Australian Government
Australian Pesticides and Veterinary Medicines Authority

Pre-application assistance (PAA) – APVMA written assistance

Applicant name:	FISHERIES RESEARCH AND DEVELOPMENT CORPORATION
PAA ID:	136871
Assistance tier:	2
Product name:	CCD Trimetsulpha and A.F.S TRIMSUL ANTIMICROBIAL SOLUBLE POWDER / Marine and freshwater finfish / Susceptible bacterial infections
Date advice provided	18/10/2022

Summary of proposed application

Obtain advice on data requirement to contribute to a trimethoprim-sulfadiazine minor use permit application to treat susceptible bacterial infections in marine and freshwater finfish.

APVMA advice

The APVMA has reviewed your pre-application assistance application and provides the following advice under each of the relevant risk areas. Please note, advice has only been provided for technical areas requested by you in the PAA application form. Further data may be required to support a minor use permit application.

Human health (toxicology and worker health and safety)

You are proposing to use two registered products, of which 42336 is approved for use in poultry, pigs and cattle, and 36528 in chicken and pigeons, to be used for treating freshwater fish under minor use permit. A toxicology assessment would not be required for registered products, however WH&S module 6.3 assessment will be required to establish first aid instructions and safety directions for the minor use label. This will be based on the formulation's acute hazard and repeat exposure risk from the use of the product.

You should provide information on the intended use pattern(s), i.e., application equipment, method, and rate of the application to assist in the worker exposure risk assessment.

Residues and trade

The considered use is for the in-feed application to marine and freshwater finfish for up to 10 days for the treatment of bacterial infections, in conjunction with a 1000-degree days withholding period.

The combination formulation of trimethoprim and sulphadiazine is currently registered for administration to cattle, sheep, goats, pigs, horses and poultry through various routes of administration. The administration of trimethoprim and sulphadiazine to fish has not previously been assessed.

For assessment, the residues definition of the considered active ingredients in fish will need to be addressed. The submission of a scientific argument and supporting literature and/or international assessments may be appropriate. In addition, the scientific argument as outlined in the current PAA submission documentation, along with full versions of all literature and/or international assessments as referenced, is considered appropriate for an initial assessment of a minor use permit under a Module 5.5. The submitted information and argument will be evaluated during assessment.

A Trade Advice Notice consultation may be required should finite residues be expected at the proposed WHP.

Environment

The proposed minor use involves a new use situation for the registered antibiotic products in marine and freshwater finfish compared to the existing uses of the products in terrestrial situations on farm animals (poultry, pigs, cattle and horses). For veterinary medicinal products assessments, the APVMA adopts VICH guidelines[1] (CVMP/VICH 2000) on data requirements and assessment of environmental safety. If the assessment ends in VICH phase I, then a module is not required for the minor use. The Part 7 package must include sufficient information on the aquacultural production system(s) to inform Questions 8-12 of the VICH phase I decision tree (aquatic branch).

If it is determined that a VICH phase II assessment is required, then a module 7.3 assessment applies and you must submit sufficient data to inform the assessment. You have proposed to submit ecotoxicology and degradation data for marine and freshwater systems (Giang et al. 2015), which can be used to inform the assessment, if necessary. In addition, sufficient data must also be supplied regarding metabolism and excretion data in the treated aquatic animals, the fate and behaviour of the active substances in the environment, and effects on non-target aquatic species that are likely to be at risk from exposure. The following information on each active constituent is required to inform the environmental assessment as per VICH guidelines, which can be satisfied in part with available published information:

- OECD 308: degradation in aquatic systems
- OECD 203: acute toxicity to fish (one freshwater species, one saltwater species)
- OECD 202: acute toxicity to *Daphnia magna*
- Acute toxicity to saltwater crustacean (e.g. ISO 14669, OPPTS 850.1035)
- OECD 201: growth inhibition test on freshwater algae
- Growth inhibition test on saltwater algae (e.g. ISO 10253, OPPTS 850.5400).

Efficacy and target animal safety

The proposed minor use involves treatment of susceptible bacterial infections in marine and freshwater finfish using a product currently registered for the treatment of infections in Poultry, Pigs, Cattle and Calves.

It is noted that you are not seeking advice on efficacy but have provided a reference to support that sulfadiazine/trimethoprim is a broadly effective antimicrobial against a range of fish pathogenic aerobic bacteria. Please note, to satisfy the efficacy criteria you will also have to provide:

- Evidence to support the recommended dose rate, duration of treatment and route of administration.
- Evidence to support the efficacy of the product for all proposed indications in the target species.

Under target animal safety, you have requested that the APVMA assess some published references and indicate if its adequate to fulfill the target safety requirement of a minor use permit application for trimethoprim-sulfadiazine use in marine and freshwater finfish. Data cannot be assessed as part of the PAA process.

Evidence to demonstrate the safety of the product in the target species following administration by the proposed route and for the proposed duration of use will be required. For a minor use permit, a scientific argument supported by literature references may be submitted.

It is noted that you are seeking to use the trimethoprim—sulfadiazine products in marine and freshwater finfish which is a wide group covering various species. Target animal safety will have to be demonstrated in all target species as you have defined them unless you can justify not doing so. If data is available only for a single species, you will have to include a scientific argument in your submission justifying why efficacy in a single species should be extrapolated to the whole group.

The APVMA recommends that in your submission you should consider any genus/family differences and environmental conditions and production systems differences which may impact the target animal safety. This is particularly important if you are providing data/literature based on studies conducted overseas.

To satisfy the target animal safety aspect of the safety criteria, you should:

[1] https://vichsec.org/en/guidelines/pharmaceuticals/pharma-safety/environmental-safety.html

- ensure the studies in the literature you submit include appropriate target animal safety assessment parameters
- demonstrate the safety of the product in target species following repeated dose administration via the proposed route
- demonstrate the safety of the product for the proposed length of treatment, or longer than via the proposed route. The dosage of a veterinary medicinal product (as in mammals) is principally a function of treatment concentration and exposure period
- address possible adverse effects on development (malformations) if the medication is applied to young fish (embryos, larvae and juveniles) and the product can easily interfere with growth.
- consider the range of sizes and weights of fish recruited for studies in the literature you are submitting, as the same treatment might not have the same effect in fish of different sizes.
- determine the safety of excipients and justify any lack of appropriate data. Excipients normally used in pharmaceutical products for terrestrial animals might not be well tolerated by aquatic species.

A module 8.3 efficacy and target animal safety assessment will be required.

Special data:

When applying for a permit, for use of a product containing an approved antibiotic active constituent in a new species, a special data module 10.2 may be required. Determination of the risk to antibiotic resistance and whether a module 10 would not be required cannot be made in this PAA as more information would be required before making a decision. An assessment on whether the off label use in this application could increase the use of the antibiotics or increase the risk to public health will be undertaken when the permit application is received by the APVMA.

International assessments

The APVMA will consider relevant international assessments, provided the data supporting the assessment are also provided. Guidance for the submission of international data can be found on the APVMA website at apvma.gov.au/node/14186.

Resulting application

The likely item number for this application is Item **21**.

As stated above, the advice provided is for the technical areas requested by you in the PAA application form. There may be further data requirements to support a product variation or minor use permit application, resulting in additional modular assessments where advice was not requested. The modules, timeframes and fees applicable (based on the current fee structure) for the modules identified above are found on our website: https://apvma.gov.au/node/1088. **Please note:** Applications may still be subject to recategorisation under section 70B of the Agricultural and Veterinary Chemicals Code. If recategorisation is required, you will be given the reasons why the modules are to be changed and the opportunity to respond.

If additional information is requested under section 159 of the Agricultural and Veterinary Chemicals Code during the assessment of the application, an extended timeframe as outlined in Schedule 6 of the Agricultural and Veterinary Chemicals Code Regulations will apply.

The assistance provided by the APVMA is based on the information provided in your pre-application assistance request. If the information you have provided is not complete or correct, that could limit the effectiveness of the assistance provided by the APVMA.

The APVMA gives no undertaking that any application lodged after receiving pre-application assistance will be approved.

Outcome

If you require clarification of any issues addressed in this request for pre-application assistance, please contact your case manager. If you are seeking advice on additional/new questions, you will need to apply for further pre-application assistance under a new application. More information is available at apvma.gov.au/node/108.

When submitting this record in support of an application please ensure you include it in your information list.

Feedback

The APVMA welcomes your feedback on our PAA service and the assistance provided to you throughout this process.

If you would like to provide feedback, please complete the *pre-application assistance feedback form*, available at apvma.gov.au/node/97841 and return it via email to casemanagement@apvma.gov.au.