Date of Approval: February 13, 2008

# FREEDOM OF INFORMATION SUMMARY

## SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-068

BAYTRIL 100

Enrofloxacin
Injectable Solution
Beef and Non-Lactating Dairy Cattle

To provide for the use of enrofloxacin in female dairy cattle less than 20 months of age.

Sponsored by:

Bayer HealthCare LLC
Animal Health Division

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## I. GENERAL INFORMATION:

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|---|---|
| **A. File Number:** | NADA 141-068 |
| **B. Sponsor:** | Bayer HealthCare LLC<br>Animal Health Division<br>P.O. Box 390<br>Shawnee Mission, KS 66201<br><br>Drug Labeler Code: 000859 |
| **C. Proprietary Name(s):** | BAYTRIL 100 |
| **D. Established Name(s):** | Enrofloxacin |
| **E. Pharmacological Category:** | Antimicrobial |
| **F. Dosage Form(s):** | Injectable solution |
| **G. Amount of Active Ingredient(s):** | 100 mg/mL |
| **H. How Supplied:** | 100 and 250 mL bottles |
| **I. How Dispensed:** | Rx |
| **J. Dosage(s):** | Single-Dose Therapy: 7.5 - 12.5 mg/kg of body weight (3.4 - 5.7 mL/100 lb).<br><br>Multiple-Day Therapy: 2.5 - 5.0 mg/kg of body weight (1.1 - 2.3 mL/100 lb). Treatment should be repeated at 24-hour intervals for three days. Additional treatments may be given on days 4 and 5 to animals that have shown clinical improvement but not total recovery. |
| **K. Route(s) of Administration:** | Subcutaneous injection |
| **L. Species/Class(es):** | Beef and non-lactating dairy cattle |
| **M. Indication(s):** | For the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* (previously *Haemophilus somnus*) in beef and non-lactating dairy cattle. |

**N. Effect(s) of Supplement:** To provide for the use of enrofloxacin in female dairy cattle less than 20 months of age.

## II. EFFECTIVENESS:

### A. Dosage Characterization:

This supplemental approval does not change the previously approved dosages. The FOI Summary for the original approval of NADA 141-068 dated July 24, 1998, contains dosage characterization information for cattle.

### B. Substantial Evidence:

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-068 dated July 24, 1998, contains a summary of studies that demonstrate effectiveness of the drug for cattle.

## III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-068 dated July 24, 1998, contains a summary of target animal safety studies for cattle.

## IV. HUMAN FOOD SAFETY:

### A. Toxicology:

The information in the Toxicology section (with the exception of the determination of the microbiological acceptable daily intake (ADI) and the confirmation of the final ADI as described in Section A.3 below) was previously described in the FOI Summary for NADA 140-828 dated October 4, 1996. That information is being provided again in this FOI Summary because approval of NADA 140-828 was withdrawn by the Agency on August 1, 2005 (70 FR 44105), for reasons not related to these studies.

#### 1. Summary of Toxicology Studies

##### a. Acute Oral Single Dose Studies in Rats, Mice, Rabbits, and Dogs: Report #73075

Study Dates: June 1984 to August 1984

Study Director: Dr. M. Schmidt, Bayer Institute of Technology, Wuppertal, Germany

Identity of Substance and Dosage Form: Technical drug substance, oral suspension

Species and Strain of Test Animals: Rats (Wistar), Mice (BOR:CFW1), Rabbits (Chinchilla), Dogs (Beagle)

Number of Animals of Each Sex in Each Group: Rats: 5, Mice: 5, Rabbits: 2, Dogs: 2

Levels and Duration of Dosing:
Rats: 630; 1,000; and 5,000 mg/kg – single day
Mice: 1,000; 2,000; 4,000; and 5,000 mg/kg – single day
Rabbits: 320; 500; 800; 1,200; and 2,000 mg/kg – single day
Dogs: 1,000 and 5,000 mg/kg – single day

Route of Drug Administration: Oral

Parameters Studied and Discussion of Results:

Clinical Signs: Observations for 14 days. Symptoms observed were reduced mobility, trembling, tonic convulsions, labored breathing, and staggering gait. Signs appeared as early as 15 minutes after exposure with some persisting for 10 days.

Gross Necropsy: Pulmonary congestion and hemorrhage were seen at necropsy.

Conclusions: Oral LD50's:
Male and Female Rats = >5,000 mg/kg
Male Mice = >5,000 mg/kg
Female Mice = 4,336 mg/kg
Male and Female Rabbits = ~500 to 800 mg/kg
Male and Female Dogs = Not established due to vomition

**b. 90-Day Oral Toxicity Study in Rats: Report #73194**

Study Dates: September 1984 to December 1984

Study Director: R.L. Kowalski, Miles Laboratories, Elkhart, Indiana

Identity of Substance and Dosage Form: Technical drug substance, incorporated into feed

Species and Strain of Test Animals: Rats (Sprague-Dawley)

Number of Animals of Each Sex in Each Group: 15

Levels and Duration of Dosing: 0; 500; 2,000; and 7,500 ppm for a minimum of 91 consecutive days

Route of Drug Administration: Oral

Parameters Studied and Discussion of Results:

Clinical Signs and Survival: No test article-related signs of toxicity and no deaths occurred.

Physical Examination: Weekly examinations, including direct ophthalmoscopy at termination, were not suggestive of any test article-related effect.

Body Weights: Statistically significant reduction in mean body weight was observed in males and females of the high-dose group.

Food Consumption: Feed intake was slightly increased for the high-dose animals.

Hematology: No treatment-related trends were observed in these parameters.

Clinical Chemistries: Total protein levels were significantly decreased for both sexes in the high-dose group after 6 and 13 weeks. Aspartate aminotransferase was decreased in the high-dose males after 6 and 13 weeks. A decrease in total bilirubin occurred in the high-dose males. A dose-dependent increase in inorganic phosphorous was reported in males and females after 13 weeks.

Urinalysis: There was a dose-dependent trend toward decreasing urine sodium output in males of the mid- and high-dose groups at 6 weeks and in females of the mid- and high-dose groups after 13 weeks.

Organ Weights: Heart weights were decreased in mid- and high-dose animals. Mean prostate weights were significantly lower in mid- and high-dose males. Liver weights were decreased at the high-dose levels.

Gross Pathology: Swollen external ears and distention of the cecum were primarily found in the high-dose animals.

Microscopic Pathology: Auricular chondropathy was observed in all groups including the controls, but appeared to be dose-related (1 control, 1 low-dose, 6 mid-dose, and 10 high-dose). Microscopic changes of questionable relationship to the test article were observed in the knee joints of 3 of 30 rats of the high-dose group. Microscopic changes occurred in the epididymides and testes of male rats from the high-dose group. These changes appeared to represent degenerating spermatids.

Conclusions: The no observed effect level (NOEL) for this study is 500 ppm (40 mg/kg body weight (BW)/day).

**c. 90-Day Oral Toxicity Study in Dogs: Report #73146**

Study Dates: September 1984 to December 1984

Study Director: M.C. Porter, Miles Laboratories, Elkhart, Indiana

Identity of Substance and Dosage Form: Technical drug substance, incorporated into feed

Species and Strain of Test Animals: Canine (Beagle)

Number of Animals of Each Sex in Each Group: 4

Levels and Duration of Dosing: 0; 320; 800; and 2,000 ppm for 91 consecutive days

Route of Drug Administration: Oral

Parameters Studied and Discussion of Results:

Clinical Signs and Survival: Scattered incidences of emesis and an aversion to the test diet were observed during the early phase in mid-dose and high-dose animals. No adverse effect upon physical condition or deaths occurred in test animals which were 12 to 13 months of age at initiation of the study.

Physical Examination: Conducted prior to treatment and at termination, including ophthalmoscopy. No adverse effects were observed.

Body Weights: Mean body weights (recorded at weekly intervals during the course of the study) were not affected.

Food Consumption: Diet consumption returned to normal after the initial aversion phase.

Hematology: No adverse effects were observed at the three evaluation times during the course of the study, including termination.

Clinical Chemistries: Evaluations were performed at three times, including termination. Serum globulin/total protein was decreased at the early stages, but returned to normal as the study progressed.

Urinalysis: Evaluations were performed at three times, including termination. No adverse effects were observed.

Organ Weights: Organ weights were within the normal historical range for the laboratory.

Gross Pathology: No drug-related effects were observed.

Microscopic Pathology: A high incidence of lipofuscin pigment was observed in the epithelial cells of the proximal convoluted tubules of the kidneys for the high-dose animals, but was mild in intensity. The initial ages of the dogs used on the study were beyond the sensitive periods for the development of joint or testicular lesions associated with quinolone compounds in growing animals.

Conclusions: No toxic effects were observed in this study, but a definitive conclusion was not established because the test animals were older than stated in the guidelines.

**d. Additional Subchronic Oral Toxicity Study in Dogs: Report #73775**

Study Dates: May 1986 to August 1986

Study Director: M.C. Porter, Miles Laboratories, Elkhart, Indiana

Identity of Substance and Dosage Form: Technical drug substance, incorporated into feed

Species and Strain of Test Animals: Canine (Beagle)

Number of Animals of Each Sex in Each Group: 4

Levels and Duration of Dosing: 0; 100; 320; and 2,500 ppm for 91 consecutive days

Route of Drug Administration: Oral

Parameters Studied and Discussion of Results:

Clinical Signs and Survival: Daily observations were conducted. No deaths occurred, but abnormal gait and/or posture was observed in the high-dose animals by the second week of the study.

Physical Examination: Physical examinations, including direct ophthalmoscopy, were conducted pre-treatment and at termination with the only finding described in the clinical signs section. Radiographic examination revealed that neither bone growth nor density was significantly affected.

Body Weights: Body weights (recorded at weekly intervals) and body weight gains were not significantly different for treated and control animals.

Food Consumption: Diet consumption (recorded daily) was not affected.

Hematology: Samples collected at 2 and 6 weeks as well as at termination showed no abnormal findings.

Clinical Chemistries: Evaluations performed at 2 and 6 weeks and at termination showed no abnormalities.

Urinalysis: Urine samples collected after weeks 2 and 6 and at termination had crystal formations in dogs receiving the high-dose treatment.

Organ Weights: Absolute and relative organ weights for treated animals did not differ significantly from those of controls, but testicular weights were higher in the treated animals.

Gross Pathology: Superficial erosions of articular cartilage surfaces were seen in all high-dose dogs and one mid-dose male with no joint lesions in the remaining mid-dose or low-dose animals.

Microscopic Pathology: Microscopically, the joint lesions were characterized by splitting of the articular cartilage surface and disorganization of chondrocytes. Necrosis and disintegration of hyaline cartilage was seen in some cases.

A marked variation occurred in the appearance of testes including stage of maturity, diameter of lumen of seminiferous tubules, and vacuolar changes in the lining cells of the tubules. One dog from the control group and three dogs from the mid-dose group had signs of testicular maturity as evidenced by the production of tail-containing spermatozoa. None of the low-dose or high dose animals had any evidence of tailed-spermatozoa. Three dogs from the control group and one each from the mid- and high-dose groups had immature testes that were characterized by small seminiferous tubules with little or no lumen containing a single layer of spermatogonial cells. Testes from four dogs, one each from the low- and high-dose groups and two from the mid-dose group, contained seminiferous tubules with dilated lumen and often more than a single layer of lining cells. The same finding, but less advanced, was seen in one dog of the control group. Vacuolar change in the apical parts of the spermatogonial cells occurred in two dogs of the low-dose group, three dogs of the high-dose group, and one control animal. The tubular morphology observed for the two low-dose and three high-dose animals appeared to be beyond the normal limits.

Conclusions: A NOEL of 100 ppm (equivalent to 3 mg/kg BW/day) was set for this study following conduction of additional subchronic dog studies.

**e. Additional Subchronic Oral Toxicity Study in Male Dogs: Report #73788**

Study Dates: June 1987 to September 1987

Study Director: M.C. Porter, Miles Laboratories, Elkhart, Indiana

Identity of Substance and Dosage Form: Technical drug substance, incorporated into feed

Species and Strain of Test Animals: Canine (Beagle)

Number of Animals of Each Sex in Each Group: 4 (males only)

Levels and Duration of Dosing: 0; 10; 20; 40; and 3,200 ppm for 92 consecutive days

Route of Drug Administration: Oral

Parameters Studied and Discussion of Results:

Clinical Signs and Survival: No deaths occurred. Overt indications of toxicity were limited to the musculoskeletal system in high-dose dogs.

Physical Examination: Observations for appearance and behavior, including ophthalmoscopy, were done daily and prior to termination. Abnormalities are described in the clinical signs section.

Body Weights: Body weights were recorded weekly. Body weight gains were not affected except in the high-dose animals during the first 5 weeks of the study.

Food Consumption: Diet consumption was similar for all groups, including controls.

Organ Weights: Absolute and relative testicular weights for treated animals did not differ meaningfully or in a dose-related manner from those of the controls.

Gross Pathology: Testes and epididymides were examined for all dogs at termination. No gross lesions or abnormalities were noted.

Microscopic Pathology: The microscopic appearance of the testes was variable due to stages of sexual maturity. All dogs were considered within normal physiologic limits except for one dog in the high-dose group which had distinct bilateral degenerative changes.

Conclusions: The NOEL for this study is 40 ppm (approximately 1.2 mg/kg BW per day).

**f. Additional Subchronic Toxicity Study in Male Dogs Followed by a 13-Week Withdrawal: Report #73789**

Study Dates: June 1987 to December 1987

Study Director: M.C. Porter, Miles Laboratories, Elkhart, Indiana

Identity of Substance and Dosage Form: Technical drug substance, incorporated into feed

Species and Strain of Test Animals: Canine (Beagle)

Number of Animals of Each Sex in Each Group: 4 (males only)

Levels and Duration of Dosing: 0, 10, and 40 ppm for 92 consecutive days

Route of Drug Administration: Oral

Parameters Studied and Discussion of Results:

Clinical Signs and Survival: No deaths occurred and no overt indications of toxicity were observed.

Physical Examination: No abnormalities were observed in examination at pretreatment and at termination which included ophthalmoscopy.

Body Weights: Body weight gains were not adversely affected.

Food Consumption: Diet consumption was similar for all groups including controls.

Organ Weights: Absolute and relative testicular weights for treated animals did not differ meaningfully or in a dose-related manner from those of controls.

Gross Pathology: No gross lesions were noted in the testes and epididymides.

Microscopic Pathology: No test article-related changes occurred in either testes or epididymides with both organs appearing normal and containing normal, mature spermatozoa.

Conclusions: The NOEL for this study is 40 ppm.

**g. Teratology (Segment II) Study in the Rat: Report #73159**

Study Dates: September 1984 to October 1984

Study Director: G.R. Clemens, Miles Laboratories, Elkhart, Indiana

Identity of Substance: Technical drug substance

Species and Strain of Test Animals: Rat (Charles River)

Number of Animals of Each Sex in Each Group: 28 (females only)

Levels and Duration of Dosing: 0, 50, 210, and 875 mg/kg for 10 consecutive days from the $6^{th}$ through the $15^{th}$ day of gestation

Route of Drug Administration: Oral gavage

Parameters Studied and Discussion of Results:

Maternal Survival and Signs of Toxicity: All dams survived and there were no remarkable observations attributable to the test article.

Food Consumption and Body Weights: Food consumption was significantly higher in the high-dose group, but overall weight gain was significantly reduced in that group.

Reproductive Performance: There were no statistically significant differences in any reproductive parameter for any test article group when compared with the control.

Fetal Parameters: Fetal weights for both males and females were significantly reduced for the high-dose group. Male and combined fetal weights were significantly reduced also for the mid-dose group. No gross morphological

external and visceral changes attributable to the test article were observed in the fetuses, but they were generally smaller in the high-dose group compared to the controls.

Skeletal Examination: There was no increase in incidence of common skeletal variations, but a statistically significant delay in ossification was observed in the mid- and high-dose groups which accompanied the overall reduction in body weights for these groups.

Conclusions: The NOEL for this study is 50 mg/kg BW per day.

**h. Embryotoxicity/Teratogenicity Study in the Rabbit: Report #73705**

Study Dates: Conducted in two phases: January 1986 and January 1989

Study Director: H. Becker, Research and Consulting Co., Itingen, Switzerland

Identity of Substance: Technical drug substance

Species and Strain of Test Animals: Rabbit (Chinchilla)

Number of Animals of Each Sex in Each Group: 16 (females only)

Levels and Duration of Dosing: 0, 1, 5, 25, and 75 mg/kg BW from Day 6 through Day 18 post-breeding

Route of Drug Administration: Oral gavage

Parameters Studied and Discussion of Results:

Maternal Survival and Signs of Toxicity: No treated dams died; one high-dose dam aborted on Day 19.

Food Consumption and Body Weights: Mean food consumption was similar for the three lower-dosed groups, but a statistically significant decrease was noted for the high-dose females. This group also had a slightly decreased body weight gain.

Reproductive Performance: No statistically significant differences were observed for the three lower-dosed groups. Treatment at the higher dose caused increased post-implantation loss.

Fetal Parameters: No differences occurred in mean body weights of fetuses in the treated groups. Malformations observed were considered to be incidental and within the normal spontaneous range.

Skeletal Examination: No test article or dose-related differences were evident and the stage of development in all groups was similar.

Conclusions: The NOEL for this study is 25 mg/kg BW per day.

**i. Specialized Male Fertility Study in the Rat: Report #73800**

Study Dates: May 1986 to December 1986

Study Director: G.R. Clemens, Miles Laboratories, Elkhart, Indiana

Identity of Substance and Dosage Form: Technical drug substance, incorporated into feed

Species and Strain of Test Animals: Rat (Sprague-Dawley)

Number of Animals of Each Sex in Each Group: 60 (males only)

Levels and Duration of Dosing: 0 and 7,500 ppm for 90 consecutive days

Route of Drug Administration: Oral

Parameters Studied and Discussion of Results:

The study design consisted of treating males for 90 days with interim sacrifices at 3, 6, 9, and 13 weeks. Fifteen males from each group were retained, placed on control diet, and then mated during the late treatment phase and at intervals during the recovery phase to non-treated females. The females were terminated on Day 20 of gestation and evaluated for reproductive indices.

Clinical Signs and Survival: There were no overt effects on appearance and/or behavior of the males during the study

Food Consumption and Body Weights: Feed consumption and body weight gain were significantly decreased during the exposure period with both returning to normal by the end of the recovery period.

Male Breeding Performance: Libido was unaffected, but a significant decrease occurred in fertility.

Male Testes/Weights and Histopathology: There was an increase in mean testicular weight during the treatment period, but by the end of the recovery period, the weights were significantly less than the controls. Epididymidal weights for the test article group were lower than the control group throughout the study. Abnormal sperm were observed in the treated animals after Week 3, but a nearly complete reversal of this change occurred during the recovery period.

Female Reproductive Performance: An adverse effect was seen on fertility of the untreated females at the initial mating (last 2 weeks of treatment phase), but during each successive breeding, fertility improved and was judged to return to normal by the $7^{th}$ week of the recovery phase.

Conclusions: The treatment of 7,500 ppm caused a marked reduction in male fertility due to the adverse effect on sperm development. Functional fertility

returned to normal for 13 of the 15 males during the withdrawal period, but two continued to have complete bilateral testicular atrophy and subsequent infertility.

**j. 90-Day Feeding Study Followed by a 13-Week Withdrawal in Male Rats: Report #73812**

Study Dates: June 1987 to December 1987

Study Director: J.J. Bare, Miles Laboratories, Elkhart, Indiana

Identity of Substance and Dosage Form: Technical drug substance, incorporated into feed

Species and Strain of Test Animals: Rat (Sprague-Dawley)

Number of Animals of Each Sex in Each Group: 135 (males only)

Levels and Duration of Dosing: 0; 125; 500; and 7,500 ppm for 91 consecutive days

Route of Drug Administration: Oral

Parameters Studied and Discussion of Results:

The study design consisted of treating males for a period of 91 days with a subgroup receiving 7,500 ppm terminated after 14 days on the diet. Fifteen animals from each group were terminated after 91 days. The remaining animals were maintained on a control diet for another 90 days and then terminated. Testes and epididymides were evaluated.

Clinical Signs and Survival: One low-dose animal died, but no other deaths occurred. No signs of toxicity were observed.

Body Weights: There was no effect on weight gain in the low or mid-dose groups. The high-dose animals had a statistically significant decrease in body weight gain during the treatment phase, but gained weight rapidly during the reversible phase.

Physical Examination: All animals appeared to be in good physical condition.

Histopathology: Abnormal spermatozoa were present in the testes of 10 of the 15 high-dose rats terminated at Day 14. At the end of the withdrawal period, no abnormal spermatozoa were detected in the testes, but bilateral testicular atrophy was seen in two high-dose males.

Organ Weights: At both terminations, a dose-dependent decrease in mean epididymal weights occurred which was statistically significant in the mid- and high-dose groups. There was a significant increase in weight of testes in the high-dose group at the Day 91 sacrifice.

Conclusions: The NOEL for this study is 125 ppm (approximately 9.9 mg/kg BW per day).

**k. Two-Generation Reproduction Study in Rats: Report #73314**

Study Dates: November 1984 to August 1985

Study Director: G.R. Clemens, Miles Laboratories, Elkhart, Indiana

Identity of Substance and Dosage Form: Technical drug substance, incorporated into feed

Species and Strain of Test Animals: Rat (Sprague-Dawley)

Number of Animals of Each Sex in Each Group: 120 in the $F_0$ generation

Levels and Duration of Dosing: 0; 500; 2,000; and 7,500 ppm for two generations

Route of Drug Administration: Oral

Parameters Studied and Discussion of Results:

Clinical Observations: No overt toxicity signs were observed at any dietary concentration. General behavior and appearance was essentially normal for the $F_0$ and $F_1$ generations. Swollen pinnae were reported in both the $F_0$ and $F_1$ generations.

Body Weight and Food Consumption: Body weights for the high-dose males and females of the $F_0$ and $F_1$ generations were significantly reduced during most of the study. A significant reduction in food intake for the $F_0$ and $F_1$ generation was seen in the high-dose males.

Reproductive Performance of $F_0$ and $F_1$ Males: Libido was unaffected and breeding performance was considered favorable for males of both generations.

Reproductive Performance of $F_0$ and $F_1$ Females: No meaningful alteration occurred in any reproductive parameter for dams exposed to 500 ppm or 2,000 ppm of test article in the diet. There was a marked reduction in reproductive performance in the dams receiving 7,500 ppm level. The parameters affected included increased gestation length, pregnancy rates, total pups born, litter size, number of implantations, and birth index. These parameters were significantly reduced in the high-dose group.

Neonatal Growth and Development: There was no increase in the number of still births for any dose group from either generation when compared to the controls. The high-dose level had significantly reduced neonatal survival and neonatal weight gains during lactation. Unilaterally, small testes were reported.

Microscopic Pathology: No changes occurred in the female reproductive tissues. Spermatic morphological alterations were seen in the high-dose males from both generations. Cecal dilatation, unilateral testicular atrophy, and reduced prostatitis were observed in the various treatment groups. Histopathological evaluations of the pinnae were not conducted.

Conclusions: The NOEL for this study is 2,000 ppm (165 mg/kg BW per day).

**l. Additional Two-Generation Reproduction Study in Rats: Report #73892**

Study Dates: May 1986 to February 1987

Study Director: R.L. Kowaski, Miles Laboratories, Elkhart, Indiana

Identity of Substance and Dosage Form: Technical drug substance, incorporated into feed

Species and Strain of Test Animals: Rat (Sprague-Dawley)

Number of Animals of Each Sex in Each Group: 120 in the $F_0$ generation

Levels and Duration of Dosing: 0; 125; 300; and 2,000 ppm for two generations

Route of Drug Administration: Oral

Parameters Studied and Discussion of Results:

Clinical Observations: No adverse behavioral effects or signs of toxicity were attributed to the test article at any of the three concentrations.

Food Consumption: Food consumption was not affected by consumption of the test substance.

Reproductive Performance of Males: Male libido was unaffected by the dietary intake of the test compound.

Reproductive Performance of Females: No effects occurred upon performance. Estrus cycle and fertility in general (pregnancy rates, implantation, and litter size) for animals of the treated groups compared favorably with those of the controls.

Neonatal Growth and Development: No meaningful alterations occurred in neonatal development at any of the exposure levels. There was a slight, but significant decrease in body weight gain in the $F_2$ generation.

Microscopic Pathology: The only definite test article-related change was seen in the testes and epididymides of mid- and high-dose $F_0$ and $F_1$ males. The change was characterized as abnormal spermatozoa.

Organ Weights: Epididymal weights of the high-dose groups were decreased in both the $F_0$ and $F_1$ generation with the variation in the $F_1$ being statistically significant.

Conclusions: The NOEL for this study is 125 ppm.

**m. Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay: Report #73055**

Study Dates: July 1984 to October 1984

Study Director: M.A. Cifone, Litton Bionetics, Kensington, Maryland

Identity of Substance: Technical drug substance

Species and Strain of Test Animals: Rat (Fischer)

Number of Animals of Each Sex in Each Group: Not Applicable

Levels and Duration of Dosing: 1 µg/mL to 500 µg/mL

Route of Drug Administration: Cell culture perfusion

Parameters Tested and Discussion of Results:

The test material did not induce significant changes in the nuclear labeling of primary rat hepatocytes for an applied concentration range of 1 µg/mL to 200 µg/mL. Treatment with 500 µg/mL was lethal. There was no dose-related response according to the criteria used to evaluate unscheduled DNA synthesis (UDS).

Conclusions: The test material was negative in the Primary Rat Hepatocyte UDS Assay under the conditions tested.

**n. Mammalian Cell Chromosomal Aberration Mutagenicity Assay: Report #74165**

Study Dates: December 1987 to June 1988

Study Director: R. Taalman, Hazleton Biotechnologies, Veenendaal, Netherlands

Identity of Substance and Dosage Form: Technical drug substance, *in vitro*

Species and Strain of Test Animals: Chinese Hamster Ovary Cells (CHO-WBI)

Number of Animals of Each Sex in Each Group: Not Applicable

Levels and Duration of Dosing:
Non-activated: 25, 50, 100, and 250 µg/mL
Activated: 1, 100, 250, and 500 µg/mL

Route of Drug Administration: Infusion into cell culture

Parameters Tested and Discussion of Results:

Duplicate Chinese Hamster Ovary Cell cultures were used to measure chromosomal aberrations in presence and absence of a metabolic activation system.

The test article was considered positive for chromosomal aberration induction under the non-activation conditions. In the activation part of the assay, the test article did not exhibit clastogenic activity assessed by lack of chromosomal aberrations.

Conclusions: The test material was positive for mutagenic activity in this assay.

**o. Rat Bone Marrow Chromosomal Aberration Mutagenicity Assay: Report #74166**

Study Dates: July 1986 to November 1986

Study Director: J. Boatman, Life Science Research Limited, Suffolk, England

Identity of Substance and Dosage Form: Technical drug substance, suspension

Species and Strain of Test Animals: Rat (CD)

Number of Animals of Each Sex in Each Group: 5 and/or 15

Levels and Duration of Dosing: 0; 40; 200; and 1,000 mg/kg; single dose

Route of Drug Administration: Oral gavage

Parameters Tested and Discussion of Results:

The effect of enrofloxacin on chromosomal structure was investigated in bone marrow cells of the rat following acute oral administration. Two hours before the surviving animals were sacrificed, bone marrow cell division was arrested at metaphase by the administration of a spindle poison. At termination, bone marrow cells were harvested and metaphase chromosome spreads were prepared on microscope slides. The mitotic index was calculated for each animal, giving an indication of the gross toxicity affecting the division of bone marrow cells. Fifty metaphases were examined from each animal and all observed chromosomal aberrations were recorded.

Conclusions: This assay was sensitive to the positive control chlorambucil, but no significant damage to chromosomal structure in rat bone marrow was seen following administration of the test article. Enrofloxacin was negative in the Rat Bone Marrow Chromosomal Aberration Mutagenicity Assay under the conditions tested.

**p. Salmonella/Microsome Assay to Evaluate for Point-Mutagenic Effects (Ames Test): Report #72213**

Study Dates: November 1984 to December 1984

Study Director: B. Herbold, Institute of Toxicology, Wuppertal, Germany

Identity of Substance and Dosage Form: Technical drug substance, agar/bacterial cell culture

Species and Strain of Test Animals: *Salmonella typhimurium* (LT-2); TA 1535, TA 100, TA 1537, TA 98

Number of Animals of Each Sex in Each Group: Not Applicable

Levels and Duration of Dosing: 8; 40; 200; and 1,000 µg per plate

Route of Drug Administration: Agar/plate inoculation

Parameters Tested and Discussion of Results:

The test article was tested in the Ames Assay for the induction of bacterial mutation using four histadine-auxotrophs of *Salmonella typhimurium*. The drug concentrations were evaluated with and without the S-9 metabolic activator. Positive controls were used.

Conclusions: The Agency concluded that this microbial assay did not satisfy the criteria for a valid test to assess the mutagenicity of an antimicrobial compound.

**q. Study of Chronic Toxicity and Carcinogenicity in Mice: Report #74229**

Study Dates: October 1986 to October 1988

Study Director: E. Bomhard, Institute of Toxicology, Wuppertal, Germany

Identity of Substance and Dosage Form: Technical drug substance, incorporated into feed

Species and Strain of Test Animals: Mouse (B6C3F1)

Number of Animals of Each Sex in Each Group: 50

Levels and Duration of Dosing: 0; 1,000; 3,300; and 10,000 ppm for 24 months

Route of Drug Administration: Oral

Parameters Studied and Discussion of Results:

Ten additional mice of both sexes were assigned per treatment, plus 10 of each sex at 20,000 ppm for interim sampling at 12 months.

Inspection of Animals: The body surfaces, orifices, eyes, general behavior, posture, breathing, and excretion products of the treated animals did not show any unusual features compared to the controls.

Ophthalmological Investigations: There was no evidence of treatment-induced damage to the eyes in the groups receiving up to and including 3,300 ppm at the end of the study. The females in the 10,000 ppm group showed clearly elevated incidence of focal lenticular opacity. No histological correlation could be assigned to the effect.

Mortality: A slightly higher increase in mortality of the males in the 3,300 ppm group and females in the 10,000 ppm group was observed.

Body Weights: Body weights were determined once a week. The animals in the two lower dosed groups had significantly higher body weights than the controls; the 10,000 ppm group occasionally had higher body weights, and the 20,000 ppm group had body weights comparable to the controls.

Food Consumption: Intake was monitored once a week. There was no difference in the groups receiving up to and including 10,000 ppm when compared to the controls.

Hematology: The total white blood cell counts were decreased in the 3,300 and 10,000 ppm groups for the males and in the 3,300 ppm group for the females. Significantly lower hemoglobin, hematocrit, MCV, and MCH values were seen at the 10,000 ppm level.

Clinical Chemistries: Samples obtained after 12 and 24 months showed lower alkaline phosphatase levels at the 3,300 and 10,000 ppm levels. A dose-dependent trend was observed in total protein values with the reduction in total plasma protein attributed to a decrease in the globulin fraction.

Gross Pathology: No specific findings were observed at the 12-month sacrifice. After 24 months, a dose-dependent increase in the incidence of cecal dilation was observed. Males treated at 1,000 ppm; 3,300 ppm, and 10,000 ppm had an incidence of 4.0%, 42.0%, and 82.0% respectively. Females had an incidence of 26.0% at 3,300 ppm and 64.0% at 10,000 ppm.

Organ Weights: No changes occurred in absolute or relative organ weights except for increases in female kidneys receiving 10,000 ppm.

Microscopic Pathology: On histopathological examination, there was neither an increase in the incidence nor a decrease in the time of appearance of tumors in the dosed groups compared to the controls. Intrahepatic bile-duct changes were detected in the 3,300 and 10,000 ppm dose groups. Focal papillary mucosal hyperplasia in the gall bladder was observed in the 3,300 ppm males and the 10,000 ppm females.

Conclusions: A NOEL of 1,000 ppm (323 mg/kg BW/day) was determined for all effects. There was no evidence of carcinogenic effects in mice dosed with 1,000 to 10,000 ppm enrofloxacin for two years.

**r. Study of Chronic Toxicity and Carcinogenicity in Rats: Report #74230**

Study Dates: August 1986 to September 1988

Study Director: E. Bomhard, Institute of Toxicology, Wuppertal, Germany

Identity of Substance and Dosage Form: Technical drug substance, incorporated into feed

Species and Strain of Test Animals: Rat (Wistar)

Number of Animals of Each Sex in Each Group: 60

Levels and Duration of Dosing: 0; 770; 2,000; and 6,000 ppm for 105 weeks

Route of Drug Administration: Oral

Parameters Studied and Discussion of Results:

Ten additional rats of both sexes were assigned to the above stated treatments, plus 10 of each sex at 10,000 ppm for interim sampling at 12 months.

Inspection of Animals: The body surfaces, orifices, general behavior, posture, breathing, and excretion products of the treated animals did not show any unusual features compared to the controls.

Ophthalmological Investigations: No evidence of treatment-induced changes in the refractile media, the ocular fundus, or the pupillary reflex after one year and at the end of the study.

Mortality: Mortality increased in both males and females at the 6,000 ppm level.

Body Weights: The body weight development of males was highly retarded at the 10,000 ppm level with a slight retardation at 6,000 ppm. Slight growth reduction was recorded for females at 10,000 ppm. Body weights were recorded weekly until Week 13 and then every 2 weeks.

Food Consumption: Intake was monitored once a week. There was a significant increase in food consumption for both males and females at the 10,000 ppm level. Levels up to and including 6,000 ppm did not differ appreciably from the controls.

Hematology: Investigations were carried out after 6, 12, and 18 months and at the end of the study. Leukopenia was seen in the 770 to the 10,000 ppm groups for both males and females. Temporarily decreased erythrocyte, hemoglobin, hematocrit, and MCV values were observed at the higher doses.

Clinical Chemistries: Samples were obtained from 6, 12, and 18 months and at the end of the study. Total protein was significantly decreased in males at all doses and at all sampling intervals. Total protein decreases were less for females.

Urinalysis: Analysis was performed at 6 month intervals. Overall, the results indicated that the test substance did not lead to toxicologically relevant kidney damage.

Gross Pathology: A statistically significant increase in the incidence of hepatic cysts was found in both sexes treated with 2,000 and 6,000 ppm, and a biologically significant increase in males treated with 770 ppm. Both sexes showed a significant increase in the incidence of dilated cecum after treatment with 6,000 ppm. Size of testes was reduced and consistency altered in male treatments at 2,000 to 10,000 ppm.

Organ Weights: Absolute and relative liver weights were decreased in males at 2,000 ppm and above. The same changes were seen in the females at the interim, but not at the study termination. In the 6,000 ppm males, absolute weights of the brains, testes, and adrenals were significantly decreased, but the relative weights were no different than the controls.

Microscopic Pathology: The incidence of bile duct hyperplasia in the liver increased in a dose-related manner in all treatment groups and both sexes. Sclerotic changes were statistically significant from 770 ppm in the males and from 2,000 ppm in females. Cystic bile duct hyperplasia increased with drug exposure from 770 ppm in the males and 2,000 ppm in females. A marked increase in the incidence of cardiomyopathy was seen in males at the 6,000 ppm dose and in females dosed at 770 ppm and above. There was also a significant increase in the number of subendocardial proliferative lesions in males and females at the highest dose, as well as an elevated number of subendocardial mesenchymal tumors. There was a marked increase in the number of sarcolemmal nuclei in skeletal muscles of animals at the 6,000 ppm treatment. This lesion is generally associated with degenerative changes in the muscle fibers. Marked degenerative changes were also noted in the sciatic nerve. Fewer females in the treated groups showed mammary alveolar development and milk secretions than the control animals.

Conclusions: A NOEL was not established for this study due to the incidence of bile duct hyperplasia and cardiomyopathy. There was no evidence of carcinogenic effects in rats dosed with 770 to 6,000 ppm of enrofloxacin for two years.

**s. Chronic Toxicity Study in Rats after Administration in Feed Over a Period of Two Years: Report #74387**

Study Dates: July 1989 to July 1991

Study Director: K. Leser, Institute of Toxicology, Wuppertal, Germany

Identity of Substance and Dosage Form: Technical drug substance, incorporated into feed

Species and Strain of Test Animals: Rat (Wistar)

Number of Animals of Each Sex in Each Group: 50

Levels and Duration of Dosing: 0, 100, and 500 ppm for 24 months

Route of Drug Administration: Oral

Parameters Studied and Discussion of Results:

Histological evaluation was limited to the heart and liver. Additionally, 10 rats of each sex per group were used for an intermediate necropsy after 12 months.

Inspection of Animals: Twice daily observations with a detailed inspection once a week did not detect abnormalities in body surfaces, orifices, general behavior, posture, respiration, or excreta.

Ophthalmological Investigations: There was no evidence of any treatment-related changes after one year or at the end of the study.

Mortality: No statistically significant differences were observed compared to the controls.

Body Weights: Weights were recorded weekly. Treated rats had comparable gains compared to the corresponding controls.

Food Consumption: Feed intake was determined on individual animals weekly until Week 13 and then every 4 weeks. There were no significant differences compared to the controls.

Hematology: Investigations were conducted after 6, 12, 18, and 24 months on 10 rats per group. There was no evidence of treatment-related damage.

Clinical Chemistries: Samples were evaluated at 6, 12, 18, and 24 months. No correlation was observed between parameter values and dose or time in the study period.

Urinalysis: Analysis was performed on 10 rats per dose per sex at 27, 52, 79, and 104 weeks. No effects of toxicological significance were reported.

Gross Pathology: No abnormalities were noted at the interim sacrifices. A trend toward an increased number of swollen livers was observed in males at final necropsy.

Organ Weights: No toxicological significance was attached to the differences observed.

Microscopic Pathology: Sclerotic bile duct hyperplasia was more common in treated males and females than in the control animals. The incidence increased in males after 52 and 104 weeks of treatment at 100 and 500 ppm dose levels. By 104 weeks, there were as many affected males in the 100 ppm dose group and the lesions were of equal severity. As the incidence at 52 weeks is approximately the same as at 104 weeks, it can be concluded that treatment accelerates the development of bile duct sclerosis in male rats. In females, there was an increased incidence of bile duct hyperplasia at 104 weeks in the 500 ppm group. The average severity increased in both the 100 and 500 ppm dose levels when compared to the control females. The total number of females affected was markedly less than the number of males. No evidence of carcinogenicity was seen in the hearts or livers in this study.

Conclusions: A NOEL was not seen in this study due to the significant increase in bile duct hyperplasia in all treated males. However, the Agency established a NOEL at 100 ppm after considering the spectrum of data from all of the chronic rat studies and opinions submitted to CVM. The 100 ppm NOEL corresponds to doses of 5.3 and 7.2 mg enrofloxacin/kg BW per day for male and female rats, respectively.

**t. Evaluation of Bile Duct Hyperplasia in Male Rat Livers: Report #74388**

Study Completion: May 1992

Study Director: R. Squire, John Hopkins School of Medicine, Baltimore, Maryland

Identity of Substance and Dosage Form: Technical drug substance, incorporated into feed

Species and Strain of Test Animals: Rat (Wistar)

Number of Animals of Each Sex in Each Group: 50

Levels and Duration of Dosing: 0, 100, and 500 ppm for 24 months

Route of Drug Administration: Oral

Parameters Studied and Discussion of Results:

Dr. Squire conducted a second and independent histological evaluation of the liver slides for the male rats from both the interim and terminal kills for the previously described Study No. 74387. This assessment was arranged and conducted at the request of Bayer. The conclusions were: “There was an increase over controls in the incidence of bile duct hyperplasia in both dose groups at the interim kill, although this was probably a spurious finding. At the terminal kill, an increased incidence occurred only at the 500 ppm level. No clear effect on lesion severity was noted in any group. The 100 ppm dose was a no-effect level in this study”.

**u. Chronic Toxicity Study in Rats with Administration in Feed Over a Period of Two Years: Report #74472**

Study Dates: April 1991 to April 1993

Study Director: K. Leser, Institute of Toxicology, Wuppertal, Germany

Identity of Substance and Dosage Form: Technical drug substance, incorporated into feed

Species and Strain of Test Animals: Rat (Wistar)

Number of Animals of Each Sex in Each Group: 50

Levels and Duration of Dosing: 0, 10, and 50 ppm for 24 months

Route of Drug Administration: Oral

Parameters Studied and Discussion of Results:

Histological evaluation was limited only to the liver. An additional 10 rats per group received the test substance in the same doses and were used for an interim necropsy after 12 months.

Inspection of Animals: Observations were conducted twice daily with a detailed inspection once a week. There were no treatment-related increases in the incidence of unusual findings.

Ophthalmological Investigations: The examination yielded no evidence of any treatment-induced changes after 1 or 2 years of treatment.

Mortality: No influence of the test drug on mortality was suggested by the numbers of rats that died or by their distribution between the individual treatment groups.

Body Weights: Weights were recorded once a week. Treated rats had comparable weights to the controls.

Food Consumption: Feed intake was determined once a week until Week 13 and then every 4 weeks. Quantities consumed were not substantially different from the values in the control rats.

Hematology: Samples were obtained on 10 rats per group after Weeks 27, 79, and 104. The investigations yielded no evidence of damage to red or white blood cell parameters in either sex at any time.

Clinical Chemistries: No treatment-related changes were reported.

Urinalysis: Analysis was performed on 10 rats per dose per sex at the intervals stated for hematology investigations with no findings of toxicological significance.

Gross Pathology: There was no evidence of any treatment-related damage in the rats dying spontaneously, after 12 months or at the end of the study.

Organ Weights: No significant differences were seen in either absolute or relative organ weights.

Microscopic Pathology: Histological readings were conducted on one part of the left hepatic lobe and one part of the right hepatic lobe. The incidence and severity of bile duct hyperplasia in the treated female and male rats was comparable with the control.

Conclusions: No apparent treatment-related effects were noted in Wistar rats administered 10 or 50 ppm of enrofloxacin in the feed.

**v. Pathology Working Group on a Two-Year Chronic Feeding Study with One-Year Interim Kill in Rats on the Compound Bay Vp 2674**

This assessment by the Pathology Working Group was arranged and conducted at the request of the Agency. It included a review of the heart tissues from all the rats of the chronic study conducted by Bayer (Report No. 74230).

Report Date: November 1992

Study Director: W. Hall, V.M.D., Ph.D., Pathology Associates, Inc., Frederick, Maryland

Conclusions: The endocardial neoplasms and Schwann cell-like hyperplasia were not considered by the Pathology Working Group to be treatment-related for the following reasons:

a) the incidence of endocardial neoplasia in male and female rats was not statistically significant ($P > 0.05$) [the statistically positive trend in endocardial neoplasia in females was not considered to be biologically significant by the Pathology Working Group because of the low numbers (0/50 controls vs. 3/50 high-dose) and the reduced incidence in controls compared to historical data];

b) the incidence in endocardial neoplasms seen in dosed male rats compared with controls did not increase with higher doses;

c) the incidence of endocardial Schwann cell-like hyperplasia was low and did not support an increased incidence of endocardial neoplasia in high-dose rats [the statistically positive trend in Schwann cell-like hyperplasia in males and females was not considered to be biologically significant by the Pathology Working Group because of the low numbers (0/48 or 50 controls vs. 2/50 high-dose)]; and

d) all other endocardial hyperplastic lesions were considered to be reactive in nature in response to an underlying myocardial lesion.

**2. Determination of No Observed Effect Level (NOEL) for chronic exposure.**

The safe concentrations of total residues of enrofloxacin were determined from the lowest NOEL in the most sensitive species tested in the various toxicology studies conducted. Studies considered in establishing the Acceptable Daily Intake (ADI) are summarized below.

Table 1. Summary of studies conducted to establish the ADI.

| Study | Study Number | No-Observed Effect Level (NOEL) |
|---|---|---|
| Subchronic Oral Toxicity in Dogs | No. 73775 | 3 mg/kg |
| Chronic Toxicity and Carcinogenicity Study in Mice | No. 74229 | 323 mg/kg |
| Chronic Toxicity in Rats | No. 74387 | 5.3 mg/kg |
| Two-Generation Rat Reproductive Toxicity Study | No. 73892 | 125 mg/kg |
| Embryotoxicity/Teratogenicity Study in the Rabbit | No. 73705 | 25 mg/kg |

The Agency concluded that under the given exposure conditions in the two-year rodent studies, a significant increased frequency or distribution of tumors were not noted. The Subchronic Oral Toxicity Study in Dogs (Study No. 73775) was concluded to be the most appropriate study (based upon the lowest NOEL) to determine the ADI. The NOEL for establishing the ADI is 3 mg/kg BW/day.

**3. Acceptable Daily Intake (ADI)**

General Toxicology ADI

$$\text{Acceptable Daily Intake (ADI)} = \frac{\text{Lowest NOEL}}{\text{Safety Factor}}$$

A safety factor of 1000 was used because the NOEL was from a subchronic study.

$$\text{The lowest NOEL is 3 mg/kg, so the ADI} = \frac{3\ \text{mg/kg BW/day}}{1000}$$

$$= 0.003\ \text{mg/kg BW/day}$$

Microbiological ADI

A microbiological ADI was determined following the recommendations in FDA GFI #159 "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI". Of the two

endpoints of health concern, a microbiological ADI was determined for "disruption of the colonization barrier". The ADI for disruption of the colonization barrier is 34.65 mcg/kg BW/day or 2.08 mg/person/day.

The studies performed for determining the microbiological ADI for disruption of the colonization barrier were the following:

- A Minimum Inhibitory Concentration (MIC) study performed with enrofloxacin against the recommended representative bacteria of the human intestinal flora (Study No. DWS/014/96). The data from this study was used to calculate the $MIC_{calc}$ to be applied in the formula recommended in GFI #159.
- An *in vitro* fecal binding study performed by incubating selected concentrations of enrofloxacin with increasing concentrations of sterilized feces collected from three different donors for time periods between 0 and 12 hours (Study No. DWS/020/04). The data from this study showed that approximately 2% of enrofloxacin active residues remain available for interaction with the colonic flora. This value was applied to the formula recommended in GFI #159.

The studies used to address the need for determining an ADI for the endpoint of increase in the population of resistant bacteria in the human colon were preliminary *in vitro* susceptibility studies performed in a fed batch culture model of the human colonic flora. The test system containing fecal slurries from healthy human volunteers was subjected to extended exposure of enrofloxacin residue concentrations to study the prevalence and susceptibility of *Bacteroides fragilis* group (BfG, target bacteria selected for addressing this endpoint). The data from these studies showed that non-susceptible BfG are already present in feces of a number of human volunteers (Study No. DWS #021/04). Therefore, because of (a) the results of the baseline susceptibility studies in human volunteers; (b) the potential minimal impact of a low free drug concentration on the development of novel resistant BfG and (c) relevant published data, it was determined that there was no need to pursue a microbiological ADI for the endpoint of increase in the population of resistant bacteria in the colon.

Consequently, the microbiological ADI for enrofloxacin residues is 34.65 mcg/kg BW/day or 2.08 mg/person/day. Since the microbiological ADI is higher than the general toxicological ADI, the final ADI for enrofloxacin residues is the general toxicological ADI (0.003 mg/kg BW/day or 0.18 mg/person/day).

**4. Safe Concentrations (SC) for Total Residues**

The calculation of the SCs is based on the General Principles for Evaluating the Safety of Compounds used in Food-Producing Animals (FDA/CVM, revised July 1994).

$$\text{Safe Concentration (SC)} = \frac{\text{Acceptable Daily Intake (ADI) x Human Weight}}{\text{Consumption Value}}$$

The average human weight is approximately 60 kg. The daily consumption values of edible tissues of cattle are approximated as 300 g for muscle, 100 g for liver, 50 g for kidney, and 50 g for fat.

$$\text{SC (muscle)} = \frac{.003 \text{ mg/kg BW/day x 60 kg BW}}{0.3 \text{ kg/day}} = 0.6 \text{ mcg/kg} = 0.6 \text{ ppm}$$

$$\text{SC (liver)} = \frac{.003 \text{ mg/kg BW/day x 60 kg BW}}{0.1 \text{ kg/day}} = 1.8 \text{ mcg/kg} = 1.8 \text{ ppm}$$

$$\text{SC (kidney)} = \frac{.003 \text{ mg/kg BW/day x 60 kg BW}}{0.05 \text{ kg/day}} = 3.6 \text{ mcg/kg} = 3.6 \text{ ppm}$$

$$\text{SC (fat)} = \frac{.003 \text{ mg/kg BW/day x 60 kg BW}}{0.05 \text{ kg/day}} = 3.6 \text{ mcg/kg} = 3.6 \text{ ppm}$$

## B. Residue Chemistry:

### 1. Summary of Residue Chemistry Studies

Total residue depletion, metabolism, comparative metabolism, and residue depletion data have been summarized in the FOI Summary for the original approval of NADA 141-068 dated July 24, 1998.

### 2. Target Tissue and Marker Residue Assignment

The marker residue is desethylene ciprofloxacin and the target tissue in cattle is liver (See FOI Summary for NADA 141-068 dated July 24, 1998).

### 3. Tolerance Assignments

A tolerance of 0.1 ppm for desethylene ciprofloxacin has been established in the liver of cattle (See FOI Summary for NADA 141-068 dated July 24, 1998).

### 4. Withdrawal Time

A withdrawal period of 28 days is assigned for both uses of the 10% enrofloxacin injectable solution, either as a single subcutaneous dose of 7.5 mg/kg to 12.5 mg/kg, or as a multiple dose subcutaneous treatment at up to 5 mg/kg for up to 5 days (see FOI Summary for NADA 141-068 dated July 24, 1998). These same withdrawal periods apply to female dairy cattle under 20 months of age.

## C. Microbial Food Safety:

This supplemental approval allows for a modification to the label of approved enrofloxacin (as BAYTRIL 100) 100 mg/mL injectable solution for treatment of bovine respiratory disease. The supplement allows for the restriction reading, "Do not use in cattle intended for dairy production." to be changed to read, "Do not use in female dairy cattle 20 months of age or older. Use of enrofloxacin in this class of cattle may cause milk residues." The current supplement allows for those therapeutic claims already established for beef cattle to be applied to dairy cattle less than 20 months of age.

The sponsor provided a hazard characterization and microbial food safety qualitative risk assessment addressing potential human illness caused by fluoroquinolone-resistant *Campylobacter* spp., *Salmonella* spp., or multi-drug resistance (MDR) *Salmonella* spp. attributable to consumption of contaminated ground beef, followed by treatment with a human antibiotic of the fluoroquinolone class.

The qualitative risk assessment included a release assessment to describe the probability that enrofloxacin and its use in the dairy farm environment will result in emergence or selection of resistant *Campylobacter*, *Salmonella*, and MDR *Salmonella* attributed to the proposed use of enrofloxacin in dairy heifers; an exposure assessment to describe the likelihood of human foodborne exposure to *Campylobacter*, *Salmonella*, and MDR *Salmonella* following consumption of ground beef from treated dairy heifers, and a consequence assessment to describe potential human health consequences arising from exposure to the defined foodborne pathogens or resistance determinants by considering the human medical importance of fluorquinolones in the treatment of human gastrointestinal diseases.

Based upon the Agency's evaluation of the information submitted by the sponsor, and in consideration of the current fluoroquinolone and quinolone susceptibility profiles of *Salmonella spp*., *E.coli*, and *Campylobacter spp*., including their prevalence in the food commodity of concern (ground beef) and target animal (dairy cattle), and taking into considerations the proposed use conditions of BAYTRIL 100 in female dairy cattle under 20 months of age, the overall risk of enrofloxacin use in female dairy cattle less than 20 months of age is high. This estimation was based on individual rankings of the outcomes of the components of the qualitative risk assessment: medium for the release assessment, medium for the exposure assessment, and high for the consequence assessment. The ranking of high for the consequence assessment is based on the medical importance of fluoroquinolone (Table A1, GFI #152). Since ciprofloxacin, an analogue of enrofloxacin, is the empiric drug of choice to treat a majority of clinical gastrointestinal infections, the drug is currently ranked as critically important to human medicine. The overall risk estimation for the proposed use of enrofloxacin in female dairy cattle less than 20 months of age is adequately addressed by the Agency's **Category 1** risk management strategies: prescription only marketing status, injectable, limited number of animals – treated individually, monitoring by the National Antimicrobial Resistance System.

Conclusions regarding microbial food safety for enrofloxacin (as BAYTRIL 100) 100 mg/mL injectable solution presented here apply only to the proposed supplement allowing for the use of enrofloxacin (as BAYTRIL 100) 100 mg/mL injectable solution in female dairy cattle under 20 months of age, and are not applicable to any other NADAs (including supplements) containing enrofloxacin without further assessment.

### D. Analytical Method for Residues:

The FOI Summary for the original approval of NADA 141-068 dated July 24, 1998, contains the analytical method summaries for enrofloxacin in cattle.

## V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to BAYTRIL 100:

**For use in animals only. Keep out of the reach of children.** Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following ocular or dermal exposures. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight. For customer service or to obtain product information, including a Material Safety Data Sheet, call 1-800-633-3796. For medical emergencies or to report adverse reactions, call 1-800-422-9874.

## VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514. The data demonstrate that BAYTRIL 100, when used according to the label, is safe and effective for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* (previously *Haemophilus somnus*) in beef and non-lactating dairy cattle. Additionally, data demonstrate that residues in food products derived from beef and non-lactating dairy cattle treated with BAYTRIL 100 will not represent a public health concern when the product is used according to the label.

### A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). This decision was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product to treat BRD, and (b) restricting this drug to use by or on order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues.

**B. Exclusivity:**

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the use of enrofloxacin in female dairy cattle less than 20 months of age, for which this supplement is approved.

**C. Supplemental Applications:**

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR §514.106(b)(2)).

**D. Patent Information:**

The sponsor did not submit any patent information with this application.

## VII. ATTACHMENTS:

Facsimile Labeling:

a. BAYTRIL 100 – multiple insert
b. BAYTRIL 100 – 100 mL unit label
c. BAYTRIL 100 – 100 mL unit carton
d. BAYTRIL 100 – 100 mL case shipping label
e. BAYTRIL 100 – 100 mL case storage label
f. BAYTRIL 100 – 250 mL unit label
g. BAYTRIL 100 – 250 mL unit carton
h. BAYTRIL 100 – 250 mL case shipping label
i. BAYTRIL 100 – 250 mL case storage label