Approval Date: April 03, 1996

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

ANADA 200-050

B. Sponsor

Rhone-Merieux, Inc.
P.O. Box 459
2116 8th Avenue South
Ft. Dodge, Iowa 50501

C. Proprietary Name

Neomycin 325 Soluble Powder

D. Established Name

neomycin sulfate

E. Dosage Form

Soluble powder

F. How Supplied

3.5 Oz (100 g) packages

G. Dispensing Status

OTC vf. Amount of Active Ingredient: 50 g neomycin/3.5 Oz

H. Dosage Regimen

10 mg/lb body weight daily in divided doses for a maximum of 14 days

I. Route of Administration

Orally in drinking water or milk

J. Species/Class

Cattle (excluding veal calves), Swine, Sheep, and Goats

K. Indication

For the treatment and control of colibacillosis (bacterial enteritis) caused by *Escherichia coli* susceptible to neomycin sulfate.

L. Reference Listed New Animal Drug

Upjohn Company / Neomix ® 325 / NADA 011-315

M. Effect of Supplement

To increase the tolerance in the target tissue, kidneys, to 7.2 ppm and to decrease the withdrawal periods to 1 day in cattle, 2 days in sheep, and 3 days for swine and goats.

II. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS

The basis for the original approval of this ANADA was published in 60 FR 14217, March 16, 1995.

III. HUMAN FOOD SAFETY

Tolerance

The tolerance for neomycin residues in the uncooked edible tissues of cattle, swine, sheep, and goats was originally established at 0.25 ppm (21 CFR 556.430). The tolerance is being revised using the new food consumption factors as described in the FDA/CVM July 1994 guideline entitled, "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals" (59 FR 37499). A tolerance of 7.2 ppm is established for residues of parent neomycin (marker residue) in the kidney (target tissue), 7.2 ppm in fat, 3.6 ppm in liver, 1.2 ppm in muscle of cattle, swine, sheep, and goats. A tolerance of 0.15 ppm is established for neomycin in milk.

Studies Establishing the Withdrawal Period

Four separate residue depletion studies were conducted by Colorado Animal Research Enterprises Inc. (CARE), Fort Collins, Colorado under VMF 5154. The purpose of the studies was to determine the depletion of neomycin in swine, cattle, sheep, or goats following administration of 10 mg neomycin sulfate/pound body weight/day through drinking water for 14 days.

1. Ten male and ten female swine weighing approximately 100 lbs each were administered neomycin sulfate at 10 mg/lb/day for 14 days through the drinking water. One male and one female swine served as controls. The swine were sacrificed in groups of four (2M, 2F) at 0, 1, 3, 7, and 14 days after the last dose. Samples of kidney, liver, muscle, and fat were taken and assayed for residues. Only kidney had detectable amounts of residues.

   Geometric Mean Kidney Tissue Neomycin Residues from Swine Medicated with 10 mg/lb/day for 14 Days through Drinking Water (n=2)

Withdrawal Time in Days	**Geometric Mean Neomycin Levels (ppm) - Female**	**Geometric Mean Neomycin Levels (ppm) - Male**
0	1.63	2.52
1	0.79	2.92
3	0.46	1.34
7	0.44	0.65
14	0.34	0

   Limit of Quantitation is 0.5 ppm.

2. Ten steers and ten heifers weighing approximately 525 lbs each were administered neomycin sulfate at 10 mg/lb/day for 14 days through drinking water. One steer and one heifer served as controls. The treated cattle were sacrificed in groups of four (2M, 2F) at 0, 1, 3, 7, and 14 days after the last dose (only 3 animals were sacrificed on day 7 of withdrawal due to the death of one heifer). Kidneys, liver and samples of muscle and fat were assayed for residues. Only kidney had detectable amounts of residues.

   Geometric Mean Kidney Tissue Neomycin Residues from Cattle Medicated with 10 mg/lb/day for 14 Days through Drinking Water (n=2)

Withdrawal Time in Days	**Geometric Mean Neomycin Levels (ppm) - Female**	**Geometric Mean Neomycin Levels (ppm) - Male**
0	2.40	3.16
1	3.35	2.37
3	1.87	1.48
7	--	0.52
14	0	0

   Limit of Quantitation is 0.5 ppm.

3. Ten wethers and ten ewes weighing approximately 110 lbs each were administered neomycin sulfate at 10 mg/lb/day for 14 days through drinking water. One wether and one ewe served as controls. The treated sheep were sacrificed in groups of four (2M, 2F) at 1, 3, 7, 14, and 21 days after the last dose. Kidneys, liver and samples of muscle and fat were assayed for residues. Only kidney had detectable amounts of residues.

   Geometric Mean Kidney Tissue Neomycin Residues from Sheep Medicated with 10 mg/lb/day for 14 Days through Drinking Water (n=2)

Withdrawal Time in Days	**Geometric Mean Neomycin Levels (ppm) - Female**	**Geometric Mean Neomycin Levels (ppm) - Male**
1	1.28	0.62
3	0	0.45
7	--	0

   Limit of Quantitation is 0.5 ppm.

4. Ten female and ten male goats weighing approximately 65 lbs each were administered neomycin sulfate at 10 mg/lb/day for 14 days through drinking water. One female goat and one male goat served as controls. The treated goats were sacrificed in groups of four (2M, 2F) at 12, 24, 48, 72, and 96 hours after the last dose. Kidneys, liver and samples of muscle and fat were assayed for residues. Only kidney had detectable amounts of residues.

Geometric Mean Kidney Tissue Neomycin Residues from Goats Medicated with 10 mg/lb/day for 14 Days through Drinking Water (n=2)

Withdrawal Time in Days	**Geometric Mean Neomycin Levels (ppm) - Female**	**Geometric Mean Neomycin Levels (ppm) - Male**
12	1.002	0.732
24	1.50	2.61
48	1.09	2.20
72	0.81	1.04
96	0.36	0.84

Limit of Quantitation is 0.5 ppm.

A weighted least squares regression line was fit to tobit maximum likelihood (ML) estimates of central location for each time point. The weights were based on ML estimates of dispersion. This accommodates values below the limit of quantitation and above the limit of detection. Using a statistical tolerance limit for the 99th percentile of the population with 95% confidence, the following withdrawal times were calculated for animals treated with 10 mg/lb/day neomycin sulfate for 14 days through drinking water:

Animals treated with 10 mg/lb/day neomycin sulfate for 14 days through drinking water	**Withdrawal Time in Days**
Swine	3
Goats	3
Sheep	2
Cattle (excluding veal calves)	1

Regulatory Method for Residues

The regulatory analytical method for detection of residues of the drug is a microbiological test using *Staphylococcus epidermidis* suspension. The method is published by the Food and Drug Administration, "Antibiotic Residues in Milk, Dairy Products and Animal Tissues: Methods, Reports, and Protocols", revised October 1968, reprinted December 1974.

IV. AGENCY CONCLUSIONS

Neomycin sulfate, codified in 21 CFR Parts 520.1484(c)(3) and 556.430, is approved for marketing as a soluble powder for the treatment and control of colibacillosis (bacterial enteritis) caused by *Escherichia coli* susceptible to neomycin sulfate in cattle (excluding veal calves), swine, sheep, and goats.

The data submitted in support of this supplemental ANADA requesting an increase in the tolerance satisfy the requirements of section 512 of the Act and demonstrate that neomycin sulfate (Neomycin 325 Soluble Powder) at a dose of 10 mg/lb/day for 14 days orally in the drinking water, will produce concentrations of residues in the kidneys (target tissue) in cattle, swine, sheep, and goats which are below the accepted tolerance (7.2 ppm) by the following revised withdrawal periods. The withdrawal period for cattle is 1 day, sheep is 2 days, and swine and goats is 3 days.

Under the Center's supplemental approval policy, this is a Category II change [21 CFR 514.106(b)(2)(x)and(xi)]. The approval of this change, a recalculation of the tolerance, is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. The change in tolerance allows for a decrease in the withdrawal period. Accordingly, this approval did not require a reevaluation of the safety or effectiveness data in the parent application.

Under section 512(c)(2)(F)(iii) of the Federal Food , Drug, and Cosmetic Act (21 U.S.C. 360b(c)(2)(F)(iii)), this approval does not qualify for marketing exclusivity because the application does not contain reports of new clinical or field investigations (other than bioequivalence or residue studies) or new human food safety studies (other than bioequivalence or residue studies) essential to the approval and conducted or sponsored by the applicant.

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.