Date of Approval Letter: March 12, 2004

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 095-143

TERRAMYCIN 50, TERRAMYCIN 100, and TERRAMYCIN 200
Type A Medicated Articles
(oxytetracycline)

"to establish a zero-day pre-slaughter withdrawal period for cattle administered oxytetracycline at 10 mg/lb body weight per day for 14 days"

Sponsored by:
Phibro Animal Health

1. GENERAL INFORMATION:

a. File Number:	NADA 095-143
b. Sponsor:	Phibro Animal Health 710 Route 46 East Suite 401 Fairfield, New Jersey 07004 Drug Labeler Code: 066104
c. Established Name:	Oxytetracycline (from oxytetracycline dihydrate base) equivalent to oxytetracycline hydrochloride
d. Proprietary Names:	TERRAMYCIN 50, TERRAMYCIN 100, TERRAMYCIN 200
e. Dosage Form:	Type A Medicated Article
f. How Supplied:	50 lb (22.6 kg) bags
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	TERRAMYCIN 50: 50 g/lb; TERRAMYCIN 100: 100 g/lb; TERRAMYCIN 200: 200 g/lb
i. Route of Administration:	Oral, via feed
j. Species/Class:	Chickens, turkeys, swine, cattle, sheep
k. Recommended Dosage and Indications:	Chickens: Increased rate of weight gain and improved feed efficiency – 10-50 g/ton, feed continuously. Control of infectious synovitis caused by *Mycoplasma synoviae*; control of fowl cholera caused by *Pasteurella multocida* susceptible to oxytetracycline – 100-200 g/ton, feed continuously for 7-14 days. Control of chronic respiratory disease (CRD) and air sac infection caused by *Mycoplasma gallisepticum* and *Escherichia coli* susceptible to oxytetracycline – 400 g/ton, feed continuously for 7-14 days. Reduction of mortality due to air sacculitis (air sac

infection) caused by *Escherichia coli* susceptible to oxytetracycline – 500 g/ton, feed continuously for 5 days.

Turkeys: For growing turkeys for increased rate of weight gain and improved feed efficiency – 10-50 g/ton, feed continuously. Control of hexamitiasis caused by *Hexamita meleagridis* susceptible to oxytetracycline – 100 g/ton, feed continuously for 7-14 days. Control of infectious synovitis caused by *Mycoplasma synoviae* susceptible to oxytetracycline – 200 g/ton, feed continuously for 7-14 days. Control of complicating bacterial organisms associated with bluecomb (transmissible enteritis, coronaviral enteritis) susceptible to oxytetracycline – 25 mg/lb of body weight daily, feed continuously for 7-14 days.

Swine: Increased rate of weight gain and improved feed efficiency – 10-50 g/ton, feed continuously. Treatment of bacterial enteritis caused by *Escherichia coli* and *Salmonella choleraesuis* susceptible to oxytetracycline and treatment of bacterial pneumonia caused by *Pasteurella multocida* susceptible to oxytetracycline – 10 mg/lb of body weight daily, feed continuously for 7-14 days. For breeding swine for control and treatment of Leptospirosis (reducing the incidence of abortion and shedding of leptospirae) caused by *Leptospira pomona* susceptible to oxytetracycline – 10 mg/lb of body weight daily, feed continuously for not more than 14 days.

Calves including Preruminating (Veal) Calves, Beef Cattle, and Non-Lactating Dairy Cattle: For calves (up to 250 lb) for increased rate of weight gain and improved feed efficiency – 0.05-0.1 mg/lb of body weight daily, feed continuously. For calves (250-400 lb) for increased rate of weight gain and improved feed efficiency – 25 mg/head/day, feed continuously. For growing cattle (over 400 lb) for increased rate of weight gain, improved feed efficiency,

	and reduction of liver condemnation due to liver abscesses – 75 mg/head/day, feed continuously. For prevention and treatment of the early stages of shipping fever complex – 0.5 to 2.0 g/head/day, feed 3-5 days before and after arrival in feedlots. Treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia (shipping fever complex) caused by *Pasteurella multocida* susceptible to oxytetracycline – 10 mg/lb of body weight daily, feed continuously for 7-14 days. Sheep: Increased rate of weight gain and improved feed efficiency – 10-20 g/ton, feed continuously. Treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to oxytetracycline - 10 mg/lb of body weight daily, feed continuously for 7-14 days.
l. Pharmacological Category:	Antimicrobial
m. Effect of Supplement:	This supplement establishes a zero-day pre-slaughter withdrawal period for cattle administered oxytetracycline at 10 mg/lb/day for 14 days.

2. EFFECTIVENESS:

No further effectiveness data were required for the approval of this supplemental application.

3. ANIMAL SAFETY:

No further target animal safety data were required for the approval of this supplemental application.

4. HUMAN SAFETY:

a. Toxicity:

No further basic toxicology studies were required for the approval of this supplemental application. However, CVM currently requires the sponsors to submit an assessment concerning the effects of antimicrobial residues present in the edible tissues of food animals on the intestinal flora of the consumer. The assessment submitted by the sponsor to comply with the human food safety requirements for antimicrobial drugs showed that the consumption of oxytetracycline residues present in edible tissues of cattle treated with 10 mg/lb/day for 14 days would not adversely affect the human intestinal flora, even when the complete meal basket is consumed in one day.

b. Safe Concentrations of Total Residues:

As documented in the FOI Summary dated March 28, 1996, for NADA 113-232. The safe concentration for total tetracycline microbiological activity was limited to 1 ppm in the total diet (1.5 mg/person/day) (61 FR 67453), equal to an ADI of 25 micrograms per kilogram of body weight per day.

c. Tolerance for the Marker Residue:

Tolerances for oxytetracycline have been codified previously under 21 CFR 556.500 (61 FR 67453, December 23, 1996; 66 FR 46370, September 5, 2001). Tolerances are established for the sum of residues of the tetracyclines in tissues of beef cattle, dairy cattle, calves, swine, sheep, chickens, turkeys, catfish, lobsters, and salmonids as follows: 2 parts per million (ppm) in muscle, 6 ppm in liver, 12 ppm in fat and kidney, and 0.3 ppm in milk.

d. Study Establishing the Withdrawal Period in Cattle:

Phibro Study Number USD123-016

1. Purpose: A tissue residue study was conducted to quantify the concentration of oxytetracycline activity in edible tissues of cattle after oral administration, in feed, of oxytetracycline at a dose of 11 mg of oxytetracycline hydrochloride activity/lb of body weight (BW) for 14 days.

2. Investigators: Colorado Animal Research Enterprises (CARE), 6200 E. County Rd. 56, Fort Collins, CO 80524

3. Animals: six crossbred beef steers and six heifers

4. Dosage form and dosage: medicated feed at a dose of 11 mg oxytetracycline hydrochloride/lb BW/day for 14 consecutive days.

5. Parameters measured and assay: Oxytetracycline (parent) residues were measured in liver, kidney, muscle, and fat using the regulatory analytical (microbiological) method. LOQ for liver and kidney was 100 ppb; for muscle and fat the LOQ was 75 ppb (microassay).

6. Results: Oxytetracycline concentrations in the edible tissues of treated cattle are summarized in Table 6.1.

Table 6.1: Concentration of oxytetracycline (ppm) in the tissues of cattle treated with oxytetracycline medicated feed at a dose of 11 mg/lb/day and slaughtered at practical zero withdrawal.

Gender	Tissue			
	Kidney	Liver	Muscle	Fat
Heifers	1.818±0.439	0.671±0.175	0.181±0.057	ND*
Steers	1.312±0.704	0.796±0.211	0.197±0.091	ND
Overall	1.247±0.563	0.734±0.196	0.189±0.073	ND

*Residues were not detected in fat.

These data were used to calculate the single point 99th percentile upper tolerance limit (with 95% confidence) for oxytetracycline residues at zero withdrawal for kidney, liver, and muscle. The upper tolerance limit values are summarized in Table 6.2.

Table 6.2: Calculated tissue-specific upper tolerance limits (ppm) for oxytetracycline residues in cattle treated with medicated feed at a dose of 11 mg/lb/day and slaughtered at practical zero withdrawal.

Gender	Tissue		
	Kidney	Liver	Muscle
Heifers	3.40	1.56	0.47
Steers	4.88	1.87	0.66
Overall	3.36	1.47	0.46

The calculated upper tolerance limit value for each tissue is significantly less than the tissue-specific tolerance codified under 21 CFR 556.500. Therefore, it is concluded that the use of the oxytetracycline Type A Medicated Articles in cattle to provide oxytetracycline at doses up to 10 mg/lb body weight/day qualifies for a zero withdrawal.

e. Regulatory Method for Residues:

The regulatory analytical method for detection of residues of the drug is a microbiological test using *Bacillus cereus* var. *mycoides* (ATCC 11778). The method is as published by the Food and Drug Administration, "Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Method, Reports, and Protocols," revised October 1968, reprinted December 1974.

f. Microbial Food Safety Assessment:

This NADA supplement establishes a zero-day pre-slaughter withdrawal period for cattle treated with 10 mg oxytetracycline/lb body weight per day for 14 days. Because this change to NADA 095-143 does not change the product indication, dose, duration, or other conditions of use beyond the change in withdrawal period, an evaluation of Microbial Food Safety was determined not to be necessary at this time for this supplemental approval to this approved product.

5. 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 of the implementing regulations. The data demonstrate that TERRAMYCIN 50, TERRAMYCIN 100, and TERRAMYCIN 200 Type A Medicated Articles are safe at a zero-day pre-slaughter withdrawal period when these products are administered to cattle for 14 days at a level of 10 mg/lb body weight/day in feed.

The Center for Veterinary Medicine has concluded that, for this product, adequate directions of use by the layperson have been provided and the product will have over-the-counter (OTC) status. Label directions provide detailed instructions in plain language. The drug product is not a controlled substance. Thus, the NADA retains OTC status, and the labeling is adequate for the intended use.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

Under the Center's supplemental policy (21 CFR 514.106(b)(2)), this is a Category II change. The approval of this change required a reevaluation of certain safety data in the parent application.

6. ATTACHMENTS:

Facsimile labeling is attached as indicated below:

A. TERRAMYCIN 50, TERRAMYCIN 100, and TERRAMYCIN 200 Type A Medicated Articles

B. Oxytetracycline Type B and C Blue Bird labels