Date of Approval: November 23, 2009

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-299

RESFLOR GOLD

Florfenicol and Flunixin Meglumine (in 2-pyrrolidone and triacetin)
Injectable Solution
Beef and Non-Lactating Dairy Cattle

For treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*, and control of BRD-associated pyrexia in beef and non-lactating dairy cattle

Sponsored by:

Intervet, Inc.

TABLE OF CONTENTS

I. GENERAL INFORMATION:

A. File Number:	NADA 141-299
B. Sponsor:	Intervet, Inc. 56 Livingston Avenue Roseland, New Jersey 07068 Drug Labeler Code: 000061
C. Proprietary Name:	RESFLOR GOLD
D. Established Name:	Florfenicol and flunixin meglumine (in 2-pyrrolidone and triacetin)
E. Pharmacological Categories:	Antimicrobial and non-steroidal anti-inflammatory (NSAID)
F. Dosage Form:	Injectable solution
G. Amount of Active Ingredients:	300 mg florfenicol and 16.5 mg flunixin (27.37 mg flunixin meglumine) per mL
H. How Supplied:	100, 250, and 500 mL glass vials
I. How Dispensed:	Rx
J. Dosage:	40 mg florfenicol/kg body weight (BW) and 2.2 mg flunixin/kg BW once (equivalent to 2 mL/15 kg BW or 6 mL/100 lbs)
K. Route of Administration:	Subcutaneous
L. Species/Classes:	Cattle/Beef and non-lactating dairy
M. Indication:	RESFLOR GOLD is indicated for treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*, and control of BRD-associated pyrexia in beef and non-lactating dairy cattle.

II. EFFECTIVENESS:

RESFLOR GOLD is a combination of florfenicol and flunixin meglumine. Florfenicol is approved as NUFLOR Injectable Solution (NADA 141-063) and NUFLOR GOLD Injectable Solution (NADA 141-265) in beef and non-lactating dairy cattle. Flunixin meglumine is approved as BANAMINE Injectable Solution (NADA 101-479) in beef and non-lactating dairy cattle.

A. Dosage Characterization:

The dose of florfenicol in RESFLOR GOLD [40 mg florfenicol/kg body weight (BW)] is identical to the approved subcutaneous (SC) dose of florfenicol in NUFLOR Injectable Solution and NUFLOR GOLD Injectable Solution. The dose of flunixin (as flunixin meglumine) in RESFLOR GOLD (2.2 mg flunixin/kg BW) is identical to the approved dose of flunixin in BANAMINE Injectable Solution.

B. Substantial Evidence:

1. Natural Infection Clinical Field Study

a. Title: "An Evaluation of the Clinical Efficacy and Antipyretic Effect of RESFLOR GOLD […] and the Clinical Efficacy of NUFLOR GOLD in Comparison to Saline for the Treatment of Naturally Occurring Bovine Respiratory Disease; a Multi-center Pivotal Field Trial. Study No. C05-126-00. March 2006 to April 2006."

b. Study Investigators and Locations:

David T. Bechtol, D.V.M., Palo Duro Consultation Research and Feedlot, Canyon, TX
Breck D. Hunsaker, D.V.M., Ph.D., Horton Feedlot and Research Center, Wellington, CO
Edward G. Johnson, D.V.M., Johnson Research, LLC, Parma, ID
Kelly F. Lechtenberg, D.V.M., Ph.D., Midwest Veterinary Services, Inc., Oakland, NE

c. Study Design:

i. *Objective:* To demonstrate the effectiveness of RESFLOR GOLD for the treatment of bovine respiratory disease (BRD) and control of BRD-associated pyrexia compared to NUFLOR GOLD Injectable Solution and saline.

ii. *Test Animals:* Four-hundred eighty-six male (castrated and intact) and female pure- and cross-bred beef calves, five to eight months old, weighing 316 to 664 lbs, were enrolled in the study.

iii. *Experimental Design:* The study was conducted at four sites. At each site, calves were randomly assigned to treatment groups and allocated to pens. Males and females were randomized and penned separately. Calves were penned in blocks of four, and study pens were filled to capacity (eight calves per pen) in consecutive order. Treatments were commingled within pens, and the individual calf was the experimental unit. Calves were enrolled in the study when they were diagnosed with BRD and met the enrollment criteria of either a depression score ≥ 2 and rectal temperature ≥ 104.0 °F, or respiratory score ≥ 2 and rectal temperature ≥ 104.0 °F. The following clinical scoring scales were used:

Depression Scoring Scale:

0 = Normal: bright, alert, and responsive.

1 = Mildly depressed: may stand isolated with its head held down or ears drooping, but will quickly respond to minimal stimulation.

2 = Moderately depressed: may stand isolated with its head down; may show signs of muscle weakness (standing cross-legged or knuckling when walking); shows a delayed response to minimal stimulation or requires greater stimulation before showing a response.

3 = Severely depressed: may be recumbent and reluctant to rise, or if standing isolated, may be reluctant to move; ataxia, knuckling, or swaying may be evident when moving; eyes dull; head carried low with ears drooping; possible excess salivation/lacrimation.

Respiratory Scoring Scale:

0 = Normal: no abnormal respiratory symptoms are present; respiratory rate and effort are appropriate for the environment.

1 = Mild respiratory distress: serous nasal or ocular discharge and/or cough.

2 = Moderate respiratory distress: mucous or mucopurulent nasal or ocular discharge and/or increase in respiratory rate or effort.

3 = Severe respiratory distress: marked increase in respiratory rate or effort, including one or more of the following: open-mouth breathing, abdominal breathing, and/or extended head.

iv. *Test Article Administration:* Calves were administered one of two test articles or a control article. The first test article was RESFLOR GOLD (florfenicol and flunixin meglumine in 2-pyrrolidone and triacetin) injectable solution. The second test article was NUFLOR GOLD

(florfenicol in 2-pyrrolidone and triacetin) Injectable Solution (NADA 141-265). The control article was saline (0.9% sodium chloride) injectable solution. Treatments were administered SC in the left side of the neck once on the day of enrollment (Day 0). The maximum volumes per injection site were 10 mL for RESFLOR GOLD and 15 mL for both NUFLOR GOLD Injectable Solution and saline.

v. *Treatment groups:* The treatment groups are described below in Table 1.

Table 1. Treatment Groups.

Treatment	**Dosage**	**No. of Enrolled Animals[1]**
Saline	2 mL/15 kg[2] BW SC once	162
RESFLOR GOLD	40 mg florfenicol/kg BW and 2.2 mg flunixin/kg BW (2 mL/15 kg BW) SC once	161
NUFLOR GOLD Injectable Solution	40 mg florfenicol/kg BW (2 mL/15 kg BW) SC once	163

[1]One site (40 animals in each of the three treatment groups, for a total of 120 animals) was excluded from the analysis of treatment success for BRD due to a protocol deviation. This protocol deviation did not affect the analysis of change in rectal temperature; therefore, all four sites were included in the analysis of change in rectal temperature.

[2]Volume equivalent to RESFLOR GOLD and NUFLOR GOLD Injectable Solution dosages.

vi. *Measurements and Observations:*

a) *Treatment Success for BRD:* From Day 0 to Day 11, calves that were moribund due to BRD and calves with depression or respiratory scores of 3, regardless of rectal temperature, were classified as treatment failures and removed from the study. Calves that died or were euthanized were necropsied. Mortalities due to BRD were classified as treatment failures. From Day 3 to Day 10, calves with depression or respiratory scores ≥ 2 and rectal temperatures ≥ 104.0 °F were classified as treatment failures and removed from the study. On Day 11, all calves remaining on-study were classified as treatment successes if they had respiratory and depression scores ≤ 1 and rectal temperatures < 104.0 °F. All other calves were classified as treatment failures.

The criteria used to evaluate the effectiveness of RESFLOR GOLD for the treatment of BRD were:

- A statistically significantly greater proportion of treatment successes among calves in the RESFLOR GOLD treatment group compared to the saline control treatment group; and
- Non-inferiority of the treatment success rate among calves in the RESFLOR GOLD treatment group compared to the NUFLOR GOLD Injectable Solution treatment group.

Nasal swabs were collected for bacterial culture pre-treatment (all enrolled calves) and post-treatment (calves classified as treatment failures prior to removal). In addition, cultures were performed on lung tissue samples collected from necropsied calves. The criterion used to include a pathogen in the indication was that at least 30 isolates were obtained from at least 30 calves in the study.

b) *Change in Rectal Temperature:* On Day 0, rectal temperature was obtained on each calf pre-treatment and 6 hours post-treatment.

The criteria used to evaluate the effectiveness of RESFLOR GOLD for the control of BRD-associated pyrexia were:

- A statistically significantly greater proportion of calves whose rectal temperatures decreased by ≥ 2.0 °F from pre-treatment to 6 hours post-treatment in the RESFLOR GOLD treatment group compared to the saline control treatment group; and
- A statistically significantly greater mean decrease in rectal temperature from pre-treatment to 6 hours post-treatment for calves in the RESFLOR GOLD treatment group compared to the NUFLOR GOLD Injectable Solution treatment group; and
- A statistically significantly greater mean decrease in rectal temperature from pre-treatment to 6 hours post-treatment for calves in the RESFLOR GOLD treatment group compared to the saline control treatment group.

vii. Statistical Analysis:

a) *Treatment Success for BRD:* The treatment success rate for BRD was analyzed using a generalized linear mixed effect model with binomial error, logit link, and Kenward-Rogers degrees of freedom, with fixed effect of treatment and with random effects of site, treatment by site, pen within site, and treatment by pen within site. Statistical tests were conducted at the two-sided 0.05 level of significance. After establishing significance of overall treatment effect, the contrast between RESFLOR GOLD and saline was evaluated. An

unconditional exact test of non-inferiority was then conducted to determine whether RESFLOR GOLD was non-inferior to NUFLOR GOLD Injectable Solution, employing a 15% margin of non-inferiority evaluated at the one-sided 95% level of confidence.

b) *Change in Rectal Temperature:* Analyses of rectal temperature and proportion success rate in reducing rectal temperature ≥ 2.0 °F used mixed effect linear models, with fixed effect of treatment and with random effects of site, treatment by site, treatment by pen, pen within site, and treatment by pen within site. The model for rectal temperature was normal with identity link, and the model for proportion success rate in reducing rectal temperature ≥ 2.0 °F was binomial with logit link. Statistical tests were conducted at the two-sided 0.05 level of significance. Appropriate contrasts were reported only after establishing significance of overall treatment effect.

d. Results:

i. *Treatment Success for BRD:* Three-hundred fifty-six calves were included in the analysis of treatment success for BRD. The treatment success rate for BRD for the RESFLOR GOLD treatment group (68.4%) was statistically significantly greater (p = 0.0255) compared to the treatment success rate for BRD for the saline control treatment group (42.9%). RESFLOR GOLD was non-inferior to NUFLOR GOLD Injectable Solution for the treatment of BRD, with a one-sided 95% lower confidence bound for the difference between the two treatments equal to -13.2%, within the specified 15% margin of non-inferiority. One-hundred eighty-three isolates of *Mannheimia haemolytica*, 139 isolates of *Pasteurella multocida*, and 84 isolates of *Histophilus somni*, were obtained from more than 30 calves in the study.

ii. *Change in Rectal Temperature:* Four-hundred seventy-six calves were included in the analysis of change in rectal temperature. The proportion of calves whose rectal temperatures decreased ≥ 2.0 °F from pre-treatment to 6 hours post-treatment was statistically significantly greater (p = 0.0019) in the RESFLOR GOLD treatment group compared to the saline control treatment group. The mean decrease in rectal temperature from pre-treatment to 6 hours post-treatment was statistically significantly greater (p = 0.0031) in the RESFLOR GOLD treatment group compared to the NUFLOR GOLD Injectable Solution treatment group. The mean decrease in rectal temperature from pre-treatment to 6 hours post-treatment was statistically significantly greater (p = 0.0002) in the RESFLOR GOLD treatment group compared to the saline control treatment group.

e. Adverse Reactions: No adverse reactions associated with the administration of RESFLOR GOLD were observed.

f. Conclusions: The results of this study demonstrate that RESFLOR GOLD, when administered as a single SC dosage of 40 mg florfenicol/kg BW and 2.2 mg flunixin/kg BW, is effective for treatment of BRD associated with *M. haemolytica*, *P. multocida*, and *H. somni* and control of BRD-associated pyrexia in beef and non-lactating dairy cattle.

2. Determination of Minimum Inhibitory Concentrations (MICs)

The (MICs) of florfenicol were determined for BRD isolates obtained from calves enrolled in BRD field studies in the U.S. in 2006 using methods recommended by the Clinical and Laboratory Standards Institute (M31-A2). Isolates were obtained from pre-treatment nasal swabs from all calves enrolled at four sites, post-treatment nasal swabs from treatment failures in the RESFLOR GOLD and saline control treatment groups at three sites, and lung tissue from one calf that died in the saline control treatment group. The results are shown below in Table 2.

Table 2. Florfenicol MIC Values* of Indicated Pathogens Isolated from Cattle with Naturally-Occurring BRD.

Indicated pathogens	**Year of isolation**	**Number of isolates**	**MIC_{50}** ** **(µg/mL)**	**MIC_{90}** ** **(µg/mL)**	**MIC range (µg/mL)**
Mannheimia haemolytica	2006	183	1.0	1.0	0.5 to 32
Pasteurella multocida	2006	139	0.5	0.5	≤ 0.125 to 16
Histophilus somni	2006	84	≤ 0.125	≤ 0.125	≤ 0.125 to 0.25

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.

** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

III. TARGET ANIMAL SAFETY:

A. Systemic Safety:

Systemic target animal safety for the use of RESFLOR GOLD in cattle was demonstrated by conducting a target animal safety study in cattle using an initial florfenicol-flunixin injectable solution formulation, conducting a bioequivalence study using the initial formulation and RESFLOR GOLD, and conducting an injection site safety study using RESFLOR GOLD. The FOI Summary for the original approval of NADA 141-265 (NUFLOR GOLD Injectable Solution) dated March 21, 2008, contains a summary of a study titled "Florfenicol (SCH 25298)/2-Pyrrolidone/Triacetin Formulation: Subcutaneous Injection Target Animal Safety Study in Cattle," Study No. 03410. This study supports the safety of the excipients in RESFLOR GOLD (2-pyrrolidone and triacetin). These excipients

are used in the same concentration in both NUFLOR GOLD Injectable Solution and RESFLOR GOLD.

1. Target Animal Safety Study

a. Title: "SCH 529752 [Initial Florfenicol-Flunixin Formulation]: Subcutaneous Injection Target Animal Safety Study in Cattle." Study No. 01503.

b. Study Director: Terry TerHune, DVM, PhD

c. Study Location: HMS Veterinary Development, Inc.
Tulare, California

d. General Study Design:

i. *Purpose*: To assess the safety of an initial florfenicol-flunixin formulation when administered to cattle by subcutaneous injection at 0X, 1X, 3X, and 5X the proposed clinical dose equivalent to 40 mg of florfenicol/kg body weight (BW) and 2.2 mg of flunixin/kg BW for three consecutive days (3X the intended duration). The study was conducted in compliance with FDA's Good Laboratory Practice Regulations (21 CFR Part 58).

ii. *Animals*: Thirty-two crossbred commercial cattle (16 castrated males and 16 females), age 8 to 12 months, weighing 142 to 251 kg at the start of the treatment period, were used in the study.

iii. *Test articl*e: The initial formulation, containing 300 mg of florfenicol/mL and 16.5 mg flunixin (as flunixin meglumine)/mL, was administered at a 1X, 3X, or 5X dose. A 0.9% saline solution, administered at a volume equivalent to the 5X dose, was used as a placebo control.

iv. *Study Design*: The acclimation period began on Day -21. On Day -8, four females and four castrated males were selected and randomized to each of four treatment groups (0X, 1X, 3X, and 5X). The test article was administered by subcutaneous injection on the dorsolateral sides of the neck once daily for three consecutive days starting on Day 1. A maximum volume of 10 mL was injected per site.

v. *Measurements and Observations*: Physical examinations were conducted on all animals on Days -14, -9, -7, -1, and then 24 hours after the first and third doses. Vital signs (rectal temperature, respiratory rate, heart rate, mucous membrane color, and capillary refill time) were recorded daily starting on Day -14. Animals were observed twice daily beginning on Day -14 for survival, general condition, and any abnormal clinical signs. Cattle were weighed on Days -21, -14, -9, -7, -1, prior to each dose, and

prior to necropsy. Feed and water consumption were measured daily beginning on Day -14. Blood samples were collected from all cattle on Days -14, -10, -7, -1, and 24 hours after the first and third doses for determination of serum chemistry, hematology, and coagulation parameters. Blood was collected prior to the first dose and at 2, 4, 6, 8, 12, and 24 hours after dosing for plasma florfenicol and flunixin concentrations. Urine and fecal samples were collected for analysis on Days -14, -10, -7, -1, and 24 hours after the first and third doses. All animals were euthanized by captive bolt on the day after final dosing. Complete gross necropsy, histopathologic evaluation, and organ weight analyses were performed.

vi. *Statistical Methods*: All continuous variables were analyzed using a mixed model. Variables measured multiple times were analyzed using repeated measures analysis of covariance (ANCOVA) using the average baseline values as covariates. Statistical comparisons of treatment effects were performed at the 0.1 level of significance; comparison of treatment and sex, or treatment and time and sex were performed at the 0.05 level of significance.

e. Results: Mild to moderate injection site swellings were recorded on Days 2 and 4 in all animals in the 1X, 3X, and 5X groups, which persisted through Day 4 (the day of necropsy). On Days 3 and 4, the 1X, 3X, and 5X groups showed statistically significantly ($P < 0.1$) lower average feed and water consumption compared with the control group. Body weights were mildly decreased and numerically lower in the 1X, 3X, and 5X groups, compared with the control group. No test article-related changes were observed in serum chemistry, hematology, coagulation, fecal analysis, or organ weights.

Test article-related macroscopic lesions were limited to injection site reactions and included mild to marked reddish-tan discoloration, thickening, and edema, with minimal discoloration or creamy masses that rarely extended to the muscle. Histopathologic lesions in all groups included minimal to moderate acute edema/fibrin, minimal to mild acute hemorrhage, minimal to moderate acute/subacute inflammation, and rare chronic, moderate focal abscesses. Test article-related histopathologic lesions also included occasional minimal to mild acute muscle degeneration. The lesions tended to increase in severity in the 3X and 5X groups.

Peak plasma concentrations for both drugs occurred 2 to 6 hours post-injection. On Day 1, the average C_{max} and AUC values for florfenicol and flunixin plasma concentration did not rise above values achieved following the administration of the 3X proposed dose. Accordingly, the systemic exposures to florfenicol and flunixin in those animals enrolled in the 5X group were effectively the same as the corresponding drug exposures in animals enrolled in the 3X dose group. On Day 3, there were

dose-proportional increases in the average AUC value for florfenicol plasma concentrations and dose-proportional increases in the average C_{max} and AUC values for flunixin plasma concentrations; however, the average C_{max} value of the florfenicol plasma concentrations on Day 3 did not rise above that achieved in the 3X dose group. There were no gender-related differences with the florfenicol component and there were no conclusive gender-related differences with the flunixin component.

f. Conclusions: Administration of the initial florfenicol-flunixin formulation at 1X, 3X, and 5X the proposed dose (at 3X the proposed duration) may cause decreased feed consumption (and associated decrease in body weight) and decreased water consumption. No other adverse effects were seen. The use of the initial florfenicol-flunixin formulation at the intended proposed dose of 40 mg of florfenicol/kg BW and 2.2 mg of flunixin/kg BW administered subcutaneously once is safe in cattle.

2. Bioequivalence Study:

a. Title: "SCH 529752: Comparison of Florfenicol-Flunixin/ 2-Pyrrolidone/Triactin Formulation to [an Initial Florfenicol-Flunixin Formulation] in a Single-Dose Bioequivalence Crossover Study of Florfenicol and Flunixin in Cattle." Study Number SN 06244.

b. Study Director: Patrick W. Lockwood, DVM

c. Study Location: Schering-Plough Animal Health
Terre Haute, Indiana

d. General Study Design:

i. *Purpose*: To demonstrate the relative bioavailability of florfenicol and flunixin administered as the revised commercial florfenicol-flunixin/ 2-pyrrolidone/triacetin formulation (RESFLOR GOLD) as compared to an initial florfenicol-flunixin formulation. A pivotal target animal safety study was conducted with the initial formulation. This study serves to bridge the findings from the target animal safety study conducted using the initial formulation to RESFLOR GOLD.

ii. *Animals*: Twenty-eight beef cattle (14 castrated males, 14 intact females) of feedlot age were evaluated in the study. Animals were divided into two treatment groups, each containing 7 males and 7 females.

iii. *Test Article Administration*: The initial formulation and RESFLOR GOLD were used. Both formulations (test articles) contained 300 mg florfenicol/mL and 16.5 mg flunixin (as flunixin meglumine)/mL, and were administered as a single subcutaneous dosage of 40 mg florfenicol/kg body weight (BW) and 2.2 mg flunixin/kg BW. Injections were given in the neck with a maximum injection volume of

10 mL per injection site. After a minimum 48 day washout period, the administration of the test article in the two treatment groups was reversed.

iv. *Study Design*: Randomized, two-period, two-sequence, two-treatment crossover study.

v. *Statistical Methods*: Product relative bioavailability assessments were based upon comparisons of product values for the area under the plasma concentration-time curve (AUC) from time zero to the last quantifiable concentration (AUC_{0-t}) and peak concentration (C_{max}) for the active components, florfenicol and flunixin. The individual subject values for these parameters were transformed (natural logs) prior to statistical comparison. An analysis of variance (ANOVA) was run on the Ln-AUC_{0-t} and Ln-C_{max}, where subject nested within sequence was the random effect and treatment and period were the fixed effects. The resulting residual error term was used to generate the 90% confidence interval about treatment least square means.

vi. *Measurement and Observations*: At specified intervals during the study, the following parameters were evaluated: clinical observations, abnormal feed consumption, body weight, and plasma florfenicol and flunixin concentrations. Blood was collected from each animal at 0 (pre-dose), 5, 10, 15, 30, and 45 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, and 144 hours post-dose. Plasma samples were analyzed for florfenicol and flunixin concentrations using a validated liquid chromatographic double mass spectrometry (LC-MS/MS) method. Serial plasma concentrations of florfenicol and flunixin were subjected to non-compartmental pharmacokinetic analysis once for each treatment phase using WINNONLIN Professional Version 5.1.1 (Pharsight Corporation, Mountain View, CA).

e. Results:

i. Mortalities: None.

ii. Clinical Observations: Injection site swellings were reported in both test-article treatment groups and were described as small, large, hard, diffuse and/or severe. Swellings were observed 2 to 3 days after dosing and tended to resolve between 15-36 days post-injection. No other abnormal general health observations were noted during the study.

iii. Laboratory Analysis: The florfenicol and flunixin extent of absorption (AUC_{0-t}) was equivalent when the cattle were dosed with the revised and initial formulations. The greater peak florfenicol concentrations observed following administration of the revised formulation were determined to be clinically insignificant. The tabular results of the relative bioavailability study are provided in Table 3 (florfenicol) and Table 4 (flunixin). The relative bioavailability profiles for florfenicol and flunixin are shown in Figure 1 (florfenicol) and Figure 2 (flunixin).

Table 3. Mean and Percent Coefficient of Variation (%CV) for Florfenicol Pharmacokinetic Parameters.

	Formulation		AUC_{0-t}[1] (ng*hr/mL)	AUC_{0-inf}[2] (ng*hr/mL)	C_{max}[3] (ng/mL)	T_{max}[4] (hr)	$T_{½}$[5] (hr)	MRT_{0-inf}[6] (hr)
	Revised Formulation	N	28	28	28	28	28	28
		Mean	242527	247577	11151	6.25	28.5	27.29
		%CV	18	17	36	62	35	43
	Initial Formulation	N	27	26	27	27	26	26
		Mean	233214	240753	9914	8	32.6	33.8
		%CV	22	24	45	37	43	43
Relative bioavailability		Ratio (Revised/Initial)	1.04	1.03	1.12	0.78	0.87	0.80
Confidence Limit		Lower bound	0.99	N/D[7]	0.98	N/D[7]	N/D[7]	N/D[7]
		Upper bound	1.09	N/D[7]	1.3	N/D[7]	N/D[7]	N/D[7]

[1] AUC_{0-t} = Area under the plasma-concentration-time curve from time zero to the last quantifiable concentrations
[2] AUC_{0-inf} = AUC from time zero to infinity
[3] C_{max} = Maximum plasma concentration
[4] T_{max} = Time at which C_{max} was observed
[5] $T_{½}$ = Terminal elimination half-life.
[6] MRT_{0-inf} = Mean residence time from time zero to infinity
[7] N/D = Not determined

Table 4. Mean and Percent Coefficient of Variation (%CV) for Flunixin Pharmacokinetic Parameters.

	Formulation		AUC_{0-t}[1] (ng*hr/mL)	AUC_{0-inf}[2] (ng*hr/mL)	C_{max}[3] (ng/mL)	T_{max}[4] (hr)	$T_{½}$[5] (hr)	MRT_{0-inf}[6] (hr)
	Revised Formulation	N	28	27	28	28	27	27
		Mean	13370	14448	1913	1.14	9.5	11.4
		%CV	37	35	41	84	34	37
	Initial Formulation	N	27	23	27	27	23	23
		Mean	13750	14803	2838	1.06	8.8	9.5
		%CV	223	24	45	37	43	43
Relative bioavailability		Ratio (Revised/Initial)	0.97	0.98	0.67	0.67	0.00	1.09
Confidence Limit		Lower bound	0.84	N/D[7]	0.58	N/D[7]	N/D[7]	N/D[7]
		Upper bound	1.10	N/D[7]	0.77	N/D[7]	N/D[7]	N/D[7]

[1] AUC_{0-t} = Area under the plasma-concentration-time curve from time zero to the last quantifiable concentrations

[2] AUC_{0-inf} = AUC from time zero to infinity

[3] C_{max} = Maximum plasma concentration

[4] T_{max} = Time at which C_{max} was observed

[5] $T_{½}$ = Terminal elimination half-life.

[6] MRT_{0-inf} = Mean residence time from time zero to infinity

[7] N/D = Not determined

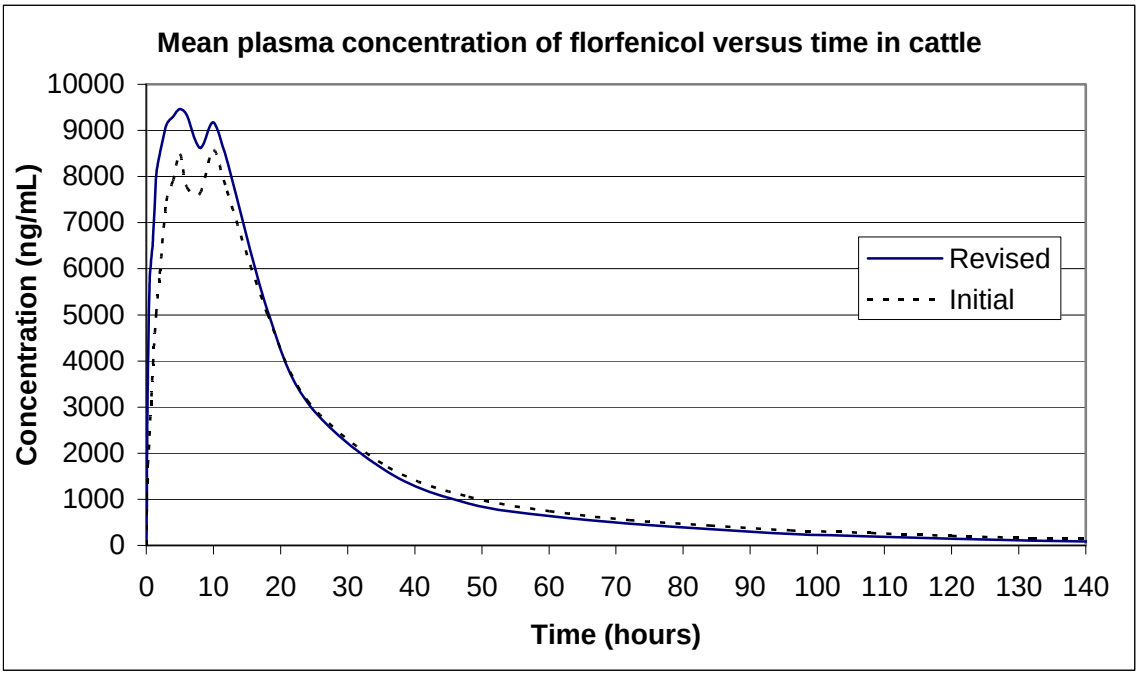

Figure 1. Mean plasma concentration of florfenicol versus time in cattle following subcutaneous administration of the revised and initial formulations at a florfenicol dose of 40 mg/kg.

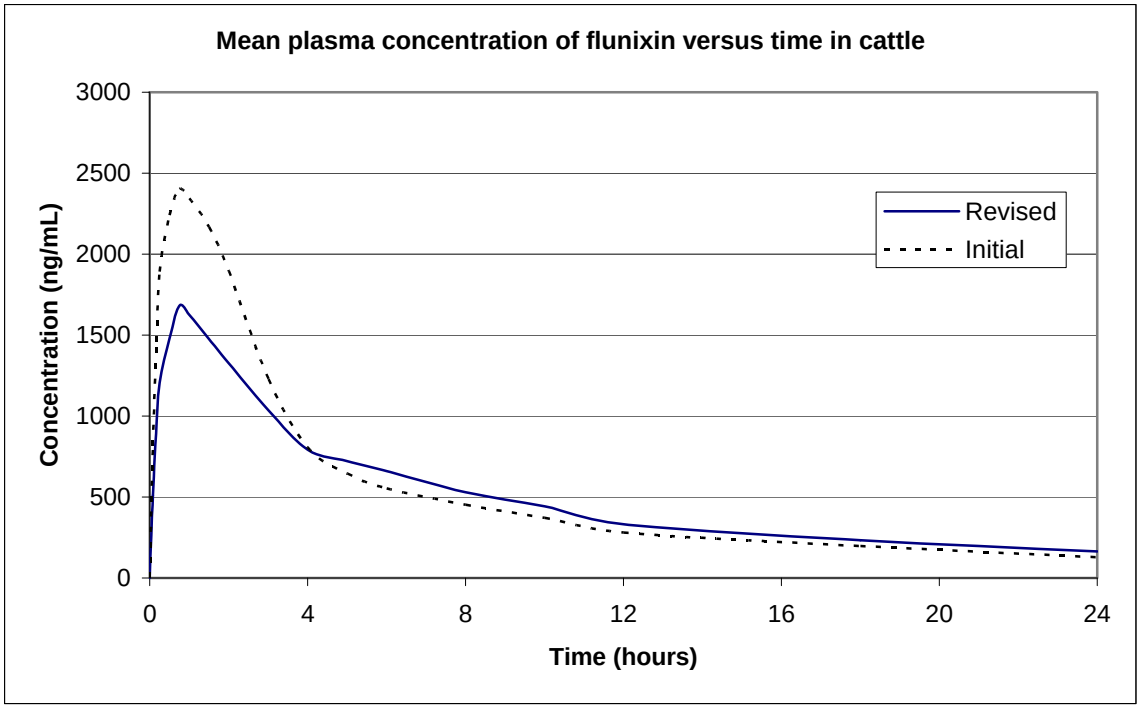

Figure 2. Mean plasma concentration of flunixin versus time in cattle following subcutaneous administration of the revised and initial formulations at a flunixin dose of 2.2 mg/kg.

f. Conclusion: The extent of florfenicol exposure associated with RESFLOR GOLD is approximately equivalent to that associated with the initial florfenicol-flunixin formulation. The slightly higher average peak concentrations of florfenicol observed with RESFLOR GOLD will not alter the margin of safety observed with the initial formulation. Similarly, the relative exposure (rate and extent) of flunixin following injection of RESFLOR GOLD is less than or equal to the rate and extent of absorption following injection of the initial formulation. Accordingly, this pharmacokinetic study successfully bridges RESFLOR GOLD to the Target Animal Safety study conducted using the initial formulation (Study No. 01503).

B. Injection Site Irritation Study:

1. Title: "(Florfenicol-Flunixin)/2-Pyrrolidone/Triacetin Formulation: Subcutaneous Injection Target Animal Safety Study in Cattle." Study No. 06063.

2. Study Director: Terry N. TerHune, DVM, PhD

3. Study Location: HMS Veterinary Development, Inc.
   Tulare, CA 93274

4. General Study Design:

a. *Purpose*: To assess the resolution of injection site irritation of florfenicol and flunixin meglumine in 2-pyrrolidone/triacetin injectable solution (RESFLOR GOLD) when administered to cattle by a single subcutaneous (SC) injection at the proposed clinical dose of 40 mg of florfenicol/kg BW and 2.2 mg of flunixin/kg BW. As part of the pathologic evaluation, special emphasis was placed on the identification of gross lesions that would require trim-out at the time of slaughter if the animal was being processed for food for human consumption. The study was conducted in compliance with FDA Good Laboratory Practice (GLP) Regulations (21 CFR Part 58).

b. *Animals*: Twenty healthy crossbred commercial (Angus and Hereford) cattle (10 castrated males and 10 females), age 18 months, weighing 325 to 396 kg on Day -7, were enrolled in the study. All cattle received the identical treatment and dosage regimen. A control group was not included.

c. *Test article*: The revised formulation of florfenicol and flunixin containing 300 mg of florfenicol/mL and 16.5 mg flunixin (as flunixin meglumine)/mL in 2-pyrrolidone/triacetin, was administered to cattle as a single subcutaneous dose of 40 mg of florfenicol/kg BW and 2.2 mg of flunixin/kg BW divided into five to seven injection sites per animal, split between both sides of the neck. Injection sites were numbered from one to three on the left side of the neck, caudal to cranial. Injection sites were numbered four to seven on the right side of the neck, caudal to cranial. The injections were given approximately 4 inches apart. A maximum volume of 10 mL was injected per site.

d. *Study Design*: Twenty healthy cattle were selected from a pool of 24 cattle on Day -5 of a 21 day acclimation period. Two females and two castrated males were randomly assigned to each of five treatment groups. The test article was administered on Day 0, 14, 28, 42, or 45; all animals were euthanized and necropsied on Day 91 as shown in Table 5.

Table 5. Control and Treatment Groups.

Treatment Group	Treatment Day	Number and Sex of Animals	Necropsy (Number of Days Post-Injection)
1	0	2 males and 2 females	91
2	14	2 males and 2 females	77
3	28	2 males and 2 females	63
4	42	2 males and 2 females	49
5	45	2 males and 2 females	46

e. *Measurements and Observations:* Complete physical exams were performed on Day -15, -7, and -1 by the study veterinarian. General health observations were recorded daily beginning Day -21 (the start of the acclimation period) and ending Day 91 (the day of necropsy). Injection sites were visually inspected daily for swelling and drainage by designated study personnel. Swelling dimensions were measured beginning 2 days prior to and a minimum of 14 days after the injection was administered, or until the swelling was gone. Gross necropsy consisted of a complete gross pathologic evaluation and scoring of all injection sites at four tissue levels (external skin surface, subcutaneous tissue, surface of the musculature, and deep muscle). Photographs were taken at each tissue level of each injection site. Two standard injection sites from each animal were examined histologically. Other sites were collected as determined by the study pathologist.

5. Results:

a. *Mortalities*: None.

b. *General Health Observations*: No abnormal general health observations were noted during the study.

c. *Clinical Injection Site Observations*: Injection site swelling was observed in all animals 2 to 4 days after administration of the test article. At 23 days post-injection, half of the animals had visually apparent injection site swellings. The swelling resolved in all animals with the exception of one animal in the final treatment group whose swelling persisted 47 days post-injection (the day of necropsy).

d. *Gross Pathology Results*: At necropsy, macroscopic changes of the subcutaneous tissue consisted of discoloration, thickening, and cystic spaces. Macroscopic changes of the exposed muscle surface consisted of discoloration and one cystic space. There were no macroscopic changes of the skin surface or deep muscle tissue. The size of the subcutaneous tissue and exposed muscle surface discolorations tended to decrease over time but persisted at least 91 days after dosing. The results are summarized in Table 6.

Table 6. Summary of Injection Site Gross Lesions (Incidence by Group).

	Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**
	91 days post-dose	77 days post-dose	63 days post-dose	49 days post-dose	46 days post-dose
Total Number of Injection Sites	22	23	23	23	23
Total Number of Gross Subcutaneous Lesions	6	10	12	16	9
Total Number of Gross Exposed Muscle Surface Lesions	8	8	10	6	7
Total Number of Gross Deep Muscle Lesions	0	0	0	0	0

e. *Histopathology Results*: There were no abnormalities found at the skin surface. Microscopic alterations of the subcutaneous and exposed muscle surface consisted of low-grade (minimal/mild) fibrosis, chronic inflammation, hemosiderin (pigment indicating prior hemorrhage), and cystic spaces (seromas). There were two sites (in different animals) that showed histopathologically (but not macroscopically) chronic inflammation in the deep muscle, 91 days post-injection. Histopathology confirmed that inflammation was present and that the incidence and severity were time-dependent.

6. Conclusions: Subcutaneous injection of RESFLOR GOLD at 40 mg of florfenicol/kg BW and 2.2 mg of flunixin/kg BW administered once, at up to 10 mL per site, is safe in beef and non-lactating dairy cattle. RESFLOR GOLD, when administered as directed, may induce a transient reaction at the site of injection and underlying tissues that may result in trim loss of edible tissue at slaughter.

IV. HUMAN FOOD SAFETY:

A. Toxicology:

1. Summary of Toxicology Studies

In vitro and *in vivo* toxicity studies performed with florfenicol were conducted to support the original approval of florfenicol in cattle. Summaries of all toxicology studies for florfenicol are addressed in the FOI Summary for NUFLOR Injectable Solution (NADA 141-063) that was approved for use in cattle on May 31, 1996. This was codified on August 15, 1996 (61 FR 42383).

No new toxicity studies were conducted to support the current NADA. However, an assessment of the effect of microbiologically active florfenicol residues on human intestinal flora after consumption of edible tissues of cattle was submitted for the current NADA. The information was reviewed and the conclusion was drawn that the amount of microbiologically active residues present in the colon after consumption of meat from animals treated with RESFLOR GOLD (florfenicol and flunixin meglumine in 2-pyrrolidone and triacetin) is too low to produce any adverse effect on the human intestinal flora. This conclusion was reached considering the following data:

a. The concentration of residues in the tissues at the withdrawal time considering the worst case scenario, which would be the residues at the injection site. (Data was taken from a residue depletion study performed with an initial florfenicol-flunixin formulation.) After reviewing bioequivalence data comparing the initial formulation with RESFLOR GOLD, it was concluded that both formulations are equivalent for the purpose of assessing effects of florfenicol residues on human intestinal flora.

b. The percentage of residues with antimicrobial activity.

c. The consumption factor for edible tissues.

d. The percentage of residues excreted in feces.

2. Determination of No Observed Effect Level (NOEL) for chronic exposure and the NOEL for acute exposure (if applicable).

Determination of NOEL for florfenicol is addressed in the FOI Summary for NUFLOR Injectable Solution (NADA 141-063) that was approved for use in cattle on May 31, 1996. This was codified on August 15, 1996 (61 FR 42383).

3. Acceptable Daily Intake (ADI)

Calculations of the ADI for florfenicol are addressed in the FOI Summary for NUFLOR Injectable Solution (NADA 141-063) that was approved for use in cattle on May 31, 1996. This was codified on August 15, 1996 (61 FR 42383).

4. Safe Concentrations for Total Residues (edible tissues and injection sites, if applicable)

Assignment of Safe Concentrations for florfenicol is addressed in the FOI Summary for NUFLOR Injectable Solution (NADA 141-063) that was approved for use in cattle on May 31, 1996. This was codified on August 15, 1996 (61 FR 42383).

B. Residue Chemistry:

1. Summary of Residue Chemistry Studies

The total residue depletion and metabolism in the target species and comparative metabolism in the toxicological species are summarized in the FOI Summaries for florfenicol dated May 31, 1996, and for flunixin meglumine dated May 5, 1998, under NADAs 141-063 and 101-479, respectively. The two pivotal studies summarized below were conducted to support the use of florfenicol and flunixin meglumine in beef and non-lactating cattle. The first is a total residue depletion study of ^{14}C-flunixin in cattle after SC injection, a primary goal of which was to quantify free flunixin in injection site muscle samples by the validated LC-MS/MS method and to determine the marker:total residue ratio. The second study was conducted to permit the assignment of a withdrawal period for the combination in cattle.

a. Residue Chemistry Study

i. Title: "SCH 529752: An Injection Site Total Residue Depletion Study of ^{14}C-Flunixin in Cattle Following Subcutaneous (SC) Administration," Study Number 02487

ii. Study Director and Laboratory:

Testing Facility (in-life): Lian Wen, Ph.D.
Principal Investigator
ABC Laboratories Missouri
Columbia, MO 65202

Analytical Facility (Phase I): (Total Residue Analysis)	Lian Wen, Ph.D. Principal Investigator ABC Laboratories Missouri Columbia, MO 65202
Analytical Facility (Phase II): (Marker Residue Analysis)	Dave Liu, Ph.D. Principal Investigator Xenobiotics Laboratories, Inc. Plainsboro, NJ 08536
Analytical Facility (Phase III): (Radioprofiling Analysis)	Mohammad Mushtaq, Ph.D. Study Director Schering-Plough Research Institute Lafayette, NJ 07848.

iii. Objective: The major objective of this GLP study was to determine the ratio of the marker residue, flunixin free acid, to the total radioactive residue in injection site muscle because the previous total residue depletion study of ^{14}C-flunixin meglumine in cattle (NADA 101-479) used intravenous administration. In addition, the total radioactive residue in limited samples of liver, kidney, fat, and excreta was quantified and residue profiling of injection site muscle was performed.

iv. Test Animals: Nineteen Hereford cattle (11 castrated males and 8 intact females) were randomly selected for the study. Based on day of tissue analysis, the animals were divided into seven groups numbered I, IA, II, III, IV, V, and VI. Groups I, IA, III, and V had two males and one female per group and Groups II and IV had one male and two females per group. Group VI contained one male control. The cattle in Groups IA and I through V were dosed in an identical fashion. The male control in Group VI received no treatment.

v. Route of Administration and Duration of Dosing: Single SC injection.

vi. Radioisotope: ^{14}C-Flunixin N-methyl glucamine (NMG) was universally ring-labeled. ^{14}C-Flunixin-NMG and unlabeled flunixin-NMG were added to a formulation containing unlabeled florfenicol and the subsequent radiopurity and specific activity of the ^{14}C-flunixin free acid was >98.6% and 1.809 µCi/mg flunixin free acid, respectively.

vii. Animal Dosing: The formulation was administered once SC at three to four sites (≤ l0 mL per injection site) in the neck. The target dose was 2.2 mg of ^{14}C-flunixin free acid and 40 mg florfenicol/kg BW The cattle (mean weight 218.6 kg, n=18) received a mean actual dose of 2.24 mg of ^{14}C-flunixin free acid/kg BW based on the nominal concentration.

viii. Excreta/Tissue Collection: The treated animals were euthanized on Days 7 (Groups I and IA), 14 (Group II), 21 (Group III), 28 (Group IV) and 35 (Group V) post-dose. Urine and feces were collected from Group IV animals at 24-hour intervals up to 14 days post-dose. Injection site (IS) muscle samples were taken from Groups I through V and IA, and liver, kidney, muscle (leg and loin), and fat (renal and peritoneal) were taken from Groups I through V.

ix. Residue Analysis: Quantitation of ^{14}C-content in injection site muscle, extracted injection site muscle (Groups I through V and IA), liver, kidney, leg and loin muscle, and fat (Group I only), and feces (Group IV only) was by radiocombustion or solubilization followed by liquid scintillation counting. Urine (Group IV only) was assayed directly by liquid scintillation counting. The content of the marker residue, flunixin free acid, was determined by a validated LC-MS/MS method. Three IS muscle specimens from two cattle (Group I) containing sufficient radioactivity [> 0.1 ppm total radioactive residue (TRR)] were selected for radioprofiling by HPLC. A procedure involving serial organic solvent extraction followed by solid-phase extraction (SPE) of the extracts was used to prepare the residues for HPLC analysis. Extractable and unextractable residues were determined using five aliquots for each sample and the extractable residues for each sample were combined for HPLC analysis.

x. Results: Relevant data from this study are provided in Tables 7 through 10 below.

Table 7: Recovery of Dose in Cattle Excreta by 14 Days Post-Dose.

Group	Urine	Feces	Total
IV (Mean)	34.23	56.58	90.82

Table 8: Total Radioactive Residues (ppm, as Flunixin Free Acid Equivalents) in Cattle Liver, Kidney, Leg and Loin (LL) Muscle, and Fat in Group I, 7 days Post-Dose (Mean ± Standard Deviation).

Residue	Liver	Kidney	LL Muscle	Fat
TRR	0.018 ± 0.002 (n = 3)	0.011 ± 0.004 (n = 3)	BLQ[1] (n = 3)	BLQ (n = 3)
LOQ	0.006	0.006	0.013	0.010
[1] TRR value below the respective limit of quantitation				

Table 9: Total Radioactive Residue (ppm, as ^{14}C-Flunixin Free Acid Equivalents), Marker Residue (ppm, Flunixin Free Acid), and Marker:Total Residue Ratio in Injection Site Muscle (Mean ± Standard Deviation as Applicable).

Residue	Group I (Day 7)	Group IA (Day 7)	Group II (Day 14)	Group III (Day 21)	Group IV (Day 28)	Group V (Day 35)
TRR	0.087 ± 0.060 (n = 9)	0.083 ± 0.030 (n = 9)	0.034 ± 0.023 (n = 6)	0.019 ± 0.006 (n = 3)	0.023 (n = 2)	BLQ[1]
Flunixin Free Acid	0.0393 ± 0.0342 (n = 9)	NTF[2]	0.0052 ± 0.0047 (n = 10)	0.0020 ± 0.0012 (n = 8)	0.0034 ± 0.0043 (n = 4)	0.0010 (n = 2)
Flunixin Free Acid (%)	40.7 ± 9.0 (n = 9)	NA[3]	22.7 ± 5.0 (n = 6)	15.0 ± 4.9 (n = 3)	22.0 (n = 2)	NA

[1] TRR values were below the limit of quantitation of 0.013 ppm
[2] Not tested for
[3] Not applicable

Table 10. Extraction and Metabolite Profiling of ^{14}C-Flunixin Residues by HPLC in Selected IS Muscle Samples, Group I (7 days post-dose).

Sample:	IM1-ISM-S2	IF1-ISM-S2	IF1-ISM-S3
TRR (ppm[1])	0.189	0.145	0.139
Extraction (n=5)			
Mean % Extractable	76.1	67.1	59.1
Mean % Unextractable	18.2	28.8	13.2
Mean % Recovery	94.2	98.6	90.3
HPLC of Extractable Residue			
% Flunixin	96.4	85.5	80.4
% Unk-1	0.5	3.0	5.1
% Unk-2	2.9	6.8	4.2
Level in Tissue (ppm[1])			
Flunixin	0.139	0.083	0.066
Unk-1	0.001	0.003	0.004
Unk-2	0.004	0.007	0.003

[1] ppm in ^{14}C-flunixin free acid equivalents

xi. Conclusions: The primary purpose of this study was to determine the flunixin marker to total residue ratio in injection sites of cattle so that a value for making decisions regarding the safety of the injection site could be established. Flunixin meglumine when used alone requires a 4-day withdrawal period (21 CFR 522.970), so the ratio at that time would be most relevant. However, the earliest sacrifice interval in this study was 7 days, at which time the ratio was 40.7 ± 9.0%. Because the ratios declined to 22.7 and 15% at 14 and 21 days of withdrawal (Table 10 above), the ratio at 4 days likely would have been somewhat higher than 40.7%. The agency concluded that the value of 40% for decisions about flunixin residues at the injection site at 4 days would be a conservative estimate.

The safe concentration for flunixin in muscle is 0.1 ppm. Applying the agency's standard value of 10X the muscle value, the safe concentration for injection site muscle is 1 ppm. Using the ratio of 40%, the agency calculated a value of 400 ppb flunixin free acid for making decisions about the safety of the injection site.

b. Residue Depletion Study

i. Title: "SCH 529752 (Florfenicol-Flunixin/2-Pyrrolidone/Triacetin Formulation): A Final Residue Depletion Study of Florfenicol Amine and Flunixin in Cattle Following SC Administration of SCH 529752 Injectable," Study Number 05515

ii. Study Director and Laboratory:

Testing Facility (In life):	Patrick Lockwood, D.V.M. Principal Investigator Schering-Plough Animal Health 2458 No. Chamberlain Street Terre Haute, IN 47805
Analytical Laboratory:	Christopher L. Wrzesinski, M.S. Study Director Schering-Plough Research Institute 144 Route 94 South Lafayette, New Jersey 07848

iii. Objective: The objective of this GLP study was to quantify flunixin free acid and florfenicol amine, as the marker residues for flunixin and florfenicol, respectively, in liver, kidney, muscle, injection site muscle, and fat (flunixin only) as a function of time after SC administration of a combination of flunixin meglumine and florfenicol (RESFLOR GOLD). Only data for liver are discussed.

iv. Test Animals: Twenty-nine Hereford cattle (15 castrated males and 14 intact females), 6 to 12 months of age, weighing 230 to 292 kg were selected for the study. Based on the day of tissue collection, they were divided into eight groups numbered I through VIII. Groups I through VII each contained two males and two females and were dosed in an identical fashion. Group VIII contained one male control and received no treatment. One Group VI animal (number 688) was removed from the study on Day 28.

v. Test Article: RESFLOR GOLD

vi. Treatment Regimen: The test article was administered as a single SC dose in the neck at a dose of 40 mg florfenicol/kg and 2.2 mg flunixin/kg.

vii. Collection Intervals: Tissues were collected at Day 14 (Group I), Day 21 (Group II), Day 28 (Group III), Day 35 (Group IV), Day 42 (Group V), Day 49 (Group VI), and Day 56 (Group VII) post-dose.

viii. Tissues Collected: Liver, kidney, muscle, fat, injection site muscle.

ix. Residue Analysis: Florfenicol amine and flunixin free acid were analyzed in the target tissue, liver, by the respective official determinative procedure.

x. Results: The results of this study are provided in Table 11, below.

Table 11. Residues of Florfenicol Amine and Flunixin Free Acid in Liver (ppb).

Group	Days Post-Dose	Sex	Animal	Florfenicol Amine (ppb)	Flunixin Free Acid (ppb)
I	14	M	653	9190	ND[1]
		M	659	4930	ND
		F	677	8840	ND
		F	680	3720	BLQ[2]
Mean	**(N = 4)**			**6670**	**BLQ**
SD				**2760**	

Group	Days Post-Dose	Sex	Animal	Florfenicol Amine (ppb)	Flunixin Free Acid (ppb)
II	21	M M F F	650 693 663 676	6360 6070 6940 5750	ND ND ND BLQ
Mean SD	**(N = 4)**			**6280 506**	**BLQ**
III	28	M M F F	660 674 662 670	3390 5600 2750 3960	NTF[3]
Mean SD	**(N = 4)**			**3930 1220**	
IV	35	M M F F	655 687 679 690	1420 1580 1690 2450	NTF
Mean SD	**(N = 4)**			**1790 457**	
V	42	M M F F	656 684 657 666	1000 867 881 940	NTF
Mean SD	**(N = 4)**			**922 60.9**	
VI	49	M F F	668 648 686	337 561 619	NTF
Mean SD	**(N = 3)**[2]			**506 149**	
Vll	56	M M F F	678 683 646 673	295 312 304 443	NTF
Mean SD	**(N = 4)**			**339 70.0**	
Vlll	Control	M	665	**BLQ**	**BLQ**

[1] Not detected
[2] Below the limit of quantitation as tissue equivalent of lowest standard (16 ppb)
[3] Not tested for

2. Target Tissue and Marker Residue Assignment

The marker residue for florfenicol in cattle is florfenicol amine and the target tissue is liver (21 CFR 556.283). The marker residue for flunixin meglumine in cattle is flunixin free acid and the target tissue is liver (21 CFR 556.286).

3. Tolerance Assignments

The tolerances for florfenicol amine are 3.7 ppm in cattle liver and 0.3 ppm in cattle muscle (21 CFR 556.283). The tolerances for flunixin free acid are 125 ppb in cattle liver and 25 ppb in cattle muscle (21 CFR 556.286).

4. Withdrawal Time

The data in Table 11, above, show that florfenicol determines the withdrawal period for the combination of florfenicol and flunixin meglumine. The data for florfenicol were statistically analyzed using FDA's 99% tolerance limit with 95% confidence algorithm. Based on the statistical analysis, the agency assigned a withdrawal period of 38 days.

C. Microbial Food Safety:

The Agency used a qualitative risk assessment to evaluate available microbial food safety information for florfenicol in combination with flunixin meglumine for treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni,* and control of BRD-associated pyrexia in beef and non-lactating dairy cattle. This risk assessment procedure involved conducting:

1. A *release assessment* to describe the probability of emergence of resistant bacteria or resistance determinants in cattle following the use of florfenicol under the proposed conditions of use;

2. An *exposure assessment* to describe the likelihood of human exposure to any resistant bacteria or resistance determinants through consumption of edible products from florfenicol-treated animals;

3. A *consequence assessment* to describe the potential human health consequences of exposure to resistant bacteria or resistance determinants by considering the human medical importance of chloramphenicol in the treatment of human infectious diseases.

From this assessment, it was determined that the microbial food safety risk associated with this use of florfenicol in combination with flunixin meglumine is medium. A risk estimation of medium is compatible with the proposed conditions of use for this product: prescription only, single injection of individual animals with 40 mg of florfenicol/kg BW in combination with 2.2 mg of flunixin/kg BW.

D. Analytical Method for Residues:

1. Analytical Method

The FOI Summary for the original approval of NUFLOR Injectable Solution under NADA 141-063 dated May 31, 1996, contains the analytical method summary for florfenicol in cattle. The FOI Summary for the supplemental approval of BANAMINE Injectable solution under NADA 101-479 dated May 5, 1998, contains the analytical method summaries for flunixin in cattle.

2. Availability of Method

The methods are available from the Center for Veterinary Medicine, FDA, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY:

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

WARNINGS: NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. This product contains materials that can be irritating to skin and eyes. Avoid direct contact with skin, eyes, and clothing. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. Consult a physician if irritation persists. Accidental injection of this product may cause local irritation. Consult a physician immediately. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information.

For customer service or to obtain a copy of the MSDS, call 1-800-211-3573. For technical assistance or to report suspected adverse reactions, call 1-800-219-9286.

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 RESFLOR GOLD, when used according to the label, is safe and effective for treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*, and control of BRD-associated pyrexia 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 RESFLOR GOLD will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

Labeling restricts this drug to use by or on order of a licensed veterinarian. This decision was based on the following factors: (1) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this

product to treat BRD; and (2) 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)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval.

C. Patent Information:

RESFLOR GOLD is under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
6,790,867	January 24, 2023

For current information on patents, see the Animal Drugs @ FDA database (formerly the Green Book) on the FDA CVM internet website.

VII. ATTACHMENTS:

Facsimile Labeling:
A. 100 mL bottle
B. 100 mL carton
C. 100 mL bottle Product Information insert
D. 250 mL bottle with attached, pull-out Product Information insert
E. 500 mL bottle with attached, pull-out Product Information insert