Oxytetracycline Immersion Clinical Field Trials - INAD 9033

2008 Annual Summary Report on the Use of Oxytetracycline Immersion Therapy in Field Efficacy Trials

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Summary

Oxytetracycline for immersion therapy (OTIMM) has been used in aquaculture to control mortality in a variety of fish caused by certain bacterial pathogens, particularly among fish not yet trained to consume medicated feed. In calendar year 2008 (CY08), the efficacy of OTIMM was evaluated under compassionate Investigational New Animal Drug (INAD) #9033 in eight disease trials. Efficacy trials were conducted at four state fish hatcheries and one private hatchery and involved approximately 0.1 million fish. The purpose of conducting such trials under INAD #9033 was to collect ancillary efficacy data to support a new animal drug approval for OTIMM. Efficacy was based on whether or not mortality of infected fish decreased when treated with OTIMM. Overall results showed that 100% of the OTIMM trials appeared efficacious.

Introduction

Oxytetracycline has historically been the drug of choice when diagnostic evidence shows salmonids to have furunculosis, caused by *Aeromonas salmonicida*; bacterial hemorrhagic septicemia, caused by *A. hydrophila* and other closely related

bacteria; pseudomonas disease, caused by *Pseudomonas sp.*; enteric redmouth, caused by *Yersinia ruckeri*; flavobacteriosis, caused by *Flavobacteria columnare*, *F. psychrophila*, or closely related yellow pigmented gliding bacteria as described in U. S. Food and Drug Administration (FDA) Public Master File #5456; or vibriosis caused by *Vibrio anguillarum, V. ordalli* or other closely related bacteria.

In warmwater fish culture, oxytetracycline has been found to be efficacious for the control of bacterial hemorrhagic septicemia, pseudomonas disease, and enteric septicemia of catfish caused by *Edwardsiella ictaluri*. Fish culturists have also reported oxytetracycline to be effective against systemic and external flavobacteriosis in catfish, sturgeon, paddlefish, temperate basses, sunfishes, and other fish species.

Oxytetracycline treatment therapy has been shown to be effective, whether administered as a medicated feed or as a bath immersion. Immersion therapy is often the only option when treating young fish not accustom to feeding on man-made fish diets. Reluctance or refusal of young fish to consume such feed excludes medicated feed treatment as a therapy option.

Although integrated fish health management practices are often successful in preventing the occurrence of the above-described diseases, adverse environmental conditions, uncontrollable water supplies, and other culture-related factors can lead to severe disease outbreaks requiring prompt treatment to prevent significant losses of fish valuable to natural resource stewardship. Treatment with antibacterial therapeutants

can effectively prevent losses of cultured fish species caused by a variety of fish diseases. Such treatments also reduce the discharge of infectious agents into the environment, thereby reducing the spread of disease to both cultured and wild fish. Although relying on administering therapeutic treatment to sick fish if and when they get sick is not the preferred option, it is critical that such an option exists.

Treatment strategies for the use of OTIMM have been designed to meet the needs of individual fish species and life stages, the physical configuration of the fish culture facility, and environmental conditions. The overall objective of OTIMM efficacy trials were to minimize the impact of disease on fish health, fish quality, and survival in order to fully meet fishery management objectives. As many factors can affect the success or failure of OTIMM, data were collected with respect to a number of parameters to help determine appropriate use patterns for OTIMM under routine fish culture conditions. These data should provide valuable information with respect to potential OTIMM use patterns in aquaculture.

Purpose

The purpose of this report is to summarize the results of CY08 supplemental OTIMM field efficacy trials. However, it is also expected that these data will be used to enhance the existing OTIMM database that has been established from previous years trials for the purpose of supporting an approval of an initial label claim for OTIMM use in aquaculture.

Facilities, Materials, and Methods

1. Participating Facilities

Four state fish hatcheries and one private hatchery used OTIMM in eight separate field efficacy trials during CY08 to control mortality in a variety of fish caused by a variety of bacterial and other infectious pathogens. Water temperature during treatments at the various testing facilities ranged from 45.0 - 78.4 °F, with a mean treatment temperature of 66.3 °F.

2. Oxytetracycline used in trials

All oxytetracycline used in CY08 trials was Terramycin-343 soluble powder, supplied by Pfizer, Inc., Lee's Summit, Missouri. Pfizer's over-the-counter Terramycin-343 soluble powder contains 343 grams of active oxytetracycline hydrochloride per pound. Pfizer's Terramycin-343 was the only form of oxytetracycline used by fish culturists to treat fish under INAD #9033 during the reporting period.

3. Drug dosages

One treatment regimen is allowed in the Study Protocol for INAD #9033. During CY08, OTIMM was administered as a bath treatment at a concentration of 20 mg/L for 1 hour for one - four days in eight trials.

Fish Species

1. Species of fish treated

Five fish species, including one salmonid and four non-salmonids were treated during CY08. Treated fish ranged in length from 2.3 - 10.0 in; mean length was 6.5 in. Species treated included:

Salmonids

Rainbow trout (*Oncorhychus mykiss*)

Non-salmonids

Largemouth bass (*Micropterus salmoides*)

Pallid Sturgeon (*Scaphirhynchus albus*)

Lake sturgeon (*Acipenser fulvescens*)

White sturgeon (*A. transmontanus*)

2. Diseases treated

Test fish were treated with OTIMM to control mortality caused by either external columnaris, bacterial gill disease, *Aeromonas hydrophila*, or external flavobacteriosis (mixed bacteria).

Data Collected

1. Pathologists Reports

Fish health pathology reports provide essential information with respect to disease confirmation and general fish health. Pathology reports were submitted with 63% of the CY08 trials.

2. Mortality data

As stated in the Study Protocol, mortality data was to be collected 5 days prior to treatment, during treatment, and 10 d post-treatment. Investigators were strongly encouraged to collect mortality data on a daily basis.

Discussion of Study Results

1. General observations on the efficacy of OTIMM 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 summary data for all trials; and Table 3 describes all trials conducted during CY08 under INAD #9033).

A. Efficacy of OTIMM at 20.0 mg/L for 1 hour for 1 day

OTIMM was used at 20.0 mg/L for 1 hour for 1 day in two trials involving largemouth bass and rainbow trout diagnosed with external flavobacteriosis

(mixed bacteria) (Table 1). Results indicated that OTIMM treatments appeared efficacious in both trials.

B. Efficacy of OTIMM at 20.0 mg/L for 1 hour for 3 - 4 days

OTIMM was used at 20.0 mg/L for 1 hour for 3 - 4 days in six trials involving lake sturgeon, pallid sturgeon, and white sturgeon diagnosed with bacterial gill disease, external columnaris, and *Aeromonas hydrophila* (Table 1). Results indicated that OTIMM treatments appeared efficacious in all trials.

2. Observed Toxicity

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

Current Study Protocol for OTIMM INAD #9033

Please see the attached current study protocol for OTIMM INAD #9033. Please note no changes have occurred to this study protocol.

Facility Sign-up List

Please see "Table 4. Facilities and Names of Investigators" for facilities that signed-up to participate in the OTIMM INAD #9033 during CY08. Facilities not listed in Appendix III-a of the current OTIMM INAD #9033 study protocol have been highlighted.

Correspondence sent to OTIMM Participants

Please see the attached correspondence that was sent to all OTIMM participants after the AADAP Office received their sign-up form for calendar year 2008.

Number of Treated Fish under Treatment Use Authorization

Total number of treated fish during CY08 was 123,546. The total number of treated fish to count against the treatment use authorization dated October 1, 2007 is 123,546.

Summary of Study Results

Oxytetracycline as an immersion therapeutant was used at a dosage of 20 mg/L for 1 hr daily, and treatments were administered for 1 - 4 days. Five fish species were treated with OTIMM, and trials involved approximately 0.1 million treated fish. Treated fish ranged in size from 2.3 - 10.0 in. Water temperature during treatments ranged between 45.0 and 78.4 ^{o}F. All of the trials appeared efficacious. No evidence of toxicity or adverse effects related to OTIMM treatment were reported. Although these data will be considered ancillary efficacy data, they should provide useful corroborative data to support an initial label claim for OTIMM. It is anticipated that additional ancillary efficacy data will continue to be collected in the future under INAD #9033. In future trials conducted under INAD #9033, efforts will continue to be directed towards the generation of high quality data.

Table 1. Summary of CY08 OTIMM Treatment Trial Results - efficacious results

Facility	Number of Trials	Fish Species	Number of Fish	Fish Size (in)	Treatment Duration (hrs)	Dose (mg/L)	Number of Treatments	Disease	Temp. (^{o}F)
Manning SFH	1	LMB	35,000	2.30	1	20	1	External Flaovobacteriosis	68.0
Lost Valley SFH	2	LST	546	5.50	1	20	3	*Aeromonas Hydrophila*	60.8
Blind Pony SFH	2	PLS	2,800	5.40	1	20	4	External Columnaris	77.7 - 78.4
French River SFH	1	RBT	70,000	7.80	1	20	1	External Flaovobacteriosis	45.0
Sterling Caviar LLC	2	WHS	15,200	10.0	1	20	4	BGD	70.0

Table 2. Summary Data Regarding CY08 OTIMM Efficacy Trials

Total Number of Trials Conducted:	8
Number of efficacious trials:	8
Total Number of Fish Treated:	**123,546**
Number of fish treated in efficacious trials	123,546
Treatment Regimens Used:	
20 mg/L static bath for 1 hr; 1 day	2 trials
20 mg/L static bath for 1 hr; 3days	2 trials
20 mg/L static bath for 1 hr; 4days	4 trials
Treatment Water Temperature (°F):	45.0 - 78.4
Size of Treated Fish (in):	2.3 - 10.0
Species Treated:	
Rainbow trout (*Oncorhychus mykiss*)	
Largemouth bass (*Micropterus salmoides*)	
Pallid Sturgeon (*Scaphirhynchus albus*)	
Lake sturgeon (*Acipenser fulvescens*)	
White sturgeon (*A. transmontanus*)	