

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 044-759

B. Sponsor

Hoechst-Roussel Agri-Vet Co.
P.O. Box 2500
Route 202-206
Somerville, NJ 08876-1258

C. Proprietary Name

Flavomycin®

D. Established Name

bambermycins

E. Dosage Form

Three (3) Type A Medicated Articles in 50 lb. multi-walled bags. The Type A Medicated Articles contain 2 g bambermycins per pound, 4 g bambermycins per pound, and 10 g bambermycins per pound.

F. Dispensing Status

OTC

G. Dosage Regimen

1-4 g bambermycins/ton (in a Type C medicated feed) to supply 10-20 mg bambermycins/hd/day.

H. Route of Administration

Orally by mixing the Type A Medicated Article into cattle supplements (Type B Medicated Feed) and complete cattle feed (Type C Medicated Feed)

I. Indication

For increased rate of weight gain and improved feed efficiency in cattle fed in confinement for slaughter.

J. Effect of Supplement

21 CFR 558.95 currently provides for the use of bambermycins in poultry and swine. This supplement provides for the use of bambermycins in cattle fed in confinement for slaughter for increased rate of weight gain and improved feed efficiency.

II. EFFECTIVENESS

A. Pivotal Dose Titration Studies:

This New Animal Drug Application is based on adequate and well-controlled studies demonstrating the effectiveness of bambermycins for increased rate of weight gain and improved feed efficiency in feedlot cattle. The pivotal studies are dose titration studies in which the parameters measured are the same parameters as measured in clinical (field) studies. These studies were conducted using similar protocols so the results may be pooled and summarized.

The 1830 test animals used in these nine (9) feedlot studies were crossbred animals of European breeds. There were 6 to 20 steers or heifers per pen with each treatment replicated 4 to 6 times. The initial animal weights ranged from 400 to 900 lbs. and the studies were terminated when the animals reached slaughter weights and condition (1,000 to 1,200 lbs.). Feeding periods ranged from 84 to 238 days depending on initial weights and energy level in the diet. Low energy (high roughage/low concentrate) to high energy (low roughage/high concentrate) diets were fed. Bambermycins was administered via the feed in the following doses: 0.0, 2.5, 5.0, 10.0, 20.0, and 40.0 mg bambermycins per head per day. The results from the nine (9) studies are summarized as follows:

1. Trial No. 946-1 - A Dose Titration Study

Investigator:

E.S. Erwin & Associates, Inc.
 P.O. Box 237
 Tolloson, Arizona 85353

Monitor:

Max W. Moeller
 Hoechst-Roussel Agri-Vet Company
 P.O. Box 2500
 Route 202-206
 Somerville, New Jersey 08876

This study was conducted using 200 animals. The cattle were fed for 238 days. There were 10 animals per pen and 5 replications of each treatment. The results were as follows:

| | Bambermycins (mg/hd/day) | | | |
|---------------------------------|---------------------------------|-------------|-------------|-------------|
| | 0.0 | 10.0 | 20.0 | 40.0 |
| Average Daily Gain (lbs) | 2.10 | 2.11 | 2.12 | 2.14 |
| Feed Efficiency (F/G) | 7.49 | 7.45 | 7.40 | 7.42 |

2. Trial No. 946-2 - A Dose Titration Study

Investigator:

R. Hollis Klett
Texas Tech University Center
P.O. Box 7
Panrex, Texas 79069

Monitor:

Max W. Moeller
Hoechst-Roussel Agri-Vet Company
P.O. Box 2500
Route 202-206
Somerville, New Jersey 08876

This study was conducted using 200 animals. The cattle were fed for 169 days. There were 10 animals per pen and 5 replications of each treatment. The results were as follows:

| | Bambermycins (mg/hd/day) | | | |
|---------------------------------|---------------------------------|-------------|-------------|-------------|
| | 0.0 | 10.0 | 20.0 | 40.0 |
| Average Daily Gain (lbs) | 2.65 | 2.58 | 2.79 | 2.59 |
| Feed Efficiency (F/G) | 7.11 | 8.15 | 7.49 | 8.08 |

3. Trial No. 946-3 - A Dose Titration Study

Investigator:

Kenneth S. Eng
Eng Inc.
P.O. Box R
Casa Grande, Arizona 85222

Monitor:

Max W. Moeller
Hoechst-Roussel Agri-Vet Company
P.O. Box 2500
Route 202-206
Somerville, New Jersey 08876

This study was conducted using 192 animals. The cattle were fed for 136 days. There were 8 animals per pen and 6 replications of each treatment. The results were as follows:

| | Bambermycins (mg/hd/day) | | | |
|---------------------------------|---------------------------------|-------------|-------------|-------------|
| | 0.0 | 10.0 | 20.0 | 40.0 |
| Average Daily Gain (lbs) | 2.46 | 2.75 | 2.60 | 2.63 |
| Feed Efficiency (F/G) | 8.31 | 7.07 | 7.56 | 7.59 |

4. Trial No. 946-4 - A Dose Titration Study

Investigator:

Kenneth S. Eng
 Eng Inc.
 P.O. Box R
 Casa Grande, Arizona 85222

Monitor:

Max W. Moeller
 Hoechst-Roussel Agri-Vet Company
 P.O. Box 2500
 Route 202-206
 Somerville, New Jersey 08876

This study was conducted using 192 animals. The cattle were fed for 140 days. There were 8 animals per pen and 6 replications of each treatment. The results were as follows:

| | Bambermycins (mg/hd/day) | | | |
|---------------------------------|---------------------------------|-------------|-------------|-------------|
| | 0.0 | 10.0 | 20.0 | 40.0 |
| Average Daily Gain (lbs) | 1.96 | 2.00 | 2.10 | 2.03 |
| Feed Efficiency (F/G) | 10.48 | 10.13 | 9.61 | 9.91 |

5. Trial No. 946-7 - A Dose Titration Study

Investigator:

R. Hollis Klett
 Texas Tech University Center

P.O. Box 7
Panrex, Texas 79069

Monitor:

Robert J. Grant
Hoechst-Roussel Agri-Vet Company
P.O. Box 2500
Route 202-206
Somerville, New Jersey 08876

This study was conducted using 200 animals. The cattle were fed for 185 days. There were 10 animals per pen and 5 replications of each treatment. The results were as follows:

| | Bambermycins (mg/hd/day) | | | |
|---------------------------------|---------------------------------|-------------|-------------|-------------|
| | 0.0 | 10.0 | 20.0 | 40.0 |
| Average Daily Gain (lbs) | 2.17 | 2.28 | 2.33 | 2.30 |
| Feed Efficiency (F/G) | 8.84 | 8.66 | 8.60 | 8.35 |

6. Trial No. 946-8 - A Dose Titration Study

Investigator:

J.P. Fontenot
Virginia Polytechnic Institute
Department Animal Science
Blacksburg, Virginia 24061

Monitor:

Robert J. Grant
Hoechst-Roussel Agri-Vet Company
P.O. Box 2500
Route 202-206

Somerville, New Jersey 08876

This study was conducted using 108 animals. The cattle were fed for 160-195 days depending on replication. There were 6 to 8 animals per pen (depending on replication) and 4 replications of each treatment. The results were as follows:

| | Bambermycins (mg/hd/day) | | | |
|---------------------------------|---------------------------------|-------------|-------------|-------------|
| | 0.0 | 10.0 | 20.0 | 40.0 |
| Average Daily Gain (lbs) | 2.10 | 2.09 | 2.10 | 2.21 |
| Feed Efficiency (F/G) | 4.62 | 14.65 | 14.55 | 14.38 |

7. Trial No. 946-10 - A Dose Titration Study

Investigator:

E. Hatfield
 University of Illinois
 264 Animal Science Lab
 Urbana, Illinois 61801

Monitor:

Robert J. Grant
 Hoechst-Roussel Agri-Vet Company
 P.O. Box 2500
 Route 202-206
 Somerville, New Jersey 08876

This study was conducted using 108 animals. The cattle were fed for 84 days. There were 6 animals per pen and 6 replications of each treatment. The results were as follows:

| | Bambermycins (mg/hd/day) | | |
|---------------------------------|---------------------------------|------------|-------------|
| | 0.0 | 5.0 | 10.0 |
| Average Daily Gain (lbs) | 2.97 | 3.22 | 3.39 |
| Feed Efficiency (F/G) | 7.00 | 6.49 | 6.11 |

8. Trial No. 946-11 - A Dose Titration Study

Investigator:

Merlin Voorhees
 Missouri Slope Feedlot, Inc.

Onida, South Dakota 57564

Monitor:

Robert J. Grant
Hoechst-Roussel Agri-Vet Company
P.O. Box 2500
Route 202-206
Somerville, New Jersey 08876

This study was conducted using 360 animals. The cattle were fed for 111 days. There were 20 animals per pen and 6 replications of each treatment. The results were as follows:

| | Bambermycins (mg/hd/day) | | |
|---------------------------------|---------------------------------|------------|-------------|
| | 0.0 | 5.0 | 10.0 |
| Average Daily Gain (lbs) | 3.14 | 3.21 | 3.20 |
| Feed Efficiency (F/G) | 6.4 | 6.48 | 6.43 |

9. Trial No. 946-13 - A Dose Titration Study

Investigator:

Merlin Voorhees
Missouri Slope Feedlot, Inc.
Onida, South Dakota 57564

Monitor:

Robert J. Grant
Hoechst-Roussel Agri-Vet Company
P.O. Box 2500
Route 202-206
Somerville, New Jersey 08876

This study was conducted using 270 animals. The cattle were fed for 93 days. There were 15 animals per pen and 6 replications of each treatment. The results were as follows:

| | Bambermycins (mg/hd/day) | | |
|---------------------------------|---------------------------------|-------------|-------------|
| | 0.0 | 10.0 | 20.0 |
| Average Daily Gain (lbs) | 2.76 | 2.97 | 3.02 |
| Feed Efficiency (F/G) | 10.10 | 9.46 | 9.39 |

A randomized complete block design was used for all studies and the data were pooled by Analysis of Variance to determine the significance of the effect of bambermycins on average daily gain (ADG) and feed efficiency (FIG). A weighted regression analysis was used because the error mean squares were heterogeneous. Additionally the pooled analysis was conducted using the treatment means from each experiment weighted by the reciprocal of its error mean square. The data were analyzed by least squares and effective ranges were determined by nonoverlapping confidence intervals. Based on the results of the least squares analysis and the regression analysis a range of 10-20 mg bambermycins/hd/day was approved for increased rate of weight gain and improved feed efficiency. Data from this pooled analysis are presented in the following table.

POOLED ANALYSIS

| | Bambermycins (mg.hd/day) | | | | | | |
|------------------|---------------------------------|------------|------------|-------------|-------------|-------------|----------------|
| | 0.0 | 2.5 | 5.0 | 10.0 | 20.0 | 40.0 | EMS (2) |
| ADG (lbs) | 2.52 | 2.53 | 2.57a | 2.58** | 2.61*** | 2.60** | 2.068 |
| F/G | 8.898 | 8.912 | 8.756 | 8.694* | 8.667g | 8.670g | 0.000221 |

(1) Superscripts denote significance compared to control as follows:

- a = (P is less than 0.10)
 - * = (P is less than 0.05)
 - ** = (P is less than 0.025)
 - *** = (P is less than 0.01)
- (2) EMS = Error Mean Square

III. TARGET ANIMAL SAFETY

Pivotal Study No. 36660 Target Animal (Beef Cattle) Safety and Drug Tolerance Study with Bambermycins (Flavomycin)

Investigator:

Analytical Bio-Chemistry Laboratories, Inc.
7200 E. ABC Lane
Columbia, Missouri 65202

Pivotal Target Animal Safety and Drug tolerance studies were conducted using thirty-six (36) yearling beef steers and heifers weighing between 500 and 685 pounds at study initiation.

Species and Strain: Cattle, Crossbred calves

Weight: 500 to 685 lbs (227 to 311 kg)

Number per Group: 4/sex/group (TAS)

2/sex/group (Drug Tolerance)

Dosage Form: Oral

Dosage Used: 0, 20, 100, 300 mg/head/day (TAS)

1500 mg/head/day (Drug Tolerance)

Frequency: Fed continuously

Start Date: February 17, 1988

End Date: May 11, 1988

The highest approved use level of bambermycins is 20 mg/hd/day. This was established as the 1 X dose level. Multiples of the highest use level were then tested as follows (mg/hd/day): control (0.0 mg), 1 X (20.0 mg), 5X (100.0 mg), 15X (300 mg) and 75X (1500 mg). The 75X dose was the drug tolerance portion of this study and was fed for 21 days. Bambermycins was fed continuously from study initiation to slaughter for the 1 X, 5X, and 15X groups. The duration of treatment for these groups was 150 to 166 days or a normal growing finishing period for feedlot steers and heifers. The 75X calves were fed bambermycins for 21 days, then deparated for 23 days prior to sacrifice and disposal. They were observed twice daily for any adverse effects attributable to bambermycins. Blood samples were drawn from the 75X animals prior to initiation and on days 10, 21, 25 and 30. These samples were assayed for bambermycins residues. The control, 1 X, 5X and 15X cattle were observed once daily for abnormal behavior, depression, anorexia, urine or feces abnormalities and abnormal skin or hair coat. Blood samples were collected prior to initiation of treatments and on days 45, 90, 135 and just prior to slaughter. The following assays and cell counts (hematology) were done on all samples.

Serum Chemistries

- Glucose

- Potassium
- Calcium
- Sodium
- Chloride
- Aspartate aminotransferase (AST)
- Total Protein
- Albumin
- Globulin
- Amylase
- Total and direct bilirubin
- Creatinine

Hematology

- White blood cell count
- Red blood cell count
- Differential white blood cell count
- Packed cell volume
- Mean corpuscular hemoglobin concentration
- Platelet count (from ratio of platelets to RBC)

The control, 1 X, 5X, and 15X cattle were sacrificed at the end of the study and the weights of the major organs (heart, liver, spleen, kidneys and lungs) were obtained. Additionally the following list of tissues were collected for histopathological examinations: pituitary gland, thyroid glands, parathyroid glands, adrenal glands, spleen, liver, kidneys, bone with marrow and marrow smear. A complete necropsy was conducted on each animal. Carcass quality evaluations were conducted and each carcass was evaluated for quality grade, yield grade, rib eye area, marbling and fat thickness.

Results

The calves remained healthy and exhibited no observable adverse effects in any of the treatments. There were no adverse effects on feed efficiency and average daily gain. The results from the remaining parameters measured were summarized as follows:

- There were no changes, due to the drug, in the blood chemistry or hematology variables that are of biological importance to the target animal.
- No gross lesions or abnormalities were observed in any tissues.
- There were no significant findings in the necropsy and histopathology reports.
- There were no significant differences in organ weights.

There were no significant findings in the carcass quality evaluations.

No adverse effects due to bambarmycins were seen in the 75X cattle (drug tolerance study). No bambarmycins residues were detected in any of the blood samples from the 75X animals.

IV. HUMAN FOOD SAFETY

A. Toxicity Tests:

1. Two Year Dietary Carcinogenicity Study in Mice

Study No.: 327-048

Starting Date: March 10, 1980

End Date: March 12, 1982

Study Director: Malcolm Blair, Ph.D.

Identification of Substance and Dosage Form: Powder (mycelia)

Species and Strain: Charles River CD ® 1 strain

Number of Animals Per Sex Per Treatment: 50/sex/group

Drug Levels Tested and Duration of Dosing: 0, 1, 2, and 4% of diet (0.0, 466.0, 932.0, and 1864.0 g/ton)

Route of Administration: Oral, fed continuously

The study was conducted at International Research and Development Corp., Matrawan, Michigan 49071. The purpose of the study was to evaluate the carcinogenicity of bambermycins (Flavomycin ®) mycelium cake in a two year feeding study. Bambermycins was offered in the diet at concentrations of 0, 1, 2, and 4 percent. The actual level of bambermycins in the diets was 0.0, 466.0, 932.0, and 1,864.0 grams per ton of diet. Fifty (50) male and 50 female mice were initiated at each dosage level and in each of two control groups.

The mice were observed daily for signs of overt toxicity and for mortality. Individual body weights and food consumptions were recorded weekly for the first 14 weeks and once every two weeks thereafter. Complete necropsies were performed on all mice that died or were sacrificed during the study. At the termination of the study, all surviving mice were sacrificed by carbon dioxide asphyxiation and necropsied. Representative tissues were fixed in formalin and stained in hematoxylin and eosin for histopathological examination.

No treatment-related effects were seen after 18 months of treatment (chronic toxicity portion of the study). After two years of treatment, there were no toxicologically significant treatment-related macroscopic or microscopic changes of neoplastic or non-neoplastic nature in mice of either sex or at any dosage level.

2. Long-Term Dietary Study in Rats Exposed In Utero

Study No.: 327-049

Starting Date: March 12, 1980

End Date: July 9, 1982

Study Director: Malcolm Blair, Ph.D.

Identification of Substance and Dosage Form: Powder (mycelia)

Species and Strain: Charles River COBS®

CD® strain

Number of Animals Per Sex Per Treatment: 50-60/sex/group

Drug Levels Tested and Duration of Dosing: 0, 1, 2, and 4% of diet (0.0, 466.0, 932.0, and 1864.0 g/ton)

Route of Administration: Oral, fed continuously

The study was conducted at International Research and Development Corp., Matrawan, Michigan 49071. Bambermycins was offered in the diet at concentrations of 0, 1, 2, and 4 percent. The actual level of bambermycins in the diets was 0.0, 466.0, 932.0, and 1,864.0 grams per ton of diet. Sexually mature rats were divided in two control and three treatment groups consisting of 50 males and 50 females each. These rats were used to produce offsprings to be used in the chronic study to evaluate the toxicological and carcinogenic potential of bambermycins with exposure beginning in utero. The bambermycins mycelia was administered orally two weeks before mating of the Fo generation. Following weaning, sixty (60) F1 pups per sex per group were initiated in the chronic phase of the study.

During the in utero phase of the study, parental animals and pups were observed for mortality and signs of overt toxicity twice a day. Individual parental body weights and food consumptions were measured except during mating periods. Maternal body weights were recorded at specified intervals during gestation and lactation. Reproductive and litter parameters assessed included male and female fertility indices, parturition, gestation length, litter size, mean number of viable and stillborn pups, pup survival, and mean pup body weight during lactation.

In the chronic phase of the study, the rats were observed twice daily for appearance, behavior, signs of overt toxicity, moribundity, and mortality. Individual body weights and food consumptions were measured weekly for the first 14 weeks and every other week thereafter. Ophthalmoscopic examinations were conducted during weeks 2, 13, 26, 51, 78, and 104. Clinical laboratory tests were performed on 10 rats/sex/group at 3, 6, 12, 8, 24 months of the study. The clinical laboratory tests included hematological, clinical chemistry, and urinalysis determinations.

After 12 months of dosing in the chronic phase of the study, 10 rats/sex/group were sacrificed and necropsied. All rats that died, those sacrificed in extremis, and all survivors at termination of study were also necropsied. Weights of brain, kidneys, liver, heart, spleen, testes, thyroid/parathyroid, ovaries, and adrenals were recorded for animals sacrificed at 12 months and at study termination. A complete set of tissues was fixed and stained for histological examination in all control groups and high dose rats, and all animals that died or were sacrificed in extremis. All gross lesions, masses, and their regional lymph nodes were also histologically examined.

No treatment-related effects were seen during the in utero phase of the study. At termination of the chronic toxicity phase of the study (one year interim report), the only changes observed were increases in the relative and absolute weights of livers and kidneys particularly in the 4% and some of the 2% groups. Females of the 2% group had an increase in absolute and relative liver weight and absolute kidney weight. Males of this group also had increased liver and kidney weights. Only the relative kidney weight of the 2% males was higher than the controls.

Consequently, the NOEL for the 1-year chronic toxicity study is 1% of mycelial bambermycins in the feed.

After two years of treatment, no differences were seen in appearance, behavior, survival rate, body weight gain and food consumption. The only effect observed was an increase in absolute and relative liver and kidney weights mainly in the males of the 4% group. No macroscopic or microscopic lesions of either neoplastic or non-neoplastic nature, or hematological, biochemical and urinary changes occurred in any group after an in utero exposure followed by two years of oral administration of bambermycins mycelia.

Consequently, bambermycins mycelia was found to be non-carcinogenic in 2-year chronic feeding studies in rats and mice.

Several toxicity studies were performed between 1962 and 1968 at Hoechst A.G., Frankfurt, Germany. They include a two-year reproduction study in rats, a chronic (2 year) feeding toxicity study in rats, sub-acute (90 days) oral toxicity studies in rats and dogs, and oral acute toxicity studies in rats and mice.

The two-year reproduction study (RR-1-64) collected data from five generations when bambermycins mycelia was fed at 0 and 25 mg/kg of feed to rats. The only effect observed was a slightly lower number of litters in the treated groups compared to the controls. No differences were found in litter size, pup weight, and pup mortality. The chronic feeding study in rats also showed no adverse effects on body weight, mortality, hematology, liver glycogen, blood sugar levels, urinalysis, organ weights, or histopathology when bambermycins mycelia was fed at 0 and 50 mg/kg of feed.

The 90-day rat study showed no effects on body weight gain, feed consumption, mortality, behavior, functional tests, hematology, urinalysis, organ weights, or histopathology when bambermycins was fed at 0, 1,000 (mycelia), and 10,000 mg (semi-purified) bambermycins per kg of feed. The 90-day dog study also showed no adverse effects on body weight, general condition, hematology, blood glucose levels, urinalysis, or hematology when bambermycins was fed to 17-month old dogs at 400 and 4,000 mg/kg of feed in the mycelial and semi-purified forms.

Oral acute toxicity studies in rats and mice showed no toxicity in rats given up to 40 g mycelia per kg body weight (containing 90 mg bambermycins) within 8-1/16 hours. In mice, no effects were seen with up to 90 g/kg body weight of mycelia containing 202.5 mg bambermycins when given within 7-1/2 hours. When purified bambermycins was used no effects occurred with 10 grams/kg body weight in one single application or with two applications, each of 10 grams/kg body weight, given within a two hour interval.

A teratology study for bambermycins was not required because: a) all the toxicity studies demonstrated that bambermycins is non-toxic when given at doses of up to 1,000 times the highest use level (20 mg/head/day), b) study number 327-047 showed no effects on reproductive or litter parameters when rats were exposed to the drug In Utero, and c) study number RR-1-64 showed no adverse or teratogenic effects in rats exposed to high levels of bambermycins through 5 generations.

B. Safe Concentration of Residues

Based on the 1-year toxicity portion of the 2-year toxicity carcinogenicity study in rats, the NOEL for mycelial bambarmycins was 1%. Considering a daily product intake of 571 mg/kg, a 100-fold safety factor, and a purity of the product of 5.12%, the calculated safe concentration for pure bambarmycins in muscle is 35 ppm. However, for the reasons discussed in Section C, the safe concentration for bambarmycins in muscle is being limited to 3 ppm. Since only minimal or no signs of toxicity were observed even at the very highest doses, radiolabelled metabolism and residue studies were not required for the bambarmycins.

C. Residue Depletion and Metabolism:

Study No.: U.S. Cattle Residue Study

Starting Date: December 4, 1972

End Date: February 9, 1973

Study Director: M.E. Tomlinson
Oakdale Farms
Midlothian, VA 23113

Id of Substance and Dosage Form: premix, 5 g activity/kg

Species and Strain: Angus

Number of Animals Per Sex Per Treatment: at 0 mg: 1 steer at 400 mg: 4 steers, 2 heifers

Drug Levels Tested and Duration of Dosing: 0, 400 mg/hd/day

Route of Administration: Oral, fed 1 lb/day

A cattle tissue residue study was conducted in which unlabeled bambarmycins was fed to one animal at 0 mg/hd/day and to six animals at 400 mg/hd/day (400 mg/hd/day is 20 times the highest approved dose). Six animals were fed 400 mg/hd/day for sixty-six (66) days. The animals were slaughtered while on medication (no withdrawal). After a 66-day feeding period no bambarmycins residues were found in the kidney, liver, muscle, skin and fat from these treated animals.

Because a study in cattle showed that residues are below the detection limit of the method (0.0125 ppm), a tolerance will not be set and a method will not be required. Since the actual residue levels are far lower than the calculated safe concentration and safe concentrations are limited to the level of residues that is required for appropriate use of the drug, the 35 ppm concentration will not be assigned to bambarmycins. A safe concentration of 3 ppm in muscle is being assigned instead. This level permits the appropriate use in the target species and is consistent with current concepts concerning allowable residues of antibiotics in food-producing animals.

D. Withdrawal Time:

A zero (0) withdrawal time is established for bambermycins because no residues are found in any tissue after bambermycins is fed at many times the approved use level.

Studies were conducted to determine the effect of bambermycins on the quantity, prevalence, and duration of salmonella shedding and on antimicrobial resistance in indigenous coliforms and salmonella in cattle (J. Anim. Sci. 44(5): 734 and J. Anim. Sci. 45(6): 1239). These studies were conducted to meet the requirements of 21 CFR 558.15. The use of bambermycins in cattle feed did not increase the quantity, prevalence or duration of salmonella shedding. There was no increase in the frequency of resistance in the indigenous coliforms or salmonella.

E. Regulatory Methods:

A regulatory tissue assay method is not required because of the establishment of a zero (0) withdrawal period in cattle. However, the research method, a microbiological assay method is used to assay tissues for bambermycins residues. The method titled, "Quantitative Agar Well Plate Assay of Bambermycins (Flavomycin) in Organs and Tissues" is on file at the Center for Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD. 20855.

V. AGENCY CONCLUSIONS

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

Under the Center for Veterinary Medicine's supplemental new animal drug application policy (21 CFR 514.106), this is a Category II change providing for the use of bambermycins in feedlot cattle. However, this action did not require a reevaluation of the safety and effectiveness data in the parent application.

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 approval because the supplemental application contains reports of new clinical or field investigations and human food safety studies essential to the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the claims of increased rate of weight gain and improved feed efficiency in cattle fed in confinement for slaughter for which the application was approved.

VI. LABELING (ATTACHED)

1. Flavomycin ® -2
2. Flavomycin ® -4
3. Flavomycin ® -10)
4. Bluebird labeling for Type C Medicated Feeds.

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

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

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

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.