

Date of Approval: July 6, 2008

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 038-439

TERRAMYCIN 200 for Fish

Oxytetracycline dihydrate
Type A medicated article
Fish

1. For the control of mortality in freshwater-reared salmonids due to coldwater disease associated with *Flavobacterium psychrophilum*
2. For the control of mortality in freshwater-reared *Oncorhynchus mykiss* due to columnaris disease associated with *Flavobacterium columnare*
3. To remove the limitation on treating salmonids in water temperatures below 9 °C
4. To add to the label the previously approved indication for marking of skeletal tissue in Pacific salmon

Sponsored by:

Phibro Animal Health

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I. GENERAL INFORMATION:

- A. File Number:** NADA 038-439
- B. Sponsor:** Phibro Animal Health
65 Challenger Rd., 3d floor
Ridgefield Park, NJ 07660

Drug Labeler Code: 066104
- C. Proprietary Name:** TERRAMYCIN 200 for Fish
- D. Established Name:** Oxytetracycline (from oxytetracycline dihydrate)
equivalent to oxytetracycline hydrochloride
- E. Pharmacological Category:** ANTIMICROBIAL
- F. Dosage Form:** Type A medicated article
- G. Amount of Active Ingredient:** 200 g oxytetracycline/lb
- H. How Supplied:** 50 lb bag
- I. How Dispensed:** OTC
- J. Dosages:** Salmonids and catfish: 2.5 to 3.75 g
oxytetracycline/100 lb of fish/day for 10 days

Pacific salmon: 250 mg/kg of fish/day
administered as the sole ration for 4 consecutive
days

Freshwater-reared salmonids: 3.75 g
oxytetracycline/100 lb of fish/day for 10 days

Freshwater-reared *Oncorhynchus mykiss*: 3.75 g
oxytetracycline/100 lb of fish/day for 10 days

Lobsters: 1 g oxytetracycline/lb of medicated
feed administered as the sole ration for
5 consecutive days
- K. Route of Administration:** Oral via feed

- L. Species/Classes:** Salmonids, catfish, Pacific salmon, freshwater-reared salmonids, freshwater-reared *Oncorhynchus mykiss*, and lobsters
- M. Indications:**
- Salmonids: Control of ulcer disease caused by *Hemophilus piscium*, furunculosis caused by *Aeromonas salmonicida*, bacterial hemorrhagic septicemia caused by *Aeromonas liquefaciens*, and pseudomonas disease.
- Catfish: Control of bacterial hemorrhagic septicemia caused by *Aeromonas liquefaciens*, and pseudomonas disease.
- Pacific salmon: For marking of skeletal tissue.
- Freshwater-reared salmonids: Control of mortality due to coldwater disease associated with *Flavobacterium psychrophilum*.
- Freshwater-reared *Oncorhynchus mykiss*: Control of mortality due to columnaris disease associated with *Flavobacterium columnare*.
- Lobsters: Control of gaffkemia caused by *Aerococcus viridans*.
- N. Effects of Supplement:** This supplement provides for the addition of an indication for the control of mortality in freshwater-reared salmonids due to coldwater disease associated with *Flavobacterium psychrophilum*, the addition of an indication for the control of mortality in freshwater-reared *Oncorhynchus mykiss* due to columnaris associated with *Flavobacterium columnare*, removal of the limitation on treating salmonids in water temperatures below 9 °C, and the addition to the label of the previously approved indication for marking of skeletal tissue in Pacific salmon.

II. EFFECTIVENESS:

The data summarized in this section are publicly available and contained in Investigational New Animal Drug Files 009-006 and 009-332 sponsored by the U.S. Fish & Wildlife Service, Aquatic Animal Drug Approval Partnership Program.

Effectiveness studies were conducted using TERRAMYCIN 100 or TERRAMYCIN 100D that were mono-alkyl (C8-C18) trimethylammonium oxytetracycline (quaternary salt) formulations. As described in the Freedom of Information (FOI) Summary for NADA 038-439 dated June 30, 2006, CVM concluded that a change in the active ingredient in the Type A medicated article product from the quaternary salt to oxytetracycline dihydrate creates no concerns regarding the effectiveness of TERRAMYCIN 200 for Fish for use in fish.

The decision to remove the limitation on treating salmonids in water temperatures below 9 °C was based on residue chemistry. The indication for the marking of skeletal tissue in Pacific salmon has already been codified in 21 CFR 558.450(d)(2). No additional data on the effectiveness of these two claims is necessary.

A. Dosage Characterization:

This supplemental approval does not change the previously approved dosage range.

B. Substantial Evidence:

Addition of the indication for the control of mortality in freshwater-reared salmonids due to coldwater disease associated with *Flavobacterium psychrophilum*

1. Clinical Field Study

- a. Title: “Efficacy of Oxytetracycline-Medicated Feed to Control Mortality of Fingerling Coho Salmon (*Oncorhynchus kisutch*) Caused by Coldwater Disease.” Study Number BOZ-98-OTF-03.
- b. Study Director: James D. Bowker
- c. Investigator: Larry Telles
- d. Study Location: U.S. Fish and Wildlife Service
Quilcene National Fish Hatchery
Quilcene, WA

e. Study Design:

- 1) Objective: To evaluate the effectiveness of oxytetracycline administered in feed at a dosage of 3.7 g oxytetracycline/100 lb of fish/day for 10 consecutive days to control mortality in fingerling coho salmon due to coldwater disease associated with *Flavobacterium psychrophilum*.
- 2) Study Animals: Approximately 83,600 coho salmon fingerlings.
- 3) Test Article/Controls: The test article was a Type C medicated feed containing oxytetracycline that delivered a dose of 3.7 g/100 lb of fish/day for 10 consecutive days. Control animals were fed a non-medicated commercial salmonid feed. The target dose was verified with a feed assay.
- 4) Procedure: The test fish originated from a single concrete raceway experiencing increased mortality. Ten fish from the raceway were examined (body surface, fins, gills, and internal organs), kidney inocula were cultured and examined for the presence of systemic bacteria, and stained kidney imprints were examined microscopically for the presence of systemic bacteria. Coldwater disease was determined to be the cause of increased mortality in the fish. Test fish were randomly transferred to 12 test tanks. Fish in six tanks were fed oxytetracycline-medicated feed, and fish in the other six tanks were fed non-medicated control feed. The treatment groups were assigned to the tanks using a completely randomized design. Treatments began the day following allocation of fish to the test tanks. Fish were treated with medicated feed (3.7 g oxytetracycline/100 lb of fish/day) or non-medicated control feed for 10 consecutive days. Mortality was observed for an additional 14 days after the end of the treatment period.
- 5) Measurements: Mortality and water quality parameters were recorded at specified intervals throughout the study.
- 6) Statistical Analysis: A generalized linear model was used to analyze the ratios of cumulative mortality to total fish. The group effect was tested at significance level $\alpha = 0.05$.

- f. Results: Mortality rates are included in the following table.

Table 1. Mean percent cumulative mortality rates at the end of the 14-day post-treatment period.

Oxytetracycline Dose (g/100 lb of fish/day)	Mean Percent Cumulative Mortality Rate
0	2.0 (841/41,759)
3.7	0.8 (324/41,840)
p-value < 0.0001	

The mean water temperature was 8.8 °C, and the mean dissolved oxygen concentration (DO) was 11.2 mg/L. Water hardness, alkalinity, and pH were 32 mg/L (as CaCO₃), 30 mg/L (as CaCO₃), and 7.5, respectively.

- g. Conclusions: The results from this study demonstrate the effectiveness of oxytetracycline-medicated feed administered at a dosage of 3.7 g oxytetracycline/100 lb of fish/day for 10 consecutive days to control mortality in coho salmon due to coldwater disease associated with *F. psychrophilum*.

2. Clinical Field Studies

The effectiveness of oxytetracycline-medicated feed to control mortality in freshwater-reared salmonids due to coldwater disease associated with *F. psychrophilum* was supported by a series of field studies conducted under INAD 009-332 involving rainbow trout and cutthroat trout. In six of sixteen studies in which coldwater disease was diagnosed by pathology, reductions in mortality were obtained at rates similar to those seen during Study BOZ-98-OTF-03 following the administration of oxytetracycline-medicated feed. Oxytetracycline was administered at doses of 3.35 to 3.92 g/100 lb of fish/day for 10 consecutive days during these six studies. In the ten other studies, reductions in mortality were observed, but the reductions were not as large as the reduction observed during Study BOZ-98-OTF-03.

The results of these studies and Study BOZ-98-OTF-03 provide substantial evidence of the effectiveness of oxytetracycline-medicated feed administered at a dose of 3.75 g oxytetracycline/100 lb of fish/day for 10 consecutive days to control mortality in freshwater-reared salmonids due to coldwater disease associated with *F. psychrophilum*.

Addition of the indication for the control of mortality in freshwater-reared *Oncorhynchus mykiss* due to columnaris disease associated with *Flavobacterium columnare*

3. Clinical Field Study

- a. Title: “The Efficacy of Oxytetracycline-Medicated Feed to Control Mortality of Juvenile Steelhead Trout *Oncorhynchus mykiss* Caused by Columnaris, (Causative Agent *Flavobacterium columnare*)” Study Number BOZ-98-OTF Study #1.
- b. Study Director: James D. Bowker
- c. Investigator: Dan Free
- d. Study Location: U.S. Fish and Wildlife Service
Coleman National Fish Hatchery
Anderson, CA
- e. Study Design:
 - 1) Objective: To evaluate the effectiveness of oxytetracycline administered in feed at a dose of 3.75 g oxytetracycline/100 lb of fish/day for 10 consecutive days to control mortality in steelhead trout due to columnaris disease associated with *Flavobacterium columnare*.
 - 2) Study Animals: Approximately 17,320 steelhead trout juveniles.
 - 3) Test Article/Controls: The test article was a Type C medicated feed containing oxytetracycline that delivered a dose of 3.75 g oxytetracycline/100 lb of fish/day for 10 consecutive days. Control animals were fed a non-medicated commercial salmonid feed. The target dose was verified with a feed assay.
 - 4) Procedure: Fish from tanks experiencing increased mortality were examined (body surface, fins, gills, and internal organs), and spleen inocula were cultured and evaluated for the presence of systemic bacteria. Columnaris disease was confirmed as the cause of increased mortality in two tanks serving as the source of test fish. The investigator transferred what he estimated as one-third of the fish in a source tank to each of six test tanks. Fish in three tanks were fed oxytetracycline-medicated feed, and fish in the other three tanks were fed non-medicated control feed. The treatment groups were assigned to the tanks using a completely randomized design. After a four-day acclimation period, fish were treated with medicated feed (3.75 g oxytetracycline/100 lb of fish/day) or non-

medicated control feed for 10 consecutive days. Mortality was observed for an additional 10 days after the end of the treatment period.

- 5) **Measurements:** Mortality and water quality parameters were recorded at specified intervals throughout the study.
 - 6) **Statistical Analysis:** A generalized linear model was used to analyze the ratios of cumulative mortality to total fish. The group effect was tested at significance level $\alpha = 0.05$. The natural logarithm of pre-treatment mortality rates was included in the model as a covariate.
- f. **Results:** Mortality rates are included in the following table.

Table 2. Mean percent cumulative mortality rates at the end of the 10-day post-treatment period.

Oxytetracycline Dose (g/100 lb fish/day)	Mean Percent Cumulative Mortality Rate [†]
0	27.7 (2,019/7,059 [‡])
3.75	13.8 (928/6,900)
p-value < 0.0001	

[†] The mean percent cumulative mortality rates are derived from the least squares means from the analysis.

[‡] Total numbers of fish per dose group do not include those fish that died during the acclimation period.

The mean water temperature was 14.9 °C, and the mean DO was 9.8 mg/L. Water hardness was 32 mg/L (as CaCO₃).

- g. **Conclusions:** The results demonstrate the effectiveness of oxytetracycline-medicated feed administered at 3.75 g oxytetracycline/100 lb of fish/day for 10 consecutive days for the control of mortality in freshwater-reared steelhead trout associated with columnaris disease associated with *F. columnare*.

4. Clinical Field Study

- a. **Title:** “The Efficacy of Oxytetracycline-Medicated Feed to Control Mortality Caused by Columnaris, Causative Agent *Flavobacterium columnare*, of Juvenile Steelhead Trout *Oncorhynchus mykiss*” Study Number BOZ-98-OTF-02.
- b. **Study Director:** James D. Bowker
- c. **Investigator:** Dan Free

- d. Study Location: U.S. Fish and Wildlife Service
Coleman National Fish Hatchery
Anderson, CA
- e. Study Design:
- 1) Objective: To evaluate the effectiveness of oxytetracycline administered in feed at a dose of 3.75 g oxytetracycline/100 lb of fish/day for 14 consecutive days to control mortality in steelhead trout due to columnaris disease associated with *F. columnare*.
 - 2) Study Animals: Approximately 76,800 steelhead trout juveniles.
 - 3) Test Article/Controls: The test article was a Type C medicated feed containing oxytetracycline that delivered a dose of 3.75 g oxytetracycline/100 lb of fish/day for 14 consecutive days. Control animals were fed a non-medicated commercial salmonid feed. The target dose was verified with a feed assay.
 - 4) Procedures: Based on the clinical signs observed, columnaris disease was determined as the cause of increased mortality in seven tanks serving as the source of test fish. Equal weights of fish were transferred to twelve test tanks. Treatment groups were assigned to the tanks using a completely randomized design. Treatments began the day following allocation of fish to the study tanks. Fish in ten tanks were treated with medicated feed (3.75 g oxytetracycline/100 lb of fish/day) for 14 consecutive days. Mortality was observed for an additional 11 days after the end of the treatment period. Oxytetracycline administration was initiated in the two control tanks 12 days after the start of the study due to the mortality rates in these tanks.
 - 5) Measurements: Mortality and water quality parameters were recorded at specified intervals throughout the study.
- f. Results: Mortality rates are included in the following table.

Table 3. Mean percent cumulative mortality rates at the end of the 11-day post-treatment period.

Oxytetracycline Dose (g/100 lb of fish/day)	Mean Percent Cumulative Mortality Rate
0	23.3 (3,003/12,865)
3.75	7.7 (4,932/63,954)

The mean water temperature was 15.4 °C, and the mean DO was 9.4 mg/L. Water hardness at the facility was 32 mg/L.

- g. Conclusions: The results support the effectiveness of oxytetracycline-medicated feed administered at 3.75 g oxytetracycline/100 lb of fish/day for 14 consecutive days for the control of mortality in freshwater-reared steelhead trout due to columnaris disease associated with *F. columnare*.

5. Clinical Field Study

- a. Title: “The Efficacy of Oxytetracycline-Medicated Feed to Control Mortality of Juvenile Steelhead Trout *Oncorhynchus mykiss* Caused by Columnaris, Causative Agent *Flavobacterium columnare*, Study #04” Study Number BOZ-98-EFF-04.
- b. Study Director: James D. Bowker
- c. Investigators: Daniel Carty and John Scott
- d. Study Location: U.S. Fish and Wildlife Service
Coleman National Fish Hatchery
Anderson, CA
- e. Study Design:
- 1) Purpose: To evaluate the effectiveness of oxytetracycline-medicated feed administered at a dosage of 3.75 g oxytetracycline/100 lb of fish/day for 10 consecutive days to control mortality due to columnaris associated with *F. columnare* in steelhead trout.
 - 2) Study Animals: Approximately 32,120 steelhead trout juveniles.
 - 3) Test Article/Controls: The test article was a Type C medicated feed containing oxytetracycline that delivered a dose of 3.75 g oxytetracycline/100 lb of fish/day for 10 consecutive days. Control animals were fed a non-medicated commercial salmonid feed. The target dose was verified with a feed assay.
 - 4) Procedure: Fish from two of the four tanks serving as the source of test fish with columnaris were examined. The body surface, fins, gills, and internal organs were examined and gill, kidney, spleen, and external skin lesion inocula were cultured and evaluated for the presence of systemic bacteria. Fish were originally held in four reference tanks. Fish from each reference tank were equally divided between two test tanks. During the study, fish were held in a total of eight tanks. Fish in four tanks were fed oxytetracycline-medicated feed, and fish in the other four tanks were fed non-medicated control feed. Treatments began the day following allocation of fish to the study tanks. Fish were treated with medicated feed (3.75 g oxytetracycline/100 lb of fish/day) or non-medicated control

feed for 10 consecutive days. Mortality was observed for an additional 14 days after the end of the treatment period.

5) **Measurements:** Mortality and water quality parameters were recorded at specified intervals throughout the study.

f. **Results:** Mortality rates are included in the following table.

Table 4. Mean percent cumulative mortality rates at the end of the 14-day post-treatment period.

Oxytetracycline Dose (g/100 lb of fish/day)	Mean Percent Cumulative Mortality Rate
0	76.8 (12,693/16,533)
3.75	17.8 (2,789/15,585)

The mean water temperature was 18.0 °C, and the mean DO was 9.1 mg/L. Mean water hardness and alkalinity were 34 mg/L (as CaCO₃) and 51 mg/L (as CaCO₃), respectively.

g. **Conclusions:** Results from this study support the effectiveness of oxytetracycline-medicated feed administered at a dosage of 3.75 g oxytetracycline/100 lb of fish/day for 10 consecutive days to control mortality in freshwater-reared steelhead trout due to columnaris disease associated with *F. columnare*.

6. Justification That the Evidence of Effectiveness has Inferential Value for All Freshwater-Reared *Oncorhynchus mykiss*

a. **Report Title:** “Justification to consider studies that demonstrate drug efficacy on freshwater-reared steelhead trout or rainbow trout be sufficient to satisfy the effectiveness requirements for all freshwater-reared *Oncorhynchus mykiss*.”

b. **Author:** U.S Fish and Wildlife Service
Aquatic Animal Drug Approval Partnership Program
Bozeman, MT

c. **Report Summary:** *Oncorhynchus mykiss* are native to western North America with both resident and anadromous migrating life history forms found throughout their range. The resident form is known as rainbow trout and the anadromous (migrating to sea or large lakes) form is known as steelhead trout. Originally, the two life history forms of *O. mykiss* were classified as two distinct species based on morphology and behavior, but they have been reclassified as a single species. Consequently, *O. mykiss* populations are now divided into subspecies based primarily on morphological evidence, many of

which exhibit both resident and anadromous migratory life history patterns. Modern genetic analysis has confirmed that not only do steelhead and rainbow trout belong to the same species, but the degree of relatedness among *O. mykiss* populations is generally associated with geographic proximity, not life history type, and suggests that steelhead and rainbow trout are polyphyletic and the result of parallel evolution rather than members of two distinct lineages.

The techniques used to culture young rainbow and steelhead trout are virtually identical. During the time that these fish are held in captivity, there are virtually no morphological or physiological differences between the two. Fish production data for 2005 were provided, which showed that of a total of 118 million *O. mykiss* cultured in 2005, 87 million were rainbow trout, 31 million were pre-hatchery release steelhead trout, and 0.009 million steelhead were kept as broodstock. All life stages of rainbow trout may be reared or held as broodstock and may be subject to treatment with one or more drugs (including medicated feeds) during their captivity. However, virtually no steelhead trout that have returned from the ocean are kept for an extended period of time at a hatchery after they have spawned. Returning adult steelhead trout do not eat and must be retrained to feed, which is often difficult to accomplish and therefore most of these fish are killed and removed.

References to cited material were provided.

- d. Conclusions: CVM agrees that the genetic relatedness and culture similarities between rainbow trout and hatchery-reared steelhead trout (versus out-migrated steelhead trout) are sufficiently similar, and therefore we conclude that data that demonstrate the effectiveness of oxytetracycline-medicated feed to control mortality due to columnaris disease in hatchery-reared steelhead trout have inferential value for all subspecies of *O. mykiss*.

III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. A FEDERAL REGISTER Notice for the original approval of NADA 038-439 published on September 23, 1970, and this dosage has been codified in 21 CFR 558.450(d)(2) for other indications for salmonids. As described in the FOI Summary for NADA 038-439 dated June 30, 2006, CVM concluded that a change in the active ingredient in the Type A medicated article product from the quaternary salt to oxytetracycline dihydrate creates no concerns regarding the target animal safety of TERRAMYCIN 200 for Fish for use in fish.

IV. HUMAN FOOD SAFETY:

A. Toxicology:

An acceptable daily intake (ADI) of 25 micrograms per kilogram of body weight per day previously has been codified for total tetracycline residues (chlortetracycline, oxytetracycline, and tetracycline) (21 CFR 556.500).

An assessment of the effects of microbiologically active residues of oxytetracycline on the human intestinal flora was conducted.

B. Residue Chemistry:

1. Residue Data

Tissue residue depletion data for fish and lobster are described in Public Master Files 003-265 and 005-028 and NADA 038-439.

Tissue depletion data demonstrating that a 21-day withdrawal period is an adequate amount of time for residues to deplete to below the tolerance at water temperatures below 9 °C are found in references in the public literature:

H. Bjorklund and G. Bylund. Temperature-related absorption and excretion of oxytetracycline in rainbow trout (*Salmo gairdneri* R.). *Aquaculture*. 84: 363-372, 1990.

R.L. Herman, D. Collis, and G.L. Bullock. Oxytetracycline residues in different tissues of trout. U.S. Dept. of Interior, Technical Papers of the Bureau of Sport Fisheries and Wildlife, No. 37, August, 1969.

M.D. Jacobsen. Withdrawal times of freshwater rainbow trout, *Salmo gairdneri* Richardson, after treatment with oxolinic acid, oxytetracycline and trimethoprim. *Journal of Fish Diseases*. 12: 29-36, 1989.

I. Nordlander, H. Johnson, and B. Osterdahl. Oxytetracycline residues in rainbow trout analyzed by a rapid HPLC method. *Food Additives and Contaminants*. 4(3): 291-296, 1987.

A. Rogstad, V. Hormazabal, O. Ellingsen, and K. Rasmussen. Pharmacokinetic study of oxytetracycline in fish. I. Absorption, distribution, and accumulation in rainbow trout in freshwater. *Aquaculture*. 96: 219-226, 1991.

R. Aoyama, K. McErlane, and H. Erber. High-performance liquid chromatographic analysis of oxytetracycline in Chinook salmon following administration of medicated feed. *Journal of Chromatography*. 588: 181-186, 1991.

R. Namdari, S. Abedini, and F.C.P. Law. Tissue distribution and elimination of oxytetracycline in seawater Chinook and coho salmon following medicated-feed treatment. *Aquaculture*. 144: 27-38, 1996.

2. Target Tissue and Marker Residue Assignment

The target tissue for fish is muscle with adhering skin except for species such as catfish where the skin is not typically consumed. For catfish, the target tissue is just muscle. For lobster, the target tissue is muscle. The marker residue is oxytetracycline.

3. Tolerance Assignments

The tolerance of 2 ppm for oxytetracycline in finfish and lobster muscle previously has been codified (21 CFR 556.500).

4. Withdrawal Times

The withdrawal times are 21 days for salmonids and catfish and 30 days for lobsters.

C. Microbial Food Safety:

Microbial food safety information for oxytetracycline dihydrate for the supplement to NADA 038-439 was evaluated using a qualitative risk assessment approach. The supplement provides for the new therapeutic indications: (1) for the control of mortality in freshwater-reared salmonids due to coldwater disease associated with *Flavobacterium psychrophilum*; and (2) for the control of mortality in *Oncorhynchus mykiss* due to columnaris disease associated with *Flavobacterium columnare*.

The microbial food safety assessment was based on a *hazard characterization* and *qualitative risk assessment*, including 1) a *release assessment* to describe the probability that oxytetracycline dihydrate and its use in freshwater-reared salmonids will result in the emergence of resistant bacteria or resistance determinants in treated salmon and/or trout under proposed conditions of use; 2) an *exposure assessment* to describe the likelihood of human exposure to resistant bacteria or resistance determinants through consumption of edible products from treated salmon and/or trout; and 3) a *consequence assessment* to describe potential human health consequences arising from exposure to defined resistant bacteria or resistance determinants by considering the human medical importance of tetracyclines used in the treatment of human infectious diseases.

Based upon evaluation of the information submitted by the sponsor, and in consideration of the impact of the small additional quantity of oxytetracycline dihydrate used, the relatively small number of new fish treated as a result of the supplement, and the low relevance of tetracyclines in human medicine for treating

illnesses attributable to food-borne pathogens associated with fish species, the Agency has determined that the overall risk estimation associated with the use of the product under the newly proposed conditions of use is low, integrated from individual rankings of high to medium for the *release assessment*, low for the *exposure assessment*, and medium to low for the *consequence assessment*. This risk estimation is compatible with the proposed use of oxytetracycline dihydrate in feed in freshwater-reared salmonids.

D. Analytical Method for Residues:

The analytical method for detection of oxytetracycline is a microbiological assay using *Bacillus cereus* var. *mycoides*. This method may be found in “Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Methods, Reports, and Protocols” (revised October 1968, reprinted December 1974), National Center for Antibiotic and Insulin Analysis, FDA, Washington, DC 20204. The method is available from CVM, FDA, 7500 Standish Pl., Rockville, MD 20855.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to TERRAMYCIN 200 for Fish:

“Certain components of animal feeds, including medicated premixes, possess properties that may be a potential health hazard or a source of personal discomfort to certain individuals who are exposed to them. Human exposure should, therefore, be minimized by observing the general industry standards for occupational health and safety.

Precautions such as the following should be considered: dust masks or respirators and protective clothing should be worn; dust-arresting equipment and adequate ventilation should be utilized; personal hygiene should be observed; wash before eating or leaving a work site; be alert for signs of allergic reactions- seek prompt medical treatment if such reactions are suspected.”

“Not for human use.”

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that TERRAMYCIN 200 for Fish, when used according to the label, is safe and effective for the control of mortality in freshwater-reared salmonids due to coldwater disease associated with *Flavobacterium psychrophilum* and for the control of mortality in freshwater-reared *Oncorhynchus mykiss* due to columnaris disease associated with *Flavobacterium columnare*. Additionally, data demonstrate that residues in food

products derived from salmonids treated with TERRAMYCIN 200 for Fish will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity:

TERRAMYCIN 200 for Fish in the dosage form and for the intended uses approved by FDA, for the control of mortality in freshwater-reared salmonids due to coldwater disease associated with *Flavobacterium psychrophilum* and for the control of mortality in freshwater-reared *Oncorhynchus mykiss* due to columnaris disease associated with *Flavobacterium columnare*, qualifies for seven years of exclusive marketing rights under section 573(c) of the Federal Food, Drug, and Cosmetic Act (the act) because it has been declared a designated new animal drug by FDA under section 573(a) of the act.

C. Supplemental Applications:

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR §514.106(b)(2)).

D. Patent Information:

The sponsor did not submit any patent information with this application.

VII. ATTACHMENTS: