

Oxytetracycline Medicated Feed Clinical Field Trials - INAD 9006

Year 2001 Annual Summary Report on the Use of Oxytetracycline Medicated Feed in Clinical Field Efficacy Trials

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Summary

The efficacy of oxytetracycline medicated feed (OTF) was evaluated in seven disease control trials during calendar year (CY) 2001. Trials were conducted at three U.S. Fish and Wildlife Service (Service) National Fish Hatcheries (NFH) to control mortality caused by the following fish diseases: (1) bacterial coldwater disease, or (2) columnaris. Fish species treated included a variety of salmonids and (1) channel catfish *Ictalurus punctatus*, (2) white sturgeon *Acipenser transmontanus*, (3) white seabass *Atractoscion nobilis*, (4) hybrid striped bass (white bass x striped bass), tilapia *Tilapia mossambica*, largemouth bass *Micropterus salmoides*, walleye *Stizostedion vitreum*, and red abalone *Haliotis rufescens*. The use of OTF by the Service has been granted by the U. S. Food and Drug Administration under Compassionate Investigational New Animal Drug Exemption #9006 for the purpose of collecting pivotal and ancillary efficacy data to support a new animal drug approval for OTF.

Oxytetracycline-medicated feed efficacy trials conducted during CY2001 involved approximately 2.4 million fish. The use of OTF has been approved for use in

aquaculture by the U.S. Food and Drug Administration (FDA). However, 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 included the use of oxytetracycline medicated feed at 3.75 - 7.0 g/100 lbs fish/day for 10 - 15 days at water temperatures below 48.2° F, and 3.89 - 10.0 g/100 lbs fish/day for 10 - 14 days at water temperatures above 48.2° F. Approximately 29% of the trials appeared efficacious, while 71% 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 2001 supplemental OTF field efficacy studies. It is also expected that data from studies in this report 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

A total of 3 U.S. Fish and Wildlife Service (Service) National Fish Hatcheries (NFH) used OTF to control mortality 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 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 a one of the above described dosages for the prescribed duration. The one exception involved a trial in which fish were treated at 10.0g/100lbs of fish/10days. Based on the

small size of the test fish when treated, they would not have been available for human consumption for at least 350 days.

Fish Species and Fish Diseases Involved in CY 2001 Trials

1. Species of fish treated

The following fish species were treated during CY 2001:

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

2. Diseases treated

The following diseases were treated during CY 2001:

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

Data Collected

1. Pathologist's reports

Pathologist reports were submitted with studies conducted at Dworshak NFH and 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 2001 Study Results

1. General observations on the efficacy of OTF

A. Efficacy at 3.75 - 7.0 g/100 lbs fish/day for 10 - 15 days at water temperatures below 48.2° F

OTF was used at 3.75 - 7.0 g/100 lbs fish/day for 10 - 15 days in 1 trial involving chinook salmon, and in 1 trial involving coho salmon diagnosed with bacterial coldwater disease (Table 2). Mean water temperature during treatment for each trial was 40.7 and 48.0°F respectively. Both trials were characterized as inconclusive.

B. Efficacy at 3.89 - 10.0 g/100 lbs fish/day for 10 - 14 days at water temperatures above 48.2° F

OTF was used at 3.89 - 10.0 g/100 lbs fish/day for 10 - 14 days at water temperatures above 48.2° F in 5 trials. Trials involved steelhead trout and chinook salmon diagnosed with columnaris and CWD (Tables 1 - 2). Mean water temperature during treatment for each trial ranged between 54.0 - 70.0°F. Treatment appeared to be efficacious in two trials, while treatment results from three trials were characterized as inconclusive.

2. Observed Toxicity

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

Summary of Study Results

Oxytetracycline medicated feed was used at dosages ranging from 3.75 - 10.0 g/100 lbs fish per day. Treatment duration ranged from 10 - 15 days. Three different salmonid species were treated with OTF, and trials involved approximately 2.4 million treated fish. Treated fish ranged in size from 1.40 - 2.40 in. Water temperature during treatments ranged from 40.7 - 70.0°F, with a mean trial treatment temperature of 56.3°F.

Approximately 29% of the trials appeared efficacious, while 71% were characterized as inconclusive. The preponderance of treatment trials characterized as inconclusive were actually because, in most cases, treated fish were moved after into other rearing units (i.e., split into multiple or combined with other rearing unit) at the end of the treatment period. As a result, no 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 any trial. 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 2001 Oxytetracycline Medicated Feed Efficacy Results - Efficacious Studies

Hatchery	Number of Efficacious Trials	Fish Size (in.)	Fish Species	Number of Fish	Disease	Number of Treatment Days	Dose (g/100 lbs)	Temp. (°F)
Coleman NFH	1	2.25	STT	555,000	Columnaris	14	3.89	63.0
Dworshak NFH	1	1.70	STT	48,000	CWD	10	10.0	54.0

Table 2. Summary of CY 2001 Oxytetracycline Medicated Feed Efficacy Results - Inconclusive Studies

Hatchery	Number of Inconclusive Trials	Fish Size (in.)	Fish Species	Number of Fish	Disease	Number of Treatment Days	Dose (g/100 lbs)	Temp. (°F)
Dworshak NFH	1	1.40	CKS	212,697	CWD	15	7.0	40.7
Coleman NFH	1	2.40	FCS	830,000	Columnaris	10	7.00	70.0
Makah NFH	1	2.40	COS	185,000	CWD	10	3.75	48.0
Coleman NFH	1	2.25	STT	255,000	Columnaris	14	3.89	63.0
Makah NFH	1	2.20	STT	281,000	CWD	7.50	10	55.6

Table 3. Summary Data Regarding CY 2001 Oxytetracycline Medicated Feed Efficacy Studies

Total Number of Fish Treated:	<u>2,366,697</u>
Number of fish treated in efficacious studies	603,000
Number of fish treated in inconclusive studies	1,763,697
Total Number of Trials:	7
Rearing Units in Efficacious Studies	2
Rearing Units in Inconclusive Studies	5
Treatment Regimes Used:	
3.75 - 7.0 g/100 lbs fish/day for 10 - 15 days (below 48.2°C)	2 trials
3.89 -10.0 g/100 lbs fish/day for 10 - 14 days (above 48.2°F)	5 trials
Treatment Water Temperature (°F):	
Temperature Range	40.7 - 70.0
Mean Trial Temperature	56.3
Size of Treated Fish (in.):	
Size Range	1.40 - 2.40
Species Treated:	coho salmon (<i>Oncorhynchus kisutch</i>) steelhead trout (<i>O. mykiss</i>) chinook salmon (<i>O. tshawytscha</i>)
