Date of Approval Letter: January 24, 2002

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 048-761

AUREOMYCIN® 50 Granular, AUREOMYCIN® 90 Granular,
and AUREOMYCIN® 100 Granular

(chlortetracycline) Type A Medicated Articles

"To allow for top-dress route of administration as a Type C medicated feed for the following claim. Calves, beef and non-lactating dairy cattle. For the treatment of bacterial enteritis caused by *Escherichia coli* and for bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline."

Sponsored by :

ALPHARMA, INC.

I. GENERAL INFORMATION

NADA Number: 048-761

Sponsor: Alpharma, Inc.
One Executive Drive
Fort Lee, New Jersey 07024

Established Name: Chlortetracycline

Proprietary Name: AUREOMYCIN® 50, 90 or 100 GRANULAR

Marketing Status: over-the-counter

Effects of the Supplement: Provides for top dressing AUREOMYCIN® at the rate of 10 mg chlortetracycline (equivalent to chlortetracycline hydrochloride) per pound of bodyweight of Type C medicated feeds for cattle.

II. INDICATIONS FOR USE

Calves, beef and non-lactating dairy cattle. Treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* organisms susceptible to chlortetracycline.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

A. *Dosage Form:* Type A medicated article

B. *Route of Administration:* Oral, in feed. These drugs are administered orally *ad libitum*.

C. *Recommended Dosage:* 500 to 4000 g/ton (complete medicated cattle feed), to provide 10 mg chlortetracycline/lb bodyweight

4000 to 20,000 g/ton (top-dress), to provide 10 mg chlortetracycline/lb bodyweight

Feed for not more than 5 days.

IV. EFFECTIVENESS

A. Effectiveness of Dose

The Drug Efficacy Study Implementation (DESI) of the National Academy of Science and National Research Council (NAS/NRC) provided for use of chlortetracycline at the dose described above (FR 61, 35949 - 35958, July 9, 1996).

Pharmacokinetic Study - RVI Study No. CD-98-09

1. *Objectiv*e: To determine whether chlortetracycline (CTC) when fed as a top-dress to growing caves is bioequivalent to CTC when mixed in the complete ration of growing calves.

2. *Investigato*r: Ross W. Miller, D.V.M.
   Roche Vitamins Animal Health Research Station
   Wrightstown, New Jersey 08562-9801

3. *Design and Methods*: Twenty-four calves were divided into 2 groups of 12 in a two-treatment, two-period, two-sequence crossover design. One group of calves was dosed with 10 mg chlortetracycline per pound bodyweight mixed into a high roughage diet and the other group was dosed with 10 mg chlortetracycline per pound bodyweight top-dressed on the same diet.

4. *Test Article Administration*: Chlortetracycline was administered by providing the same medicated supplement to both treatment groups for five consecutive daily feedings. Twenty-three days of non-medicated feed were provided between dosing periods of the study.

5. *Sampling*: Blood samples were collected immediately prior to the fifth daily dose and at 3, 6, 9, 12, 18, 24, 30, 36, 48, 60, 72, 84, 96, and 108 hours after cattle received the fifth daily dose of chlortetracycline. Serum was analyzed by microbiological methods for activity of chlortetracycline.

6. *Results*: The bioequivalence of chlortetracycline when administered as either a top-dress formulation or as a complete feed was confirmed on the basis of peak drug concentrations (C_{max}) and the extent of systemic exposure (area under the curve, AUC). Since chlortetracycline is associated with a terminal elimination half-life of approximately 15 hours, five sequential days of dosing results in near steady state conditions (where 5 multiples of $t_{1/2}$ results in approximately 97% steady state concentrations). This point was illustrated by the similar predose (hrs zero) values seen on days 4 and 5 and hr 24 values after the fifth dose (Table 4.1). Therefore, AUC_{0-24} values that are estimated after dose 5 should be comparable to those AUC_{0-inf} values after a single dose.

Table 4.1: Hr zero concentrations

Day	Time	TRT 1	TRT 2
4	Hr 0	0.134	0.151
5	Hr 0	0.173	0.162
5	Hr 24	0.157	0.157

The *results* of the relative bioavailability study are summarized in Table 4.2.

Table 4.2. Summary of bioequivalence study results

	Top Dress (TRT 1)	Mixed (TRT 2)	Ratio TRT 1/TRT 2	90% Confidence interval (relative to TRT 2)
AUC_{0-24}	4.2135	4.4133	0.95	89.7 - 115.3
C_{max}	0.2205	0.2049	1.08	95.3 - 121.5
t_{max}*	10.56	10.13	1.04	
λ_z	0.04497 ($t_{½}$ = 15.4 hrs)	0.04325 ($t_{½}$ = 16.0 hrs)	1.04	96.7 - 111.2

*Parametric confidence intervals not appropriate since t_{max} is a discrete variable.

7. *Conclusion***:** There was no indication that administering chlortetracycline in a top-dress fashion influenced its absorption or elimination based on levels of chlortetracycline in serum. Therefore, top-dressing is not expected to affect the therapeutic activity of chlortetracycline.

V. ANIMAL SAFETY

1. *Objective*: Study No. FD32:1301 was conducted to obtain safety information on AUREOMYCIN® (chlortetracycline) when administered to cattle in their feed at a rate of 10, 20, or 30 mg chlortetracycline per pound bodyweight.

2. *Investigator:* H. Berger, and J.H. Colavita
American Cyanamid Company, Building 301, Agriculture Research Division, Princeton, New Jersey

3. *Methods:* Sixteen beef steers were allotted by weight to four treatment groups, each receiving one of four experimental rations providing either 0, 10, 20, or 30 mg chlortetracycline per pound bodyweight per day. Rations were fed for 42 days. Bodyweights and pen feed consumption were determined during the experimental period and periodic blood samples were collected for various blood chemistry and hematology measurements. Steers were observed daily for symptoms of toxicity.

4. *Results*: No differences were detected in gross feed intake, weight gain, or hematological characteristics during the study. However, some statistically significant ($P<0.05$) differences were noted between the control and the treated groups for albumin, total bilirubin and SGOT. These differences in serum chemistry attributes were not directly related to dose of chlortetracycline or duration or exposure to the various dose rates. Although statistical differences were detected for these characteristics, all mean values were within accepted normal ranges for each respective characteristic and were judged to be of no biological significance.

5. *Conclusion*: There was no indication that administering chlortetracycline in a dose up to 30 mg per pound bodyweight had any deleterious affect on cattle physiology. Therefore, in cases where cattle of mixed health compete for feed,

i.e., where potentially variable feed intake exists between cattle within a pen, over-consumption of the 10 mg per pound bodyweight dose rate would not be expected to adversely impact health.

VI. HUMAN SAFETY

A. *Toxicity Studies:* Safety of the approved product, chlortetracycline premix, has been established by data in the original application, NADA 48-761.

B. *Tolerance and Acceptable Daily Intake:* Tolerances for chlortetracycline in edible tissue of beef and non-lactating dairy cattle are established as 2 ppm in muscle, 6 ppm in liver, and 12 ppm in fat and kidney.

C *Residue Study Confirming the Withdrawal Time:*

1. *Objective*: This study (RVI Study No. CD-98-04) was conducted to determine if feeding chlortetracycline to cattle at the rate of 10 mg per pound bodyweight as a top-dress is likely to cause a residue of chlortetracycline, at zero withdrawal, that is greater than the published tolerance.

2. *Investigator*: Ross W. Miller, D.V.M.
Roche Vitamins Animal Health Research Station
Wrightstown, New Jersey 08562-9801

3. *Design and Methods*: Ten calves were divided into 2 groups. The control group (2 steers and 2 heifers) received a diet without chlortetracycline and served to verify that methods were suitable for detection of tissue residues. The treated group (3 steers and 3 heifers) was dosed with 1 mg lasalocid per 2.2 pounds bodyweight and 10 mg chlortetracycline per pound bodyweight for 14 days. Lasalocid was included to provide residue data on the combination use of the drugs for another application. Chlortetracycline was dosed by top-dressing a medicated supplement on the diet after the complete ration was delivered to the feed bunk. Kidneys and livers were collected from both treatment groups within 12 hours after consumption of their respective diets on the 14th day of feeding. The concentration of chlortetracycline in kidney was determined by the approved microbiological method. The concentration of lasalocid in liver was determined by an established HPLC method.

4. *Results*:

Mean Residues of Lasalocid in Liver and Chlortetracycline in Kidney Collected from Cattle Treated with Feed Containing 1 mg lasalocid per 2.2 pounds bodyweight (mixed into diet) and 10 mg chlortetracycline per pound bodyweight (provided as a top dressing) for 14 days.		
Withdrawal Time in Hours	Lasalocid (ppm)	Chlortetracycline (ppm)
0	0.042 ± 0.025	1.730 ± 0.965

Samples of control kidney were fortified with lasalocid and control liver were fortified with chlortetracycline. The data showed that the presence of lasalocid did not interfere with the assay of chlortetracycline and the presence of chlortetracycline did not interfere with the assay of lasalocid.

Residues of lasalocid and chlortetracycline were below their respective tolerances at zero withdrawal, the established withdrawal period for each of the drugs, thereby indicating an absence of interference.

D. *Regulatory Method:* The regulatory method for detection of chlortetracycline residues is a microbiological test using *Bacillus cereus* var. *mycoides* (ATCC 11778) as the test organism (Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Methods, Reports, and Protocols, Food and Drug Administration, Washington, D.C., 1968.) This method is on file at the Center for Veterinary Medicine, Food and Drug Administration, HFV-199, 7500 Standish Place, Rockville, Maryland 20855.

VII. AGENCY CONCLUSIONS

The information submitted in support of this supplemental NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act (FFDCA) and 21 CFR Part 514 of the implementing regulations. The data demonstrate that top-dressing and mixing chlortetracycline in complete feed provide the same therapeutic effect and that no deleterious effects occur in cattle consuming up to 30 mg chlortetracycline per pound bodyweight.

The data demonstrate that residues of chlortetracycline provided as a top-dressing were below the tolerance at zero withdrawal.

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

In accordance with 21 CFR 514.106 (b)(2)(iv), 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 qualifies for a categorical exclusion from the requirement of preparing an environmental assessment in accordance with 21 CFR 25.33(a)(1).

Under Section 512(c)(2)(F)(iii) of the FFDCA, this approval for food-producing animals qualifies for 3 years of marketing exclusivity, because the application contains substantial evidence of the effectiveness of the drug involved, 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 of the application and conducted or sponsored

by the applicant. The three years of marketing exclusivity applies only to the claim for

administration of chlortetracycline to cattle as a top-dress on feed for the treatment of enteritis and pneumonia.

VIII. APPROVED PRODUCT LABELING

A. Facsimile label - AUREOMYCIN® 50 GRANULAR Type A Medicated Article

B. Facsimile label - AUREOMYCIN® 90 GRANULAR Type A Medicated Article

C. Facsimile label - AUREOMYCIN® 100 GRANULAR Type A Medicated Article

D. Blue Bird CTC Top-Dress Type C Cattle Feed Medicated

E. Blue Bird CTC Type C Cattle Feed Medicate

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, Maryland 20857