data should animals showing such signs be left in enclosures. In all circumstances, humane endpoints should be applied as soon as sufficient data has been obtained".	
358	1	Comment: The term "different tanks" is used in the text. Could "different" be interpreted as different in shape or volume? Proposed change: "Therefore, at least two groups kept under identical conditions but in separate identical tanks should always be used."	Partly accepted The text has been edited for clarification.
365	2	Comment: It is suggested that animals should not have been exposed to the challenge organism if possible. Since there is the potential for significant changes in the outcome of studies where animals have previously been exposed to an organism, it would seem appropriate to strengthen this text to indicate that a specific justification is required to use such animals. Proposed change: ~~"The test animals should not previously have been exposed to the challenge organism, if possible~~ Specific justification must be given for the use of test animals where they have previously been exposed to the	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		challenge organism, since such exposure has the potential to alter study results"	
380	2	Comment: Similar comment to that above relating to lines 78-82 above. Proposed change: "Where modelling evidence does not suffice, the dosage recommendations ~~should~~ may need to be supported by studies showing the adjustments necessary to retain a satisfactory effect at the lowest and highest water temperature recommended."	Partly accepted The concern is addressed, even though the proposed text is not accepted.
382	2	Comment: Similar comment to that above relating to lines 172-173 Proposed change: "Where read – across cannot be justified, tests ~~must~~ may need to be carried out in seawater and/or freshwater, as relevant to the proposed use."	Partly accepted The concern is addressed, even though the proposed text is not accepted.
409	2	Comment: European legislation on experiments on animals EU Directive 86/609 requires the use of the minimum number of animals to achieve the scientific objective. This needs to be considered during the design of the study.	Not accepted The concern is considered sufficiently addressed in the guideline. .

428	2	Comment: Justification of the number of fish to be post-mortemed is not given. Suggest set criteria such as: Proposed changes**:** “include post mortem examination of ~~at least six individuals from each group~~ sufficient fish to allow for variability in response and accurate diagnosis. 6 individuals from each group have been shown to be sufficient in some studies.”	Partly accepted However, the recommendation for a minimum number of 6 fish from each group has been maintained.
443	2	Comment: Similar comment to that above relating to lines 248-249 that “vehicle” may be more appropriate than “saline” for a placebo group. Proposed change: “a group treated with placebo (either ~~saline~~ vehicle or test formulation without active ingredient) or left untreated, for comparison with the test product under evaluation”.	Partly accepted The concern is addressed, even though the proposed text is not accepted.