Date of Approval: March 21, 2008

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-265

NUFLOR GOLD Injectable Solution

Florfenicol (with 2-pyrrolidone and triacetin)

Beef and Non-Lactating Dairy Cattle

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

Sponsored by:

Schering-Plough Animal Health

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-265
B. Sponsor:	Schering-Plough Animal Health Corp. 556 Morris Ave. Summit, NJ 07901 Drug Labeler Code: 000061
C. Proprietary Name:	NUFLOR GOLD Injectable Soltuion
D. Established Name:	Florfenicol (with 2-pyrrolidone and triacetin)
E. Pharmacological Category:	Antimicrobial
F. Dosage Form:	Sterile injectable solution
G. Amount of Active Ingredient:	300 mg florfenicol/mL
H. How Supplied:	100, 250, and 500 mL glass vials
I. How Dispensed:	Rx
J. Dosage:	40 mg florfenicol/kg body weight once
K. Route of Administration:	Subcutaneous in the neck
L. Species/Classes:	Cattle/Beef and non-lactating dairy
M. Indication:	NUFLOR GOLD Injectable Solution is indicated for treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida*, and *Histophilus somni* in beef and non-lactating dairy cattle.

II. EFFECTIVENESS:

A. Dosage Characterization:

Dosage characterization for NUFLOR GOLD Injectable Solution was based on the comparability of plasma florfenicol concentrations following subcutaneous (SC) injection of NUFLOR GOLD Injectable Solution and NUFLOR Injectable Solution (NADA 141-063). A crossover study was conducted in 24 feeder calves (12 males, 12 females) to compare the relative bioavailability of florfenicol when administered as NUFLOR GOLD Injectable Solution versus NUFLOR Injectable Solution.

Calves were divided into two treatment groups, each containing six male and six female calves. The calves were first administered NUFLOR GOLD Injectable Solution as a single SC injection of 40 mg florfenicol/kg body weight (BW) with a maximum injection site volume of 15 mL. After a 56-day washout period, NUFLOR Injectable Solution was administered as a single SC injection of 40 mg florfenicol/kg BW with a maximum injection site volume of 10 mL. Blood was collected from each calf before dosing (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 60, 72, 84, 96, 108, and 120 hours after dosing. Area under the curve (AUC) was calculated from time zero to the last quantifiable concentration (AUC_{last}) using the linear trapezoidal rule. Other pharmacokinetic estimates included the maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life ($T_{½}$), and duration of time during which drug concentrations exceeded 0.5 µg (mcg)/mL (T > 0.5 µg/mL), and 1.0 µg/mL (T > 1.0 µg/mL). Florfenicol pharmacokinetics were generated using WinNonlin version 4.1.

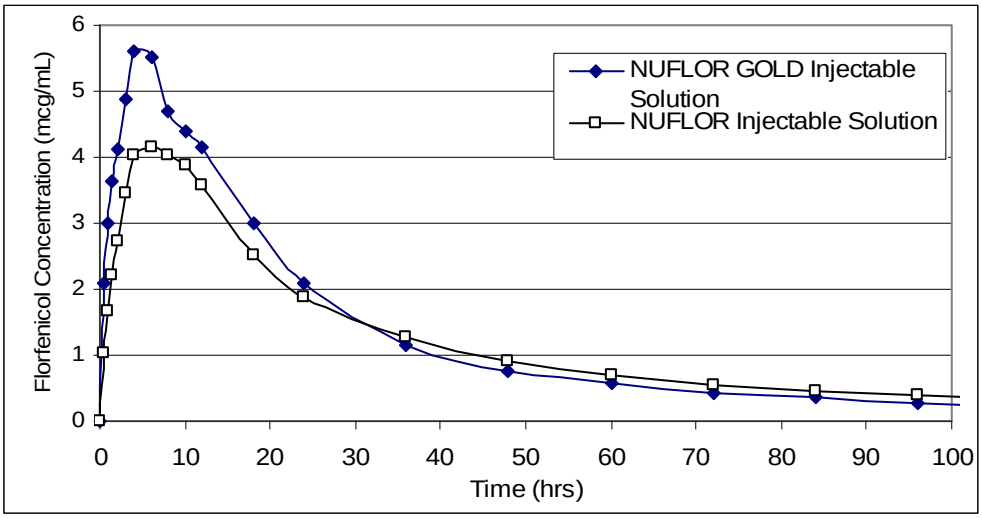
The pharmacokinetics of florfenicol after SC injection of NUFLOR GOLD Injectable Solution or NUFLOR Injectable Solution to cattle are described below in Table 1. and Figure 1.

Table 1. Pharmacokinetic Parameter Values for Florfenicol Following SC Injection of 40 mg Florfenicol/kg BW to Feeder Calves (n = 24)

	NUFLOR GOLD Injectable Solution				NUFLOR Injectable Solution			
	C_{max} (µg/mL)	T_{max} (hr)	AUC_{last} (µg*hr/mL)	$T_{1/2}$ (hr)	C_{max} (µg/mL)	T_{max} (hr)	AUC_{last} (µg*hr/mL)	$T_{1/2}$ (hr)
n	24	24	24	23[2]	24	24	24	23[2]
Mean	5.93	5.0[1]	150.2	37.67	4.69	6.0[1]	141.78	51.79
% CV	38.3	2.0-12.0[1]	20.9	27.3	47.3	2.0-10.0[1]	27.0	42.0

C_{max}: Maximum plasma concentration
T_{max}: Time at which C_{max} was observed
AUC_{last}: Area under the curve from time zero to the last quantifiable concentration
$T_{1/2}$: Terminal elimination half-life
% CV: Percent coefficient of variance
[1]T_{max} is presented as the median value or range of observed values (minimum to maximum)
[2]$T_{1/2}$ value could not be accurately estimated for one calf

Figure 1. Mean Florfenicol Plasma Concentration versus Time Following SC Injection of NUFLOR GOLD Injectable Solution or NUFLOR Injectable Solution in Cattle



B. Substantial Evidence:

1. Natural Infection Clinical Field Study

a. Title: An Evaluation of 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 NUFLOR GOLD Injectable Solution for the treatment of BRD compared to 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 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:

<u>Depression Scoring Scale</u>:

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.

<u>Respiratory Scoring Scale</u>:

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 increased 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: The test article was NUFLOR GOLD (florfenicol with 2-pyrrolidone and triacetin) Injectable Solution. 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 volume per injection site was 15 mL.

v) Treatment Groups: The evaluated treatment groups are described below in Table 2.

Table 2. Treatment Groups

Treatment	Dosage	No. of Animals[2]
Saline	2 mL/15 kg[1] BW SC once	122
NUFLOR GOLD Injectable Solution	40 mg florfenicol/kg BW (2 mL/15 kg BW) SC once	123

[1]Volume equivalent to NUFLOR GOLD Injectable Solution dosage

[2]One site was excluded from the analysis due to a protocol deviation

A third treatment group was included in the study, but the results from this treatment group were not used as part of substantial evidence of effectiveness.

vi) Measurements and Observations: The pivotal variable was the treatment success rate for BRD on Day 11. 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. Nasal swabs were collected for 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 effectiveness of NUFLOR GOLD Injectable Solution for the treatment of BRD was evaluated by comparing the proportion of treatment successes in the NUFLOR GOLD Injectable Solution treatment group to the saline control treatment group.

vii) Statistical Methods: The treatment success rate for BRD was analyzed using a generalized linear mixed effect model with binomial error and

logit link, with fixed effect of treatment and with random effects of site, treatment by site, pen within site, and treatment by pen within site. The statistical model employed the Kenward-Rogers approximation to determine the denominator degree of freedom for hypothesis tests.

After establishing statistical significance of overall treatment effect, the contrast between NUFLOR GOLD Injectable Solution and saline was evaluated. Statistical tests were conducted at the two-sided 0.05 level of significance.

d. Results: Three-hundred fifty-six calves were included in the analysis of treatment success for BRD. The treatment success rate for BRD for the NUFLOR GOLD Injectable Solution treatment group (71.7%) was statistically significantly greater ($p = 0.0162$) compared to the treatment success rate for BRD for the saline control treatment group (42.9%). The BRD pathogens *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* were isolated from study calves. Minimum inhibitory concentration (MIC) data are summarized below in Table 3.

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

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

2. Determination of MICs

The MICs of florfenicol were determined for *M. haemolytica*, *P. multocida*, and *H. somni* isolates obtained from calves enrolled in the BRD clinical field study described above 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 three sites, post-treatment nasal swabs from treatment failures in the NUFLOR 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 3.

Table 3. Florfenicol MIC Values[1] of Indicated Pathogens Isolated from Cattle with Naturally-Occurring BRD

Indicated pathogens	Year of isolation	No. of isolates	MIC_{50}[2] (µg/mL)	MIC_{90}[2] (µg/mL)	MIC range (µg/mL)
Mannheimia haemolytica	2006	158	1.0	1.0	0.5 to 32
Pasteurella multocida	2006	103	0.5	0.5	≤ 0.125 to 16
Histophilus somni	2006	85	≤ 0.125	≤ 0.125	≤ 0.125 to 0.25

[1]The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown

[2]The MIC to encompass 50% and 90% of the isolates, respectively

III. TARGET ANIMAL SAFETY:

A. Toxicity Study:

1. Title: Florfenicol (SCH 25298)/2-Pyrrolidone/Triacetin Formulation: Subcutaneous Injection Target Animal Safety Study in Cattle. Study No. 03410. May 2004 to June 2004.

2. Study Director and Location:

   Terry TerHune, D.V.M., Ph.D., HMS Veterinary Development, Inc., Tulare, CA

3. Study Design:

   a) Objective: To assess the safety of NUFLOR GOLD (florfenicol with 2-pyrrolidone and triacetin) Injectable Solution when administered to cattle by SC injection at doses of 40, 120, and 200 mg florfenicol/kg BW (1X, 3X, and 5X the labeled dose) for three consecutive days (3X the labeled duration).

   The study was conducted in compliance with FDA's Good Laboratory Practice (GLP) requirements.

   b) Test Animals: Twenty-four cross-bred commercial cattle (12 castrated males and 12 non-pregnant females), five to seven months old, weighing 139 to 200 kg at the start of the treatment period.

   c) Experimental Design: On Day -21, 40 cattle were assigned to pens using a simple randomization procedure. On Day -8, 12 castrated males and 12 non-pregnant females were determined healthy and selected for the study based on physical examination findings, clinical pathology, and body weight. Cattle were randomly allocated to one of four treatment groups, as shown below in Table 4. Test and control articles were administered on Days 1, 2, and 3. All cattle were euthanized and necropsied on Day 4.

   Table 4. Treatment Assignments

Group	Treatment	NUFLOR GOLD Injectable Solution Dosage (mg florfenicol/kg BW)	No. of Animals	
			Male	Female
1	Control (saline)	0	3	3
2	1X	40	3	3
3	3X	120	3	3
4	5X	200	3	3

d) Test Article Administration: NUFLOR GOLD Injectable Solution was administered SC at a dose of 40, 120, or 200 mg florfenicol/kg BW once every day for three consecutive days. Injections were administered in the left lateral neck on Day 1, right lateral neck on Day 2, and left lateral neck on Day 3. Saline at an equivalent volume to the 5X dose (0.6667 mL/kg BW) was used as the control article. A maximum of 15 mL was injected at each site.

e) Measurements and Observations: Physical examinations were performed on Days -14, -9, -7, -1, 2, and 4. Temperature, respiratory rate, heart rate, mucous membrane color, and capillary refill time were recorded daily from Day -14 to Day 4. Body weights were collected on Days -21, -14, -9, -7, -1, 2, and 4. Feed and water consumption were measured daily from Day -14 to the end of the study (Day 4). Blood samples for hematology and serum chemistry were collected on Days -14, -10, -1, 2, and 4. Clinical observations of appetite, body condition, eyes, respiration, nasal discharge, locomotion/musculature, skin and hair coat, behavioral attitude, feces, and urine were made twice daily, Day -14 through Day 4. Plasma florfenicol concentration samples were collected on Days -1, 1, and 2. Gross pathology and histopathology were evaluated at necropsy (Day 4).

f) Statistical Methods: Variables measured multiple times were analyzed using repeated measures analysis of covariance (ANCOVA) using the average baseline values as covariates. Main treatment effects and treatment by time interactions were evaluated at the 0.10 level of significance, and comparison of treatment by sex interactions and treatment by sex by time interactions were evaluated at the 0.05 level of significance. Variables measured only once, during necropsy, were analyzed using ANOVA, with treatment and sex as fixed effects, and with treatment evaluated at the 0.10 level of significance.

4. Results:

a) Clinical Observations: Injection site swellings were observed in all cattle in the 1X, 3X, and 5X groups. Injection site swellings were not seen in the control group. Average daily feed intake was decreased in the 1X, 3X, and 5X groups, compared to the control group. Average daily water intake was

decreased on Day 3 for the 1X group and on Days 2, 3, and 4 for the 3X and 5X groups, compared to the control group.

b) *Mortality:* All cattle survived to scheduled euthanasia.

c) *Hematology and Serum Chemistry:* Variations from the normal reference ranges were noted for some parameters, and some statistically significant differences were found. Hematocrit, hemoglobin, and red blood cells for some treatment groups had some statistically significantly lower values than the control group on various days of the study. Absolute lymphocytes, white blood cells, and absolute segmented neutrophils for some treatment groups had statistically significantly higher values compared to the control group on various days of the study. Albumin, alkaline phosphatase, globulin, phosphorus, and total protein were statistically significantly lower than the control group in some treatment groups on various days of the study. Cholesterol, direct bilirubin, total bilirubin, and aspartate aminotransferase for some treatment groups had statistically significantly higher values than the control group on various days of the study. However, no trends or patterns were found, and none of the differences were considered clinically relevant. The observed abnormalities were considered unrelated to test article administration.

d) *Gross and Histopathological Observations:* Test article-related histopathologic findings were observed in the SC injection sites and included acute edema/fibrin, acute to subacute inflammation, and acute to subacute muscle degeneration.

e) *Florfenicol Plasma Concentrations:* Florfenicol plasma concentrations at the anticipated peak of four hours after dosing tended to show dose-proportional increases. There were no obvious sex-related differences in florfenicol plasma levels observed in the study.

Florfenicol plasma concentrations at 24 hours after dosing (immediately prior to the next dose) were lower in proportion to the 1X dose so that the average 3X dose resulted in 79% of the expected exposure, and the average 5X dose resulted in only 69% of the expected exposure based upon plasma florfenicol concentrations achieved following a 1X dose.

5. Conclusion: NUFLOR GOLD Injectable Solution has an adequate margin of safety in beef and non-lactating dairy cattle when injected SC in the neck as a single dosage of 40 mg florfenicol/kg BW.

B. Injection Site Irritation Study:

1. Title: Florfenicol (SCH 25298)/2-Pyrrolidone/Triacetin Formulation: Subcutaneous Injection Site Irritation Study in Cattle. Study No. 03411. April 2004 to June 2004.

2. Study Director and Location:

Terry TerHune, D.V.M., Ph.D., HMS Veterinary Development, Inc., Tulare, CA

3. Study Design:

a) *Objective:* To evaluate the injection site tolerance of NUFLOR GOLD Injectable Solution when administered to cattle as a single SC dosage of 0.13 mL/kg BW (equivalent to 40 mg of florfenicol).

The study was conducted in compliance with FDA's GLP requirements.

b) *Test Animals:* Twenty cross-bred commercial cattle (10 castrated males and 10 non-pregnant females), 12 to 24 months old, weighing 378 to 498 kg at the beginning of the study.

c) *Experimental Design:* Prior to the beginning of treatment (Day -5), 10 healthy, castrated males and 10 healthy, non-pregnant females were selected for the study. Cattle were randomly assigned to one of five treatment groups, as shown below in Table 5. The test article was administered on Day 0, 14, 21, 28, or 35, according to treatment group. All cattle were euthanized on Day 56, corresponding to 21, 28, 35, 42, or 56 days post-injection at necropsy.

Table 5. Treatment Assignments

Group	Treatment Day	Days post-injection at scheduled necropsy	No. of Animals	
			Males	Females
1	0	56	2	2
2	14	42	2	2
3	21	35	2	2
4	28	28	2	2
5	35	21	2	2

d) *Test Article Administration:* NUFLOR GOLD Injectable Solution was injected SC in the neck at a dose of 0.13 mL/kg BW. A maximum of 15 mL was injected at each site. There were up to five injection sites per animal. No control article was used in the study.

e) *Measurements and Observations:* Cattle were observed once daily for general appearance and abnormal clinical signs. Injection sites were visually inspected and palpated daily by a veterinarian, beginning two days prior to treatment and continuing for at least 14 days after treatment or until swellings were no longer palpable. At necropsy, gross and histopathologic examination was limited to the site of injection. The external skin surface, SC tissue, neck

musculature, and deep muscle were examined at each site of injection. Special emphasis was placed on identifying gross lesions that would require trim out at slaughter.

f) *Statistical Methods:* None

4. Results:

a) *Clinical Observations:* No abnormal clinical observations were noted during the study. Injection site reactions and visible swelling on the neck were present in all treatment groups. These swellings became palpable one to two days after dosing, and resolved between 24 and 42 days post-injection.

b) *Mortality:* All cattle survived to scheduled euthanasia.

c) *Gross and Histopathologic Observations:* At necropsy, gross lesions were present at the florfenicol injection site in three of four cattle 56 days post-injection, in four of four cattle 42 days post-injection, in four of four cattle at 35 days post-injection, in four of four cattle at 28 days post-injection, and in four of four cattle at 21 days post-injection. Florfenicol-related histopathologic findings were observed in the SC injection sites and included subacute to chronic inflammation, edema, and fibrin. The severity and frequency of lesions decreased as the post-injection interval increased.

5. Conclusion: NUFLOR GOLD Injectable Solution, when administered to beef and non-lactating dairy cattle as a single SC injection at a dose of 0.13 mL/kg BW, (40 mg florfenicol/kg BW), can cause a transient local tissue reaction 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) which 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 for florfenicol. 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 NUFLOR GOLD Injectable Solution [florfenicol (with 2-pyrrolidone and triacetin)] is too low to produce any adverse effect on the human intestinal flora.

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

Determination of NOEL for florfenicol is addressed in the FOI Summary for NUFLOR Injectable Solution (NADA 141-063) which 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 is addressed in the FOI Summary for NUFLOR Injectable Solution (NADA 141-063) which 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

Assignment of Safe Concentrations for florfenicol is addressed in the FOI Summary for NUFLOR Injectable Solution (NADA 141-063) which 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

a. Residue Depletion Study

i. Title: SCH 25298: A final residue depletion study of florfenicol amine in cattle following subcutaneous administration of florfenicol 2-pyrrolidone/triacetin formulation. SPRI Study No. 03492

ii. Study Director and Laboratory:

Study Director (In life): Patrick Lockwood, D.V.M., Schering-Plough Animal Health, Terre Haute, IN
Analytical Laboratory: Xenobiotic Laboratories, Plainsboro, NJ

iii. Test Article: NUFLOR GOLD Injectable Solution

iv. Test Animals: Twenty-nine Angus cattle (14 females and 14 males treated; 1 male control), six to nine months old, weighing 178 to 227.5 kg

v. Dose: One SC injection at 40 mg florfenicol/kg BW

vi. Results:

Table 6. Uncorrected Mean Florfenicol Amine Residue Concentrations[1] (ppm) in Treated Cattle

Days Post Dose	Liver	Kidney	Muscle Leg/Loin	Injection Site Muscle	
				Surround	Core
14	7.698 0.587	0.913 0.083	0.167 0.020	0.366 0.290	120.874 86.690
21	4.978 1.374	0.584 0.158	0.113[2] 0.002	0.175 0.111	96.953 189.639
28	4.075 1.199	0.405 0.048	< LOQ	0.141 0.074	14.242 16.794
35	2.112 0.452	0.206 0.067	< LOQ	0.104 0.019	0.107 0.009
42	0.885 0.622	0.144[2] 0.059	< LOQ	0.075 0.019	0.125[3] 0.055
49	0.540 0.282	< LOQ	< LOQ	0.061[3] 0.003	0.078 0.002
56	0.387 0.144	< LOQ	< LOQ	0.059[3] 0.008	0.198[3] 0.226
Control	0.131	.009	0.010	0.009	0.007
LOQ LOD Tolerance	0.1 ppm 0.028 ppm 3.7 ppm	0.1 ppm 0.047 ppm None	0.1 ppm 0.005 ppm 0.3 ppm	0.05 ppm 0.005 ppm None	0.05 ppm 0.005 ppm None

LOQ: Limit of quantitation
LOD: Limit of detection
[1]Levels uncorrected for method recovery; all values above LOQ
[2]Mean of two values
[3]Mean of three values

b. Residue Depletion Study

i. Title: SCH 25298: A final residue depletion study of 2-pyrrolidone in cattle following subcutaneous administration in florfenicol 2-pyrrolidone/triacetin formulation. SPRI Study No. 04064.

ii. Study Director and Laboratory:

Study Director (In life): Patrick Lockwood, D.V.M., Schering-Plough Animal Health, Terre Haute, IN
Analytical Laboratory: Analytical Development Corporation, Colorado Springs, CO, and Ricerca Biosciences, Concord, OH

iii. Test Article: NUFLOR GOLD Injectable Solution

iv. Test Animals: Twenty-eight cross-bred beef cattle (14 male castrates, 14 females), eight to eleven months old, weighing 231 to 369 kg

v. Dose: One SC injection at 40 mg florfenicol/kg BW

vi. Results:

Table 7. Mean 2-pyrrolidone Concentrations in Liver and Injection Site Muscle

Group	n	Withdrawal Time	Liver, ppb Mean (SD)	Injection Site Muscle, ppb Mean (SD)
9	4	Untreated	190 (86)	44 (13)
8	3	28 Day	156 (67)	58 (29)
7	3	14 Day	150 (58)	177 (135)
6	3	10 Day	201 (42)	584 (261)
5	3	8 Day	248 (39)	585 (320)
4	3	6 Day	187 (111)	333 (211)
3	3	4 Day	116 (40)	784 (667)
2	3	2 Day	165 (38)	546 (558)
1	3	6 hr	26,875 (1680)	69,307 (5179)

SD: Standard deviation

c. Total Residue Depletion and Metabolism Study

The total residue and metabolism of florfenicol in cattle is incorporated by reference to NUFLOR Injectable Solution (NADA 141-063) which was approved for use in cattle on May 31, 1996. This was codified on August 15, 1996 (61 FR 42383).

d. Comparative Metabolism Studies

The comparative metabolism studies conducted with florfenicol in the rat are incorporated by reference to NUFLOR Injectable Solution (NADA 141-063) which was approved for use in cattle on May 31, 1996. This was codified on August 15, 1996 (61 FR 42383).

2. Target Tissue and Marker Residue Assignment

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

Because residues of 2-pyrrolidone return to background concentrations prior to the withdrawal time assigned to florfenicol (see section B.4., below), NUFLOR GOLD Injectable Solution will be regulated based on florfenicol. Thus, neither a target tissue nor marker residue assignment is needed for 2-pyrrolidone.

3. Tolerance Assignments

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

Because residues of 2-pyrrolidone return to background concentrations prior to the withdrawal time assigned to florfenicol (see section B.4., below), NUFLOR GOLD Injectable Solution will be regulated based on the depletion of florfenicol amine, the marker residue for florfenicol. Thus, a tolerance assignment is not needed for 2-pyrrolidone.

4. Withdrawal Time

Based on a tolerance of 3.7 ppm for florfenicol amine, the marker residue, in the liver, the withdrawal time for NUFLOR GOLD Injectable Solution was calculated using the Agency's statistical tolerance limit algorithm (99% tolerance limit with a 95% confidence interval). The withdrawal time is 44 days.

C. Microbial Food Safety:

The Agency used a qualitative risk assessment to evaluate available microbial food safety information for the use of NUFLOR GOLD Injectable Solution in cattle for the treatment of BRD. 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 the antimicrobial new animal drug 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 treated cattle; and (3) a consequence assessment to describe the potential human health consequences of exposure to the defined

resistant bacteria or resistance determinants by considering the human medical importance of chloramphenicol in the treatment of human infectious diseases.

It was determined that the risk associated with the use of this product is MEDIUM. An overall risk of MEDIUM is compatible with the proposed conditions of use of florfenicol in cattle: a single, SC injection in the neck at a dose of 40 mg florfenicol/kg BW for the treatment of BRD.

D. Analytical Method for Residues:

1. Determinative Method

The HPLC determinative method for cattle liver is incorporated by reference to NUFLOR Injectable Solution (NADA 141-063) which was approved for use in cattle on May 31, 1996. This was codified on August 15, 1996 (61 FR 42383).

2. Confirmatory Method

The LC/MS/MS confirmatory method is incorporated by reference to NUFLOR Injectable Solution (NADA 141-063) which was approved for use in cattle on May 31, 1996. This was codified on August 15, 1996 (61 FR 42383).

3. Availability of Method

The validated regulatory method for detection and confirmation of residues of florfenicol is available from CVM, 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 NUFLOR GOLD Injectable Solution:

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, to report suspected adverse reactions, or to obtain a copy of the MSDS, call 1-800-211-3573.

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 NUFLOR GOLD Injectable Solution, when used according to the label, is safe and effective for the treatment of BRD associated with *M. haemolytica*, *P. multocida*, and *H. somni* 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 NUFLOR GOLD Injectable Solution 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:

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

VII. ATTACHMENTS:

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