

Oxytetracycline Medicated Feed Clinical Field Trials - INAD 9006

Year 2000 Annual Summary Report on the Use of Oxytetracycline Medicated Feed in Clinical Field Efficacy Trials

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Summary

Oxytetracycline as a feed additive (OTF) was used at five U.S. Fish and Wildlife Service National Fish Hatcheries (NFH) during calendar year 2000 to evaluate its efficacy to control mortality caused by bacterial coldwater disease, columnaris, and flavobacteriosis in both salmonid and non-salmonid fish species. 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 field efficacy data on OTF for the control of these diseases, the FDA has authorized the use of this compound under the Compassionate Investigational New Animal Drug Exemption #9006. In calendar year (CY) 2000, OTF was administered under INAD #9006 in 22 disease control trials involving approximately 3.5 million fish. Treatment regimes included the use of oxytetracycline medicated feed at 4.60 - 6.0 g/100 lbs fish/day for 11- 21 days at water temperatures below 48.2° F, and 3.60 - 7.0 g/100 lbs fish/day for 10 days at water temperatures above 48.2° F. Approximately 59% of the trials appeared efficacious, 27% appeared ineffective, and 14% were characterized as inconclusive.

Introduction

The current label restricts the use of OTF 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 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 also reported that oxytetracycline medicated feed treatment is a useful tool for the control of bacterial cold water disease (CWD) and columnaris in salmonids. These two diseases, collectively termed "flavobacteriosis" are caused by *Flavobacter 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 also have been found to be responsive to OTF therapy. However, none of these latter uses are yet approved by the FDA.

Purpose

The primary purpose of this report is to summarize the results of CY 2000 supplemental OTF field efficacy studies. However, it is also expected that data from these studies will be used to enhance the existing OTF database that has been established from previous years studies for the purpose of expanding and/or extending the approved label for OTF.

Facilities, Materials, and Treatment Procedures

1. Facilities

A total of 5 U.S. Fish and Wildlife Service National Fish Hatcheries (NFH) used OTF to control mortality caused by CWD, columnaris, and flavobacteriosis.

2. OTF used in trials

The OTF used in these trials was either Terramycin 100 or Terramycin 100D, both of which contained 100 g active oxytetracycline quaternary salt per pound of premix. All Terramycin 100/100D was supplied by Pfizer, Inc., 1107 South 291 Highway, Lee's Summit, MO. However, oxytetracycline medicated feed was supplied by 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".

Fish Species and Fish Diseases Involved in CY 2000 Trials

1. Species of fish treated

Three salmonid and one non-salmonid fish species were treated during CY 2000.

Fish species treated included: rainbow and steelhead trout (*Oncorhynchus mykiss*); coho salmon (*O. kisutch*); and blue catfish (*Ictalurus furcatus*).

2. Diseases treated

The diseases treated most frequently during CY 2000 were bacterial coldwater disease and columnaris. The other disease treated for was flavobacteriosis at the Makah NFH and Uvalde NFH.

Data Collected

1. Pathologist's reports

Fish health pathology reports include: 1) a description of how the identity of 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. Pathologist reports were submitted with studies conducted at Quinalt NFH, Willard NFH, and Makah NFH.

2. Mortality data

As stated in 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 collect mortality data on a daily basis. However, daily collection of mortality data was not always possible. At production facilities that are understaffed, the collection and enumeration of mortalities can not always be conducted on a daily basis. Therefore, in some cases, mortalities were collected, counted, and recorded only once/twice per week.

Discussion of CY 2000 Study Results

1. General observations on the efficacy of OTF for the control of bacterial diseases in salmonid and non-salmonid fish

A. Efficacy at 4.60 - 6.0 g/100 lbs fish/day for 11- 21 days at water temperatures below 48.2° F

OTF was used at 4.60 - 6.0 g/100 lbs fish/day for 11- 21 days in 2 of 22 trials (9%). These trials involved coho salmon at the Willard NFH and Quinalt NFH

diagnosed with bacterial coldwater disease (Table 1). Water temperature during treatment was 43.0 - 44.0°F. Treatment appeared to be efficacious in both trials.

B. Efficacy at 3.60 - 7.0 g/100 lbs fish/day for 10 days at water temperatures above 48.2° F

OTF was used at 3.60 - 7.0 g/100 lbs fish/day for 10 days in 20 of 22 trials (91%). Trials involved rainbow and steelhead trout, and blue catfish diagnosed with columnaris and flavobacteriosis (Table 1 - 3). Water temperature during treatment was between 54 - 79°F. Treatment appeared to be efficacious in 11 trials (55%), while 6 trials (30%) appeared to be inefficacious, and 3 trials (15%) 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 3.60 - 7.0 g/100 lbs fish per day. Treatment duration ranged from 10 - 21 days. Four different species of fish were treated with OTF, and trials involved approximately 3.5 million treated fish. Treated fish ranged in size from 1.70 - 4.80 in. Water temperature during treatment ranged from 43.0 - 79.0°F, with a mean trial treatment temperature of 63.5°F. Approximately 59% of the trials appeared efficacious, 27% appeared ineffective, and 14% were characterized as inconclusive. Overall, OTF treatment appeared effective in controlling mortality caused by bacterial coldwater disease, columnaris, or flavobacteriosis. Results of trials indicated that mortality decreased during or following the treatment period, and remained at normal levels throughout the post-treatment period. Furthermore, investigators reported no evidence of toxicity or adverse effects related to OTF treatment. However, based on a lack of untreated control fish, replication, randomization, etc., it is understood that these data can only be considered as ancillary data. None-the-less, the ancillary data described above 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, 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 2000 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)
Quinalt NFH	1	1.70	COS	420,000	CWD	11	4.60	44.0
Chattahoochee Forest NFH	11	3.0 - 4.8	RBT	317,025	Columnaris	10	6.00	66.0
Willard NFH	1	2.18	COS	2,250,480	CWD	21	7.00	43.0

Table 2. Summary of CY 2000 Oxytetracycline Medicated Feed Efficacy Results - Non-efficacious Studies

Hatchery	# of Non-efficacious Trials	Fish Size (in.)	Fish Species	Number of Fish	Disease	Number of Treatment Days	Dose (g/100 lbs)	Temp. (°F)
Chattahoochee Forest NFH	6	3.00	RBT	205,625	Columnaris	10	6.0	66.0

Table 3. Summary of CY 2000 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)
Uvalde NFH	1	4.50	BCF	50,000	Flavobacteriosis	10	3.60	79.0
Makah NFH	2	1.9 - 2.0	STT	230,000	Flavobacteriosis	10	6.00	54.0

Table 4. Summary Data Regarding CY 2000 Oxytetracycline Medicated Feed Efficacy Studies

Total Number of Fish Treated: **3,473,130**

Number of fish treated in efficacious studies 2,987,505
 Number of fish treated in non-efficacious studies 205,625
 Number of fish treated in inconclusive studies 280,000

Total Number of Rearing Units Treated: **22**

Rearing Units in Efficacious Studies 13
 Rearing Units in Non-efficacious Studies 6
 Rearing Units in Inconclusive Studies 3

Treatment Regimes Used:

3.60 - 7.0 g/100 lbs fish/day for 10 days (above 48.2°C) 20 trials
 4.60 - 6.0 g/100 lbs fish/day for 11- 21 days (below 48.2°F) 2 trials

Treatment Water Temperature (°F):

Temperature Range 43.0 - 79.0
 Mean Trial Temperature 63.5

Size of Treated Fish (in.):

Size Range 1.70 - 4.80

Species Treated: rainbow trout (*Oncorhynchus mykiss*)
 coho salmon (*O. kisutch*)
 steelhead trout (*O. mykiss*)
 blue catfish (*Ictalurus furcatus*)
