Approval Date: May 4, 1990

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-913

B. Sponsor

Mobay Corporation
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201

C. Proprietary Name

Baytril® Antibacterial Injectable Solution

D. Product Established Name

Enrofloxacin

E. Marketing Status

Rx

F. Dosage Form, Routes of Administration and Recommended Dosages

The optimum dose of Baytril (brand of enrofloxacin) has been established at 2.5 mg/kg (1.13 mg/lb) of body weight administered twice daily (every 12 hours). Baytril Tablets should be given twice daily for two to three days beyond the cessation of clinical signs to a maximum of ten days. Baytril Injectable Solution may be used as the initial dose. It should be administered intramuscularly (IM) as a single dose, followed by Baytril Tablets every 12 hours. If no improvement is seen within five days, the diagnosis should be re-evaluated and a different course of therapy considered.

Dosage Chart

Weight of Dog	Baytril 22.7 mg/mL Injectable Solution	BAYTRIL (Scored)* Tablet
2.3 kg (5 lb)	0.25 mL	1 x 5.7 mg tablet twice daily
9.1 kg (20 lb)	1.00 mL	1 x 22.7 mg tablet twice daily
27.2 kg (60 lb)	3.00 mL	1 x 68.0 mg tablet twice daily

* The 5.7 and 22.7 mg tablets are single scored and the 68 mg tablet is double scored for accurate dosing.

G. Indications for Use:

Baytril® (brand of enrofloxacin) Antibacterial Tablets and Injectable Solution are indicated for the treatment of the following bacterial infections in dogs:
Dermal infections (wounds and abscesses) caused by susceptible strains of *Escherichia coli*, *Klebsiella pneumoniae* *, *Proteus mirabilis*, and *Staphylococcus aureus*.

Respiratory infections (pneumonia, tonsillitis, rhinitis) caused by susceptible strains of *Escherichia coli* and *Staphylococcus aureus*.

Urinary cystitis caused by susceptible strains of *Escherichia coli*, *Proteus mirabilis* and *Staphylococcus aureus*.

**Klebsiella* has been recognized as a significant pathogen associated with nosocomial infections in dogs. (1,2)

Glickman, L.T. Veterinary Nosocomial (Hospital-Acquired) *Klebsiella* Infections: JAVMA, V.179, No. 12, Dec. 15, 1981, 1389-1392.
Kaufman, J. Nosocomial Infections: Klebsiella. The Compendium on Continuing Education, V.6, No. 4, April 1984, 303-310.

II. STUDIES DEMONSTRATING EFFECTIVENESS

A. Pivotal Studies

1. Cross referenced to Baytril® (brand of enrofloxacin) Antibacterial Tablets, NADA 140-441, 54 FR 3444 (January 24, 1989).

The tablet NADA contains dose titration and dose confirmation model studies which establish the dose and efficacy for the tablet formulation. In addition, pharmacokinetic and body fluid/tissue level studies profile the distribution of enrofloxacin in dogs, while *in vitro* microbiological studies demonstrate the drug's activity against a variety of bacterial pathogens. Finally, both pivotal and corroborative clinical evaluations were conducted to confirm the antibacterial activity of enrofloxacin in the tablet formulation, under clinical conditions.

2. Bioequivalency (Crossover) Study of Enrofloxacin Tablet and Injectable Formulations in Dogs

H.D. McCurdy and J.D. Craven, Shawnee Mission, KS.

The purpose of this trial, conducted in accordance with the July 1985, FDA Bioequivalence Guidelines, was to compare enrofloxacin tablets (NADA 140-441) with the 2.27% injectable solution in dogs at a dose rate of 2.5 mg/kg (1.13 mg/lb) body weight for both formulations. The enrofloxacin 2.27% injectable formulation was that intended for market while the tablet formulation was that currently approved and marketed. The study compared enrofloxacin serum levels collected at established time intervals, beginning just prior to dosing and continuing for 24 hours after the single dose. Following this, the dogs were rested for seven days, then dosed again with the opposite formulation according to the same procedure.

Twenty-four purebred and mixed breed adult dogs of both sexes and a wide range of body weights were used. The dogs were in good condition at the time of the study. The study was conducted from August through October 1986. The dogs were randomly assigned to study groups so that half received the tablets and half the injectable solution. The oral formulation was given directly per os and the injectable solution by IM administration. The study was well controlled and blinded in that the laboratory conducting the assays was not advised of the treatments given. Pretreatment blood samples were used to confirm the absence of enrofloxacin in the serum before dosing. Comparisons were made between serum levels from dogs receiving the established tablet formulation, as a positive control, and those from dogs receiving the injectable formulation. The second round of a single dose, and serum collections using the opposite formulation (i.e., crossover), allowed the evaluation of each dog with each formulation.

Serum samples were submitted to an independent laboratory for analysis of enrofloxacin levels according to a standard microbiological method. Confidence intervals (90%) for area under the curve (AUC), maximum concentration (Cmax) and time to maximum concentration (Tmax) were calculated from an appropriate analysis of variance for the crossover study design. The results are presented in Table 1 and Figure 1 below. Other than the first hour when the injectable values were higher ($P<0.01$), there were no significant differences between the tablet and injectable group. Based upon this approach, the injectable formulation is at least as bioavailable as the tablet formulation. No adverse effects were observed.

Table 1. Experiment A-86-21 Summary of Daily Gain/Chick

Formulation	No. of Dogs	Pretreat	Hours after Treatment – 0.25	Hours after Treatment – 0.50	Hours after Treatment – 0.75	Hours after Treatment – 1.00	Hours after Treatment – 2.0	Hours after Treatment – 4.0	Hours after Treatment – 8.0	Hours after Treatment – 12.0
Tablet	24	0.00	0.08	0.47	0.70	0.70	0.70	0.55	0.18	0.09
Injectable	24	0.00	0.72	1.09	1.00	0.94	0.82	0.54	0.20	0.10

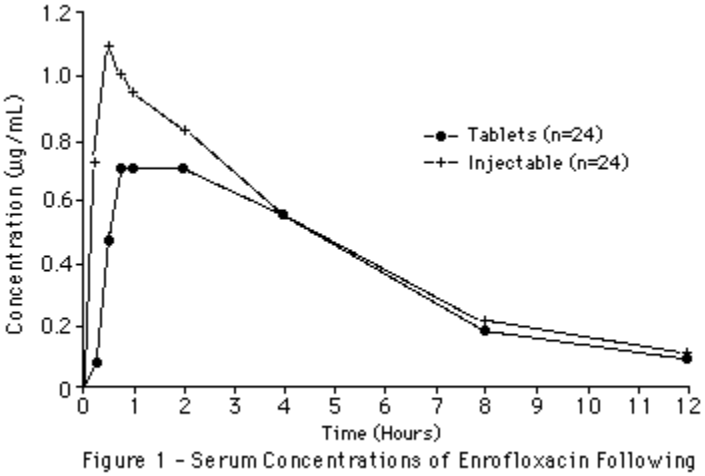

Figure 1 - Serum Concentrations of Enrofloxacin Following Either a Single Oral or Intramuscular Dose

3. Clinical Evaluation of BAY Vp 2674 (enrofloxacin) Injectable Solution plus Tablets Against Certain Bacterial Infections in Dogs.

Dr. Richard Mauldin - Oklahoma City, OK
Dr. Culver Moe Oklahoma City, OK
Dr. Sara Core Abilene, TX
Dr. Ben Baker Ft. Smith, AR
Dr. Richard Heers Tulare, CA
Dr. Ted Lamp Bellville, TX
Dr. Ken Winters Overland Park, KS

A well-controlled, blinded, clinical investigation was conducted in several geographical locations from March through May 1988. The purpose of the study was to evaluate the clinical response under actual use conditions. The investigators (listed above) conducted trials according to a uniform protocol to compare the efficacy and safety of enrofloxacin 2.27% injectable solution followed by tablets with Tribrissen Injection followed by tablets, as the positive control. The enrofloxacin 2.27% injectable formulation was that intended for market while the tablet formulation was that currently approved and marketed. The bacterial infections studied included naturally occurring conditions of the dermal, otic, respiratory, enteric, and urinary system in dogs. Selection was made on the basis of clinical signs and a bacteriological culture. Data were submitted on 40 breeds plus mixed breeds including both sexes, ages ranging from 1.5 months to 20 years and weights from 2.3 to 54.4 kg (5 to 120 lbs). Of the 128 dogs initially selected, 13 were omitted from any assessment because of protocol deviations that could be expected to influence the results. Clinical evaluations subsequently were conducted on 115 dogs, 61 dosed with enrofloxacin and 54 with the positive control. An additional 21 dogs were omitted from microbiological evaluation because of incomplete culture data. A microbiological assessment was conducted on 94 dogs, 51 with enrofloxacin and 43 with the positive control.

Details of the distribution are presented by system in Table 2.

Table 2. Clinical Trial Case Distribution

Body System	For Clinical Evaluation - Enrofloxacin	For Clinical Evaluation - Enrofloxacin	For Microbiological Evaluation - Enrofloxacin	For Microbiological Evaluation - Enrofloxacin
Dermal	28	22	27	22
Otic	16	15	13	9
Respiratory	6	9	6	7
Enteric	4	2	2	2
Urinary	7	6	3	3
Total	61	54	51	43

The dogs were assigned to a treatment group by body system according to a randomization schedule. The study was blinded in that the investigator was not informed of the drug being used until after all evaluations were completed. Both the test and control medications were administered with a single injection, at 1 mL/9.1 kg (1 mL/20 lb) body weight, followed by oral administration of tablets for the remainder of the regimen. Enrofloxacin was given at 2.5 mg/kg (1.13 mg/lb) twice daily (BID) for up to ten days. Tribrissen was dosed according to label BID. Efficacy was evaluated by three methods. The infections were rated according to a uniform scoring system, (i.e., 0 = normal through 4 = most severe). All systems, except urinary tract infections used both before and after treatment scores. Urinary tract infections were only rated after treatment. Comparison with the positive control was accomplished by comparing the percentage reduction in the score for each system. The second method of evaluation was the elimination of pathogens. This was done by comparing the results of the pretreatment and post-treatment cultures. Subjective evaluations for ease of administration, efficacy, and safety according to established uniform definitions formed the final evaluation method. Efficacy determinations were based on medical decisions. The data, therefore, are presented as means and percentages rather than with statistical analyses.

The results from each of these evaluations are presented in tabular form. Table 3 illustrates the percentage reduction in the dermal, otic, respiratory, and enteric scores and the percentage of the urinary tract scores that reached normal (score = 0) at the post-treatment examination. Enrofloxacin had a medically significant effect on lesions from those systems, comparable to Tribrissen.

Table 3. Clinical Score Evaluation

System	Treatment	Cases	% Reduction
Dermal	Enrofloxacin	28	84.8
Dermal	Tribrissen	22	80.6
Otic	Enrofloxacin	16	50.9
Otic	Tribrissen	15	49.0
Respiratory	Enrofloxacin	6	60.0
Respiratory	Tribrissen	9	82.1
Enteric	Enrofloxacin	4	100
Enteric	Tribrissen	2	100
System	**Treatment**	**Cases**	**% Normal After**
Urinary	Enrofloxacin	7	71.4
Urinary	Tribrissen	6	50.0

Culture results have been tabulated in Table 4. Over 20 genera of bacteria, involving multiple species, were isolated before treatment. Of the 170 isolates, 74 of 99 (74.7%) were eliminated following enrofloxacin treatment and 46 of 71 (64.8%) were eliminated following Tribrissen. Data were evaluated from *Staphylococcus*, *Streptococcus*, *Escherichia*, *Pseudomonas*, *Proteus*, *Bacillus*, *Acinetobacter,* and *Klebsiella* species infections. No medically significant differences were detected between the treatments with respect to bacterial response.

Table 4. Pathogen Elimination

	Percent Eliminated (Total Isolates) - Enrofloxacin	**Percent Eliminated (Total Isolates) - Tribrissen**
Dermal	82.1 (56)	67.5 (40)
Otic	61.9 (21)	50.0 (14)
Respiratory	64.3 (14)	72.7 (11)
Enteric	100.0 (2)	66.7 (3)
Urinary	66.7 (6)	66.7 (3)

Subjective evaluation results are presented in Table 5. There was essentially no difference between treatments with respect to the subjective impressions.

Table 5. Subjective Evaluations

Parameter	**Rating**	**Percent of Cases - Enrofloxacin**	**Percent of Cases - Tribrissen**
Ease of Administration	Excellent to Good	98.4	98.1
Ease of Administration	Fair to Poor	1.6	1.9
Efficacy	Excellent to Good	82.0	79.6
Efficacy	Fair to Poor	18.0	20.4
Safety	Excellent to Good	100.0	100.0

No drug related side effects were reported following dosing with either enrofloxacin or Tribrissen. It was concluded that enrofloxacin is safe and effective in treating the infections evaluated in this study.

B. Corroborative Study

Enrofloxacin Injectable Solution plus Tablets Clinical Field Trial in Dogs.

Dr. W Yates - Raytown, MO
Dr. S. Cheesman - Pine Bluff, AR
Dr. E. Schobert - Tampa, FL
Dr. D. Plumb - St. Paul, MN

A clinical investigation was conducted at several geographical locations in the US according to a uniform protocol comparing Baytril®(enrofloxacin) Injectable Solution plus Tablets with a similar regimen of Tribrissen as a positive control. The enrofloxacin 2.27% injectable formulation was that intended for market while the tablet formulation was that currently approved and marketed. The injectable formulation was given by single intramuscular injection followed by oral

administration of tablets. Enrofloxacin was given at 2.5 mg/kg (1.13 mg/lb) twice daily for up to ten days. Tribrissen was given according to the label recommended dose. One hundred twenty four case reports were submitted from December 1986 through October 1987 including infections of the dermal, respiratory, enteric, and urinary systems. Ten dogs were omitted for protocol deviations leaving 114 acceptable cases for evaluation. Those cases included 32 breeds plus mixed breeds, including 48 females and 66 males, ranging in age from ten weeks to 15 years and in weight from 2.7 to 63.5 kg (6 to 140 lbs). The infections consisted of 67 dermal, 24 respiratory, 17 urinary, and 6 enteric cases; 61 of these were treated with enrofloxacin and 53 with Tribrissen.

Efficacy was evaluated for clinical and bacteriological response. The infections were rated according to a uniform scoring system, (i.e., 0 = normal through 4 = most severe). All systems, except urinary tract infections, used both before and after treatment scores. Urinary tract infections were only rated after treatment. Comparison with the positive control was accomplished by comparing the percentage reduction in the score for each system. The second method of evaluation was the elimination of pathogens. This was done by comparing the results of the pretreatment and post-treatment cultures.

The results from each of these evaluations are presented in tabular form. Table 6 illustrates the percentage reduction in the dermal, respiratory and enteric scores and the percentage of urinary tract infections that had returned to normal (score = 0) at the post-treatment examination.

Table 6. Clinical Score Evaluation

System	**Treatment**	**Cases**	**% Reduction**
Dermal	Enrofloxacin	36	91.9
	Tribrissen	31	92.0
Respiratory	Enrofloxacin	12	84.4
	Tribrissen	12	94.4
Enteric	Enrofloxacin	3	100.0
	Tribrissen	3	50.0
System	**Treatment**	**Cases**	**% Normal After**
Urinary	Enrofloxacin	10	90.0
	Tribrissen	7	71.4

Table 7. Pathogen Elimination

	Percent Eliminated (Total Isolates) - Enrofloxacin	**Percent Eliminated (Total Isolates) - Tribrissen**
Dermal	100 (51)	98.2 (56)
Respiratory	100 (14)	94.4 (18)
Enteric	100 (2)	100 (2)
Urinary	100 (13)	75.0 (8)

III. ANIMAL SAFETY

A. Pivotal Studies

Pivotal safety studies for the use of enrofloxacin (Bay Vp 2674) in dogs with both the injectable and tablet formulations were conducted as per Good Laboratory Practice Regulations.

1. Local Tolerance Evaluation (Local Tolerance Evaluation for Intramuscular Treatment of Dogs with Bay Vp 2674 Formulation)

M. Kohlenberg of Shawnee Mission, Kansas conducted a study to evaluate for tissue irritation by administering single intramuscular injections in each rear leg to 12 male and female dogs of various breeds and a weight range of 12.3 to 16.0 kg (27.1 to 35.3 lb). The dogs were injected with the 2.27% enrofloxacin formulation intended for market, a placebo formulation without the active ingredient, a 4.54% enrofloxacin formulation and normal saline. The purpose of this study was to evaluate BAY Vp 2674 for tissue irritation as per FDA Target Species Safety Guidelines.

The study was blinded in that the necropsy observations and histopathology readings were made by an individual unaware of the treatments given. The subjective evaluations were made based on medical decisions. All important observations/findings were listed. A statistical analysis, therefore, was unnecessary to the conclusions drawn. Each dog received 2 different injections and thus each of the 4 test products was evaluated 6 times. Volumes used were equivalent to the 2.27% formulation, at a use rate of 2.5 mg/kg (1.13mg/lb). Parameters were palpations for tissue swelling, necropsy observations, and histology readings. Study duration was 10 days. No tissue swelling occurred and no clinically significant lesions were present at necropsy. Histology readings indicated adequate healing. No adverse reactions were observed in any of the treated dogs. A brief summary is presented in Table 8 below. In conclusion, the findings of the study indicated that a single intramuscular injection of a 2.27% formulation is clinically acceptable and without significant histological sequel.

Table 8. Local Tolerance Evaluation

Formulation	Total Injection Sites	Dose Rate mg/kg	Results
2.27% Soln.	6	2.5	All Groups -
Placebo of 2.27% Soln.	6	-	1. No Swelling 2. No Clinical Lesions 3. Histological – Adequate healing
4.54% Soln.	6	5.0	
Physiol. Saline	6	-	

2. Drug Tolerance Test (Drug Tolerance Test for the Use of a BAY Vp 2674 Injectable Formulation in Dogs)

M. Kohlenberg, Shawnee Mission, Kansas conducted an evaluation to define the clinical signs following a single intramuscular treatment with an excessive overdose of the 2.27% formulation intended for market. The study was blinded in that the necropsy observations and histopathology readings were made by an individual unaware of the treatments given. Also the clinical chemistry and hematology values were collected without advising laboratory personnel of the treatments. All subjective evaluations were based on medical decisions.

Four dogs (male and female) of various breeds were used with one being a nontreated control, another receiving normal saline treatment, and 2 treated with the 2.27% enrofloxacin formulation at a rate of 62.5 mg/kg or 28.4 mg/lb (25 times the use rate). The treatments were administered at multiple sites due to the larger volume of material being injected.

The dogs were evaluated for 7 days following treatment. The parameters monitored were: clinical signs, clinical chemistries, hematology, necropsy observations, and histological readings. Signs of toxicosis in the 2 treated dogs included excitation, incoordination, recumbency, convulsions, muscle tremors, salivation, vomition, alterations in respiratory rate, and slight to severe depression, but both were clinically normal within 24 hours post-treatment. They also had transient increases in CPK, SGOT, and SGPT values, but these values had essentially returned to normal at 7 days post-treatment. There were no gross or microscopic lesions. All important observations and findings were listed. Statistical analyses, therefore, were unnecessary to the conclusions drawn. A brief summary of the results is presented in Table 9 below. The study indicated that toxicity occurs after a single treatment at 25x with recovery within 24 hours and defined the clinical signs of the toxic syndrome.

Table 9. Drug Tolerance Results Summary

Formulation	No. of Dogs	Dose Rate mg/kg	Observations
2.27% Solution	2	62.5	Significant toxicosis. Both recovered within 24 hr. No gross or histopathology changes at necropsy
Physiol. Saline	1	-	Normal
Untreated	1	-	Normal

3. General Safety Study (Safety Evaluation for the Use of a BAY Vp 2674 Injectable Formulation Followed by a BAY Vp 2674 Tablet Formulation)

M. Kohlenberg of Shawnee Mission, Kansas conducted a study in 16 adult, male and female Beagle dogs in groups of 4 with a combination of the 2.27% injectable formulation intended for market and the approved 22.7 mg tablet currently being marketed. The purpose of this study was to evaluate for clinical signs and histopathology following dosing at 1, 3, and 5x doses for a 3x duration. This study was blinded in that necropsy evaluations and histopathology readings were made by an individual unaware of the treatments. Also the clinical chemistry and hematology values were collected without advising the laboratory personnel of the treatments. Subjective evaluations were made based on medical decisions. Four dogs served as nontreated controls. Initially, 3 intramuscular injections were administered to each animal at rates of 2.5, 7.5, or 12.5 mg/kg (respectively 1.13, 3.40, or 5.67 mg/lb) followed by oral treatment at the same dosage rate for a total duration of 30 days. Treatments were twice daily and thus each dog received a combination of 3 injections followed by 57 oral treatments. Parameters evaluated were clinical signs, body weights, clinical chemistries, hematology, necropsy observations, and histological readings. All important observations

and findings were listed. Statistical analyses, therefore, were unnecessary to the conclusions drawn. The results have been summarized in Table 10 below. No adverse effects occurred in any of the parameters and the study concluded an adequate safety margin based upon treatment at 5 times the use rate for 3 times the labeled duration.

Table 10. General Safety Observations

Formulation	No. of Dogs	Dose Rate mg/kg	Observations
Non-treated	4	-	-
2.27% Solution plus 22.7 mg tablet formulations used in all treated groups.	4	2.5	No drug-related adverse effects observed in any treated group.
2.27% Solution plus 22.7 mg tablet formulations used in all treated groups.	4	7.5	No drug-related adverse effects observed in any treated group.
2.27% Solution plus 22.7 mg tablet formulations used in all treated groups.	4	12.5	No drug-related adverse effects observed in any treated group.

4. Study in Female Breeding Dogs (Safety Evaluation for BAY Vp 2674 in Female Breeding Dogs)

A. Stuke and J. Magerkurth of Topeka, Kansas conducted a reproductive safety study in 15 adult female Beagle breed dogs with the 22.7 mg enrofloxacin tablet. The purpose of this study was to evaluate libido and safety in female breeding dogs following multiple treatments with the approved market tablet formulation. Before treatment the dogs were randomly assigned to one of three groups. Four dogs served as the nontreated controls, 5 received treatments orally of 2.5 mg/kg (1.13 mg/lb) twice daily for a total of 5 mg/kg (2.27 mg/lb) per day and 6 were treated orally with 7.5 mg/kg (3.40 mg/lb) twice daily for a total of 15 mg/kg (6.80 mg/lb) per day. Each female received treatments for 10 consecutive days at each of 4 stages of reproduction (prior to breeding, early pregnancy, late pregnancy and lactation). Parameters monitored included number of pups born alive, average number of pups born alive per female, number of dead pups at birth, average number of dead pups per female, average body weight (birth, 2 and 4 weeks of age), average daily body weight gain, number of pups alive at 4 weeks of age per female. Blinding was not appropriate since the monitored parameters could be measured by objective means. Results of this study (Groups 1,2,3) and the 1987 historical control data for the kennel are presented in Table 11 below.

Table 10. Comparison of Reproductive Performances with Historical Controls: Groups 1, 2, and 3

Parameter	Historical Controls	Group 1 (Non-Treated Controls)	Group 2 (5 mg/kg/day)	Group 3 (15 mg/kg/day)
Number of Females Whelping	82	4	5	6
Total Number of Pups Born	494	27	38	33
Number of Pups Born Alive	494	27	35	32
Average Number of Pups Born Alive / Female	5.5	6.8	7	5.3
Number of Dead Pups At Birth	40	0	3	1
Average Number of Dead Pups / Female	0.48	0	0.6	0.17
Average Body Weight at Birth (kg)	0.301	0.291	0.267	0.306
Average Body Weight at 2 Weeks (kg)	0.766	0.854	0.777	0.871
Average Body Weight at 4 Weeks (kg)	1.216	1.260	1.277	1.463
Average Daily Gain (gm/day)	32.6	34.3	35.8	41.1
Number of Pups Alive at 2 Weeks	-*	24	27	27
Number of Pups Alive at 4 Weeks	411*	24	27	27
Average Number of Pups Alive at 4 Weeks / Female	5.0**	6.0	5.4	4.5

* Data not available
** Parameter evaluated at 6 Weeks for Historical Controls

B. Corroborative Studies

Corroborative safety studies were conducted by Mobay Corporation, Animal Health Division, Shawnee Mission, Kansas and in the laboratories of Drs. M. L. Sharp, Vernon, Texas and Robert Young of Modesto, California. Additionally, clinical field trial safety studies were conducted by 11 veterinary practitioners in various geographical areas of the United States.

1. Bioequivalency of Enrofloxacin Tablet and Injectable Formulations (Bioequivalency of BAY Vp 2674 Tablet and Injectable Formulations in Dogs)

H. D. McCurdy of Shawnee Mission, Kansas conducted a bioequivalency study in 24 adult male and female dogs of various breeds using a cross-over design. The tablet (5.7 and 22.7 mg) formulation, given orally as the positive control, was compared to the 2.27% injectable formulation, as the test group, administered via intramuscular route. The enrofloxacin 2.27% injectable formulation was that intended for market while the tablet formulation was that currently marketed and approved. The study was well controlled and blinded in that the laboratory conducting the assays was not advised of the treatment

given. Serum levels were monitored following single treatments at 2.5 mg/kg (1.13 mg/lb). The 2 formulations were deemed bioequivalent based upon statistical analysis of the data. Based upon bioequivalence, reference is made to the preclinical safety evaluations conducted for NADA 140-441 (5.7, 22.7, and 68.0 mg enrofloxacin tablets) as this formulation's safety was previously confirmed in well-controlled studies.

Additional details concerning the study may be found beginning on page 2 (section IV.A.2.) of this FOI Summary.

2. Comparison of Two Injectable Formulations for Local Tolerance (Local Tolerance Evaluation and Comparison in Dogs for the Use of BAY Vp 2674 Formulations When Administered as Single Treatments)

M. Kohlenberg of Shawnee Mission, Kansas evaluated single subcutaneous and intramuscular treatment of 10 dogs with 2 injectable formulations (2.5 and 2.27%) at a rate of 2.5 mg/kg (1.13 mg/lb) in a local tolerance study. The enrofloxacin 2.27% injectable solution was that intended for market while the 2.5% was a preliminary formulation. The dogs were male and female, adults and of various breeds. Each animal received a total of 4 injections (one subcutaneous and one intramuscular with each of the 2 formulations). The test animals each served as their own control. They were observed for clinical signs, pain responses, tissue swellings, necropsy at 21 days and microscopic readings. No clinically significant side effects were observed, but the histologist confirmed the 2.27% formulation to be preferred based upon less tissue reactivity. The lesions were in a healing process at necropsy.

3. Preliminary Safety Evaluation (Safety Evaluation for the Use of an Injectable BAY Vp 2674 Formulation Followed by Administration of BAY Vp 2674 Tablets to Dogs)

M. Kohlenberg of Shawnee Mission, Kansas conducted a preliminary uncontrolled safety evaluation in 20 male and female adult dogs of varied breeding with a combination treatment of oral (22.7 mg tablets, approved and marketed) and injectable (2.27% intended for market) formulations. Ten dogs received a single subcutaneous treatment at either 2.5 or 5.0 mg/kg (respectively 1.13 or 2.27 mg/lb) followed by the tablet orally at the rate of 2.5 or 5.0 mg/kg (respectively 1.13 or 2.27 mg/lb) twice daily for 7 days. The other 10 dogs received the same treatment scheduled except the initial treatment was via intramuscular route. Parameters included observations for pain at treatment, palpation for tissue swelling, necropsy observations and histology. The study concluded these combinations are clinically acceptable.

4. Additional Preclinical Safety Evaluations Conducted in Laboratory / Clinical Conditions (Safety Evaluations of Baytril® Injectable/Tablets in Dogs)

M. Sharp of Vernon, Texas and R. Young of Modesto, California conducted additional safety evaluations with 88 dogs (male and female, greater than 8 months of age and of 29 breeds). Each dog received a single enrofloxacin intramuscular injection with the 2.27% formulation followed by twice daily enrofloxacin tablet treatment orally for the remainder of the 10 day regimen.

The enrofloxacin 2.27% injectable formulation was that intended for market while the tablet formulation was that currently approved and marketed. Each treatment was at a 2.5 mg/kg (1.13 mg/lb) rate. In addition, 28 dogs received treatment with Tribrissen (positive control) as per labeled directions (injection followed by tablets) for comparative purposes. Parameters included monitoring for pain, tissue swelling and clinical signs. With the injections, there was a 2.3% incidence of moderate tissue swelling following enrofloxacin treatment and a 32.1% incidence of slight to moderate pain following the Tribrissen injections. Two cases of emesis were observed following treatment with each of the 2 products. This evaluation further confirmed safety for the combination injectable and tablet enrofloxacin treatment.

5. Confirmation of Safety in Clinical Field Trials

Confirmation of safety for a single intramuscular injection followed by oral tablet treatment was achieved in clinical field trials conducted by 11 veterinary practitioners at 10 geographic locations. Additional details concerning the investigators, etc. may be found beginning on page 4 (section IV.A.3.) and page 7 (section IV.B.) of this FOI Summary. Enrofloxacin treatment (injection followed by tablets) was administered to 122 dogs. The enrofloxacin 2.27% injectable formulation was that intended for market while the tablet formulation was that currently approved and marketed. Enrofloxacin was administered at 2.5 mg/kg (1.13 mg/lb) twice daily for up to 10 days. Breeds of dogs treated were representative of the canine population. Weight range for the treated animals was 2.7 to 63.5 kg (6 to 140 lbs.). Age range was 1.5 months to 20 years. No evidence of drug potentiation was observed for concurrent treatment with enrofloxacin and a variety of other animal health products. No side effects were reported in the enrofloxacin treated dogs. The veterinary practitioners rated safety for enrofloxacin treatments as excellent in 77% of the cases and good in the remaining 23%. These trials used Tribrissen (injection followed by tablets) as the positive control.

IV. HUMAN SAFETY

A. Human Food Safety

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is labeled for use in dogs, which are non-food animals.

B. Human Safety Relative to Possession, Handling and Administration

The labeling contains an adequate warning statement: "WARNING: Keep out of reach of Children."

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. The data consist of adequate and well controlled studies, including field investigations, demonstrating effectiveness and adequate tests to demonstrate safety to the target animal. Dermal infections (wounds and abscessed) caused by susceptible strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Staphylococcus aureus*.

Respiratory infections (pneumonia, tonsillitis, rhinitis) caused by susceptible strains of *Escherichia coli* and *Staphylococcus aureus*.

Urinary cystitis caused by susceptible strains of *Escherichia coli*, *Proteus mirabilis* and Staphylococcus aureus.

A differential diagnosis and monitoring of a patient's progress require the professional expertise of a veterinarian. Professional diagnosis, including testing, is necessary to determine the nature of the infection, e.g. to determine whether the infection is bacterial or of some other cause. Laymen are unable to make this diagnosis for the conditions indicated for this drug because different causative organisms may produce the same signs in the animal. For proper monitoring, a veterinarian must determine the parameters to be measured, how often the measurement is to take place, and whether recovery is taking place. Therefore, the labeling for this product must contain the veterinary prescription legend.

Under Section 512(c)(2)(F)(ii) of the Generic Animal Drug and Patent Term Restoration Act of 1988, this new animal drug application qualifies for three years of marketing exclusivity.

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.