

Oxytetracycline Medicated Feed Clinical Field Trials - INAD 9006

Year 2002 Annual Summary Report on the Use of Oxytetracycline Medicated Feed in Clinical Field Efficacy Trials

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Summary

Oxytetracycline-medicated feed (OTF) has been used effectively in the U. S. under compassionate INAD Exemption #9006 to control mortality in a variety of fish caused by common fish bacterial pathogens. In calendar year (CY) 2002 the efficacy of OTF was evaluated at two U.S. Fish and Wildlife Service (Service) National Fish Hatcheries (NFH) in three disease trials to control mortality in two different salmonid species, involving 257,000 fish, caused by either bacterial coldwater disease or columnaris. Fish species treated included coho salmon (*Oncorhynchus kisutch*) and steelhead trout (*O. mykiss*).

Although the use of OTF has been approved for use in aquaculture by the U.S. Food and Drug Administration (FDA), the current label limits drug use to the control of only specific bacterial diseases of fish at water temperatures not below 48.2° F (9° C). Label guidelines do not permit use of oxytetracycline for the control of bacterial coldwater disease, columnaris, enteric redmouth, bacterial kidney disease, or vibriosis.

To accommodate the needs of aquaculture and to collect clinical OTF field efficacy data for the control of these diseases, the FDA has authorized the use of this compound under the Compassionate Investigational New Animal Drug Exemption #9006.

Treatment regimes used during CY2002 included the use of oxytetracycline medicated feed at 7.0 g/100 lbs fish/day for 14 days at water temperatures below 48.2° F, and 11.2 g/100 lbs fish/day for 13 days at water temperatures above 48.2° F. Overall results from field efficacy trials showed that approximately 67% of the trials appeared efficacious, while 33% were characterized as inconclusive.

Introduction

The current oxytetracycline-medicated feed (OTF) label restricts its use of to the control of furunculosis in salmonids caused by *Aeromonas salmonicida*, and bacterial hemorrhagic septicemia in salmonids and catfish caused by *A. hydrophila* or *Pseudomonas sp.* Oxytetracycline medicated feed has been shown to be highly effective in controlling mortality caused by these diseases, especially when predisposing environmental stresses are reduced at the time of treatment (Warren 1991). However, the current FDA approved label for OTF limits allowed dosages to a range of 2.5 - 3.75 grams of active drug per 100 pounds of fish per day for 10 days, and limits use to water temperatures "not below 48.2° F (9° C)." These label restrictions severely limit the overall utility of approved OTF use in aquaculture.

Fish culturists have reported that oxytetracycline medicated feed treatment is a useful tool for the control of bacterial cold water disease (CWD) and columnaris in salmonids. Both diseases, collectively termed "flavobacteriosis", are caused by *Flavobacterium psychrophilus* and *F. columnaris*. Enteric redmouth, caused by *Yersinia ruckeri*, vibriosis caused by various members of the genus *Vibrio*, and other less common bacterial diseases of fish have also been found to be responsive to OTF therapy. However, none of these latter uses are yet approved by the FDA.

Purpose

The purpose of this report is to summarize the results of CY 2002 supplemental OTF field efficacy studies. It is also expected that data in this report on controlling mortality in salmonids caused by coldwater disease and columnaris will be used to enhance the existing OTF database that has been established from studies of previous years for the purpose of expanding and/or extending the approved label for OTF.

Facilities, Materials, and Treatment Procedures

1. Facilities

Two U.S. Fish and Wildlife Service (Service) National Fish Hatcheries (NFH) used OTF to control mortality in fish caused by CWD and columnaris.

2. OTF used in trials

Either Terramycin 100 or Terramycin 100D, both of which contained 100 g active oxytetracycline quaternary salt per pound of premix, were used in all trials. All Terramycin 100/100D was supplied by Pfizer, Inc., 1107 South 291 Highway, Lee's Summit, MO. It should be noted that oxytetracycline-medicated feed used in the treatment trials was purchased from several different fish feed manufacturers.

3. Drug dosages and duration

As described in the Study Protocol for INAD #9006, Investigators were allowed to use OTF either within the current label range of 2.5 - 3.75 grams of active drug per 100 lbs of fish per day, or at dosages up to 7.0 grams of active drug per 100 lbs of fish per day. Treatment duration was restricted to either 10 days, or "up to 21 days." With one exception, all trials were conducted using one of the above described dosages for the prescribed duration. The one exception involved a trial in which fish were treated at 11.2 g/100lbs of fish/13days. Based on the small size of the test fish when treated, they would not have been available for human consumption for at least 180 days.

Fish Species and Fish Diseases Involved in CY 2002 Trials

1. Species of fish treated

The following fish species were treated during CY 2002:

1. Coho salmon *Oncorhynchus. Kisutch*
2. Steelhead trout *O. mykiss*

2. Diseases treated

The following diseases were treated during CY 2002:

1. bacterial coldwater disease, causative agent *Flavobacterium psychrophilum*
2. columnaris, causative agent *F. columnare*

Data Collected

1. Pathologist's reports

A pathology report was submitted with the study conducted at Coleman NFH.

Fish health pathology reports typically include: 1) a description of how the identity of the 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

According to the Study Protocol, mortality data was to be collected for at least 10 days prior to treatment, during the treatment period, and for at least 30 days post-treatment. Investigators were strongly encouraged to document daily mortality. However, daily collection of post-treatment mortality data was not always possible due to factors such as fish being moved into other tanks and fish being stocked to rivers and other bodies of water.

Discussion of CY 2002 Study Results

1. General observations on the efficacy of OTF

A. Efficacy at 7.0 g/100 lbs fish/d for 14 d at water temperatures below 48.2° F

OTF was used at 7.0 g/100 lbs fish/d for 14 d in two trials involving coho salmon diagnosed with bacterial coldwater disease (Table 1). Mean water temperature during treatment for each trial was 43.0°F. Both trials appeared to be successful.

B. Efficacy at 11.2 g/100 lbs fish/d for 13 d at water temperatures above 48.2° F

OTF was used at 11.2 g/100 lbs fish/d for 13 ds at water temperatures above 48.2° F in one trial involving steelhead trout diagnosed with columnaris (Table 2). Mean water temperature during treatment was 66.5°F. Treatment was characterized as inconclusive because insufficient post-treatment mortality was recorded and fish had a secondary parasite (costia) present during the treatment period.

2. Observed Toxicity

No toxicity or adverse effects relating to OTF treatment were reported in two trials. However, in one trial, the Investigator noted that the fish were “flighty” and reluctant to eat on treatment day 5.

Summary of Study Results

Oxytetracycline medicated feed was used at dosages ranging from 7.0 - 11.2 g/100 lbs fish per d. Treatment duration ranged from 13 - 14 d. Two different salmonid species were treated with OTF, and trials involved approximately 257,000 treated fish. Treated fish ranged in size from 2.10 - 3.40 in. Water temperature during treatments were either 43.0 or 66.5°F. Two of the three trials appeared efficacious, while the remaining trial was characterized as inconclusive. The treatment trial characterized as inconclusive

was actually because insufficient post-treatment mortality records were available. Results of trials that appeared to be effective indicated that mortality decreased during or following the treatment period, and remained at normal levels throughout the post-treatment period. In addition, Investigators reported no evidence of toxicity or adverse effects related to OTF treatment in two trials. However, in one trial, the Investigator noted that the fish were “flighty” and reluctant to take feed on treatment day 5. In spite of the fact that no efficacy trial utilized untreated control fish, replication, randomization, etc., and that these data will be considered ancillary, information summarized in this report should provide useful corroborative data to support a future expanded label claim for OTF. It is anticipated that additional ancillary efficacy data will continue to be collected under INAD #9006. In future trials conducted under INAD 9006, and that efforts will be directed towards the generation of higher quality data.

References

Warren, J.W. 1991. Diseases of hatchery fish. U.S. Fish and Wildlife Service, Portland, Oregon, 92 p.

Table 1. Summary of CY 2002 Oxytetracycline Medicated Feed Efficacy Results - Efficacious Studies

Hatchery	Number of Efficacious Trials	Fish Size (in.)	Fish Species	Number of Fish	Disease	Dose (g/100 lbs)	Number of Treatment Days	Temp. (°F)
Willard NFH	2	2.7 - 3.4	COS	249,146	CWD	7.0	14	43.0

Table 2. Summary of CY 2002 Oxytetracycline Medicated Feed Efficacy Results - Inconclusive Studies

Hatchery	Number of Inconclusive Trials	Fish Size (in.)	Fish Species	Number of Fish	Disease	Dose (g/100 lbs)	Number of Treatment Days	Temp. (°F)
Coleman NFH	1	2.10	STT	8,082	Columnaris	11.2	13	66.5

Table 3. Summary Data Regarding CY 2002 Oxytetracycline Medicated Feed Efficacy Studies

Total Number of Fish Treated:	<u>257,228</u>
Number of fish treated in efficacious studies	249,146
Number of fish treated in inconclusive studies	8,082
Total Number of Trials:	3
Efficacious Trials	2
Inconclusive Trials	1
Treatment Regimes Used:	
7.0 g/100 lbs fish/day for 14 days (below 48.2°C)	2 trials
11.2 g/100 lbs fish/day for 13 days (above 48.2°F)	1 trial
Treatment Water Temperature (°F):	
Temperature Range	43.0 & 66.5
Size of Treated Fish (in.):	
Size Range	2.10 - 3.40
Species Treated:	coho salmon (<i>Oncorhynchus kisutch</i>) steelhead trout (<i>O. mykiss</i>)
