

EFFICACY OF VETERINARY MEDICINAL PRODUCTS FOR USE IN FARMED AQUATIC SPECIES

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CONTENTS

- I. INTRODUCTION
- II. PRECLINICAL TRIALS
 - 1. GENERAL CONSIDERATIONS
 - 2. TOLERANCE
 - 3. PHARMACOLOGY
 - 4. MICROBIOLOGY AND PARASITOLOGY
- III. CLINICAL TRIALS
 - 5. GENERAL CONSIDERATIONS
 - 6. PERFORMANCE OF TRIALS

EFFICACY OF VETERINARY MEDICINAL PRODUCTS FOR USE IN FARMED AQUATIC SPECIES

I. INTRODUCTION

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

This document provides special guidance in respect of the documentation of efficacy and tolerance of medicinal products for use in aquatic species. The guidance should remain flexible to allow scientific discretion in the design and conduct of studies which will yield the maximum necessary information on a product.

In the context of this document, the consideration of efficacy and tolerance only relates to those products regulated by Directive 81/851/EEC and does not refer, for example, to zootechnical feed additives. Immunological veterinary products are excluded from the scope of this guideline.

The investigations outlined should be considered in relation to any particular submission, but may not be applicable or economically justified for all medicinal products for use in aquaculture. If items are modified or omitted, justification should be provided.

While in principle, the results of all trials should be applicable irrespective of where they are carried out, nevertheless, the applicant should take into account the various conditions (e.g. climatic, disease, etc.) which prevail in the Member States where the product is to be marketed.

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

- Veterinary medicinal product intended for farmed aquatic species
Any medical product intended for farmed aquatic species excluding immunological veterinary medicinal products.
- Aquatic species
All animal species, including their reproductive and resting stages and reproduction products, living in sea or fresh water and intended for human consumption, with the exception of amphibia, reptiles, mammals, birds and ornamental fish.

All aquatic species shall be identified by their colloquial name followed in parenthesis by the Latin or Linnean description.

For practical reasons aquatic species are, as defined above, included in the concept of “fish” in this paper.

II. PRECLINICAL TRIALS

1. GENERAL CONSIDERATIONS

1.1 Instructions to investigators

To facilitate the evaluation of the documentation of target species tolerance and pharmacology, a summary should be given on the name and complete composition of the medicinal product, similarities to other medicinal products, pharmacological category, mode of action, dosage form, target animal species, recommended dosage, route(s) of administration, proposed indications and contra-indications, side effects, restrictions on use withdrawal period, and preferably a statement of the reason(s) for the development of the product.

1.2 Test reports

All experimental techniques should be described in such details as to allow them to be reproduced. The investigator should establish their validity. There must be a strict definition of all conditions under which the trials are performed.

The documentation should include, depending on the purpose of the trial, such items as:

- description of test animals; species, number, sex and maturation status, age, length and/or weight, source, history of diseases/infections and known vaccination status;
- feeding; type, amount, distribution, appetite;
- water quality parameters; temperature, O₂, NH₃/NH₄⁺, salinity, pH, flow, hardness;
- other environmental factors of importance;
- concomitant treatment;
- methods of observation and evaluation;
- where applicable, the information should include a complete description of the management.

The description of the analytical methods used to determine the content of the active molecule and its active metabolites should cover the principle of the method and relevant properties showing the suitability of the method, e.g. selectivity, accuracy, detectability and precision. When tracer methods are used, the place of incorporation and the specific activity of the tracer should be stated if known.

2. TOLERANCE

2.1 General remarks

Tests for assessment of target species tolerance should be performed in the main target species, as defined by the investigator. Studies performed in one species of fish are considered relevant for evaluation of tolerance in another species of fish of the same genus or taxonomic family provided they are maintained in the same environmental conditions.

Extensive testing may be required for compounds with a novel molecular structure or compounds not previously approved for aquatic species. Only limited investigation would be necessary, for example, for a new salt or ester of a compound which is toxicologically well characterised in relevant species.

The test animals should be healthy and of the species or closely related species for which the product is intended. Treated and control animals should be handled identically except for the exposure to the product.

The water quality should be relevant to the proposed use of the product and the species of fish to be tested.

Diseased animals will not be required routinely for safety testing. If the product has a narrow margin of safety, it may be necessary to perform a safety evaluation in diseased fish. The latter can be incorporated in the clinical studies.

Excipients normally used in the general pharmaceutical field may not be well tolerated by aquatic species. Based on literature survey and/or preliminary data, studies could be needed and if so, designed to cover tolerance for excipients as well as for the active substance.

2.2 Single dose toxicity

Studies of single dose toxicity should be conducted in such a way that studies of acute toxicity are revealed and the mode of death assessed as far as reasonably possible. A quantitative evaluation of the approximate lethal dose and information on the dose-effect relationship should be obtained. The tests should generally include clinical observations and a necropsy examination of all individuals, if possible.

It is recommended to carry out studies in finfish according to principles in the OECD guideline 203: "Fish, Acute Toxicity Test" modified as described below, or in accordance with other internationally recognised guidelines. Test methods for other aquatic species are left to the discretion of the investigator.

2.2.1 Selection of species

Studies performed in one species of fish are considered as relevant in another species of the same genus or taxonomic family.

2.2.2 Administration of test substance

The route(s) of administration should correspond with the intended one(s).

2.2.2.1 Waterborne administration

Dipping, bathing or "top dressing" on the water surface are considered as waterborne administration. The test substance should be administered in the same manner as intended for the finished product.

2.2.2.2 Oral administration

It is recommended to administer the test substance orally by gavage. Control fish should in the same manner be administered the test substance deprived of the active substance. Great care should be taken to ensure that each fish receives the proper dose.

2.2.2.3 Injections

The test substance should be administered by injection. Control fish should be administered by injection. Control fish should be administered the solution deprived of the active substance in the same manner. The same volume of test solution should preferably be administered to all the fish.

2.2.3 Test substance

It is recommended to use a similar formulation to the finished medicinal product, if possible.

Substances intended for administration by oral 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).

2.2.4 Dosage and duration of exposure

At least 3 dose levels should be tested, the highest dose ensuring, if possible, a high degree of toxic effects. For waterborne treatment, a suitable exposure period should be chosen based on the duration of treatment. The choice of dose levels and duration of exposure must be justified by the applicant.

2.2.4.1 Waterborne administration

The controls should be exposed to the same concentration(s) of auxiliary substance(s), e.g. dispersal agents, as used in the trials with the highest concentration of the test substance.

2.2.4.2 Oral administration

The maximum dose should not exceed 2 000 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 requested dose. These limitations are given for practical reasons.

2.2.5 Conditions of exposure

The following conditions as recommended:

Stocking:	Semistatic test:	<ul style="list-style-type: none"> - waterborne administration: max. 1 g/l; - oral administration: max. 5 g/l or 5 kg/fish; - injections: max. 5 g/l;
	Flow trough	- higher loading is acceptable

Group size and number: Min. 10 fish per group. Min. 2 tanks per dose and 2 control tanks.

Temperature: The temperature(s) chosen should be relevant to the proposed use of the product.

Fish size: It is recommended to use fish of the size, age and physiological status for which the product is intended, if possible.

Water quality: Relevant to the species to be tested and to the proposed use of the product; fresh water and/or sea water. Water quality parameters, such as temperature, oxygen content, salinity, flow, pH, NH₃/NH₄⁺ and hardness should be monitored.

2.2.6 Holding

The fish to be tested should be in good health and have good appetite during two weeks of acclimatisation. The allocation of fish in groups should be done randomly 1–2 weeks before the trial starts, using a recognised method.

2.2.7 Reporting

As a conclusion of the single dose toxicity trials, it is sufficient to state the approximate lethal concentration. If the lethal dose is above 2 000 mg/kg, this is to be stated without performing further trials. Post mortem examination should be performed on all fish. For further guidance, item 1.2 and OECD guideline for testing of chemicals 204: “Fish, Prolonged Toxicity Test, 14-Day Study” should be consulted.

2.3 Repeated dose toxicity

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

It is recommended to carry out studies in finfish according to the principles in the OECD guideline for testing of chemicals 204, modified as described below, or in accordance with other internationally recognised guidelines. Test methods for other aquatic species are left to the discretion of the investigator.

2.3.1 Selection of species

See item 2.2.1

2.3.2 Administration of test substance

See item 2.2.2

2.3.2.1 Waterborne administration

See item 2.2.2.1

2.3.2.2 Oral administration

It is recommended to administer the test substance in the same manner as intended for therapeutic use of the final product, e.g. mixed in feed or as a special oral dosage form. Detailed records on feed uptake and concomitant daily dose should be given. The controls should be administered the test substance deprived of the active substance in the same manner as the test fish.

2.3.2.3 Injections

See item 2.2.2.3

2.3.3 Test substance

See item 2.2.3

2.3.4 Dosage and duration of exposure

The dose level(s) should be chosen by evaluating the information obtained from the studies of single dose toxicity giving attention to the proposed therapeutic dose.

Having regard to the recommended therapeutic dosage scheme, the duration of exposure shall be justified by the investigator.

2.3.5 Conditions of exposure

See item 2.2.5

2.3.6 Holding

See item 2.2.6

2.3.7 Observations and reporting

All handling procedures and test conditions should preferably be reported daily throughout the entire test period including a pre-treatment, treatment and a post-treatment period. Relevant water quality parameters, e.g. temperature, salinity, O₂, NH₃/NH₄⁺, hardness, pH and flow, should be monitored clinical observations, e.g. behaviour, signs of adverse effects, appetite and mortality should also be recorded.

Necropsy examination of all fish that die should be performed, as well as histopathological examination of injection site(s), all grossly affected organs and known or suspected target organs. If necessary also surviving fish should be examined.

For further guidance, item 1.2 and OECD guideline 204 should be consulted.

2.4 Tolerance – finished product

2.4.1 General remarks

It will normally be possible to derive the documentation of tolerance from the toxicological and clinical studies.

2.4.2 Therapeutic index

Normally, a therapeutic index should be given for the finished medicinal product or an essentially similar formulation, i.e. same chemical(s), same particle size and dosage form.

The therapeutic index should as a minimum be stated as the margin between the maximum proposed therapeutic dose and the dose causing adverse effects. It may be sufficient to indicate a minimum or approximate value for this factor if it can be shown that the dose. For medicinal products intended for repeated administration, the maximum proposed duration of use should also be considered in the evaluation.

2.4.3 Adverse reactions and side effects

The nature and frequency of adverse drug reactions (ADRs) and side effects are to be stated. Thorough monitoring during all the clinical trials will normally be a sufficient basis.

2.4.4 Interactions

Signs of interactions should be carefully observed during the clinical trials. This applies particularly to medicinal products likely to be used concurrently.

3. PHARMACOLOGY

3.1 Chemical and pharmacological summary

To facilitate evaluation of the pharmacological documentation, certain chemical and pharmacological data should be included as an introduction, even if they are presented at a

greater length elsewhere in the submission. In addition to the information in the summary of product characteristics, the following should be given:

- Chemical structure;
- Molecular weight;
- pK_a ¹¹;
- Solubility.

3.2 General remarks

Studies in target species are required for the assessment of the pharmacological effects. All studies should be performed under relevant conditions for the proposed use of the product.

3.3 Pharmacodynamics

The pharmacodynamic effects, including the mode of action of the active ingredient(s) which form the basis for the recommended use of the product, should be described, if known.

Desired effects as well as side effects, preferably dose-related, are to be reported. Special emphasis should be placed on quantitative aspects. ED_{50} values should be provided if possible.

3.4 Pharmacokinetics

3.4.1 General considerations

Thorough pharmacokinetic studies are required in main target species. The studies should demonstrate the time course of the concentrations of the substance and its metabolites in body fluids, tissues and excreta taking into account the intended use of the finished product if considered relevant for the assessment of clinical efficacy.

If relevant, pharmacokinetic studies should be carried out at different water temperatures.

In the case of new combinations of substances of which the pharmacokinetics in the target species are generally known in veterinary medical science, studies may be limited to an investigation of possible pharmacokinetic interactions if justified by the results of the toxicological and clinical studies.

3.4.2 Performance of tests

For substances only intended for single administration, single dose studies are sufficient. If a product is intended for repeated administration, information should be given on reaching and maintenance of a steady state or on possible accumulation.

The test substance should be administered by the route intended for therapeutic use of the finished product.

Due to the high degree of inter-individual differences observed in fish, samples from several fish per timepoint (10 are recommended or less if statistically justified) are required for analyses. For repeated blood sampling from an individual fish, results from at least 4 individuals are required. The investigator shall justify the number of fish samples.

¹¹ the negative logarithm of the dissociation constant

3.4.3 Absorption

The time course of the concentration of the active substance in blood, serum or plasma and eventually in target tissue(s), at which pharmacological and toxicological effects are obtained, should be stated. Both the rate and extent of absorption should be described if possible e.g. as C_{max} , T_{max} , and AUC.

3.4.3.1 Bioavailability

Absolute bioavailability (intravenous versus intended administration) or relative bioavailability (intra-peritoneal versus intended administration) of the finished medicinal product should be stated for products intended for oral administration or injection when efficacy is dependent on tissue or plasma concentration. Absolute bioavailability is preferred, but relative bioavailability can be accepted if justified by the investigator.

Bioavailability for pre-mixes should be determined by administration of a medicated feed prepared by the procedure recommended by the manufacturer.

3.4.4 Distribution

The primary distribution should be outlined specifying the tissues or organs where especially high concentrations of the active molecule and its metabolites are to be found. Any retention of the active molecule and its metabolites are to be found. Any retention of the active substance or its metabolites in organs or tissues should be reported, if possible with approximate concentrations and time course. Whole-body autoradiography can be a useful method for studies of distribution.

Where appropriate, the magnitude of extravascular distribution should be calculated and stated, e.g. as apparent volume of distribution (litres per kg body weight).

3.4.5 Metabolism

The metabolism or biotransformation of active substance should, if possible, be documented both quantitatively and qualitatively. Presence of metabolites should be discussed. Possible influence of dose, pathological conditions and environmental factors on metabolism should be considered, if possible.

3.4.6 Elimination

The main route(s) of excretion of the active molecule and its principle metabolites should be stated. The rate of elimination (clearance) from target tissue(s), blood, plasma or serum should be stated. The most important factors influencing the rate of elimination should preferably be discussed, e.g. water temperature, salinity, O_2 content, feeding and physiological status of the fish.

3.5 Reporting

The changes of concentration of the medicine should be followed as a function of time, dose, frequency and duration of dosing, 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.

4. MICROBIOLOGY AND PARASITOLOGY

4.1 General remarks

Proof of the *in vitro* efficacy of the active substance should, if possible, be given.

For antibacterials, studies to establish minimal inhibitory concentration (MIC) and/or minimal bactericidal concentration (MBC) is claimed. It is recommended to establish the MIC 50, MIC 90, the MBC and where relevant, the MIC/MBC-ratio.

For antiparasitic agents, approximate lethal concentration for the target parasite(s) should be indicated.

4.2 Determination of MIC/MBC

MIC values for a relevant number (at least 10 if possible) of pertinent strains of each pathogen upon which effect is claimed are to be stated using established methods. In case of a pathogen of which several serotypes exist, the ten strains should represent the different serotypes. The methods of determination of MIC/MBC should be described in detail. The "type strain" of the bacterial species should be tested in the same system.

The bacterial strains should be well characterised and representative of the current disease situation isolated from the field within the last 3–5 years in the Member States in which the product is to be used. Strains with known resistance to antimicrobials should be included.

Based on MIC-values, the estimated therapeutic concentration of the substance in blood or serum and, if relevant, in target tissue(s), should be stated.

III. CLINICAL TRIALS

5. GENERAL CONSIDERATIONS

5.1 General remarks

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

Clinical trials are demanded for each proposed indication and for the main target species in which efficacy is claimed. The trials should include control groups. Normally, both trials performed under experimental conditions and full scale field trials will be required. Controlled field studies are of most benefit and should be performed in accordance with the note for guidance: *Good Clinical Practice for the Conduct of Clinical Trials on Veterinary Medicinal Products in the European Union*, considering the modifications laid out below.

Adverse effects, side-effects and target animal tolerance should be monitored during the course of the trial.

5.2 Instructions to investigators

To facilitate the evaluation of the documentation of efficacy, a summary should be given on the name and complete composition of the medicinal product, similarities to other medicinal products, pharmacological category, mode of action, dosage form, target animal species, recommended dosage, route(s) of administration, proposed indications and contraindications, side effects, restrictions of use, withdrawal period and preferably a statement of the reasons for development of the product.

The rationale for the choice of dosage, dosage intervals and route(s) of administration used in the clinical trials should be given.

6. PERFORMANCE OF TRIALS

6.1 General remarks

All studies should be performed under relevant conditions for the proposed use of the product.

6.1.1 Administration of the medicinal product

The final formulation or an essentially similar formulation should be used and administered by the route intended for therapeutic use. Positive and/or negative control groups should receive placebo treatment, when treatment is likely to stress the fish and when the auxiliary substance(s) or vehicle(s) have any effects of their own.

The daily uptake of special oral dosage forms should be recorded together with the concomitant daily dose of the active substance, if possible.

Pre-mixes should be administered as a medicated feed prepared by the procedure recommended by the manufacturer, preferably using a standardised feed. Daily feed uptake should be recorded together with the concomitant daily dose of the active substance, if possible.

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, also for side-effects, should be established.

Dose determination trials can be performed as a combination of experimental studies and field trials. Field trials are considered as giving most valuable information.

The need for differentiated dosage regimens should, if relevant, be investigated if differences in pharmacokinetics and/or efficacy occur dependant on age, size or physiological status of the fish and/or water quality parameters, such as temperature, salinity, oxygen content, hardness or pH.

The final formulation or a bioequivalent one ("essentially similar") should be used in the trials.

6.1.3 Dose confirmation trials

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

6.2 Experimental trials

The test conditions can be controlled and standardised in land or sea-based test stations for fish. Use of experimental trials can give valuable information and simplify the evaluation of the product. Experimental trials should be performed for main target species.

6.2.1 Selection of animals

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 acceptable method.

6.2.2 Selection of groups

The number and size(s) of groups should be sufficient to give statistically significant results. The investigator should justify the number and size(s) of groups.

6.2.3 Performance of tests

The investigator should justify the choice of the factors mentioned in item 6.6 “Reporting”. All trials must be planned so that suitable data are available for statistical analysis.

6.2.3.1 Challenge studies

Challenge studies with both positive and negative controls are most valuable. 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, 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 in the different groups should be reported, based on parasite counting, microbiological analyses or other pertinent investigations. A statistic presentation is useful.

6.3 Field trials

The scope of the field trials is to ensure that the medicinal product is efficacious in the diversified conditions for aquaculture found in Member States (see Part 1 “Introduction”). Recommended therapeutic dosage based on dose-response studies, kinetic data and clinical trials are to be presented.

The field studies are to be performed in established farms representative for practical use of the product.

For the main indication(s) claimed by the manufacturer, at least 3-5 clinical field trials are to be performed.

6.3.1 Selection of farms

A minimum of 3-5 farms should be selected for clinical trials. These farms should be geographically distant to optimise the possibility of diversified environmental conditions, disease situation and management practices.

Each farm 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 medicinal product. At least two of the pens or tanks should be used in the trial.

The farmer should 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 are accepted for water temperatures below 8 C.

6.3.2 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 these as a control group, which in most cases will be positive control group. The allocation of the groups should be a positive control group. The allocation of the groups should be done randomly, using an acceptable method.

The prevalence of disease, daily mortality, clinical symptoms and other relevant parameters should be comparable in the treated and control groups.

6.3.3 Performance of tests

Field trials in commercial fish farms should preferably be performed under 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.

6.3.3.1 Challenge studies

Challenge studies can be accepted if justified by the investigator. See item 6.2.3.1 for further guidance.

6.3.3.2 Diagnostical 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 autopsy 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 are normally required.

6.3.3.3 Use of control groups

All trials should include positive and/or negative control groups. Negative control groups are not demanded for contagious diseases. Negative controls can be assigned to a treatment group once an adequate estimation of difference in effect can be established.

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

6.4 Reporting

The efficacy of the medicine should be stated as a function of time, dose, frequency and duration of dosing. The criteria used for the evaluation of efficacy in the trials should be given. The data and results should be in a form which is suited for adequate statistical evaluation.

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

The clinical trials for each indication should be discussed and reported separately. Reports on all trials, whether favourable or not, should be provided. Whilst the results from separate trials should not be amalgamated, adequate summaries of groups of trials based on the same protocols should be provided. Justification of any apparent failures with relevance to the proposed recommended use of the medicinal product should be provided.

Each experimental trial or field trial should be described in detail. The documentation should *inter alia* cover:

- Description of fish; species, origin, size/weight/age, physiological status, previous diseases and therapy including vaccinations;
- Number and density of fish;
- Manner of application of the medicinal product;
- Feeding; amount, type, frequency, distribution, appetite;
- Water quality parameters; temperature, O₂, NH₃/NH₄⁺, pH, salinity, hardness, velocity or flow;
- Methods of observation and evaluation;
- Handling procedures/management practices;
- Size and number of tanks or pens in total at the farm;
- Localisation and identification of the farm.

6.5 General remarks

Data on the emergence of resistant organisms should be presented. Their possible implications should be discussed.

6.6 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.

6.7 Transfer of resistance

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