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Guideline on demonstration of target animal safety and efficacy of veterinary medicinal products intended for use in farmed finfish

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This guideline replaces the current "Guideline on the efficacy of veterinary medicinal products for use in farmed aquatic species"; last update September 1994, published in Vol. 7 (7AE22a) of "The Rules governing medicinal products in the European Union".

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu or Fax: +44 20 7418 8447

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Guideline on demonstration of target animal safety and efficacy of veterinary medicinal products intended for use in farmed finfish

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Executive summary

The revised guideline on the demonstration of target animal safety and efficacy of veterinary medicinal products intended for use in farmed finfish provides updated guidance on the preclinical and clinical aspects of the application procedure for those who seek approval of such products.

The revision replace the "Efficacy of veterinary medicinal products for use in farmed aquatic species" and takes into account the development during recent years, and feedback obtained from users of the previous guideline which was last revised in 1994.

1. Introduction (background)

Veterinary medicinal products intended for use in finfish will have to satisfy all the usual requirements for approval. This includes documentation of quality, demonstration of safety for the consumer, the user and the environment, and demonstration of efficacy and tolerance in the target species.

This document provides special guidance in respect of the documentation required to confirm efficacy and tolerance for medicinal products for use in finfish.

The procedures outlined should be considered for all submissions, but may not be applicable for all veterinary medicinal products for use in aquaculture. If certain aspects are modified or omitted, justification should be provided.

In principle the results of all trials should be applicable irrespective of where they are carried out; however, the applicant should take into account the various conditions (e.g. climatic, disease situation, water temperature and salinity) as these may influence the outcome of the studies.

2. Scope

The aim of this guideline is to provide guidance regarding the demonstration of efficacy and target animal safety for veterinary medicinal products intended for use in farmed finfish.

Immunological veterinary medicinal products are excluded from the scope of this guideline.

3. Legal basis

This document is intended to provide guidance on the demonstration of efficacy and target animal safety for veterinary medicinal products intended for use in farmed finfish.

It should be read in conjunction with Directive 2001/82/EC, as amended. Applicants should also refer to other relevant European and VICH guidelines, including those listed among the references at the end of this document.

4. General considerations

The applicant is encouraged to standardise study protocols and study reports as far as possible to facilitate the comparison of study results and the possible extrapolation between species.

If the product is intended for in-feed administration, the possible impact of the feed composition should be considered and investigated, if appropriate. The feed composition and manufacturing process may influence the medicated product with regard to physico-chemical compatibility.

Conditioning and pelleting are the main factors affecting stability during manufacture of medicated feed. These processes can subject the medicated feed to high temperature and pressures, which can cause degradation of active substances, excipients or feed constituents. Other quality points for considerations are homogeneity and segregation of these products. For further information the applicant is directed to the guideline on additional quality requirements for products intended for incorporation into animal feedingstuffs (medicated premixes) among the references listed at the end of this guideline.

To account for the fish being poikilothermic animals, the term "degree-days" should be used wherever relevant.

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. The applicant should justify their choice of maximum or minimum temperature(s) in relation to the choice of product / indication. Exceptions from carrying out studies at two different temperatures as described here should be justified by the applicant. The table below gives examples for optimal water temperatures for some fish spp.

Fish species	**Latin name**	**Optimal water temperature (s) (°Celsius)**
Atlantic salmon	*Salmo salar*	12-15
Rainbow trout	*Oncorhynchus mykiss*	14-18
Cod	*Gadus morrhua*	8-14
Sea bass	*Serranidae*	8-28
Carp	*Cyprinidae*	20-23
Halibut	*Hippoglossus hippoglossus*	8-12
Turbot	*Psetta maxima*	14-18

The origin/varying genetics of the experimental fish is important to obtain valid reproducible results, and any variation should be addressed. All finfish species shall be identified by their colloquial name followed in parenthesis by the Latin or Linnean description.

Extensive testing may be required for compounds with a novel molecular structure or compounds not previously approved for aquatic species. More limited investigations may be acceptable for a new salt or ester of a compound previously approved for the same or other relevant species.

4.1. Study reports

To facilitate the evaluation of the documentation of efficacy and target animal safety, all experimental techniques should be described in such detail as to allow them to be reproduced. The investigator should establish their validity. Each experimental trial or field trial and the conditions under which they are performed should be described in detail. Separate reports on all trials, whether favourable or not, should be provided. Adequate summaries of groups of trials based on the same protocols may be provided.

The applicant is directed to the "Guidelines for reporting the results of experiments on fish" (Brattelid and Smith, 2000) for detailed guidance on the contents of the study report.

Adverse events, side effects and target animal tolerance should be reported. An explanation of non-specific mortalities and comments on any physical or behavioural abnormalities should be provided.

For clinical studies the applicant should clearly state the onset and the duration of relevant disease outbreaks. This information will allow censoring of irrelevant mortality data, potentially threatening the statistical power of the study.

4.2. General study design

As water quality has been identified as an important element for maintaining healthy fish and ensuring valid experimental results, the water quality parameters temperature and salinity should be addressed in detail.

The efficacy of the veterinary medicinal product should be stated as a function of time, dose, frequency and duration of treatment. The criteria used for the evaluation of efficacy in the trials should be pre-determined. The results should be presented in a way that is suited for adequate statistical evaluation. The clinical trials should cover all claimed indications and each indication should be discussed and reported separately.

Statistical analysis of the results should be performed whenever relevant.

The applicant should justify the observation unit (e.g. individual fish or cage) and the number of samples collected on each sampling occasion. The sample sizes should be sufficiently high to allow for the results to be statistically significant and clinically reliable.

In studies of products intended for use against aquatic one-host parasites, like for example sea lice on salmon, sampling a limited number of fish from many cages instead of many fish from a small number of cages is recommended. This is to take into account clustering which naturally occurs with such parasites.

5. Preclinical studies

5.1. General considerations

Great care should be taken to ensure that the fish receives the required dose. For single dose studies of orally administered products it is recommended to administer the test substance orally by gavage.

For repeated dose studies of premixes intended for medicated pellets, examples of control methods applicable to trials with small and large numbers of test subjects, respectively, are given below.

5.1.1. Small number of test subjects

Count the number of pellets before they are given to the fish. After dosing, count the uneaten number of pellets and then calculate the actual dose received.

5.1.2. Large number of test subjects

Small X-ray-dense glass beads (ballotini) may be incorporated when manufacturing medicated feed pellets for the trial, at a known concentration of beads per pellet. This can be determined by X-raying the pellets. When the number of beads per pellet is known, a representative number of fish may be X-rayed to reveal the average number of pellets ingested by the fish. It is also possible, by using small and large pellets every other day, to reveal how many pellets were ingested two different days in a row (Horsberg, Hoff and Nordmo, 1996).

5.2. Pharmacology

All studies should be performed according to the expected method of use of the product in the field.

Studies in target species are as a general principle required for the assessment of the pharmacological effects. However, the mode of action and route of administration should be taken into account. For example, for an extension to a new target animal species for a waterborne sea lice product acting

directly on sea lice, pharmacological parameters in the target animal would be of no importance with regard to efficacy. However, they may be relevant to target animal safety and residue data. For sea lice products given orally, pharmacological parameters would be relevant to efficacy.

The changes in concentration of the active substance should be determined as a function of time, dose, frequency and duration of treatment, and of the route of administration of the test substance. Any observed changes should be described. From the application of appropriate models or from model-free calculations, the pharmacokinetic parameters should be derived and presented. If ED50 or EC50 are known or established from model studies, these can serve as a basis for the selection of the treatment dose.

As fish are poikilothermic, temperature related pharmacology trials should be conducted as significant temperature related effects can be expected. The applicant should justify their choice of temperatures at which the studies are conducted.

Depending on the nature of the veterinary medicinal product in question, studies on interactions with other veterinary medicinal products should be undertaken.

5.3. Pharmacodynamics

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. Desired effects as well as adverse effects and any dose dependency of these should be investigated. If relevant, the frequency of adverse effects should be reported.

If feasible, model studies should be carried out. Effects found in such model studies should be reported as a function of dose and ED_{50} or EC_{50} values should be provided, as they can serve as a basis for the selection of the treatment dose.

5.4. Pharmacokinetics

5.4.1. General considerations

It is recommended to carry out pharmacokinetic studies in finfish according to the principles in the CVMP guidelines for the conduct of pharmacokinetic studies in target animal species, as far as they may be applied to fish.

When the product is intended for fish kept in areas with varying water temperatures, pharmacokinetic studies should be carried out at different water temperatures (high end and low end of the natural variation). When the product is intended for fish kept in both seawater and freshwater, pharmacokinetic studies should be carried out in both types of water.

5.4.2. Performance of tests

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.

It is recommended that the group consists of a sufficient number of animals, as this will allow for sampling small numbers of fish without stressing the remaining fish in the group. Sampling fish out of a small group may cause stress symptoms like decreased food uptake among the remaining ones. For many species of fish the group should preferably consist of at least 1000 individuals.

5.4.3. Bioavailability

Bioavailability for premixes should be determined by administration of a medicated feed prepared by the procedure recommended by the manufacturer. The possible influence of different feed types should be considered.

Data describing the bioavailability of oral products should be provided, as this is important in the evaluation of environmental effects. Water salinity may significantly affect the bioavailability, and products must be tested under relevant conditions (fish kept in seawater and/or freshwater).

5.4.4. Distribution

Methods using radiolabelled substance, e.g. whole-body autoradiography, can be useful for studies of distribution. This may be relevant in pharmacokinetic studies of antibiotics that are intended to exert an effect on specific sites or organs. For waterborne sea lice products acting directly on the sea lice, distribution studies are less relevant.

5.4.5. Metabolism

As fish generally metabolise drugs at a lower rate than mammals and the number of metabolites are usually lower, there is less need for studies on metabolism, especially for substances where information relating to other species is available.

5.4.6. Elimination

The most important factors influencing the rate of elimination should be determined and discussed, e.g. water temperature, salinity, 0_2 content, feeding and physiological status of the fish.

5.5. Pharmacological studies of antimicrobials and antiparasitic products

For antimicrobials, pharmacological studies in finfish and the PK/PD analysis should be carried out according to the principles in the CVMP guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances. For anthelmintics, the principles of the VICH overall guideline for efficacy requirements for anthelmintics apply. For other antiparasitic products, the general pharmacokinetic guideline should be used.

5.5.1. Development of resistance

The mechanism for, and frequency of development of resistance should be discussed. Possible development of chromosomal or plasmid mediated resistance to other active substances used in farmed fish should be stated. For ectoparasiticidals, experience of development of antiparasitic resistance should be included, if relevant.

5.5.2. Transfer of resistance

The potential hazard of transferring microbial resistance to wild fish pathogens, other waterborne pathogens or human pathogens by using the medicinal product as indicated by the manufacturer should be considered.

5.6. Tolerance in target species

Target animal safety should be determined in all the target species, as defined by the investigator, unless otherwise justified. Studies performed in one species of fish may be considered relevant for the evaluation of tolerance in a second species of fish of the same genus or taxonomic family, provided that they are kept under the same environmental conditions. In such a case there must be supportive safety data from clinical trials in the second species. It may for example be considered unnecessary to carry out formal target animal safety studies in trout if such studies have been carried out on other species of salmonids, and if clinical studies in trout are available.

Excipients normally used in pharmaceutical products for terrestrial animals may not be well tolerated by aquatic species. Safety of excipients should be determined and lack of appropriate data justified.

It is important to take into account possible adverse effects on development (malformations) if the medication is applied to young fish (embryos, larvae and juveniles), and where these products can easily interfere in the growth. It is important to indicate the range of sizes and weights of fish which are recruited for the trial since the same treatment may not have the same effect in different sizes of fish.

Studies of repeated dose tolerance are relevant only for products intended for repeated dose administration.

The following points apply to all target animal safety studies:

5.6.1. Test product

It is recommended to use the final formulation of the medicinal product. Where the formulation used in studies differs from the final commercial formulation the applicant must demonstrate that the bioavailability of the formulation is the same. Substances administered by gavage should have a suitable formulation, e.g. solution, suspension, capsule or in feed. All formulations used in the tests should be assayed for the concentration of the active substances before the start of the trial(s).

5.6.2. Negative control groups

Fish have a very marked sense of taste and smell. Consequently, studies with in-feed medication should be carried out with the medicated group (using the test product), a placebo group (using the test formulation without active substance) and an untreated "feed-alone" group (i.e. 2 forms of control), otherwise the feed effect cannot be differentiated from the formulation and medication effect.

In all tests, the test product and placebo should be administered in the same manner as intended for the finished product. Untreated controls should be handled identically to treated fish.

For studies of other than in-feed medication, the control substance should be either saline or finished product deprived of the active substance. The applicant should justify their choice of control substance, taking into account that the excipients may have some effects of their own.

5.6.3. Holding

The fish to be tested should be in a normal physiological condition and be feeding well during two weeks of acclimatisation. The allocation of fish in groups should be done randomly the day prior to administration of the test product, using an appropriate method. Acclimatisation is not applicable for embryonal stages.

The following conditions of exposure are recommended:

Stocking:

Semistatic test:

- waterborne administration: max. 1 g fish/litre of water
- oral administration: max. 5 g fish/litre of water
- parenteral administration: max. 5 g fish/litre of water

Flow through:

Higher loading is acceptable

Group size and number:

The numbers of fish per group should be justified, and should not be less than 10 with a minimum of 2 tanks per dose and 2 control tanks.

Fish size:

It is recommended to use fish of the most sensitive category for which the product is intended (size/age and physiological status).

5.6.4. Necropsy and histopathology examinations

As a minimum, tissues from all fish in the highest dose group and control group should be examined macroscopically and microscopically. Where the toxicity of the test product is anticipated to be relatively high, different necropsy schemes may be required, to include gross and microscopic examinations for all fish or for randomly pre-selected fish. If lesions are found in any tissue from the highest dose group, then samples from fish in the second highest dose group of the test product should be examined macroscopically and microscopically, until a no-observable-adverse-effect-level is determined. In addition, tissues from all fish showing systemic clinical signs should be examined macroscopically and microscopically.

5.6.5. Dosage and duration of dosage

The choice of dose levels and duration of exposure must be justified by the applicant.

The chosen levels must be adequate for demonstration of a sufficient margin of safety for the veterinary medicinal product when used under field conditions. This means that the choice of dosage levels should be sufficiently high to account for the fact that varying degrees of unintended overdosing will commonly occur in practice with such types of medicinal products intended for waterborne or in-feed treatment.

For single dose studies at least 3 dose levels should be tested. The selection of dose levels and duration of the treatment period should be based on the proposed therapeutic dosing regimen.

For repeated dose studies the selection of dose level(s) and duration of the dosing period should be based on the proposed therapeutic dosing regimen and on results from single dose studies.

5.6.6. Oral administration

Detailed records on feed uptake and concomitant daily dose should be given.

The maximum dose should usually not exceed 2000 mg/kg fish. For solutions and suspensions given by gavage, the concentration of the active ingredient should be adjusted so that, if possible, no more

than 0.5 ml test solution per 100 g fish gives the required dose. These maximum dosage recommendations are given as an advice to the applicant on the practical dosage limitations in fish.

5.6.7. Waterborne administration

Dipping, bathing or "top dressing" on the water surface are methods of administration considered as waterborne administration.

Waterborne treatment must usually have a very broad margin of safety due to the difficulty of accurate dosing/estimation of water volume in raceways or sea cages.

The duration of treatment should be equal to or longer than the proposed length of treatment. Dosage of the veterinary medicinal product – like in mammals – is principally a function of treatment concentration and exposure period. For sedatives and anaesthetics for use in finfish the length of exposure period is the main parameter available for adjustment during treatment.

5.6.8. Parenteral administration

Both the test and the control product should be administered by injection. The same volume of test solution should preferably be administered to the fish in both the test and the control group. Also, the maximal volume of the veterinary medicinal product administered in one injection site and assessment of the reaction in the injection site should be provided.

6. Clinical

The main purpose of the documentation of efficacy is to prove the therapeutic value of a new veterinary medicinal product for aquatic species and to define an optimal dose and dosage regimen.

Clinical trials are required for each proposed indication and for all target species in which efficacy is claimed. For some products, such as waterborne treatments which act directly on ectoparasites and which are independent of the pharmacokinetics in the fish, clinical trials in a second species may not be required if the clinical data obtained for the main fish species can be shown to be relevant to the second species. In such cases sufficient justification for the omission of clinical studies, together with documentation of target animal tolerance is necessary.

All studies should be performed under appropriate conditions according to the proposed method of use of the product. The study/studies should for example be carried out in (a) water temperature(s) in which the test product is likely to be used considering the different climatic conditions within the community.

The studies should be blinded unless otherwise justified.

Normally, data from both laboratory and full scale field trials will be required. Where appropriate the applicant should justify the lack of relevant data.

Omission of field studies and submission of challenge studies only may be accepted if adequately justified by the investigator. For example, in case of a second species closely related to a first species for which the product is fully documented, challenge studies may be sufficient to document efficacy also in the second species.

In all studies the final formulation or an essentially similar formulation should be used and administered by the proposed route. Where a similar formulation is used, it should be justified with regard to bioavailability.

The trials should include control groups.

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). If a positive control is chosen, a veterinary medicinal product authorised according to the relevant EU requirements should preferably be used. The daily uptake of medicated feed should be recorded together with the daily dose of the active substance, if possible. Premixes should be administered as medicated feed prepared by the procedure recommended by the manufacturer, preferably using a standardised feed.

The applicant should consider/discuss all variables likely to confound results and the methods that will be used to reduce/avoid them.

If feasible and without disrupting the value of the data obtained, 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 holding unit rather than waiting for death to occur.

The nature and frequency of adverse drug reactions should be monitored and recorded.

Signs of interactions with other medicinal products or with feed should be carefully observed during the clinical trials.

6.1. Laboratory studies

The test conditions can be controlled and standardised in land or sea-based test facilities. Experimental trials should be performed for the main target species.

The fish to be included in the trials should be of similar age and size, be susceptible to the disease in question and be of known origin and health status. The allocation of fish in groups should be done randomly, using an appropriate method.

Every study should be designed to allow for appropriate statistical evaluation. A sample size analysis should be presented. Significant differences might be experienced between different groups of fish which are kept under identical conditions owing to the fact that they are kept in different tanks. Therefore, at least two groups kept under identical conditions but in different tanks should always be used. The experimental unit should be justified.

The parameters to be recorded for evaluation should be justified. The applicant should justify the statistical evaluation methods.

6.1.1. Challenge studies

Challenge models (cohabitant, waterborne, injection) and their relevance to natural conditions (time of challenge/time of treatment/infection pressure etc.) should be discussed.

The test animals should not previously have been exposed to the challenge organism, if possible. The challenge organism must be of a strain relevant for the current disease situation, and be isolated and characterised by the most appropriate method, preferably a standard method used by the national reference laboratory, which should be described in detail. The timing and performance of the challenge and the design of the study must be justified by the investigator. The results of the introduction of the challenge organism should be reported, based on parasite counting, microbiological analyses or other pertinent investigations. If appropriate a statistical analysis should be provided.

6.1.2. Dose determination trials

The purpose of the trials is to determine the optimum dose, dosage interval and total period of treatment for the claimed indications. A dose/response relationship for therapeutic effect and, if possible, for adverse effects, should be established. Dose determination trials can be performed as a combination of experimental studies and field trials. Data from well controlled experimental studies is preferred wherever relevant models are available, and field studies should serve to confirm the findings from the controlled trials. Where no or only poor models exist, more emphasis should be placed on field studies.

The dosage recommendations should be supported by studies showing the adjustments necessary to retain a satisfactory effect at the lowest and highest water temperature recommended.

Tests must be carried out in seawater and/or freshwater, as relevant to the proposed use.

6.1.3. Dose confirmation trials

Separate dose conformation trials can be replaced by field trials performed with the final formulation of the veterinary medicinal product administered in the recommended dosage regimen.

6.2. Filed studies

The scope of the field trials is to ensure that the veterinary medicinal product is efficacious and safe in the diversified conditions for aquaculture found in Member States. The field studies are to be performed in established farms. A satisfactory number of sites with conditions representative for the normal in-use conditions should be used. The applicant should justify the number of sites. The field studies should be performed in accordance with GCP as far as possible.

A product authorised according to relevant EU requirements should preferably be used in the control group(s) (positive control).

Negative controls should only be used if no product is authorised for the claimed indication. The control group can be treated once an adequate estimation of difference in effect can be established.

6.2.1. Selection of farms

The number and suitability of the sites selected for clinical trials should be justified by the applicant. These should be geographically well distributed to optimise the possibility of diversified environmental conditions, disease situation and management practices. Each site should have several pens or tanks with fish of the relevant size/age and physiological condition (e.g. smoltification, sexual maturation) for the proposed use of the veterinary medicinal product. At least two of the pens or tanks, and preferably several pairs of pens/tanks should be used in the trial. The farmer should preferably be experienced in keeping detailed records on all important factors concerning the farm and its fish. Records on the source of fish and the disease history in different pens or tanks must be kept. Previous medication, use of chemicals and vaccines should be known. Daily records of outbreaks of disease, mortality and medication are required, as well as known and stable management practice concerning e.g. hygiene, feeding, handling and use of feed additives and chemicals. Weekly records may be accepted for water temperatures below 8 °C, if justified by the applicant.

6.2.2. Selection of groups

All fish in one tank or pen are considered as one group. A minimum of two groups must be used in each trial, one of which must be a control group, which in most cases will be a positive control group.

The allocation of the groups should be done randomly, using an appropriate method. The prevalence of disease, daily mortality, clinical symptoms and other relevant parameters should be comparable in the treated and control groups at the start of the study.

6.2.3. Trial procedure

Field trials in commercial fish farms should preferably be performed in spontaneous outbreaks of the diseases for which efficacy is claimed. Trials should thus be conducted at the time of year and under conditions where a "successful natural challenge" must be defined by the investigator, and should include the method of identification of the causal agent. Information from trials performed with unsuccessful natural challenge may be provided with an explanation of the failures. All trials should be performed with adequate controls. Field trials with anaesthetics or other "non-therapeutics" should be performed with healthy fish. All trials must be planned so that suitable data are available for statistical analysis. Clinical endpoints of relevance for the proposed indication should be chosen, and primary and secondary endpoints should be specified.

6.2.4. Diagnostic criteria

The presence of the investigated diseases must be confirmed in all groups included in the trial. The criteria for establishing the diagnosis should be given. The same criteria are to be used in all trials and should include post mortem examination of at least six individuals from each group. The precise disease condition and identification of any pathogenic organism should be provided. Bacterial diseases should be diagnosed by isolating and characterising the pathogen by the most appropriate microbiological method, preferably a standard method which should be described in detail. Samples from at least 6 fish per group are recommended.

Definitions

For the purpose of this guideline, the following definitions apply:

Finfish: A term used to separate true fish from shellfish, crayfish, jellyfish etc. All the species of fish mentioned in this guideline are examples of true finfish.

Degree days: Is a measure of cooling or heating. The amount of degree days is determined by multiplying the water temperature each day with number of days. For example, 10 days with 5° C equal 50 degree days.

Positive control: A positive control group is a group treated with an authorised reference product approved for the same indication and used according to the label instructions, for comparison with the test product under evaluation.

Negative control: A negative control group is a group treated with placebo (either saline or test formulation without active ingredient) or left untreated, for comparison with the test product under evaluation.

ED_{50}: The dosage that produces a desired effect in half the test population.

EC_{50}: The concentration of a drug where 50% of maximal effect is observed

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