Oxytetracycline Immersion Clinical Field Trials - INAD 9033

2007 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 2007 (CY07), the efficacy of OTIMM was evaluated under compassionate Investigational New Animal Drug (INAD) #9033 in eight disease control/prevention trials. Efficacy trials were conducted at two state fish hatcheries and two private 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 50% of the OTIMM trials appeared efficacious, 12% appeared ineffective, and 38% were characterized as inconclusive.

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 CY07 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

Two state fish hatcheries and two private hatcheries used OTIMM in eight separate field efficacy trials during CY07 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 48.0 - 71.0 °F, with a mean treatment temperature of 62.5 °F.

2. Oxytetracycline used in trials

All oxytetracycline used in CY07 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

Two treatment regimens are allowed in the Study Protocol for INAD #9033. During CY07, 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

Four fish species, including one salmonid, two non-salmonids, and one marine species were treated during CY07. Treated fish ranged in length from 1.25 - 11.0 in; mean length was 5.2 in. Species treated included:

1. Rainbow trout (*Oncorhychus mykiss*)
2. Largemouth bass (*Micropterus salmoides*)
3. White sturgeon (*Acipenser transmontanus*)
4. Cabezon (*Scorpaenichthys marmoratus*)

2. Diseases treated

Test fish were treated with OTIMM to control mortality caused by either external columnaris, bacterial gill disease, or 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 88% of the CY07 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 ineffective trials; 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 CY07 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 six trials involving largemouth bass diagnosed with columnaris and cabezon diagnosed with

flavobacteriosis (mixed bacteria) (Tables 1 - 3). Results indicated that OTIMM treatments appeared efficacious in two trials involving largemouth bass; while treatments involving cabezon were ineffective in one trial and characterized as inconclusive in three 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 two trials involving rainbow trout and white sturgeon diagnosed with bacterial gill disease and external columnaris (Table 1). Results indicated that OTIMM treatments appeared efficacious in both trials.

2. Observed Toxicity

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

Number of Treated Fish under Slaughter Authorization

Total number of treated fish during CY07 was 103,197. The total number of treated fish to count against the slaughter authorization dated November 23, 1999 (valid through September 30, 2007) is 4,211,502; no fish were used under the current slaughter authorization dated October 1, 2007. No changes have occurred to the current OTIMM INAD #9033 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 CY07.

Summary of Study Results

Oxytetracycline as an immersion therapeutant was used at a dosage of 20.0 mg/L for 1 hr daily, and treatments were administered for 1 - 4 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 - 11.0 in. Water temperature during treatments ranged between 48.0 and 71.0 ^{o}F. Approximately 50% of the trials appeared efficacious, 12% appeared ineffective, and 38% were characterized as inconclusive. 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 CY07 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)
Manning SFH	2	LMB	34,000	1.25	1	20	1	Columnaris	71.0
Crystal Springs SFH	1	RBT	54,000	2.10	1	20	3	BGD	48.0
Sterling Caviar LLC	1	WHS	5,400	10	1	20	4	BGD & External Columnaris	70.0

Table 2. Summary of CY07 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)
The Abalone Farm, Inc.	1	CAB	546	11.0	1	20	1	Flavobacteriosis (mixed bacteria)	59.0

Table 3. Summary of CY07 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)
The Abalone Farm, Inc.	3	CAB	9,251	5.0 - 6.0	1	20	1	Flavobacteriosis (mixed bacteria)	60.0 - 61.0

Table 4. Summary Data Regarding CY07 OTIMM Efficacy Trials

Total Number of Trials Conducted:	8
Number of efficacious trials:	4
Number of ineffictive trials:	1
Number of inconclusive trials:	3
Total Number of Fish Treated:	**103,197**
Number of fish treated in efficacious trials	93,400
Number of fish treated in inefficacious trials	546
Number of fish treated in inconclusive trials	9,251
Treatment Regimens Used:	
20 mg/L static bath for 1 hr; 1 day	6 trials
20 mg/L static bath for 1 hr; 3days	1 trial
20 mg/L static bath for 1 hr; 4days	1 trial
Treatment Water Temperature (^{o}F):	48.0 - 77.0
Size of Treated Fish (in):	1.25 - 11.0
Species Treated:	
Rainbow trout (*Oncorhychus mykiss*)	
Largemouth bass (*Micropterus salmoides*)	
White sturgeon (*Acipenser transmontanus*)	
Cabezon (*Scorpaenichthys marmoratus*)	