Date of Approval Letter: April 29, 2002

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 008-804

TM-50®, TM-50®D, TM-100®, and TM-100®D Type A Medicated Articles
Contains TERRAMYCIN®

(oxytetracycline)

"removal of withdrawal period for swine"

Sponsored by:

Phibro Animal Health

I. GENERAL INFORMATION

NADA Numbers:	008-804
Sponsor:	Phibro Animal Health 710 Route 46 East Suite 401 Fairfield, New Jersey 07004
Established Names:	Oxytetracycline Type A Medicated Article
Proprietary Names:	TM-50®, TM-100®, TM-50®D, and TM-100®D
Marketing Status:	Over-the-counter (OTC)
Effect of Supplement:	This supplement establishes a zero-day withdrawal period for swine administered oxytetracycline at 10 mg/lb/day for 14 days.

II. INDICATIONS FOR USE

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 for 3 to 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.

Honey bees: (TM-50®D, and TM-100®D only): 200 mg/colony for control of American foulbrood caused by *Bacillus larvae* and European foulbrood caused by *Streptococcus pluton* susceptible to oxytetracycline.

Lobsters: Control of gaffkemia in lobsters caused by *Aerococcus viridans* – 1 g/lb of medicated feed, Feed for 5 days as the sole ration.

III. DOSAGE

A. Dosage Form: Type A Medicated Article

B. Route of Administration: Oral (mixed with feed)

C. Recommended Dose: See indications above

IV. EFFECTIVENESS

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

V. ANIMAL SAFETY

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

VI. HUMAN FOOD SAFETY

A. Toxicity Studies: NADA 008-804 was originally approved as safe for use as labeled on May 5, 1970.

B. Safe Concentrations of Total Residues: As documented in the FOI Summary dated May 31, 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: Tolerance for oxytetracycline has been codified previously under 21 CFR 556.500 (61 FR 67453; December 23, 1996). Tolerances are established for the sum of residues of the tetracyclines in tissues of beef cattle, beef calves, non-lactating dairy cattle, dairy calves, swine, sheep, chickens, turkeys, catfish, lobsters, and salmonids as follows: 2 parts per million (ppm) in muscle, 6 ppm in liver, and 12 ppm in fat and kidney.

D. Study establishing the withdrawal period in swine

Pfizer Study Number 2522D-60-97-099

1. Purpose: A tissue residue study was conducted to determine the depletion profile of oxytetracycline in uncooked porcine liver, kidney, muscle, and fat at various withdrawal times following treatment for 14 days with oxytetracycline HCl medicated feed at a dose rate of 10 mg OTC HCl/lb BW/day.

2. Investigators: This study was conducted in two phases.

Phase one: (live phase)	Southwest Bio-Labs, Inc. 401 N. 17th Street Las Cruces, NM 88085
Phase two: (microbiological analysis)	Colorado Animal Research Enterprises (CARE) 6200 E. County Rd. 56 Fort Collins, CO 80524

3. Animals: thirty crossbred swine (15 gilts and 15 barrows)

4. Dosage form and dosage: medicated feed at a rate of 10 mg OTC HCl/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 of tissue residue study:

Table 6.1. Group oxytetracycline (parent) residues (mean ± SD) in tissues from swine treated with TERRAMYCIN® in feed at a dose rate of 10 mg/lb/day for 14 days.

Group	Sacrifice Time (hr)	Parent oxytetracycline (ppb)			
		Liver	Kidney	Muscle	Fat
II	10†	379 ± 84	1680 ± 468	299 ± 83	16 ± 31
III	24	144 ± 33	538 ± 210	*	*
IV	48	*	340 ± 104	*	*
V	72	*	162 ± 19	*	*
VI	120	*	174 ± 27	*	*
VII	168	*	126 ± 26	*	*

†Times below 12 hours support assignment of a zero-day withdrawal period.
*Values were below the limit of quantitation (LOQ).

Tissue residue depletion data support the assignment of a zero withdrawal period for swine.

E. Regulatory method

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.

VII. AGENCY CONCLUSIONS

The data submitted in support of this supplemental 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 the use of TM-50®, TM-100®, TM-50®D, and TM-100®D Type A medicated articles are safe at a zero-day withdrawal

period when these products are administered to swine for 14 days at a level of 10 mg/lb body weight/day.

Tolerances are established in 21 CFR 556.500 for the sum of residues of the tetracyclines, in tissues of beef cattle, beef calves, non-lactating dairy cattle, dairy calves, swine, sheep, chickens, turkeys, catfish, lobsters, and salmonids, as follows: 2 parts per million (ppm) in muscle, 6 ppm in liver, and 12 ppm in fat and kidney.

There is reasonable certainty that the conditions of use, including directions on labeling can and will be followed in practice. Accordingly, the Agency has concluded that this product shall retain over-the-counter marketing status.

In accordance with 21 CFR 514.106(b)(2)(x) this is a Category II change which did not require reevaluation of the safety or effectiveness data in the parent application.

The Agency has carefully considered the potential environmental effects of this action and has concluded that the action is categorically excluded under 21 CFR 25.33(a)(1) from the requirement to prepare an environmental assessment.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for food-producing animals does not qualify for marketing exclusivity because the supplemental application does not contain substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food-producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval and conducted or sponsored by the applicant.

VIII. APPROVED PRODUCT LABELING (attached)

A. Facsimile label – TM-50®, TM-100®,TM-50®D, and TM-100®D Type A medicated articles- 50 lb

B. Facsimile label – Oxytetracycline Type B and C Blue Bird labels

Applicable labels may be obtained by writing to the following:

Freedom of Information Staff (HFI-35)
Food and Drug Administration, Room 12A16
5600 Fishers Lane
Rockville, MD 20857