Date of Approval: June 30, 2006

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 038-439

TERRAMYCIN 200 for Fish

Oxytetracycline dihydrate

"for the change of the active ingredient from the mono-alkyl (C8-C18) trimethylammonium oxytetracycline to the oxytetracycline dihydrate, the change of the oxytetracycline concentration from 100 g/lb to 200 g/lb, the change of the product name to reflect the change in the oxytetracycline concentration, and the addition of the approved lobster indication to the label for the control of gaffkemia caused by *Aerococcus viridans*."

Sponsored by:

Phibro Animal Health

1. 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. Established Name:	Oxytetracycline (from oxytetracycline dihydrate base) equivalent to oxytetracycline hydrochloride
d. Proprietary Name:	TERRAMYCIN 200 for Fish
e. Dosage Form:	Medicated feed
f. How Supplied:	50 lb. bag
g. How Dispensed:	Over-the-counter
h. Amount of Active Ingredients:	200 g oxytetracycline/lb
i. Route of Administration:	Oral via feed
j. Species/Class:	Salmonids, catfish, and lobsters
k. Recommended Dosage:	Salmonids and catfish – 2.5 to 3.75 g oxytetracycline/100 lb of fish for 10 days Lobsters – 1 g oxytetracycline/lb of medicated feed administered as the sole ration for 5 consecutive days.
l. Pharmacological Category:	Antimicrobial
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. Lobsters – Control of gaffkemia caused by *Aerococcus viridans.*

n. Effect(s) of the Supplement	This supplement provides for the change of the active ingredient from the mono-alkyl (C8-C18) trimethylammonium oxytetracycline to the oxytetracycline dihydrate, the change of the oxytetracycline concentration from 100 g/lb to 200 g/lb, the change of the product name to reflect the change in the oxytetracycline concentration, and the addition of the approved lobster indication to the label for the control of gaffkemia caused by *Aerococcus viridans*.

2. EFFECTIVENESS:

a. Dosage Characterization:

The Center for Veterinary Medicine (CVM) did not require dosage characterization for this supplemental approval.

b. *Substantial Evidence*

CVM did not require effectiveness studies for this supplemental approval. The change in the active ingredient in the Type A Medicated Article product from the mono-alkyl (C8-C18) trimethylammonium oxytetracycline (quaternary salt) to oxytetracycline dihydrate creates no concerns regarding the effectiveness of the TERRAMYCIN 200 for Fish Type A Medicated Article for the approved label claims for salmonids or catfish.

The bioequivalence of the two forms of oxytetracycline has been previously demonstrated in cattle, swine, and poultry. The quaternary salt and dihydrate forms of oxytetracycline have similar physical and chemical characteristics, and the solubility of the quaternary salt and dihydrate forms of oxytetracycline are similar. Oxytetracycline dissociates from the mono-alkyl (C8-C18) trimethylammonium and dihydrate components in the gastrointestinal tract. After dissolution, the free oxytetracycline is absorbed from the gastrointestinal tract into the systemic circulation. The oxytetracycline component is considered responsible for the effectiveness of the product for the approved label claims for salmonids and catfish.

This product was previously approved for lobsters for the control of gaffkemia due to *Aerococcus viridans* under NADA 038-439 published in the FEDERAL REGISTER on June 30, 1987 (52 FR 24293). The safety and effectiveness data required for that approval are contained in Public Master File 005028. The availability of that data was publicly announced in the FEDERAL REGISTER on January 13, 1986 (51 FR 1441). During the National Academy of Sciences/National Research Council/Drug Effectiveness Study Implementation review of the oxytetracycline quaternary salt products, CVM concluded that the lobster label claim was acceptable for only certain products approved under NADA 008-804. The label claim was subsequently removed from the TERRAMYCIN for Fish product label approved under NADA 038-439. The formulations of the various oxytetracycline Type A Medicated Article products are

relatively similar. For reasons identical to those stated for catfish and salmonids, the use of an oxytetracycline Type A Medicated Article product containing oxytetracycline dihydrate rather than an oxytetracycline quaternary salt creates no concerns regarding the effectiveness of TERRAMYCIN 200 for Fish for the control of gaffkemia caused by *Aerococcus viridans* for lobsters.

The concentration of oxytetracycline in the Type A Medicated Article is stated in terms of oxytetracycline hydrochloride equivalents. The change in the concentration of oxytetracycline in the Type A Medicated Article from 100 grams to 200 grams of oxytetracycline hydrochloride equivalents per pound of Type A Medicated Article will not affect the effectiveness of the product for the approved label claims. The product is administered to catfish and salmonids based on a dose stated as grams of oxytetracycline hydrochloride equivalents per 100 pounds of fish. For lobsters, the product is administered at a single feed concentration based on oxytetracycline hydrochloride equivalents.

3. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The change in the active ingredient in the Type A Medicated Article product from the mono-alkyl (C8-C18) trimethylammonium oxytetracycline (quaternary salt) to oxytetracycline dihydrate creates no concerns regarding the safety of the product for the approved label claims for catfish or salmonids. The use of an oxytetracycline Type A Medicated Article product containing oxytetracycline dihydrate rather than an oxytetracycline quaternary salt creates no concerns regarding the target animal safety of TERRAMYCIN 200 for Fish for the control of gaffkemia caused by *Aerococcus viridans* for lobsters. The basis for these decisions is the same as described in the Substantial Evidence Section of the Effectiveness Section above.

4. HUMAN SAFETY:

The impact on human food safety for the formulation change from oxytetracycline quaternary salt to oxytetracycline dihydrate was evaluated. It was determined that tissue residues from the two formulations would be identical. No new human food safety information was generated for this supplement. All human food safety assignments such as ADI, tolerance, and withdrawal periods remain the same as designated under the original approval.

A. Toxicology

An acceptable daily intake (ADI) of 25 micrograms per kilogram of body weight per day has been previously 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 under NADA 038-439. Tissue residues resulting from either source of oxytetracycline are below the tolerance at the time of human consumption.

B. Residue Chemistry

1. Residue Data

Tissue residue depletion data for fish and lobster are described in Public Master Files 003265 and 005028 and NADA 038-439.

2. Target Tissue and Marker Residue

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. Tolerances

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

4. Withdrawal period

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

C. Microbial Food Safety

For this supplemental approval, there were no microbial food safety requirements to be addressed at this time.

D. Analytical Methods for Residues

The analytical method for detection of residues 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 on file at the Center for Veterinary Medicine, 7500 Standish Pl., Rockville, MD 20855.

5. 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."

The Material Safety Data Sheet was examined and it was concluded that user safety concerns have been appropriately addressed in the labeling.

6. 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 administered according to the label, is safe and effective for the control of ulcer disease caused by *Hemophilus piscium*, furunculosis caused by *Aeromonas salmonicida*, bacterial hemorrhagic septicemia caused by *Aeromonas liquefaciens*, and pseudomonas disease in salmonids; the control of bacterial hemorrhagic septicemia caused by *Aeromonas liquefaciens* and pseudomonas disease in catfish; and the control of gaffkemia caused by *Aerococcus viridans* in lobsters. Additionally, the data demonstrate that residues in food products derived from salmonids, catfish, and lobsters treated with TERRAMYCIN 200 for Fish will not represent a public health concern when the product is used according to the label.

TERRAMYCIN for Fish, containing oxytetracycline quaternary salt, for use in food-producing animals was marketed as an over-the-counter product. Adequate directions for safe and effective use by the layperson have been provided on the label of the TERRAMYCIN 200 for Fish product, which contains oxytetracycline dihydrate. Therefore, the Center for Veterinary Medicine has concluded that the product retains over-the-counter marketing status.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for food-producing animals does not qualify for marketing exclusivity.

The agency has determined under 21 CFR 25.33(a) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

In accordance with 21 CFR 514.106(b)(2)(i) and (ii), this is a Category II change involving a change in the active ingredient concentration and in the addition of a new therapeutic claim to the label. The safety and effectiveness data in the parent application did not need to be reevaluated.

7. ATTACHMENTS:

Facsimile labeling is attached as indicated below.

TERRAMYCIN 200 for Fish 50 lb.
Oxytetracycline Type B Blue Bird salmonid and catfish feed, medicated
Oxytetracycline Type C Blue Bird salmonid and catfish feed, medicated
Oxytetracycline Type B Blue Bird lobster feed, medicated
Oxytetracycline Type C Blue Bird lobster feed, medicated