

Florfenicol Medicated Feed Clinical Field Trials - INAD 10-697

Year 2001 Annual Summary Report on the Use of Florfenicol Medicated Feed in Field Efficacy Trials

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Summary

Florfenicol-medicated feed (FMF) has been used effectively in the U. S. under compassionate INAD Exemption #10-697 to control mortality in a variety of fish caused by common fish bacterial pathogens. In calendar year (CY) 2001 the efficacy of FMF was evaluated in five disease trials involving approximately 52,000 fish to control mortality in a variety of test fish caused by bacterial coldwater disease, furunculosis, or streptococcal septicemia. Trials were conducted at one U.S. Fish and Wildlife Service National Fish Hatchery (NFH), two state fish hatcheries, and one private hatchery. In four of the trials, FMF was administered at the standard treatment dosage of 10mg/Kg fish/d for 10 d. In one trial fish were fed FMF at the same dosage for 9 d. Overall results showed that all of the trials appeared efficacious.

Introduction

Bacterial diseases are a major problem in aquaculture and account for significant losses of fish (Clarke and Scott 1989; Frerichs and Roberts 1989; Bjorndal 1990). Although the importance of environmental conditions (McCarthy and Roberts 1980; Haastein 1988; Munro and Roberts 1989) and the value of effective vaccines, where available (Ellis 1989), are acknowledged, antimicrobial therapy presently has an important role to play in aquaculture (Klontz 1987; Alderman 1988). Florfenicol is a potent, broad-spectrum, antimicrobial agent with bacteriostatic properties (Horsberg et al. 1996). It is a fluorinated analogue of thiamphenicol and is also similar in structure to chloramphenicol, both of which have been used as broad-spectrum, veterinary antibiotics (Nagata and Oka 1996).

Florfenicol has great potential for treatment of infectious diseases, and because of its high potency and safety to humans, it could become an important drug in veterinary medicine, especially with respect to animals used by humans for food (Powers et al. 1990). Additionally, because florfenicol is not currently used in human medicine, it has become a strong candidate for use in aquaculture, and there is considerable interest to obtain U.S. Food and Drug Administration (FDA) approval for its use in fish culture.

The proposed treatment strategy (i.e., dosage and duration) for the use of florfenicol-medicated feed (FMF) in fish is designed to meet the needs of individual fish

species, individual fish lots, and a variety of environmental conditions. In all cases, treatment goals are to (1) minimize the negative effects of disease on fish health, quality, and survival, and (2) help meet fishery management objectives. Because many factors can affect the success or failure of florfenicol-medicated feed therapy, supplemental efficacy data from compassionate Investigational New Animal Drug (INAD) use, as well as efficacy data from controlled, replicated studies that are scientifically valid and statistically defensible (i.e., pivotal), are needed to gain approval of FMF use in aquaculture.

Purpose of Report

The primary purpose of this report is to summarize the results of CY 2001 supplemental FMF field efficacy studies. However, it is also expected that these data will be used to enhance the FMF database for the purpose of developing an appropriate label claim for the use of this new animal drug.

Facilities, Materials, and Treatment Procedures

1. Participating Facilities

A total of 1 National fish hatchery, 2 state fish hatcheries, and 1 private hatchery (4 total facilities) used FMF to control mortality in a variety of freshwater fish caused by bacterial coldwater disease, furunculosis, or streptococcal septicemia.

2. FMF used in trials

The Aquaflor used in CY 01 trials contained 500 g of Florfenicol per kg of premix. Florfenicol is a pure compound with no inactive ingredients. All Florfenicol used was supplied as Aquaflor by Schering-Plough Animal Health, 1095 Morris Avenue, Union, NJ. Florfenicol medicated feed was prepared by either top-coating florfenicol onto commercial fish feed at the Bozeman Fish Technology Center using accepted Standard Operating Procedures, or prepared by commercial fish feed manufactures.

3. Drug dosages and duration

As described in the Study Protocol for INAD #10-697, Investigators were allowed to use FMF at 10mg of active drug per kg of fish per day for 10 d. However, in one trial fish were fed FMF medicated feed at 10mg/Kg fish/day for 9 d.

Fish Species and Fish Diseases Involved in year 2001 Trials

1. Species of fish treated

The following two salmonid species and one non-salmonid fish species were treated with FMF during CY 2001:

Salmonids:

coho salmon *Oncorhynchus kisutch*

cutthroat trout *O. clarki*

Non-salmonids:

hybrid striped bass *Morone americana* x *M. saxatilis*

2. Diseases treated

The diseases treated were bacterial coldwater disease, furunculosis, or streptococcal septicemia.

Data Collected

1. Pathologist's reports

All CY 01 trials included pathologist's reports (4 trials were pivotal studies with pathology reports included in the pivotal data submissions). Fish health pathology reports include: 1) a description of how the identity of disease agent(s) was verified; 2) disease identification records that confirm the presence of the disease agent; and 3) the name and title of the individual performing the diagnosis. Additionally, pathology reports often provide documentation that there were no secondary infections or infestations caused by unrelated disease agents in a population of test fish. Pathology reports provide essential information if efforts are to expand/extend an existing approved label.

2. Mortality data

As stated in the Study Protocol, mortality data was to be collected 10 days prior to treatment, during the treatment period, and for at least 21 days post-treatment. Investigators were strongly encouraged to collect mortality data on a daily basis. However, daily collection of pre-treatment mortality data was not always possible due to fish being moved from rearing unit to rearing unit.

Discussion of Study Results:

1. General observations on the efficacy of FMF for the control of bacterial

diseases in salmonid and non-salmonid fish (Note: Table 1 provides a summary of all efficacious trials; Table 2 provides general CY 01 summary data; and Table 3 provides a summary of all trials conducted during CY 2001 under INAD #10-697.)

A. Efficacy at 10mg/Kg fish/day for 9 days under INAD #10-697

FMF was used at 10mg/Kg fish/day for nine days in one trial involving hybrid striped bass diagnosed with streptococcal septicemia (Table 1). FMF treatment appeared efficacious in this trial.

B. Efficacy at 10mg/Kg fish/day for 10 days under Protocol FLOR-01-EFF

FMF was used at 10mg/Kg fish/day for 10 days in four trials involving coho salmon, cutthroat trout, and hybrid striped bass diagnosed with furunculosis, CWD, or streptococcal septicemia, respectively (Tables 1). FMF treatment was effective in all four trials (please refer to pivotal submission numbers FLOR-01-EFF-01, FLOR-01-EFF-02, FLOR-01-EFF-03, and FLOR-01-EFF-04 for more details on these studies).

2. Observed Toxicity

No toxicity or adverse effects relating to FMF treatment were reported.

Summary of Study Results

Florfenicol medicated feed was used at 10mg/Kg fish per day. Treatment duration ranged from 9 - 10 days. Three different fish species were treated with FMF, and trials involved approximately 52 thousand fish. Treated fish ranged in size from 1.90 - 6.40 in. Water temperature during treatment ranged from 52.0 - 86.7 °F, with a mean treatment temperature of 68.0 °F. Overall results showed that all of the treatment trials appeared effective. Investigators reported no evidence of toxicity or adverse effects related to FMF treatment. Trials conducted under the research protocol FLOR-01-EFF included use of control fish, detailed pathologist's reports documenting the disease during the trials, and will likely be accepted by CVM as supportive. Data from Study

Number 10-697-01-1 can only be considered as ancillary data because of a general lack of untreated control fish, replication, randomization, etc.. None-the-less, the ancillary data described above should provide useful corroborative data to support a new label claim for FMF. It is anticipated that additional ancillary efficacy data will continue to be collected under INAD #10-697. In future trials conducted under INAD #10-697, efforts will be directed towards the generation of higher quality data.

References

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Table 1. Summary of CY 2001 Florfenicol Medicated Feed Efficacy Results - Efficacious Trials

Hatchery	Number of Trials	Fish Species	Fish Size (inches)	Number of Fish	Disease	Number of Treatment Days	Dose (mg/kg)	Temp. (°F)
Kent SeaTech Corp.	1	SXW	6.40	30,034	Streptococcal Septicemia	9	10	86.0
Makah NFH	1	COS	3.40	1,306	Furunculosis	10	10	58.5
Murray Springs Trout SFH	1	CUT	1.90	12,977	CWD	10	10	52.0
Washoe Park Trout SFH	1	CUT	1.90	7,160	CWD	10	10	56.7
Kent SeaTech Corp.	1	SXW	5.80	300	Streptococcal Septicemia	10	10	86.7

Table 2. Summary Data Regarding CY 2001 Florfenicol Medicated Feed Efficacy Trials

Total Fish Treated: **51,777**

Number of fish treated in efficacious trials 51,777

Total number of trials: **5**

Number of efficacious trials: 5

Pivotal Studies:

Study Number: 10-697-01-3; 10-697-01-4; 10-697-01-5; 10-697-01-6

Treatment Regimes Used:

10mg/Kg fish/day for 9 days 1 trial

10mg/Kg fish/day for 10 days 4 trials

Treatment Water Temperature (°F):

Temperature Range 52.0 - 86.7

Mean Temperature 68.0

Size of Treated Fish (in.):

Size Range 1.90 - 6.40

Species Treated:

coho salmon *Oncorhynchus kisutch*

cutthroat trout *O. clarki*

hybrid striped bass *Morone americana* x *M. saxatilis*

