

Oxytetracycline Medicated Feed Clinical Field Trials - INAD 9006

1998 Annual Summary Report on the Use of Oxytetracycline Medicated Feed in Clinical Field Efficacy Trials

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Summary

Oxytetracycline in feed (OTF) was used at seven U.S. Fish and Wildlife Service National Fish Hatcheries (NFH) and one tribal hatchery during 1998 to evaluate its efficacy to control mortality caused by bacterial coldwater disease and columnaris in 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 1998, OTF was administered under INAD #9006 in 232 disease control/prevention trials involving nearly 12 million fish. Treatment regimes included the use of oxytetracycline medicated feed at 2.5 - 7 g/100 lbs fish/day for 10 - 70 days at water temperatures above 48.2° F, and 3.75 - 7 g/100 lbs fish/day for 10 - 14 days at water temperatures below 48.2° F. Approximately 97% of the trials appeared efficacious, less than 1% appeared ineffective, and approximately 2.5% 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 "flexibacteriosis" are caused by *Flexibacter 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 calendar year 1998 (CY 98) 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 7 U.S. Fish and Wildlife Service (FWS) National Fish Hatcheries (NFH) and 1 Tribal Hatchery used OTF to control mortality caused by CWD and columnaris.

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". However, the Wolfcreek NFH deviated from the Study Protocol by treating rainbow trout and brown trout at 2.5 grams of active drug per 100 lbs of fish per day for up to 70 days. Multiple (i.e. repeating) treatments were applied as a result of an extended period of high water temperatures and low dissolved oxygen levels experienced at this facility.

Fish Species and Fish Diseases Involved in CY 1998 Trials

1. Species of fish treated

Five salmonid species and one non-salmonid specie were treated during CY 98. Salmonid species treated included: rainbow and steelhead trout (*Oncorhynchus mykiss*); coho salmon (*O. kisutch*); spring chinook salmon (*O. tshawytscha*); and brown trout (*Salmo trutta*). The only non-salmonid species treated was paddlefish (*Polydon spathula*).

2. Diseases treated

The diseases treated most frequently during CY 98 were bacterial coldwater disease and columnaris. Other diseases treated were aeromonas/pseudomonas at the Dworshak NFH, and enteric redmouth at the Chattahoochee 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 Dworshak NFH, Makah NFH, and Clearwater Fish Hatchery.

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 1998 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 2.5 g/100 lbs fish/day for 14-70 days at water temperatures above 9°C

OTF was used at 2.5 g/100 lbs for 14-70 in 62 of 232 trials (26.7%). Trials involved rainbow trout and brown trout at the Wolfcreek NFH diagnosed with columnaris (Table 1). Water temperature during treatment was approximately 17.7°C. In all trials, treatment appeared to be efficacious in controlling mortality.

B. Efficacy at 3.0 g/100 lbs fish/day for 10 days at water temperatures above 9°C

OTF was used at 3.0 g/100 lbs for 10 days in 4 of 232 trials (1.7%). Trials involved paddlefish diagnosed with columnaris at the Neosho NFH (Table 3). Water temperature during treatment was approximately 20.6°C. Treatment results were inconclusive.

C. Efficacy at 3.75 g/100 lbs fish/day for 14 days at water temperatures below 9°C

OTF was used at 3.75 g/100 lbs for 14 days in 50 of 232 trials (20.7%). All trials involved coho salmon at the Willard NFH diagnosed with bacterial coldwater disease (Table 1.). Water temperature during treatment was approximately 7.1°C. In all trials, treatment appeared to be efficacious in controlling mortality.

D. Efficacy at 4.0 g/100 lbs fish/day for 10 days at water temperatures above 9°C

OTF was used at 4.0 g/100 lbs for 10 days in 2 of 232 trials (0.9%). Both trials involved steelhead trout diagnosed with coldwater disease at the Makah NFH (Table 3). Water temperature during treatment was 13.3°C in one trial, and 15.0°C in the other trial. Treatment results were inconclusive.

E. Efficacy at 6.0 g/100 lbs fish/day for 10 days at water temperatures above and below 9°C

OTF was used at 6.0 g/100 lbs for 10 days in 10 of 232 trials (4.3%). Trials involved coho salmon diagnosed with coldwater disease at the Quinalt NFH, and rainbow trout diagnosed with columnaris/enteric redmouth at the Chattahoochee NFH (Table 1). Water temperature during treatment at Quinalt NFH was approximately 6.7°C. Water temperature during treatment at Chattahoochee

NFH was approximately 18.3°C. In all trials, treatment appeared to be efficacious in controlling mortality.

F. Efficacy at 7.0 g/100lbs fish/day for 11-14 days at water temperatures above and below 9°C

OTF was used at 7.0 g/100 lbs for 11-14 days in 103 of 231 trials (44.4%). Trials involved chinook salmon, coho salmon, and steelhead trout diagnosed with coldwater disease at the Dworshak NFH, rainbow trout diagnosed with aeromonas/pseudomonas at the Dworshak NFH, and coho salmon diagnosed with coldwater disease at the Clearwater FH (Table 1). Water temperature during treatment at Chattahoochee NFH was 11.6°C. In all trials, treatment appeared to be efficacious in controlling mortality.

G. Efficacy at 7.0 g/100 lbs fish/day for 15 days at water temperatures above 9°C

OTF was used a 7.9 g/100 lbs for 15 days in a single trial. The trial involved chinook salmon diagnosed with coldwater disease at the Clearwater FH. The water temperature during treatment was approximately 12.2°C. Treatment did not appear to be efficacious in controlling mortality.

Summary of Study Results

Oxytetracycline medicated feed was used at dosages ranging from 2.5 - 7.0 g/100 lbs fish per day. Treatment duration ranged from 10 - 70 days. Six different species of fish were treated with OTF, and trials involved approximately 11.3 million treated fish. Treated fish ranged in size from 1.2 - 9.3 in. Water temperature during treatment ranged from 5.5 - 20.6°C, with a mean trial treatment temperature of 11.1°C. Approximately 97% of trial appeared effective, less than 1% appeared ineffective, and 2.5% were characterized as inconclusive. Overall, OTF treatment appeared effective in controlling mortality caused by bacterial coldwater disease or columnaris. 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 1998 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. (°C)
Wolfcreek NFH	3	4.3 - 5.6	BNT	244,000	Columnaris	14 & 31	2.5	17.7
	59	3.0 - 9.3	RBT	1,800,150	Columnaris	14 - 70	2.5	17.7
Willard NFH	50	3.20	COS	2,701,471	CWD	14	3.75	7.1
Quinalt NFH	2	6.70	COS	635,000	CWD	10	6	6.7
Chattahoochee NFH	8	7.7 - 8.3	RBT	46,693	Columnaris/ERM	10	6	18.3
Dworshak NFH	9	1.80	SCS	169,456	CWD	14	7	5.5
	1	1.20	RBT	5,322	Aeromonas/ pseudomonas	14	7	5.8
	6	2.00	COS	259,998	CWD	14	7	7.8
	86	3.7 - 5.3	STT	2,318,929	CWD	12 & 14	7	8.4
Clearwater FH	1	3.00	COS	450,000	CWD	11	7	11.6

Table 2. Summary of 1998 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. (°C)
Clearwater FH	1	4.25	SCS	81,500	CWD	15	7	12.2

Table 3. Summary of 1998 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. (°C)
Neosho NFH	4	6.00	PAH	4,500	Columnaris	10	3	20.6
Makah NFH	1	2.00	STT	92,000	CWD	10	4	13.3
	1	2.30	STT	120,000	CWD	10	4	15.0

Table 4. Summary Data Regarding 1998 Oxytetracycline Medicated Feed Efficacy Studies

Total Number of Fish Treated: **11,306,413**

Number of fish treated in efficacious studies	11,008,413
Number of fish treated in non-efficacious studies	81,500
Number of fish treated in inconclusive studies	216,500

Total Number of Rearing Units Treated: **232**

Rearing Units in Efficacious Studies	225
Rearing Units in Non-efficacious Studies	1
Rearing Units in Inconclusive Studies	6

Treatment Regimes Used:

2.5 g/100 lbs fish/day for 14-70 days (above 9°C)	62 trials
3.0 g/100 lbs fish/day for 10 days (above 9°C)	4 trials
3.75 g/100 lbs fish/day for 14 days (below 9°C)	50 trials
4.0 g/100 lbs fish/day for 10 days (above 9°C)	2 trials
6.0 g/100 lbs fish/day for 10 days (above/below 9°C)	10 trials
7.0 g/100 lbs fish/day for 11-14 days (above/below 9°C)	103 trials
7.0 g/100 lbs fish/day for 15 days (above 9°C)	1 trials

Treatment Water Temperature (°C):

Temperature Range	5.5 - 20.6
Mean Trial Temperature	11.1

Size of Treated Fish (in.):

Size Range	1.2 - 9.3
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Species Treated: rainbow trout (*Oncorhynchus mykiss*)
 chinook salmon (*O. tshawytscha*)
 coho salmon (*O. kisutch*)
 brown trout (*Salmo trutta*)
 steelhead trout (*O. mykiss*)
 paddlefish (*Polydon spathula*)
