Approval Date: July 9, 1996

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 048-761

B. Sponsor

Hoffmann-LaRoche Inc.
340 Kingsland Street
Nutley, New Jersey 07110

C. Proprietary Name

Aureomycin®

D. Established Name

Chlortetracycline (CTC)

E. Dispensing Status

OTC

F. Dosage Regimen

Chlortetracycline is supplied as a Type A Medicated Article that is administered orally by mixing the Type A Medicated Article into a supplemental cattle free-choice feed (Moorman's Special Range Minerals AU Type C Medicated Feed) to provide 0.5-2.0 mg CTC/lb bodyweight/day. The resultant supplemental feed containing chlortetracycline is to be offered free-choice continuously throughout the period in which the cattle are grazing pasture.

Warning: Discontinue use 4 days before cattle are slaughtered.

G. Indication

Control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline, in grazing beef cattle (weighing over 700 lbs).

H. Effect of Supplement

This supplemental approval provides for a supplemental cattle feed (Moorman's Special Range Minerals AU Type C Medicated Feed) to provide 0.5-2.0 mg CTC/lb bodyweight/day for the control of active infection of anaplasmosis caused by Anaplasma marginale susceptible to chlortetracycline, in grazing beef cattle (weighing over 700 lbs). The resultant supplemental feed containing chlortetracycline is offered free-choice continuously throughout the period in which the cattle are grazing pasture.

II. EFFECTIVENESS

Chlortetracycline was approved (see 53 FR 31316, dated August 18, 1988) for use in free-choice cattle feeds such as feed blocks or salt-mineral mixes. Such feeds are given to beef cattle and non-lactating dairy cattle to provide a daily minimum intake of 0.5 milligram of CTC per pound of body weight to aid in the prevention of anaplasmosis. Since only a minimum dose (which is impractical for free-choice feeding situations) was established for efficacy and not a dose range, the Agency/Sponsor needed to address setting an upper limit for CTC consumption, so that human food safety concerns would not arise. A study was conducted (summarized in the Human Food Safety Section of this FOI Summary) that establishes the upper limit as 2.0 mg CTC per pound of body weight, when a 4 day withdrawal period is observed. Thus, the daily dosage range for CTC in free-choice feeding situations is 0.5-2.0 mg of CTC per pound of body weight.

The consumption of the medicated range minerals was tested in six free-choice pasture cattle studies to establish that the average consumption of CTC was within the daily dosage range of 0.5-2.0 mg of CTC per pound of body weight.

A. Mississippi (#4941): Conducted by Drs. C. Pat Bagley and Richard Evans (Northern Mississippi Research and Extension Center) at Prairie, Mississippi. Thirty-six mixed breed heifers were pastured on bermudagrass and fescue; and fed medicated range minerals containing CTC at 8000 grams per ton. There were three replicates in this study, each containing 12 animals, with the replicates being rotated between pastures at 14 day intervals. Average daily consumption of CTC was 0.633 mg per pound of body weight. Before the study was initiated the animals were offered non-medicated range minerals for 29 days, to adapt them to consuming the free-choice product.
B. Colorado (#4942): Conducted by Dr. Kenneth Odde (Colorado State University) at the Eastern Colorado Research Center, Akron, Colorado. Thirty-six mixed breed steers were pastured on native grasses; and fed medicated range minerals containing CTC at 8000 grams per ton. There were three replicates in this study, each containing 12 animals, with the replicates being rotated between pastures at 14 day intervals. Average daily consumption of CTC was 0.961 mg per pound of body weight. Before the study was initiated the animals were offered non-medicated range minerals for 20 days, to adapt them to consuming the free-choice product.
C. Illinois (#4958): Conducted by Dr. Britt Hicks (Moorman Research Farm No. 2) at Mendon, Illinois. Twenty-four Angus steers were pastured on orchardgrass; and fed medicated range minerals containing CTC at 8000 grams per ton. There were three replicates in this study, each containing 8 animals, with the replicates being rotated between pastures at 14 day intervals. Average daily consumption of CTC was 0.887 mg per pound of body weight. Before the study was initiated the animals were offered non-medicated range minerals for 35 days, to adapt them to consuming the free-choice product.
D. Mississippi (#4944): Conducted by Dr. C. Pat Bagley (Northern Mississippi Research and Extension Center) at Pontotoc, Mississippi. Thirty mixed breed cow-calf pairs were pastured on bermudagrass; and fed medicated range minerals containing CTC at 8000 grams per ton. There were three replicates in this study, each containing 10 cow-calf pairs (plus a bull for the first twelve days of drug treatment), with the replicates being rotated between pastures at 14 day intervals. Average daily consumption of CTC for a cow-calf pair was 1.13 mg per pound of body weight. Before the study was initiated the animals were offered

non-medicated range minerals for 26 days, to adapt them to consuming the free-choice product.

E. Colorado (#4943): Conducted by Dr. Kenneth Odde (Colorado State University) at the Eastern Colorado Research Center, Akron, Colorado. Thirty mixed breed cow-calf pairs were pastured on native grasses; and fed medicated range minerals containing CTC at 8000 grams per ton. There were three replicates in this study, each containing 10 cow-calf pairs, with the replicates being rotated between pastures at 14 day intervals. Average daily consumption of CTC for a cow-calf pair was 1.86 mg per pound of body weight. Before the study was initiated the animals were offered non-medicated range minerals for 20 days, to adapt them to consuming the free-choice product.

F. Illinois (#4959): Conducted by Dr. Britt Hicks (Moorman Research Farm No. 2) at Mendon, Illinois. Thirty Hereford x Angus cow-calf pairs were pastured on fescue; and fed medicated range minerals containing CTC at 8000 grams per ton. There were three replicates in this study, each containing 10 cow-calf pairs (plus a bull for the first 39 days of drug treatment), with the replicates being rotated between pastures at 14 day intervals. Average daily consumption of CTC for a cow-calf pair was 0.52 mg per pound of body weight. Before the study was initiated the animals were offered non-medicated range minerals for 36 days, to adapt them to consuming the free-choice product.

The results of these studies indicated the average consumption of CTC fell within the daily dosage range of 0.5-2.0 mg of CTC per pound of body weight when provided in free-choice range minerals. Because the medicated free-choice range minerals provided a daily minimum intake of 0.5 milligram of CTC per pound of body weight the Agency has concluded they are effective for the control of active infection of anaplasmosis caused by Anaplasma marginale susceptible to chlortetracycline, in grazing beef cattle (weighing over 700 lbs).

III. TARGET ANIMAL SAFETY

As discussed in the Freedom of Information Summary dated February 16, 1996, that states "NADA 48-761 was originally approved as safe on November 9, 1951.

IV. HUMAN FOOD SAFETY

A. Tolerance

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

The tolerance for chlortetracycline in the edible tissues of beef cattle and nonlactating dairy cattle is 0.1 ppm in uncooked kidney, liver, and muscle (21 CFR 556.150).

B. Study Establishing the Withdrawal Period

A residue depletion study was conducted by Moorman Manufacturing, Quincy, Illinois to satisfy the human food safety requirements for chlortetracycline (CTC) at a concentration of 4 g/lb in free-choice mineral feeds for growing calves and for cows with nursing calves. The purpose of the study was to determine the depletion of CTC in cattle fed 2 mg CTC/pound body weight/day for 28 days.

Three nonmedicated control (2 steers, 1 heifer) and 24 test Hereford cattle (12 heifers and 12 steers) with an average initial weight of 598 pounds were used. Test cattle were fed AUREOMYCIN®90 chlortetracycline granular Type A medicated article mixed in supplemental feed to provide 2 mg CTC/pound body weight/day for 28 days. The control cattle were fed nonmedicated feed. After 28 days of test drug feeding, the medicated feed was withdrawn and replaced with nonmedicated feed. At 24, 36, 48, 60, 72, and 84 hours after the end of medication, two male and two female cattle were sacrificed and the appropriate tissues were assayed for residues.

Chlortetracycline Residues in Edible Tissues from Cattle Fed Two Mg of CTC/Pound of Body Weight/Day for 28 days.

Chlortetracycline Concentrations (ppm)

Withdrawal Time (hours)	Sex of Animal	Fat	Muscle	Liver	Kidney
24	male	ND*	ND	0.2974	0.4892
24	male	ND	ND	0.2065	0.4574
24	female	ND	ND	0.1928	0.3825
24	female	ND	0.0500	0.2841	0.4784
36	male	ND	ND	0.1570	0.2991
36	male	ND	ND	0.0929	0.2045
36	female	ND	ND	0.1250	0.2287
36	female	ND	ND	0.1141	0.2615
48	male	ND	ND	ND	0.1430
48	male	ND	ND	0.0757	0.1956
48	female	ND	ND	0.0550	0.1398
48	female	ND	ND	ND	0.1143
60	male	ND	ND	ND	0.1250
60	male	ND	ND	0.0723	0.1143
60	female	ND	ND	ND	0.0817
60	female	ND	ND	0.0740	0.1093
72	male	ND	ND	ND	0.0715
72	male	ND	ND	ND	0.0598
72	female	ND	ND	ND	0.0640
72	female	ND	ND	ND	0.0547
84	male	ND	ND	ND	0.0547
84	male	ND	ND	ND	0.0572
84	female	ND	ND	ND	ND
84	female	ND	ND	ND	ND

The statistical method used to calculate the withdrawal time was that described by FDA: VI. Guideline for Establishing a Withdrawal Period, September, 1986. Using a statistical tolerance limit for the 99th percentile of the population with 95% confidence, a withdrawal time of four days in kidney was assigned for cattle fed AUREOMYCIN®90 chlortetracycline granular Type A medicated article mixed in supplemental feed to provide 2 mg CTC/pound body weight/day for 28 days.

C. Regulatory Method

The validated microbiological method with minor modifications was used to measure antimicrobial activity of chlortetracycline in cattle tissue (Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Methods, Reports, and Protocols, FDA, 1968). The limit of quantitation is 0.05 ppm. The method is on file at the Center for Veterinary Medicine, Food and Drug Administration, HFV-199, 7500 Standish Place, Rockville, Maryland 20855.

V. AGENCY CONCLUSIONS

This NADA satisfies the requirements of section 512(b) of the Federal Food, Drug and Cosmetic Act, and demonstrates that chlortetracyline when used under the proposed conditions of use is safe and effective for the labeled indications.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval for food producing animals qualifies for three years of marketing exclusivity beginning on the date of the approval because the application contains reports of new clinical or field investigations (other than bioequivalence or residue studies) essential to the approval of the application and conducted or sponsored by the applicant.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change. However, this action did not require a reevaluation of the safety and effectiveness data in the parent application.

VI. LABELING

The labeling for Moorman's Special Range Minerals AU Type C Medicated feed.

Copies of applicable labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.