

Date of Approval: November 21, 2018

**FREEDOM OF INFORMATION SUMMARY**  
**SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION**

NADA 038-439

Terramycin<sup>®</sup> 100 for Fish and Terramycin<sup>®</sup> 200 for Fish

Oxytetracycline

Type A medicated article

Freshwater-reared salmonids weighing up to 55 grams

To add to the label an indication for marking the skeletal tissue of freshwater-reared salmonids weighing up to 55 grams

Sponsored by:

Phibro Animal Health Corp.

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**I. GENERAL INFORMATION**

**A. File Number**

NADA 038-439

**B. Sponsor**

Phibro Animal Health Corp.  
GlenPointe Centre East, 3<sup>d</sup> floor  
300 Frank W. Burr Blvd., suite 21  
Teaneck, NJ 07666

Drug Labeler Code: 066104

**C. Proprietary Name**

Terramycin<sup>®</sup> 100 for Fish and Terramycin<sup>®</sup> 200 for Fish

**D. Drug Product Established Name**

Oxytetracycline

**E. Pharmacological Category**

Antimicrobial

**F. Dosage Form**

Type A medicated article

**G. Amount of Active Ingredient**

100 g/lb or 200 g/lb

**H. How Supplied**

50 lb bag

**I. Dispensing Status**

VFD

**J. Dosage Regimen**

Freshwater-reared salmonids weighing up to 55 grams: 3.75 g oxytetracycline/100 lb of fish/day for 10 days

**K. Route of Administration**

Oral via feed

**L. Species/Classes**

Freshwater-reared salmonids weighing up to 55 grams

### **M. Indication**

Freshwater-reared salmonids weighing up to 55 grams: For marking the skeletal tissue

### **N. Effect of Supplement**

This supplement provides for the addition of an indication for marking the skeletal tissue of freshwater-reared salmonids weighing up to 55 grams.

## **II. EFFECTIVENESS**

Substantial evidence of effectiveness was demonstrated through a single clinical field effectiveness study in combination with supportive field studies.

### **A. Dosage Characterization**

This supplemental approval does not change the previously approved dosage for freshwater-reared salmonids.

### **B. Substantial Evidence**

#### 1. Clinical Field Study

**Title:** The Efficacy of TERRAMYCIN 200 for Fish (oxytetracycline dihydrate) Type A Medicated Article for the Skeletal Marking of Rainbow Trout *Oncorhynchus mykiss* (Study No. OTC-08-EFF-MARK-01)

**Study Dates:** February 2009 to April 2009

**Study Location:** Bozeman, MT, United States

#### **Study Design:**

**Objective:** To evaluate the effectiveness of oxytetracycline dihydrate (OTC) for skeletal marking of rainbow trout when administered in feed at 3.75 g OTC/100 lb fish/d for 10 consecutive days. The study was conducted in accordance with Good Clinical Practice standards.

Study Animals: 180 Rainbow trout with a mean body weight of 36.6 g.

**Experimental Design:** A completely randomized design was used to distribute 20 rainbow trout from two reference population tanks to each of the nine test tanks. Treatments were also assigned to the test tanks using a completely randomized design. There were six OTC-treated tanks and three non-treated (control) tanks.

Study personnel collecting all mortality, behavior, and water quality data, or evaluating marking success, were masked to treatment assignment.

**Drug Administration:** Fish received OTC medicated feed (3.75 g OTC/100 lb of fish/d) or nonmedicated feed as assigned for 10 consecutive days.

### Measurements and Observations:

General fish behavior, feeding behavior, and mortality were monitored daily during the study. Water temperature and dissolved oxygen (DO) concentration were measured daily during the study. Water hardness, alkalinity, and pH were measured three times during the study.

The OTC concentration in the feed was assayed by liquid chromatography.

On the 22<sup>nd</sup> post-treatment day, fish were euthanized and frozen for subsequent vertebral extraction and mark evaluation. Two vertebrae from each fish (immediately anterior to the dorsal fin) were evaluated under ultraviolet light (~365 nm) using a dissecting microscope.

Skeletal marking was graded on the following ordinal scale:

"0": Not marked, i.e., no detectable mark in vertebrae

"1": Marked. Faint marks observed in vertebrae and no complete mark circles in centrum bones; marks are thin; color is not bright

"2": Marked. Faint marks observed in vertebrae and complete mark circles in centrum bones; marks are not bright, usually thin lines only

"3": Marked. Good quality marks in vertebrae; complete mark circle in centrum bones; marks are easily seen; color is good; marks may be thin or thick, but color is easily distinguishable

Scores of "0" or "1" were considered failures. Scores of "2" or "3" were considered successes.

**Statistical Methods:** The planned statistical analysis for the primary response variable, skeletal marking (success vs. failure), is a generalized linear mixed model using a logit link, with tank as the experimental unit and treatment as a fixed effect. Because of the observed success rates of 0% in the control group and 100% in the treated group, the planned analysis was not numerically feasible. The Fisher's Exact test was employed as a secondary test.

### **Results:**

**Skeletal Marking:** All vertebrae evaluated from treated tanks were scored as "3"; all vertebrae evaluated from control tanks were scored as "0". The proportions of successfully treated fish in the control and treated tanks were significantly different (P-value=0.0119) based on the Fisher's Exact test.

**General Health Observations, Food Consumption, and Mortality:** Throughout the in-life phase, there was no mortality, and both treated and non-treated fish appeared to feed aggressively and behave normally.

**Water Quality:** Mean hardness, alkalinity, and pH were 293 mg/L CaCO<sub>3</sub>, 195 mg/L CaCO<sub>3</sub>, and 7.9, respectively. Mean water temperature was 10.3 °C, and mean DO was 8.2 mg/L.

**Dose Verification:** Results showed that the drug concentration in the feed was appropriate to achieve the intended dose of 3.75 g OTC/100 lbs. of fish.

**Adverse Reactions:** No adverse drug experiences were reported.

**Conclusion:** This study demonstrates that Terramycin® 200 for Fish administered at 3.75 g OTC/100 lbs. of fish per day for 10 consecutive days is effective for the skeletal marking of rainbow trout.

## 2. Summary of Supportive Field Studies

The effectiveness of OTC medicated feed for marking of skeletal tissue of freshwater-reared salmonids is supported by a series of 74 field trials conducted under INAD 009332 from 1999 through 2006. In 72 trials, administration of OTC medicated feed at doses of 2.56 to 4.0 g/100 pounds of fish/day for up to 10 days marked skeletal tissue of rainbow trout *Oncorhynchus mykiss*, cutthroat trout *O. clarkii*, or Kokanee *O. nerka* weighing 55 grams or less. In the other two trials, none of the treated fish which were sampled had a mark. In nine of the 74 trials, marks were evaluated at least two months after treatment; all but one of these trials resulted in 70% or more of evaluated fish retaining excellent or good marks. Results from these trials support the effectiveness of OTC medicated feed administered at 3.75 g/100 pounds of fish/day for 10 consecutive days to mark skeletal tissues of freshwater-reared salmonids weighing up to 55 grams.

### 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.

### IV. HUMAN FOOD SAFETY

#### A. Antimicrobial Resistance

A hazard characterization and qualitative antimicrobial resistance risk assessment for oxytetracycline in fish was evaluated. The Agency determined a fish size limitation of 55 grams was an adequate risk management strategy to mitigate concerns for emergence or selection of resistant bacteria in or on treated fish. This decision was based on information on the relationship between size and weight for freshwater-reared salmonids. The Agency determined it was necessary to limit the size to ensure that the released fish will not likely be kept for consumption.

Based upon the Agency's 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 supplemental approval, and the low importance of tetracyclines in human medicine for treating illnesses attributable to food-borne pathogens associated with fish species, it was reasonably determined that the overall risk estimation associated with the use of the product under the newly proposed conditions of use is medium. This risk estimation is compatible with the Agency's risk management strategies described above.

## **Decision Statement**

The Agency's risk estimation of medium is compatible with the proposed conditions of use and Agency's recommended risk management strategies for this use of oxytetracycline in freshwater-reared salmonids.

### **B. Effects of Residues on Human Intestinal Flora**

CVM did not require additional information on effects of oxytetracycline residues on human intestinal flora for this supplemental approval. There would be no, or negligible, oxytetracycline residues entering human colon under the proposed conditions of use (i.e., skeletal marking) - too low to affect human intestinal flora. The codified acceptable daily intake (ADI) at 25 µg/kg bw/day is the final ADI and remains protective of effects from oxytetracycline residues. The FOI Summary for the supplemental approval of NADA 038-439 dated June 30, 2006, contains summary information about the ADI for oxytetracycline and conclusions about effects of its residues on human intestinal flora.

### **C. Toxicology**

Reassessment of the codified acceptable daily intake (ADI) was not needed for this supplemental approval. This ADI is based on a review of all tetracyclines (NADA 113-232, dated May 31, 1996). The FOI Summary for the supplemental approval of NADA 038-439 (dated June 30, 2006) contains a summary information about the ADI for oxytetracycline.

### **D. Establishment of the Final ADI**

The final ADI is the codified ADI of 25 µg/kg bw/day for total tetracycline residues (chlortetracycline, oxytetracycline, and tetracycline) listed under 21 CFR 556.500.

### **E. Safe Concentrations for Total Residues in Edible Tissues (and Injection Sites, if applicable)**

Reassessment of the safe concentrations for total tetracycline residues (chlortetracycline, oxytetracycline, and tetracycline) was not needed for this approval. The safe concentration of total tetracycline residues (tetracycline, chlortetracycline, and oxytetracycline) in the muscle of fish is 2 ppm.

### **F. Residue Chemistry**

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the supplemental approvals of NADA 038-439 dated June 30, 2006, and July 6, 2008, contain a summary of residue chemistry studies for oxytetracycline in freshwater-reared salmonids.

## **G. 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. To obtain a copy of the analytical method, please submit a Freedom of Information Summary request to:

<https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm>

## **V. USER SAFETY**

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Terramycin® 100 for Fish or 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® 100 for Fish and Terramycin® 200 for Fish, when used according to the label, are safe and effective for marking the skeletal tissue of freshwater-reared salmonids weighing up to 55 grams. Additionally, data demonstrate that residues in food products derived from species treated with Terramycin® 100 for Fish and Terramycin® 200 for Fish will not represent a public health concern when the product is used according to the label.

### **A. Marketing Status**

A valid veterinary feed directive (VFD) is required to dispense this drug. Any animal feed bearing or containing this drug will be fed to animals only by or on a lawful veterinary feed directive issued by a licensed veterinarian in the course of their professional practice. In addition, the veterinary feed directives issued for this drug are not refillable.



The decision to restrict this drug to use by or upon a lawful veterinary feed directive issued by a licensed veterinarian was based on the following factors: adequate directions cannot be written to enable lay persons to appropriately use this drug product, because restricting this drug product to use by or on the order of a licensed veterinarian is critical for assuring the safe and appropriate use of this drug product in animals in order to slow or prevent any potential for the development of bacterial resistance to antimicrobial drugs, and to ensure that edible tissue derived from animals treated with this drug product is safe with regards to human consumption.

**B. Exclusivity**

This supplemental approval for Terramycin® 100 for Fish and Terramycin® 200 for Fish qualifies for SEVEN years of exclusive marketing rights beginning as of the date of our approval letter. This drug qualifies for exclusive marketing rights under section 573(c) of the FD&C Act because it is a designated new animal drug under section 573(a) of the FD&C Act. Except as provided in section 573(c)(2) of the FD&C Act, we may not approve or conditionally approve another application submitted for such new animal drug with the same intended use as Terramycin® 100 for Fish and Terramycin® 200 for Fish. Terramycin® 100 for Fish and Terramycin® 200 for Fish, as approved in our approval letter, do not qualify for marketing exclusivity under section 512(c)(2)(F) of the FD&C 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:**

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.