

Oxytetracycline Immersion Clinical Field Trials - INAD 9033

2009 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 2009 (CY09), the efficacy of OTIMM was evaluated under compassionate Investigational New Animal Drug (INAD) #9033 in six disease trials. Efficacy trials were conducted at three state fish hatcheries 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 34% of the OTIMM trials appeared efficacious, ineffective in 33% of the trials, and were characterized as inconclusive in 33% of the trials.

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 accustomed 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 CY09 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

Three state fish hatcheries used OTIMM in six separate field efficacy trials during CY09 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 40.0 - 80.5 °F, with a mean treatment temperature of 66.0 °F.

2. Oxytetracycline used in trials

All oxytetracycline used in CY09 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

According to the Study Protocol, investigators were allowed to administer OTIMM at 20 mg/L for one hour for a single treatment or one hour daily for 1 - 4 consecutive days. During CY09, OTIMM was administered as a bath treatment at a concentration of 20 mg/L for 1 hour for one - four days in five trials.

Study Protocol Deviation: Treatment regimen administered in one trial (approximately 17% of trials) deviated from the protocol. In this trial, lake sturgeon received a four day treatment and then another four day treatment on post-treatment day 6. These fish are a state listed T&E species and will not be available for human consumption. Due to the value of these fish for the recovery program, it was deemed necessary to retreat the fish with OTIMM treatments within a short period of time.

Fish Species

1. Species of fish treated

Four fish species, including one salmonid and three non-salmonids were treated during CY09. Treated fish ranged in length from 1.25 - 6.3 in; mean length was 2.4 in. Species treated included:

Salmonids

Rainbow trout (*Oncorhynchus mykiss*)

Non-salmonids

American shad (*Alosa sapidissima*)

Lake sturgeon (*Acipenser fulvescens*)

Largemouth bass (*Micropterus salmoides*)

2. Diseases treated

Test fish were treated with OTIMM to control mortality caused by either *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 33% of the CY09 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 a summary of all trials in which treatment appeared ineffective; Table 3 provides a summary of all inconclusive trials; Table 4 provides summary data for all trials; and Table 5 describes all trials conducted during CY09 under INAD #9033).

A. Efficacy of OTIMM at 20.0 mg/L for 1 hour for 1 - 8 days

OTIMM was used at 20.0 mg/L for 1 hour for 1 - 8 days in six trials involving rainbow trout, American shad, largemouth bass, and lake sturgeon diagnosed with *Aeromonas hydrophila* or external flavobacteriosis (mixed bacteria) (Tables 1 - 3). OTIMM treatments appeared effective in two trials, ineffective in two trials, and were characterized as inconclusive in two trials.

2. Observed Toxicity

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

3. Observed Withdrawal Period

All withdrawal times were either met or exceeded.

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 6. Facilities and Names of Investigators” for facilities that signed-up to participate in the OTIMM INAD #9033 during CY09. Facilities not listed in Appendix III-a of the current OTIMM INAD #9033 study protocol have been highlighted. Please note all of these facilities are in compliance with their reporting requirements to the NPDES authority.

The following facilities had OTIMM on-hand during CY09 but never used the drug:

1. Local Ocean
2. Lost Valley SFH
3. Sterling Caviar LLC

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 2009.

Number of Treated Fish under Treatment Use Authorization

Total number of treated fish during CY09 was 109,500. The total number of treated fish to count against the treatment use authorization dated October 1, 2007 is 233,046.

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 - 8 days. Four fish species were treated with OTIMM, and trials involved approximately 0.1 million treated fish. Treated fish ranged in size from 1.25 - 6.3 in. Water temperature during treatments ranged between 40.0 and 80.5 °F. Overall results showed that 34% of the OTIMM trials appeared efficacious, ineffective in 33% of the trials, and were characterized as inconclusive in 33% of the trials. 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 CY09 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	Observed Withdrawal Time (days)	Temp. (°F)
Manning SFH	2	LMB	17,500	1.3 - 1.6	1	20	1	External Flaovobacteriosis	365	68.0 - 70.5

Table 2. Summary of CY09 OTIMM Treatment Trial Results - ineffective results

Facility	Number of Trials	Fish Species	Number of Fish	Fish Size (in)	Treatment Duration (hrs)	Dose (mg/L)	Number of Treatments	Disease	Observed Withdrawal Time (days)	Temp. (°F)
Manning SFH	1	AMS	15,000	1.25	1	20	1	External Flaovobacteriosis	365	69.0
Manning SFH	1	LMB	4,000	1.60	1	20	1	External Flaovobacteriosis	365	68.0

Table 3. Summary of CY09 OTIMM Treatment Trial Results - inconclusive results

Facility	Number of Trials	Fish Species	Number of Fish	Fish Size (in)	Treatment Duration (hrs)	Dose (mg/L)	Number of Treatments	Disease	Observed Withdrawal Time (days)	Temp. (°F)
Blind Pony SFH	1	LST	3,600	2.10	1	20	8 (See study protocol deviation.)	External Flaovobacteriosis	not for human consumption	80.5
French River SFH	1	RBT	69,400	6.3	1	20	1 - 2	<i>Aeromonas Hydrophila</i>	100	40.0

Table 4. Summary Data Regarding CY09 OTIMM Efficacy Trials

Total Number of Trials Conducted: 6

Number of efficacious trials: 2

Number of ineffective trials: 2

Number of inconclusive trials: 2

Total Number of Fish Treated: 109,500

Number of fish treated in efficacious trials 17,500

Number of fish treated in ineffective trials 19,000

Number of fish treated in inconclusive trials 73,000

Treatment Regimens Used:

20 mg/L static bath for 1 hr; 1 day 4 trials

20 mg/L static bath for 1 hr; 1 - 2 days 1 trial

20 mg/L static bath for 1 hr; 4 days (with another
four day treatment on post-treatment day 6) 1 trial

Treatment Water Temperature (°F): 40.0 - 80.5

Size of Treated Fish (in): 1.25 - 6.3

Species Treated:

Salmonids

Rainbow trout (*Oncorhynchus mykiss*)

Non-salmonids

American shad (*Alosa sapidissima*)

Lake sturgeon (*Acipenser fulvescens*)

Largemouth bass (*Micropterus salmoides*)
