

Oxytetracycline Immersion Clinical Field Trials - INAD 9033

2011 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. The U.S. Food and Drug Administration has authorized the use of OTIMM under the Compassionate Investigational New Animal Drug (INAD) Exemption #9033 for the purpose of gathering efficacy data to support a new animal drug approval. In calendar year 2011 (CY11) the efficacy of OTIMM to control mortality was evaluated in 13 trials involving approximately 1.0 million fish. Trials were conducted at six different hatcheries, including two state hatcheries and four private hatcheries during this period. The compassionate study protocol under which treatments were administered allowed the investigator to use OTIMM at a dosage of 20 mg/L for 1 h for 1 - 4 days. Efficacy was based on whether or not mortality of infected fish decreased when treated with OTIMM. Overall results

showed that 70% of the OTIMM trials appeared efficacious, ineffective in 15% of the trials, and were characterized as inconclusive in 15% 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 CY11 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

Six different hatcheries, including two state hatcheries and four private hatcheries used OTIMM in 13 separate field efficacy trials during CY11 to control mortality in a variety of fish caused by a variety of bacterial pathogens. Water temperature during treatments at the various testing facilities ranged from 63.0 - 77.0 °F, with a mean treatment temperature of 70.7 °F.

2. Oxytetracycline used in trials

Oxytetracycline hydrochloride used in CY11 trials was supplied by either 1) Terramycin-343[®] soluble powder, supplied by Pfizer, Inc., Lee's Summit, Missouri, or 2) Pennox 343[®] soluble powder, supplied by PennField Animal Health, Omaha, Nebraska. Both of these over-the-counter water-soluble powder products contains 343 grams of active oxytetracycline hydrochloride per pound.

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 CY11, OTIMM was administered as a bath treatment at a concentration of 20 mg/L for 1 hour for 1 - 4 days in 13 trials.

Fish Species

1. Species of fish treated

Five fish species, four non-salmonids and one salmonid, were treated during CY11. Treated fish ranged in length from 0.75 - 60.0 in; mean length was 5.8 in.

Species treated included:

Non-salmonids

Bluegill (*Lepomis macrochirus*)

Lake sturgeon (*Acipenser fulvescens*)

Largemouth bass (*Micropterus salmoides*)

White sturgeon (*Acipenser transmontanus*)

Salmonid

Atlantic salmon (*Salmo salar*)

2. Diseases treated

Test fish were treated with OTIMM to control mortality caused by either bacterial gill disease, aeromonas/pseudomonas, 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 38% of the CY11 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 treated 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 CY11 under INAD #9033).

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

OTIMM was used at 20.0 mg/L for 1 hour for 1 - 4 days in 13 trials involving Atlantic salmon, bluegill, largemouth bass, lake sturgeon, and white sturgeon diagnosed with bacterial gill disease, aeromonas/pseudomonas, or external flavobacteriosis (Tables 1 - 3). OTIMM treatments appeared effective in nine 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

No changes have occurred to the current study protocol for OTIMM INAD #9033.

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 CY11. Please note all of these facilities are in compliance with their reporting requirements to the NPDES authority.

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 CY11.

Number of Treated Fish under Treatment Use Authorization

Total number of treated fish during CY11 was 1,046,001. The total number of treated fish to count against the treatment use authorization dated October 1, 2007 is 1,320,904.

Summary of Study Results

Oxytetracycline as an immersion therapeutant was used at a dosage of 20 mg/L for 1 hr, and treatments were administered for 1 - 4 days. Five fish species were treated with OTIMM, and trials involved approximately 1.0 million treated fish. Treated fish ranged in size from 0.75 - 60.0 in. Water temperature during treatments ranged between 63.0 and 77.0 °F. Overall results showed that 70% of the OTIMM trials appeared efficacious, ineffective in 15% of the trials, and were characterized as inconclusive in 15% 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 CY11 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. (°F)
Bingham Hatchery	1	ATS	315,033	2.70	1	20	4	BGD	63.0
Cain Fish Farm	6	LMB	75,700	0.75	1	20	4	aeromonas/ pseudomonas	72.0
Matapeake (Manning)	1	LMB	19,800	1.50	1	20	4	BGD	64.4
Sterling Caviar LLC	1	WST	184	60.0	1	20	1	BGD	70.0

Table 2. Summary of CY11 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	Temp. (°F)
Bingham Hatchery	1	ATS	604,934	1.30	1	20	4	BGD	63.0
George Washington Carver Farm	1	BLG	23,350	1.00	1	20	4	External Flaovobacteriosis	73.0

Table 3. Summary of CY11 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	Temp. (°F)
Blind Pony SFH	2	LST	7,000	2.00	1	20	4	External Flaovobacteriosis	77.0

Table 4. Summary Data Regarding CY11 OTIMM Efficacy Trials

Total Number of Trials Conducted:	13
Number of efficacious trials:	9
Number of ineffective trials:	2
Number of inconclusive trials:	2
Total Number of Fish Treated:	1,046,001
Number of fish treated in efficacious trials	410,717
Number of fish treated in ineffective trials	628,284
Number of fish treated in inconclusive trials	7,000
Treatment Regimens Used:	
20 mg/L static bath for 1 hr; 1 day	1 trial
20 mg/L static bath for 1 hr; 4 days	12 trials
Treatment Water Temperature (°F):	63.0 - 77.0
Size of Treated Fish (in):	0.75 - 60.0
Species Treated:	
<u>Non-salmonids</u>	
Bluegill (<i>Lepomis macrochirus</i>)	
Lake sturgeon (<i>Acipenser fulvescens</i>)	
Largemouth bass (<i>Micropterus salmoides</i>)	
White sturgeon (<i>Acipenser transmontanus</i>)	
<u>Salmonid</u>	
Atlantic salmon (<i>Salmo salar</i>)	
