Approval Date: July 24, 1998

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 141-068

B. Sponsor

Bayer Corporation, Agriculture Division, Animal Health
P. O. Box 390
Shawnee Mission, Kansas 66201

C. Proprietary Name

Baytril 100 Injectable Solution

D. Established Name

Enrofloxacin

E. Dosage Form

Baytril® 100 is a sterile injectable solution that contains 100 mg enrofloxacin per milliliter.

F. Dispensing Status

A prescription (Rx) product which carries the following caution statement: "Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian."

G. Dosage Regimen

Single-Dose Therapy:

7.5 to 12.5 mg/kg of body weight (3.4 to 5.7 mL/100 lb).

Multiple-Day Therapy:

2.5 to 5.0 mg/kg of body weight (1.1 to 2.3 mL/100 lb).

Repeat at 24-hour intervals for three days. For animals that are clinically improved but still exhibit some signs of disease, additional treatments may be given on Days 4 and 5.

Administered dose volume should not exceed 20 mL per injection site.

H. Route of Administration

Baytril® 100 is given via subcutaneous injection.

I. Indication

Baytril ® 100 Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Pasteurella haemolytica*, *Pasteurella multocida*, and *Haemophilus somnus*.

II. EFFECTIVENESS

The effectiveness of enrofloxacin administered daily at a dose of 2.5 mg/kg for 5 consecutive days was established in a dose range-finding study conducted with naturally-ocurring BRD. The dose range for the multiple-day therapy, 2.5 to 5.0 mg/kg administered for 3 to 5 days, was confirmed in a negatively-controlled multi-location field trial. The 2.5 mg/kg dose was evaluated at 3 field trial locations and the 5.0 mg/kg dose was evaluated at 1 trial location.

The effectiveness of the single-dose therapy, 7.5 to 12.5 mg/kg administered once, was confirmed in a a negatively-controlled multi-location field trial. The 7.5 mg/kg dose was evaluated at 3 field trial locations and the 12.5 mg/kg dose was evaluated at one trial location.

A. Pivotal Studies

1. Dose Range-Finding Study: Multiple-Day Therapy

   a. Type of Study: This was a single location, blinded dose regimen study using enrofloxacin in feedlot calves during an outbreak of BRD.

   b. Investigators:

      Jeff Davidson, D.V.M., M.P.V.M.
      Terry TerHune, D.V.M., Ph.D.
      Health Management Services
      Tulare, California 93275

   c. General Design:

      i. Purpose: The purpose of this study was to determine the efficacy of a multiple-day regimen of enrofloxacin injectable solution at four dose levels for the identification of the lowest appropriate dose.

      ii. Animals: Male Holstein calves, 4 to 5 months of age, weighing 115 to 123kg, were purchased as a large group from local auction markets, transported by truck to the research feedlot facility and commingled in large pens. A total of 48 calves with BRD were selected and randomly assigned to four groups (12 animals per group).

      iii. Controls: Twelve of the 48 animals with BRD were assigned to a negative control group and received no treatment, but were handled identically.

iv. Challenge: Transportation, commingling, and normal processing procedures represented a typical feedlot situation that was capable of inducing BRD.

v. Diagnosis: Calves in the large receiving pens were evaluated daily for signs of respiratory disease consisting of a body temperature of ≥ 40º C (104º F), clinical respiratory signs (increased rate and nasal discharge), poor attitude and depression of appetite. Nasal swabs were taken from each animal prior to treatment to determine the presence of pathogens associated with BRD.

vi. Dosage Form: The dosage form used was an aqueous solution containing 100mg enrofloxacin per milliliter.

vii. Route of Administration: The drug was administered subcutaneously.

viii. Dose: Enrofloxacin was administered at levels of 0, 1.25 mg/kg, 2.5 mg/kg, and 5.0 mg/kg of body weight as a single injection once a day for 5 days.

ix. Test Duration: The test duration was 15 days.

x. Pertinent Variables Measured: Body temperature change between Day 6 and Day 1, treatment success, lung scores, and mortality were considered primary parameters. Treatment success was based on observations of attitude, appetite, rectal temperature, and respiratory signs.

Nasal swabs were collected to verify that microorganisms contributing to respiratory disease were present and consistent with a disease outbreak in a feedlot situation. Additionally, calves that died during the study were necropsied to determine the cause of death, including appropriate bacteriologic and histopathologic evaluations.

Blinding was accomplished by having two investigators involved in the study. All calves were euthanized on the 15th day following the initiation of therapy and necropsied. Their lungs were scored for percentage of pathology.

xi. Results: Mortality was 17% (2/12) in the control group and 8% (1/12) in the 1.25 mg/kg treatment group. No mortalities occurred in the 2.5 or 5.0 mg/kg treatment groups. As summarized in Table 4.1, the 2.5 mg/kg dose group showed the greatest reduction in rectal temperature and the least lung consolidation at necropsy among the 3 enrofloxacin dose groups. The 2.5 mg/kg treatment group had the highest rate of treatment success at Day 14 of the study.

Pasteurella haemolytica was isolated from 14 (29%) of the 48 pre-treatment nasal swabs of the cattle used in this study. *Pasteurella multocida* was isolated from 6 (13%) of the same 48 swabs. *Pasteurella haemolytica* was isolated from 24 (53%) of the 45 post-

treatment lung swabs collected and *Pasteurella multocida* was isolated from 10 (22%) of the same 45 swabs. All *P. haemolytica* and *P. multocida* nasal swab isolates were susceptible to enrofloxacin.

Table 4.1. Percent treatment success on Days 8 and 14, reduction in rectal temperature on Day 6, and percent lung consolidation in cattle with naturally-occurring BRD treated daily with enrofloxacin for 5 consecutive days.

Dosage (mg/kg)	Percent Success (Day 8)	Percent Success (Day 14)	Rectal temp. (°F) reduction (Day 6)	Percent lung consolidation
0	8 (1/12)	0 (0/12)	0.85	23.70
1.25	67 (8/12)	58 (7/12)	2.25	13.98
2.5	100 (12/12)	92 (11/12)	2.47	1.97
5.0	100 (12/12)	58 (7/12)	2.39	6.20

xii. Conclusion: The results of this study demonstrated that enrofloxacin administered subcutaneously at a dose of 2.5 mg/kg/day for 5 consecutive days was an effective treatment of naturally-occurring BRD in cattle.

xiii. Adverse Reactions: No adverse reactions were reported during this study.

2. Field Study: Multiple-Day Therapy

a. Type of Study: This was a multi-location, blinded, clinical efficacy and safety study involving four locations and a total of 597 animals.

b. Investigators:

Jeff Davidson, D.V.M., M.P.V.M.
Terry TerHune, D.V.M., Ph.D.
Health Management Services
Tulare, CA 93275

Michael D. Apley, D.V.M., Ph.D.
Karen Rogers, DVM, MS
Veterinary Research and Consulting Services
Greely, CO 80634

Kelly Lechtenberg, D.V.M., Ph.D.
Mark Sunderman
Midwest Veterinary Services, Inc.
Oakland, NE 68045

Ed G. Johnson, D.V.M.
Mike Skogsberg
Johnson Research
Parma, ID 83660

c. General Design:

i. Purpose: The purpose of this study was to confirm the efficacy and safety of enrofloxacin injectable solution administered daily for 3 to 5 days at a dosage of 2.5 mg/kg or 5.0 mg/kg of body weight for the treatment of naturally occurring cases of BRD in feedlot cattle under clinical use conditions.

ii. Animals: Four to 5 month old male and female commercial crossbred calves were utilized in the study. Each of the four locations had approximately 100 animals assigned to the drug treatment group for a total of 398 head.

iii. Controls: Each of the four locations had approximately 50 animals assigned to the negative control group for a total of 199 head. Controls were handled in the same manner as those from the drug treatment group and received a placebo injection.

iv. Diagnosis: Calves were evaluated daily for signs of respiratory disease, consisting of a body temperature of ³ 40 º C (104 º F), clinical respiratory signs (increased rate and nasal discharge), poor attitude, and depression of appetite. Nasal swabs were taken from each animal prior to treatment to determine the presence of pathogens associated with BRD.

v. Dosage Form: The dosage form used was an aqueous solution containing 100mg enrofloxacin per milliliter.

vi. Route of Administration: Enrofloxacin was administered subcutaneously.

vii. Dose: Enrofloxacin was administered at two different dose levels. The animals assigned to the treatment group at three locations received 2.5mg/kg and those at the fourth location received 5.0 mg/kg for 3 to 5 consecutive days.

viii. Test Duration: The test duration was 28 days.

ix. Pertinent Variables Measured: The primary parameter for determining efficacy was treatment success on Day 28 (i.e., animals that were initially determined treatment successes on Day 6 and did not relapse by Day 28). Treatment success was based on observations of attitude, appetite, rectal temperature, and respiratory signs.

Blinding was accomplished by using two investigators in the study. Nasal cultures were taken to verify that microorganisms contributing to respiratory disease were present and consistent with a disease outbreak in a feedlot situation. Additionally, calves that died during the study were necropsied to determine the cause of death and included appropriate bacteriologic and histopathologic evaluations.

d. Results:

The 2.5 mg/kg and 5.0 mg/kg treatment groups had significantly fewer mortalities and higher treatment success rates than the negative control groups. No mortalities were observed in the enrofloxacin treatment groups at any study location. The pooled mortality for the negative control groups at the trial locations which evaluated the 2.5 mg/kg dose was 9% (14/149). Mortality in the negative control group at the trial location which evaluated the 5.0 mg/kg dose was 14% (7/50). Summaries of the treatment success results by trial location are presented in Tables 4.2 and 4.3.

Pasteurella haemolytica was isolated from 222 (37%) of the 597 pre-treatment nasal swabs collected from the cattle utilized in this study. *Pasteurella multocida* was isolated from 198 (33%) and *Haemophilus somnus* was isolated from 20 (3%) of the same 597 nasal swabs. *Pasteurella haemolytica* was isolated from 18 (86%) of the 21 post-treatment lung swabs collected from the cattle that died on study. *Pasteurella multocida* was isolated from 12 (57%) and *Haemophilus somnus* was isolated from 3 (14%) of the same 21 lung swabs. All *P. haemolytica*, *P. multocida*, and *H. somnus* nasal and lung swab isolates were susceptible to enrofloxacin.

Table 4.2. Percent treatment success on Day 6 and Day 28 in cattle with naturally-occurring BRD treated daily with enrofloxacin at a dose of 2.5 mg/kg for 3 to 5 days.

Location	**Dosage (mg/kg)**	**Percent Success (Day 6)**		**Percent Success (Day 28)**	
California	0	8	4/50	6	(3/50)
California	2.5	82	80/98	64	(63/98)
Idaho	0	30	15/50	30	(15/50)
Idaho	2.5	75	75/100	69	(69/100)
Nebraska	0	35	17/49	35	(17/49)
Nebraska	2.5	93	91/98	90	(88/98)
Total	0	24	36/149	23	(35/149)
Total	2.5	83	246/296	74	(220/296)

Table 4.3. Percent treatment success on Day 6 and Day 28 in cattle with naturally-occurring BRD treated daily with enrofloxacin at a dose of 5.0 mg/kg for 3 to 5 days.

Location	**Dosage (mg/kg)**	**Percent Success (Day 6)**		**Percent Success (Day 28)**	
Colorado	0	24	(12/50)	20	(10/50)
Colorado	5.0	60	(57/95)	54	(51/95)

e. Statistical Analysis: Each study site was first evaluated individually and then the data was pooled for analysis, where applicable. The California, Nebraska, and Idaho study sites each evaluated a dose of 2.5 mg/kg that allowed both individual and pooled analyses of the results. The Colorado site evaluated a dose of 5.0 mg/kg and was analyzed as an individual location.

f. Conclusions: The data support that enrofloxacin administered subcutaneously at a dosage of 2.5 mg/kg to 5.0 mg/kg once daily for 3 to 5 days is effective for the treatment of naturally-occurring BRD in cattle.

g. Adverse Reactions: One study site noted a few instances of swelling at the injection site 24 hours after treatment. These were not present at observation times of 48 hours or more after injection. No adverse reactions were noted by any of the other investigators.

3. Field Study: Single-Dose Therapy

a. Type of Study: This was a multi-location, blinded, clinical efficacy and safety study involving four locations and a total of 600 animals.

b. Investigators:

Jeff Davidson, D.V.M., M.P.V.M.
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Karen Rogers, D.V.M., M.S.
Veterinary Research and Consulting Services
Greely, CO 80634

David T. Bechtol, D.V.M.
Audie Waite
Agri Research Center, Inc.
Canyon, TX 79015

c. General Design:

i. Purpose: The purpose of this study was to confirm the safety and efficacy of enrofloxacin injection for the treatment of BRD in feedlot cattle under field conditions when administered as a single subcutaneous dose of either 7.5 mg/kg or 12.5 mg /kg.

ii. Animals: Four to 5 month old male and female commercial crossbred calves were utilized in the study. Body weight ranged from 145 to 292 kg. Approximately 100 animals were assigned to

the drug treatment groups at each of the four study locations for a total of 406 treated calves.

iii. Controls: At each of the four locations approximately 50 additional animals were assigned to the negative control group for a total of 204 calves. Controls were handled in the same manner as those from the drug treatment groups and received a placebo injection.

iv. Diagnosis: Calves were initially housed in large receiving pens and moved to smaller pens as they were assigned to the study. They were evaluated daily for signs of respiratory disease consisting of a body temperature of ³ 40 º C (³ 104 º F), adverse clinical signs represented by attitude, respiration, and appetite. Nasal swabs were taken from each animal prior to treatment to determine the presence of pathogens associated with BRD.

v. Dosage Form: The dosage form used was an aqueous solution containing 100 mg enrofloxacin per milliliter.

vi. Route of Administration: Enrofloxacin was administered subcutaneously.

vii. Dose: Enrofloxacin was administered at one of two different dose levels. At three investigator sites, enrofloxacin was administered one time at the dose level of 7.5 mg/kg. The fourth site used the single dose level of 12.5mg/kg.

viii. Test Duration: The test duration was 10 days.

ix. Pertinent Variables Measured: The primary parameter for determining efficacy was treatment success on Day 10 (i.e., animals that were initially determined treatment successes on Day 6 and did not relapse by Day 10). Treatment success was based on observations of attitude, appetite, rectal temperature, and respiratory signs.

Blinding was accomplished by using two investigators at each study site. Nasal swabs were taken prior to treatment and cultured for bacterial organisms. Calves which died during the study were necropsied and tissues were taken to identify respiratory pathogens.

d. Results:

The 7.5 mg/kg and 12.5 mg/kg treatment groups had significantly fewer mortalities and higher treatment success rates than the negative control groups. The pooled mortality data for the treatment groups administered a single 7.5 mg/kg dose of enrofloxacin was 3% (9/302) compared to 36% (56/154) for the negative control groups. The mortality in the treatment group administered a single 12.5 mg/kg dose of enrofloxacin was 1% (1/102) compared to 12% (6/50) in the negative control group. Summaries of the treatment success results by trial location are presented in Tables 4.4 and 4.5 below.

Pasteurella haemolytica was isolated from 222 (37%) of the 597 pre-treatment nasal swabs collected from the cattle utilized in this study. *Pasteurella multocida* was isolated from 198 (33%) and *Haemophilus somnus* was isolated from 20 (3%) of the same 597 swabs. *Pasteurella haemolytica* was isolated from 66 (92%) of the 72 post-treatment lung swabs collected from the cattle that died on study. *Pasteurella multocida* was isolated from 18 (25%) and *Haemophilus somnus* was isolated from 11 (15%) of the same 72 lung swabs. All *P.haemolytica*, *P. multocida*, and *H. somnus* nasal and lung swab isolates were susceptible to enrofloxacin.

Table 4.4. Percent treatment success on Day 6 and Day 10 in cattle with naturally-occurring BRD treated with a single injection of enrofloxacin at a dose of 7.5 mg/kg.

Location	**Dosage (mg/kg)**	**Percent Success (Day 6)**		**Percent Success (Day 10)**	
California	0	2	1/52	2	1/52
California	7.5	72	72/100	69	69/100
Colorado	0	14	7/51	12	6/51
Colorado	7.5	67	68/101	58	59/101
Texas	0	12	6/51	12	6/51
Texas	7.5	68	69/101	63	64/101
Total	0	9	14/154	8	13/154
Total	7.5	69	209/302	64	192/302

Table 4.5. Percent treatment success on Day 6 and Day 10 in cattle with naturally-occurring BRD treated with a single injection of enrofloxacin at a dose of 12.5 mg/kg.

Location	Dosage (mg/kg)	Percent Success (Day 6)		Percent Success (Day 10)	
Nebraska	0	14	7/50	14	7/50
Nebraska	12.5	88	90/102	81	83/102

e. Statistical Analysis: Each study site was first evaluated individually and then the data was pooled for analysis, where applicable. The California, Colorado, and Texas study sites each evaluated a dose of 7.5 mg/kg that allowed both individual and pooled analyses of the results. The Nebraska site evaluated a dose of 12.5 mg/kg and was analyzed as an individual location.

f. Conclusions: The data support that enrofloxacin administered as a single subcutaneous injection at a dosage of 7.5 mg/kg to 12.5 mg/kg is an effective treatment for naturally-occurring BRD in cattle.

g. Adverse Reactions: No adverse reactions were reported in this trial.

4. *In vitro* Susceptibility Study (pivotal for labeling)

a. Type of Study: This was a study to determine the *in vitro* susceptibility of selected cattle pathogens to enrofloxacin.

b. Investigator:

Don Bade
Colorado Animal Research Enterprises, Inc.
Fort Collins, CO 80524

c. Purpose: This laboratory study was designed to determine the zones of inhibition (mm) and minimum inhibitory concentrations (MICs) of enrofloxacin for pathogens known to cause disease in the bovine.

d. Samples: Isolates were collected from clinical field trials and various diagnostic laboratories and universities located in the United States. Isolates tested were from clinical cases that occurred during 1994 and 1995.

e. Procedure: The identity of each isolate was confirmed and subjected to enrofloxacin broth microdilution, disk diffusion, and agar dilution susceptibility tests. The MIC_{50} and the MIC_{90} (minimum inhibitory concentration for 50% and 90% of the isolates) for some of the isolates tested, as determined by the broth microdilution technique, are shown in Table 4.6 below.

Table 4.6. MIC values of enrofloxacin against bacteria and mycoplasma isolated from natural infections

Isolate	**No. Isolates**	**MIC_{50}**	**MIC_{90}**
Actinomyces pyogenes	105	1	1
Escherichia coli	100	0.03	0.06
Haemophilus somnus	104	0.015	0.03
Mycoplasma spp.	124	0.25	0.5
Pasteurella haemolytica	121	0.06	0.06
Pasteurella multocida	108	0.015	0.03

III. TARGET ANIMAL SAFETY

A. Pivotal Studies

1. Drug Tolerance Study:

a. Type of Study: This study evaluated the systemic tolerance of Baytril 100 (enrofloxacin 10% injectable solution) when administered subcutaneously to beef cattle at the rate of 50mg/kg for 5 consecutive days.

b. Study Director:

James A. Shmidl
Bayer Corporation
Animal Health
Shawnee Mission, Kansas

c. General Design:

i. Purpose: The study was conducted to determine the clinical profile in beef cattle following subcutaneous administration of Baytril 100

(enrofloxacin 10% injectable solution) at 50 mg/kg/day for 5 consecutive days.

ii. Animals: Two Angus breed cattle; 1 male and 1 female, weighing 250 and 270 kg at time of initial treatment.

iii. Control: One Angus breed male weighing 270 kg.

iv. Dosage Form: An aqueous solution containing 100 mg enrofloxacin per mL was used. This is the same as the marketed form of the product

v. Dose: 50 mg/kg administered daily for 5 consecutive days.

vi. Route of Administration: The drug was administered by subcutaneous injection.

vii. Study Duration: Three days following the 5 consecutive daily treatments.

viii. Pertinent Measurements/Observations: Clinical signs, body weight, hematology, clinical chemistry, gross necropsy observations, and histopathology.

d. Results:

i. Clinical Observations: Inappetence was observed in both treated animals accompanied by varying degrees of depression and incoordination in the male calf on Days 3 to 5 of drug administration.

ii. Mortality: No deaths occurred during the study.

iii. Body Weight: Body weight changes in both treated and control animals were not clinically significant.

iv. Hematology/Clinical Chemistry: A transient elevation of CPK and AST was observed in the treated animals. No other drug-related abnormalities were identified.

v. Gross and Histological Observations: No lesions were observed at necropsy and all tissues were within normal histological limits.

e. Statistical Analysis: None

f. Conclusions: It was concluded from the findings of this study that subcutaneous treatment with Baytril 100 (enrofloxacin 10% injectable solution) at the rate of 50 mg/kg/day for 5 consecutive days can induce clinical signs of inappetence, slight depression, and incoordination with transient elevations of the CPK and AST parameters, but with no histological changes in the major organ systems.

2. General Safety Study (1X, 3X, 5X)

a. Type of Study: This study evaluated the general safety of Baytril 100 (enrofloxacin) when administered subcutaneously at dosages of 5, 15, and 25 mg/kg/day for 15 consecutive days.

b. Study Director:

James A. Shmidl
Bayer Corporation
Animal Health
Shawnee Mission, Kansas

c. General Design:

i. Purpose: To determine the clinical profile in beef calves following administration of Baytril 100 (enrofloxacin 10% injectable solution) at 5, 15, and 25 mg/kg/day for 15 consecutive days.

ii. Animals: Twelve crossbred beef calves, 6 males and 6 females, weighing 170 to 240 kg at the time of initial treatment.

iii. Control: Four crossbred beef calves, 2 males and 2 females.

iv. Dosage Form: An aqueous solution containing 100 mg enrofloxacin per mL was used. This is the same as the marketed form of the product.

v. Dose: 5, 15, and 25 mg/kg/day for 15 consecutive days.

vi. Route of Administration: The drug was administered by subcutaneous injection.

vii. Study Duration: 28 days.

viii. Pertinent Measurements/Observations: Clinical observations, body weight, hematology, clinical chemistry, gross necropsy observations, and histopathology.

d. Results:

i. Clinical Observations: No clinical signs of toxicity were observed at the 5 mg/kg dose level. Two animals receiving the 15 mg/kg dose had signs of depression or incoordination. Depression was noted as early as Day 4 and incoordination as early as Day 11 of treatment. All 4 of the animals receiving the 25 mg/kg dose had signs of depression, occasional muscle fasciculation, and incoordination with most signs appearing by Day 10.

ii. Mortality: None.

iii. Body Weight: All cattle gained body weight except for one in the control group.

iv. Hematology/Clinical Chemistry: No drug-related abnormalities were identified.

v. Gross and Histological Observations: No drug-related lesions were observed at necropsy. There were no microscopic lesions in any tissues which included the articular cartilage of the stifle joint.

e. Statistical Analysis: The study data were tabulated and, as appropriate, summarized through calculation of mean and standard deviation values.

f. Conclusions: It was concluded from the findings of this study that an adequate safety margin exists for the subcutaneous treatment of cattle with Baytril 100 (enrofloxacin 10% injectable solution).

3. Local Tolerance Study

a. Type of Study: This study evaluated the local tolerance at the subcutaneous site of injection following the administration of Baytril 100 (enrofloxacin 10% injectable solution) at 5mg/kg/day for 5 consecutive days.

b. Study Director:

James A. Shmidl
Bayer Corporation
Animal Health
Shawnee Mission, Kansas 66201

c. General Design:

i. Purpose: To determine reactivity by clinical observations, palpation, necropsy observation, and histopathology.

ii. Animals: Ten beef breed cattle, males and females weighing 170 to 210 kg at the time of initial treatment.

iii. Control: Each of the cattle received physiological saline treatments on the opposite side of the neck to serve as controls.

iv. Dosage Form: An aqueous solution containing 100 mg enrofloxacin per mL was used. This is the same as the marketed form of the product.

v. Dose: 5 mg/kg/day for 5 consecutive days.

vi. Route of Administration: The drug was administered by subcutaneous injection. A different site was selected for each of 5 daily treatments.

vii. Study Duration: 70 days after the initial injection.

viii. Pertinent Measurements/Observations: Palpation of injection site at 1, 2, 3, 4, 7, 11, 18, 23, 31, 46, 60, and 70 days after the initial injection. Euthanasia, necropsy, and histopathology at 11, 18, 31, 46, and 70 days.

d. Results:

i. Palpations of Injection Sites: Based on injection site reactivity scored on a scale of 0 (no observable reaction) to 5 (severe reaction), average scores for each of the 5 injection sites for the duration of the study were less than

ii. Gross Necropsy Observations: Most observable changes occurred in the subcutaneous tissues (discoloration, thickening, and gelatinous appearance). However, some muscle discoloration was observed at a minimum of 1 injection site in all animals necropsied up to 27 days after the 5th injection.

e. Statistical Analysis: None.

f. Conclusions: The findings of this study indicate that subcutaneous treatment of cattle with Baytril 100 (enrofloxacin 10% injectable solution) can induce a transient local tissue reaction.

4. General Safety Study in Young Calves (1X, 3X, 5X)

a. Type of Study: This study evaluated the general safety of Baytril 100 (enrofloxacin) in young calves (23 days of age) when administered subcutaneously at dosages of 5, 15, and 25 mg/kg/day for 15 consecutive days.

b. Study Director:

Terry TerHune
Health Management Services
PO Box 2046
Tulare, CA 93275

c. General Design:

i. Purpose: To determine the clinical profile in young calves following treatment at 5, 15, and 25 mg/kg/day for 15 consecutive days with Baytril 100 (enrofloxacin 10% injectable solution).

ii. Animals: Eighteen Holstein breed bull calves, 23 days of age at time of initial treatment.

iii. Control: Six Holstein breed bull calves, 23 days of age.

iv. Dosage Form: An aqueous solution containing 100 mg enrofloxacin per milliliter was used. This is the same as the marketed form of the product.

v. Dose: 5, 15, and 25 mg/kg/day for 15 consecutive days.

vi. Route of Administration: The drug was administered by subcutaneous injection.

vii. Study Duration: 23 days.

viii. Pertinent Measurements/Observations: Clinical observations, body weight, hematology, clinical chemistry, gross necropsy observations, and histopathology.

d. Results:

i. Clinical Observations: No clinical signs of toxicity were observed.

ii. Body Weights: All groups achieved anticipated body weight gains.

iii. Hematology/Clinical Chemistries: No drug-related abnormalities were identified.

iv. Gross and Histological Observations: No drug-related lesions were observed at necropsy. No articular cartilage lesions were observed in the stifle joints at 2 days and 9 days following treatment with enrofloxacin at doses of 5, 15, and 25 mg/kg/day for 15 consecutive days.

e. Statistical Analysis: None.

f. Conclusions: Under the conditions of this study, no adverse effects were observed following the administration of Baytril 100 (enrofloxacin 10% injectable solution) at doses of 5, 15, and 25 mg/kg/day for 15 consecutive days to 23-day-old calves.

IV. HUMAN FOOD SAFETY

A. Toxicity Studies

Please reference the Freedom of Information Summary dated October 4, 1996, for NADA 140-828, Baytril (enrofloxacin) 3.23% Concentrate Antimicrobial Solution, for the Human Safety Toxicity Studies.

B. Safe Concentrations of Total Enrofloxacin-Related Residues

1. No-Observed-Effect-Levels (NOEL):

The tissue safe concentrations of total enrofloxacin-related residues 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 in Table 6.1.

Table 6.1. No-Observed-Effect Levels (NOEL) in toxicology studies for enrofloxacin

Study	**Study No.**	**NOEL**
Subchronic Oral Toxicity Study in Dogs	No. 73775	3 mg/kg
Chronic Toxicity & Carcinogenicity Study in Mice	No. 74229	323 mg/kg
Chronic Toxicity Study in Rats	No. 74387	5.3 mg/kg
Two-Generation Rat Reproduction Study	No. 73892	165 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 significantly increased frequency or distribution of tumors was 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 Acceptable Daily Intake (ADI).

2. Calculation of the Acceptable Daily Intake (ADI) of Total Enrofloxacin-Related Residues:

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

A safety factor of 1000 was used because the NOEL was from a subchronic study. Since the lowest NOEL is 3 mg/kg/day,

ADI

= 3 mg/kg of body weight/day / 1000

= 0.003 mg/kg of body weight/day

= 3 µg/kg of body weight/day

3. Calculation of Tissue Safe Concentrations (SC's): The calculation of the tissue safe concentrations is based on the *General Principles for Evaluating the Safety of Compounds used in Food-Producing Animals* (FDA/CVM, revised July 1994).

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

The average human weight is approximated at 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.

$$SC\ (muscle) = \frac{0.003\ mg/kg/day\ x\ 60\ kg\ bodyweight}{0.3\ kg/day} = 0.6\ mg/kg = 0.6\ ppm$$

$$SC\ (liver) = \frac{0.003\ mg/kg/day\ x\ 60\ kg\ bodyweight}{0.1\ kg/day} = 1.8\ mg/kg = 1.8\ ppm$$

$$SC\ (kidney) = \frac{0.003\ mg/kg/day\ x\ 60\ kg\ bodyweight}{0.05\ kg/day} = 3.6\ mg/kg = 3.6\ ppm$$

$$SC\ (fat) = \frac{0.003\ mg/kg/day\ x\ 60\ kg\ bodyweight}{0.05\ kg/day} = 3.6\ mg/kg = 3.6\ ppm$$

Table 6.2. Safe Concentrations (SC's) for total enrofloxacin-related residues in edible tissues of cattle using the revised food consumption factors

Edible Tissue	Amount Consumed / Day	Safe Concentration (SC)
Muscle	300 g	0.6 ppm
Liver	100 g	1.8 ppm
Kidney	50 g	3.6 ppm
Fat	50 g	3.6 ppm

Ten times (10X) the muscle safe concentration, 6 ppm, was considered as the injection site safe concentration.

C. Total Residue Depletion and Metabolism Studies

Bayer Report Nos. 106579 and 106580

Investigator: Dr. Larry R. Hall
Bayer Research Park
Stilwell, Kansas 66085

Animals Used: Cattle, Hereford cross; 186 to 213 kg at the time of dosing.

Test Substance: 10% Enrofloxacin Injectable Formulation containing 14C-enrofloxacin. The label was at a position (C-4 position of the quinolone ring) that is not susceptible to metabolism.

Treatment Regimen: Subcutaneous injections for five consecutive days at a dose rate of 5 mg enrofloxacin per kg of animal body weight per day.

Number of Animals Per Sacrifice Interval: 3 animals (2 steers and 1 heifer or 1 steer and 2 heifers)

Sacrifice Intervals: 0 (8 hours), 3, 7, and 14 days after the administration of the fifth (final) dose.

Tissues Collected: Liver, kidney, muscle, fat, and five injection sites.

1. Total Residue Depletion

   Tissue samples from each of the animals at all sampling intervals were analyzed to determine the [^{14}C] total residue depletion. The results are summarized in Table 6.3.

Table 6.3. Average total ^{14}C-residues (ppm + standard deviation) in the edible tissues of cattle treated with ^{14}C-enrofloxacin at a dose rate of 5 mg/kg/day for five consecutive days by subcutaneous injection

Sacrifice Interval; Days Post Final Dose

Tissue	**0***	**3**	**7**	**14**
Liver	10.039 (±4.359)	1.483 (±0.200)	0.902 (±0.137)	0.634 (±0.117)
Kidney	7.464 (±3.835)	0.296 (±0.035)	0.086 (±0.015)	0.066 (±0.008)
Muscle	1.539 (±0.747)	0.022 (±0.004)	0.007 (±0.003)	0.004 (±0.001)
Fat	0.607 (±0.752)	0.010 (±0.005)	0.010 (±0.008)	0.006 (±0.002)
Last Injection Site	1602.6 (± 301.5)	1.300 (± 1.892)	0.377 (± 0.210)	0.171 (± 0.063)

*0-Day Interval is actually 8 hours after the last injection.

2. Metabolism of ^{14}C-Enrofloxacin

Samples of the edible tissues of one steer and one heifer from the 0-day (8 hours following the administration of the fifth dose) sacrifice interval were analyzed. The extraction schemes removed 80 to 108% of the total radioactive residues (TRR) from the 0-day liver, kidney, muscle, fat, and injection site tissues. The extracts were analyzed by high-performance liquid chromatography (HPLC). In the injection sites, the major component was enrofloxacin (>43% of the TRR) with some ciprofloxacin (<1-40% of the TRR). In other edible tissues of enrofloxacin-treated cattle, the parent compound and 11 metabolites were found. The only significant (>10% of the TRR) compounds found in liver, kidney, and muscle were enrofloxacin and ciprofloxacin (N-deethylated enrofloxacin). The results are summarized in Table 6.4.

Table 6.4.

Amounts of enrofloxacin and its metabolites as percentages of the total radioactive residues (TRR) in liver, kidney, muscle, and fat approximately 8 hours after the last dose

Compound	Liver	Kidney	Muscle	Fat
Enrofloxacin	21-26	27-31	55-56	35-59
Ciprofloxacin	38-44	50-55	33-34	5-7
Ring-opened oxociprofloxacin	5-6	2-3	-	-
N-Formyl ciprofloxacin	5	1	-	<1-3
7-Aminofluoroquinolinic acid	3	2-3	-	-
Desethylene ciprofloxacin	3	3-4	-	-
Desethylene enrofloxacin	3-6	3-4	4-5	-
Oxociprofloxacin	2	4-6	-	-
Dioxodesethylene ciprofloxacin	1	-	-	-
(#) Dioxociprofloxacin isomers	(3)<1-2	-	-	-
Hydroxy oxociprofloxacin	<1	-	-	-
Oxoenrofloxacin	-	-	-	27-43

D. Comparative Metabolism Study in the Rat

Bayer Report No. 106547

The metabolism of enrofloxacin in Wistar Furth rats, treated via oral gavage doses, has been described in the Freedom of Information Summary dated October 4, 1996 for NADA 140-828, Baytril® (enrofloxacin) 3.23% Concentrate Antimicrobial Solution. Enrofloxacin and the metabolites, ciprofloxacin, N-formyl ciprofloxacin, desethylene ciprofloxacin, desethylene enrofloxacin, oxociprofloxacin, and oxoenrofloxacin, were observed in both the urine of rats orally dosed with ^{14}C-enrofloxacin and the edible tissues of cattle subcutaneously treated with ^{14}C-enrofloxacin. In addition, precursors for the cattle metabolites, ring-opened oxociprofloxacin, 7-aminofluoroquinolinic acid, dioxodesethylene ciprofloxacin, dioxociprofloxacin isomers, and hydroxy oxociprofloxacin, were detected in the rat urine. Therefore, the rats used in the toxicity tests were exposed to all of the enrofloxacin metabolites observed in edible tissues of cattle.

E. Determination of the Target Tissue and the Marker Residue

Using the radiolabeled residue studies summarized in Section C, liver was assigned as the target tissue and desethylene ciprofloxacin was assigned as the marker residue for cattle subcutaneously treated with 10% enrofloxacin solution.

1. Target Tissue Determination

   The amount of time required for the average total ^{14}C-residue levels in the edible tissues to deplete to the safe concentrations was 8 hours for fat and less than 3 days for liver, kidney, muscle, and injection sites which received 10 to 12 mL of dose. Liver initially contained the highest total residues, and the total ^{14}C-residues depleted to the safe concentration the slowest from the liver. Thus, liver was selected as the target tissue.

2. Marker Residue Determination

   HPLC analysis of liver samples collected at sacrifice intervals greater than 8 hours after the administration of the final enrofloxacin dose indicated that enrofloxacin and ciprofloxacin did not comprise a significant portion of the extractable residues. Therefore, neither enrofloxacin nor ciprofloxacin could be selected as the marker residue. Analysis of the 7-day liver samples demonstrated that desethylene ciprofloxacin comprised the largest portion of the extractable radioactive residues. Desethylene ciprofloxacin was also observed in the 0-, 3-, and 14-day liver samples. Thus, desethylene ciprofloxacin was selected as the marker substance in cattle liver.

F. Determination of the Tolerance for Desethylene Ciprofloxacin in Cattle Liver

Using the determinative procedure developed for the extraction and quantitation of desethylene ciprofloxacin residues in cattle liver (Section G, below), the desethylene ciprofloxacin content in the liver samples of cattle treated with ^{14}C-enrofloxacin (Section C, above) was measured. The results are summarized in Table 6.5.

Table 6.5. Average concentrations of ^{14}C-desethylene ciprofloxacin (ppm + standard deviation) in the liver of cattle treated with ^{14}C-enrofloxacin at a dose rate of 5 mg/kg/day for five consecutive days by subcutaneous injection

Withdrawal Interval (days)	**Average ppm (± standard deviation)**
0 (8 hours)	0.512 (± 0.135)
3	0.141 (± 0.032)
7	0.117 (± 0.037)
14	0.085 (± 0.011)

At approximately 65 hours post-treatment when the total enrofloxacin-related residues in the cattle liver depleted to the safe concentration of 1.8 ppm, the level of desethylene ciprofloxacin in cattle liver depleted to approximately 0.15 ppm (8.3% of the liver safe concentration).

For the single day subcutaneous treatment of cattle with enrofloxacin at a dose rate of up to 12.5 mg per kg of animal body weight, injection site residues required 5 days post dose to deplete to 10 times the muscle safe concentration. To ensure depletion of injection site residues, a conservative value of 0.1 ppm was assigned as the tolerance of desethylene ciprofloxacin (marker residue) in the liver (target tissue) of cattle treated subcutaneously with enrofloxacin (both multiple doses and single dose).

G. Determination of the Withdrawal Time

1. Multiple-day therapy (5 mg/kg/day for 5 consecutive days)

   Bayer Report No. 74503

   Investigator:

   Mr. F. Terry McNamara
   Bayer Corporation
   Animal Health
   Shawnee Mission, Kansas 66201

   Animals Used: Cattle, predominantly Angus breeding, 268 to 368 kg at the time of dosing.

   Test Substance: 10% Enrofloxacin Injectable Formulation with arginine prepared under GMP.

   Treatment Regimen: Subcutaneous injections for five consecutive days at a daily dose rate of 5 mg enrofloxacin per kg of animal body weight.

   Number of Animals Per Sacrifice Interval: 5 animals (3 steers and 2 heifers or 2 steers and 3 heifers)

   Sacrifice Intervals: 7, 14, 21, 28, and 35 days after the administration of the fifth (final) dose.

   Tissue Collected at Sacrifice: Liver.

   Results: The liver samples were analyzed using the determinative procedure (Section H, below) to follow the depletion of desethylene ciprofloxacin from the liver of cattle treated with 10% enrofloxacin injectable formulation at the maximum proposed label use rate. The average residue levels are presented in Table 6.6.

   Table 6.6. Desethylene ciprofloxacin residues in cattle liver

Withdrawal Interval (days)	Average ppm (± standard deviation)
7	0.110 (± 0.043)
14	0.082 (± 0.033)
21	0.054 (± 0.022)
28	0.038 (± 0.008)
35	0.021 (± 0.006)

2. Single-dose therapy (7.5 mg or 12.5 mg/kg administered once)

   Bayer Report No. 74660

   Investigators:

   Drs. Lorianne Fought and James A. Shmidl
   Bayer Corporation
   Animal Health
   Shawnee Mission, Kansas 66201

   Animals Used: Cattle, mixed beef breeds (Limousin, Shorthorn, Charolais, Angus, Hereford cross, Hereford, Saler, and Simmental cross), 274 to 330 kg at the time of dosing.

Test Substance: 10% Enrofloxacin Injectable Formulation with arginine prepared under GMP.

Treatment Regimen: A single subcutaneous injection at a dose rate of either 7.5mg or 12.5 mg enrofloxacin per kg of animal body weight.

Number of Animals Per Sacrifice Interval: 4 animals (2 steers and 2 heifers)

Sacrifice Intervals: For the 7.5 mg/kg dose - 3, 7, 14, 21, and 35 days post-dose. For the 12.5 mg/kg dose - 7, 14, 21, 35, and 49 days post-dose.

Tissue Collected at Sacrifice: Liver and the first injection site where the maximum 20 mL of formulation was administered.

Results: The injection site tissues were analyzed for enrofloxacin and ciprofloxacin residues. Since the enrofloxacin residue data were comparable with those determined in a radiotracer study, depletion of the total enrofloxacin-related residues from injection site tissues was estimated using the 14C-residue data contained in Bayer Report No. 106579 (Section E.1, above).

The liver samples were analyzed using the determinative procedure (Section H, below) to follow the depletion of desethylene ciprofloxacin from the liver of cattle treated once with 10% enrofloxacin injectable formulation at 7.5 mg or 12.5 mg enrofloxacin per kg of animal body weight. The average residue levels are presented in Table 6.7.

Table 6.7. Desethylene ciprofloxacin residues in cattle liver

Withdrawal Interval (days)	**Average ppm (± standard deviation)**	
	7.5 mg/kg Dose	**12.5 mg/kg Dose**
3	0.0462 (±0.00765)	-
7	0.0259 (±0.00378)	0.0307 (±0.00900)
14	0.0148 (±0.00279)	0.0167 (±0.00358)
21	0.0120 (±0.00156)	0.0134 (±0.00228)

In examining validation data, the method provided an average 101% recovery at the 0.01ppm level and was accepted as the limit of quantitation (LOQ). The average desethylene ciprofloxacin concentrations presented in Table 6.7 were calculated without values lower than 0.01ppm.

In order to ensure that the total enrofloxacin-related residues in cattle liver decline to below the safe concentration of 1.8ppm by 5days after a single day treatment with 10% enrofloxacin injectable formulation at up to 12.5mg/kg, the following approaches were employed:

(1) Pharmacokinetic analyses of residue data contained in Bayer Report Nos. 106579 and 74660 confirmed that the marker residue concentrations would be at least 3% of the total residues occurring 5 days after a 12.5 mg/kg dose of enrofloxacin;

(2) The HPLC chromatograms of the 3-, 7-, and 14-day withdrawal liver samples from both multiple-dose and single-dose studies showed qualitatively similar metabolite distributions and depletion patterns, suggesting that the proportional relationship between marker residue and total residues should be similar for both treatment regimes; and

(3) According to the marker to total residue ratios calculated in Bayer Report No.106579, the marker residue from the single day treatment regime will represent between 4% and 15% of the total residues at 5days post-dose. The average concentration of desethylene ciprofloxacin in liver at 5 days withdrawal following a single treatment of cattle with enrofloxacin at 12.5mg/kg dose rate was estimated to be approximately 0.041 ppm, assuming that there is a parallel relationship in the liver marker residue depletion from animals treated with 7.5 mg/kg dose and 12.5 mg/kg dose. In case at least 3% of the total enrofloxacin-related residues is due to desethylene ciprofloxacin at 5 days post-dose, the total drug residues in cattle liver at 5-day sacrifice interval after the 12.5 mg/kg dose would be estimated to be 1.367 ppm, which is less than the permitted liver safe concentration.

3. Withdrawal Calculation

Liver residue depletion data from the single and multiple dose studies were individually analyzed using CVM's statistical tolerance limit algorithm. Liver and injection site residue data following the subcutaneous administration of a single dose of 10%enrofloxacin injectable solution, 7.5 mg/kg or 12.5 mg/kg, support a 5-day withdrawal. Injection site residues resulting from the subcutaneous administration of the 10% enrofloxacin solution at doses up to 5mg/kg for up to 5days require 3days to deplete to 10 times the muscle safe concentration. Following the subcutaneous administration of the 10% enrofloxacin solution at doses up to 5 mg/kg for up to 5 days, liver residues deplete to 0.1ppm by 28 days post dose. A withdrawal period of 28 days is assigned for both uses of the 10%enrofloxacin injectable solution, either as a single subcutaneous treatment, 7.5mg/kg or 12.5 mg/kg, or as a multiple dose subcutaneous treatment at up to 5mg/kg for up to 5 days.

H. Regulatory Method

1. Analytical Method for the Determination and Confirmation of the Marker Residue for Enrofloxacin, Desethylene Ciprofloxacin, in Cattle Liver

The determinative and confirmatory procedures for measuring the marker residue for enrofloxacin, desethylene ciprofloxacin, in treated cattle utilizes a one-step procedure to extract conjugated and nonconjugated desethylene ciprofloxacin residues from bovine liver tissue. The quantitation of the desethylene ciprofloxacin residue in the extract is by high performance liquid chromatography (HPLC) and fluorescence detection, and the confirmation of identity is by liquid chromatography and tandem mass spectrometry.

In the determinative procedure, ground cattle liver is homogenized in a solvent consisting of methanol and water containing 150 mM HClO4 and 150 mM H3PO4 (1:1), and the slurry is heated at 70 °C for 1 hour. Precipitates are removed by centrifugation of the slurry. The pH of the resulting supernatant is adjusted using 6 M NaOH, and the precipitates formed during the addition of the NaOH are removed by centrifugation. The supernatant is analyzed by HPLC with fluorescence detection. The limit of quantitation for the determinative procedure is approximately 0.01 ppm.

In the confirmatory procedure, a sample is processed as above, and one mL of the sample extract is acidified with acetic acid and dried. The dried extract is

dissolved in the mobile phase. The procedure uses HPLC for separation and electrospray mass spectrometry/mass spectrometry (ESI/MS/MS) with selective ion monitoring (SIM) to monitor three major product ions characteristic of desethylene ciprofloxacin.

2. Method Validation

   A method trial of the determinative and confirmatory procedures was satisfactorily completed by FDA.

3. Display of the Method

   The validated regulatory analytical method for desethylene ciprofloxacin (marker residue) in cattle liver is on display in the Dockets Management Branch (HFA-305), Room 1061, 5630 Fishers Lane, Rockville, MD 20852. It is attached to this FOI Summary.

I. User Safety

User safety concerns associated with enrofloxacin have been satisfactorily addressed by establishing label warnings. In addition, a toll-free number is available on the label which users can call to report adverse events or to obtain Material Safety Data Sheets

V. 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 Title 21, Part 514 of the implementing Code of Federal Regulations (21 CFR 514). The data demonstrate that Baytril 100, a fluoroquinolone antibiotic, when administered subcutaneously to cattle as a single injection at a dose of 7.5 to 12.5 mg/kg body weight, or as a daily injection at a dose of 2.5 to 5.0 mg/kg body weight for 3 to 5 days, is safe and effective for the treatment of bovine respiratory disease (BRD) associated with *Pasteurella haemolytica*, *Pasteurella multocida*, and *Haemophilus somnus*.

Based on a battery of toxicology tests, an acceptable daily intake of 3 µg/kg body weight/day was calculated, which further yielded safe concentrations for total enrofloxacin-related residues of 0.6 ppm in muscle 1.8 ppm in liver, 3.6 ppm in kidney, and 3.6 ppm in fat. The tolerance was determined following the evaluation of both liver and injection site residues from single dose and multiple dose residue studies. A tolerance of 0.1 ppm for desethylene ciprofloxacin (the marker residue) in liver (the target tissue) is established for the subcutaneous treatment of beef cattle with enrofloxacin. The tolerance refers to the residue measured by the regulatory method described herein.

Using a tolerance of 0.1 ppm, liver and injection site residues following a single subcutaneous injection of 12.5 mg Baytril 100/kg body weight support a 5-day withdrawal period. Injection site residues resulting from the subcutaneous administration of the 10% enrofloxacin solution at doses up to 5 mg/kg for up to 5 days require 3 days to deplete to their safe concentration. Following the subcutaneous administration of the 10%enrofloxacin solution at doses up to 5 mg/kg for up to 5 days, liver residues deplete to 0.1ppm by 28 days post dose.

The Agency has assigned a 28-day withdrawal for both the single and multiple treatment regimes for Baytril 100. The Agency is confident that the assignment of a 28-day withdrawal period is consistent with the public health, as it addresses depletion of residues of desethylene ciprofloxacin, the marker residue, in both the target tissue, liver, and at the injection site. Additionally, assigning a single withdrawal period for both treatment regimes avoids label confusion, and is likely to be followed in practice.

Labeling restricts this drug to use by or on order of a licensed veterinarian. 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 bovine respiratory disease (BRD) associated with *Pasteurella haemolytica*, *Pasteurella multocida*, and *Haemophilus somnus*, (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, and (c) the rate of emergence of enrofloxacin-resistant organisms may be reduced by the involvement of veterinarians in product use.

Public health concerns associated with potential increases in fluoroquinolone-resistant bacteria have been satisfactorily addressed. The agency has established conditions of use that minimize potential adverse effects of the antimicrobial treatment, thereby reducing the number of fluoroquinolone-resistant zoonotic pathogens that may persist in treated animals until slaughter. These use conditions also minimize excretion of drug and fluoroquinolone-resistant zoonotic pathogens into the environment. In accordance with 21 CFR 530.41, extra-label use of this product in food-producing animals is prohibited. In addition, the sponsor has agreed to participate in an antimicrobial susceptibility surveillance program.

The agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact (FONSI) and the evidence supporting that finding are contained in an environmental assessment, which may be seen in the Dockets Management Branch (HFA-305), Room 1061, 5630 Fishers Lane, Rockville, Maryland 20852.

Under section 512(c)(2)(F)(ii) 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 application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant.

Baytril 100 Injectable Solution is under patent numbers U.S.4,670,444, and 5,077,429, expiring June 2, 2004, and December 31, 2008, respectively.

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.