Date of Approval: November 3, 2006

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-264

NUFLOR (FLORFENICOL), AN ANTIBIOTIC

Florfenicol
Type A medicated article for
swine

For the control of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Streptococcus suis*, and *Bordetella bronchiseptica* in groups of swine in buildings experiencing an outbreak of SRD.

Sponsored by:

Schering-Plough Animal Health Corp.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-264
B. Sponsor:	Schering-Plough Animal Health Corp. 556 Morris Ave. Summit, NJ 07901 Drug Labeler Code: 000061
C. Proprietary Name:	NUFLOR (florfenicol), An Antibiotic
D. Established Name:	Florfenicol
E. Pharmacological Category:	Antimicrobial
F. Dosage Form:	Type A medicated article containing florfenicol at 18.2 g/lb (40 g/kg), to be diluted in a finished Type C medicated feed for swine
G. Amount of Active Ingredient:	4% florfenicol (40 g/kg or 18.2 g/lb)
H. How Supplied:	50 lb (22.7 kg) paper bags, three ply, laminated
I. How Dispensed:	VFD
J. Dosage:	NUFLOR (florfenicol), An Antibiotic should be fed at a concentration of 182 g florfenicol per ton of complete feed (200 ppm). Feed continuously as the sole ration for 5 days to swine to deliver 10 mg florfenicol per kg body weight per day.
K Route of Administration:	Oral
L. Species/Class:	Swine
M. Indication:	For the control of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Streptococcus suis*, and *Bordetella bronchiseptica* in groups of swine in buildings experiencing an outbreak of SRD.

II. EFFECTIVENESS:

A. Dosage Characterization:

The effectiveness of florfenicol was evaluated for the treatment of respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida* in swine at concentrations of 0 ppm, 100 ppm, 200 ppm, or 300 ppm for five days. A total of 120 male castrated pigs with mild dyspnea and pyrexia (rectal temperature ≥ 104.5) were randomly allocated to one of four treatment groups – florfenicol at 0 ppm, 100 ppm, 200 ppm, or 300 ppm florfenicol or a negative control. Following treatment, pigs were evaluated for clinical signs of respiratory disease once daily for 12 days. On Day 12 all surviving pigs were humanely euthanized and lung lesions were evaluated. Based on the levels of florfenicol consumed and the clinical results, the 200 ppm concentration was taken to the field.

B. Substantial Evidence:

1. Clinical Field Study:

a. Study Title: Efficacy of a florfenicol (NUFLOR) feed premix for the control of Swine Respiratory Disease (SRD) in the US (Study No.: C01-154-01, -02, -03, -04, -05, -06).

b. Type of Study: Multi-location field study in swine with spontaneously occurring SRD.

c. Investigators:

Kent J. Schwartz, Team Associates, Story City, IA
Dale Mechler, Suidae, Inc., Algona, IA
Martin Mohr, St. Peter, MN
Kelly Lechtenberg, D.V.M., Ph.D., Midwest Veterinary Services, Inc., Oakland, NE
Kris Fairbanks, Rural Technologies, Inc., Brookings, SD
Chris Rumsey, Francesville, IN

d. Study Design:

Objective: To evaluate the effectiveness of florfenicol Type A medicated article in controlling naturally occurring SRD when administered as a medicated feed at a concentration of 200 ppm to deliver 10 mg florfenicol per kg BW per day for five consecutive days.

Animals: Female and castrated male crossbred swine, ranging in age from 8 to 25 weeks, with an initial body weight of 15 to 110 kg were enrolled in this

study. Pigs were obtained from locations that had a history of SRD.

Experimental Design: The study was conducted at six sites. At each site, pigs were randomly allocated to pens. Pens contained approximately 17 animals and each site contained 9 to 12 pens.

Pens (rather than individual animals) were enrolled in the study when at least 15% of the swine population in the pen (3 pigs) were diagnosed as "ill". "Ill" criteria were pyrexia (rectal temperature ≥ 104.5°F) associated with at least moderate dyspnea (respiration score of ≥ 2) and at least moderate depression (depression score of ≥ 2).

Dyspnea was assessed using the following clinical scoring scale:

0 = absent (normal character of breathing)
1 = mild (mild distress in breathing with minor abdominal effort)
2 = moderate (moderate distress in breathing, intermittent gasping/thumping with noticeable abdominal effort after exercise)
3 = severe (severe distress in breathing, continual gasping/thumping with extreme abdominal effort)

Depression was assessed using the following clinical scoring scale:

0 = absent (no depression; animal is bright, alert, and responsive; rises when investigator enters pen)
1 = mild (still responsive but less alert; may not rise when investigator enters pen)
2 = moderate (only partially responsive to stimuli; reluctant to rise under most circumstances)
3 = severe (animal recumbent, essentially non-responsive and very reluctant to move)

Once enrolled, pens were randomly assigned to treatment groups. All animals in a pen received the same treatment.

To characterize the SRD outbreak prior to treatment, 2 to 5 pigs that met the inclusion criteria were euthanized and necropsied. Lung samples were collected and cultured for the presence of SRD pathogens.

Test Article Administration: Florfenicol Type A medicated article was administered in a Type C medicated feed at a concentration of 200 ppm to deliver 10 mg florfenicol per kg BW per day for five consecutive days. Non-medicated swine grower diet was used as the negative control article. Test and control articles were administered orally for five days.

Measurements and Observations: The primary variable was the determination of treatment success on Day 7. A pig was classified as a success if rectal temperature was < 104˚F and depression and dyspnea scores were both ≤ 1. Pigs not meeting the criteria for success were classified as treatment failures.

Each pig was weighed individually on Day 0. All surviving pigs were re-weighed at study completion (Day 7). Pigs euthanized during the study were weighed prior to necropsy. Cultures were performed on lung samples. Other supportive variables recorded were mortality, total lung consolidation, body weight, perianal inflammation, rectal eversion/prolapse, fecal consistency, concurrent disease observations, and adverse events.

Statistical Analysis: The cumulative success at Day 7 was analyzed using a generalized linear mixed model with binomial errors and a default logit link. The fixed effect was treatment and the random effects were site, treatment by site, and pen nested within treatment by site. Cumulative mortality rate in each pen was analyzed using a mixed model. The fixed effect was treatment and the random effect was site. Rectal temperature and body weight were analyzed using mixed model analysis of variance/covariance. The Day 0 pre-treatment result was included as a covariate for subsequent days' analyses. The average daily weight gain was modeled using a mixed model. The fixed effect was treatment and the random effects were site, treatment by site, and pen nested within treatment by site. Ordered categorical variables recorded, including dyspnea and depression, were analyzed by the Cochran-Mantel-Haenszel Chi Square row mean score statistic, stratified by site.

e. Results: Refer to Table 1 below. The success rate was statistically significantly higher for the florfenicol-treated group (75.3%) compared to the control group (51.0%) at P = 0.006. The Day 7 mortality rate was statistically significantly lower for the florfenicol-treated group (4.4 %) compared to the control group (9.7%).

Table 1: Day 7 Results

Variable	**Florfenicol 10 mg/kg *ad libitum***	**Control**
Success, %	75.3	51.0 (p=0.0060)*
Cumulative mortality, %	4.4	9.7 (p=0.0059)**
Mean rectal temperature, ˚F	103.2	103.7 (p=0.0353)**
Total lung consolidation, %	26.7	35.1

*Using GLIMMIX, two sided test
** Least squares means, two sided test

Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica, and *Streptococcus suis* were isolated in sufficient numbers from lung swabs to be considered clinically relevant. The MIC data collected for these organisms in this study are summarized in Table 2.

Table 2: Florfenicol MIC Values Against Bacterial Isolates from Pigs with SRD

Bacteria Name	**Number of Isolates**	**MIC_{50} [a] (µg/ml)**	**MIC_{90} [b] (µg/ml)**	**MIC range (µg/ml)**
Actinobacillus pleuropneumoniae	256	0.25	0.5	$\leq$0.125-1
Pasteurella multocida	96	0.5	0.5	$\leq$0.125-0.5
Bordetella bronchiseptica	43	4	4	2-4
Streptococcus suis	65	1	2	0.5-2

[a] MIC for 50% of the isolates
[b] MIC for 90% of the isolates

f. Adverse Events: The incidence of perianal inflammation and rectal eversion was higher in the florfenicol-treated group compared to the control group. The incidence of loose, pasty, and gruel-like stool was higher in the florfenicol-treated group on Days 1 through 7 compared to the control group.

There were no other adverse events reported in the florfenicol-treated group.

g. Conclusions: The results demonstrate that florfenicol, when administered to pigs as a medicated feed for five consecutive days at a concentration of 200 ppm to deliver 10 mg florfenicol per kg BW per day was effective for the control of SRD associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Streptococcus suis*, and *Bordetella bronchiseptica*.

2. Summary of Pharmacokinetic Studies:

a. Bioavailability Study:

1) Study Title: Bioavailability of Florfenicol in Swine Following Intravenous and Oral Gavage Administration (Study No. N01-089-01).

2) Type of Study: Cross-over pharmacokinetic study to establish and evaluate the bioavailability of florfenicol.

3) Investigators:

Patrick Lockwood, D.V.M., Schering-Plough Animal Health Center, SPAH, Terre Haute, IN

Mohammad Mushtaq, Ph.D., Drug Safety and Metabolism – Animal Health, SPRI, Lafayette, NJ

4) Study Design:

Objective: To establish and evaluate the absolute bioavailability of florfenicol Type A medicated article when administered orally via gavage at 10 mg/kg BW and florfenicol injectable solution administered intravenously via ear vein at 10 mg/kg BW.

Animals: 6 male and 6 female swine, 2 to 4 months old and weighing 33 to 40 kg, were assigned to two treatment groups.

Experimental Design:

Table 3: Treatment Groups

Treatment Group	First Period Treatment	Second Period Treatment	Dose	Number of Animals
Group # 1	Nuflor Type A Medicated Article (Oral Gavage)	Nuflor Injectable 300 mg/ml (IV)	10 mg/kg	6 (3M, 3F)
Group # 2	Nuflor Injectable 300 mg/ml (IV)	Nuflor Swine Premix (Oral Gavage)	10 mg/kg	6 (3M, 3F)

Dose formulation: The Group #1 treatment was florfenicol Type A medicated article mixed in 5 mL water and light corn syrup was added up to 30 mL. The Group #2 treatment was commercially available florfenicol injectable solution.

Blood samples were collected at the following time intervals.

Group #1 (IV): 0 (Pre-dose), 0.25, 0.50, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours (± 10 minutes) after test article administration.

Group #2 (Oral Gavage): 0 (Pre-dose), 0.25, 0.50, 0.75, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours (± 10 minutes) after test article administration.

The washout period was 14 days.

Measurements: Serum levels of florfenicol were quantified by LC/MS/MS.

Pharmacokinetic Analysis: Pharmacokinetic parameter analysis was performed using non-compartmental modeling (NCA) via WinNonlin 4.0.1 (Pharsight Corporation, Mountain View, CA). Area under the swine serum concentration vs. time curve ($AUC_{0-\infty}$) was calculated by the linear trapezoidal rule, elimination half-life, and 24-hour swine serum concentration.

5) Results: Due to apparent drug extravasations, two animals were excluded from the estimation of mean IV pharmacokinetic parameter values. For one animal following oral gavage, the slope of the terminal depletion phase could not be estimated. Therefore, mean $T_{1/2}$ and $AUC_{0-\infty}$ values following oral gavage included only 11 of the 12 animals. Since three animals did not have $T_{1/2}$ value estimates following both oral and IV doses, F_{oral} was calculated on the basis of 9 of the 12 study subjects. Mean florfenicol pharmacokinetic parameters and bioavailability in swine after administration of a single 10 mg/kg BW dose of either NUFLOR (florfenicol), An Antibiotic Type A medicated article for swine (oral gavage) or NUFLOR Injectable Solution (intravenous) are tabulated in Table 4.

Table 4: Mean Florfenicol Pharmacokinetic Parameters (mean ± Standard Deviation [SD])

Parameter	Intravenous	Oral Gavage
$T_{1/2}$ (hr)*	2.81 ± 0.29	3.49 ± 0.62
Vd (mL/kg)*	963 ± 121	
Vd(ss) (mL/kg)*	957 ± 91	
Clb (mL/hr/kg)*	240 ± 40	
AUC_{last} (hr*µg/mL)*	40.51 ± 7.28	37.27 ± 14.05
$AUC_{0-\infty}$ (hr*µg/mL)*	42.69 ± 6.97	42.75 ± 9.14
F_{oral} (%)*		97 ± 16

* Pharmacokinetic parameters calculated for florfenicol included elimination half-life ($T_{1/2}$), peaking time (T_{max}), peak concentration (C_{max}), distribution volume at Steady State (Vd(ss)), clearance (Clb), area under the swine serum concentration vs. time curve from time zero to infinity ($AUC_{0-\infty}$), and bioavailability (F_{oral}).

6) Adverse Reactions: No adverse reactions occurred in this study.

7) Conclusions: Mean oral florfenicol bioavailability (F_{oral}) following an oral gavage dose was 97 ± 16% (mean ± SD). This indicates that florfenicol is completely absorbed when NUFLOR (florfenicol), An

Antibiotic Type A medicated article for swine is administered via oral gavage.

b. Pharmacokinetic Study:

1) Study Title: Pharmacokinetics of Florfenicol in Swine Following Administration of Nuflor Swine Premix in Feed for 5 days (Study No.: N01-061-01).

2) Type of Study: Pharmacokinetic study to establish and evaluate the pharmacokinetic profile of florfenicol.

3) Investigators:

Patrick Lockwood, D.V.M, Schering-Plough Animal Health Center, Terre Haute, IN
Mohammad Mushtaq, Ph.D., Drug Safety and Metabolism – Animal Health, SPRI, Lafayette, NJ

4) Study Design:

Objective: To establish the pharmacokinetic profile of florfenicol in swine following administration of florfenicol by oral route in feed, for 5 consecutive days at the dose rate of 10 mg/kg BW per day.

Animals: 6 male and 6 female crossbred swine, three to four months old, weighing an average 26.3 kg (25.5-28 kg).

Experimental Design:

Twelve healthy pigs were fed florfenicol medicated feed (200 ppm) for 5 consecutive days at a target dose rate of 10 mg/kg BW per day. Blood samples were collected from each pig as follows:

Day 0: 0 (pre-dose), 1, 2, 4, 6, 8, and 12 hours (± 15 min) after test article administration.
Day 1: 0 (pre-dose), 6, and 12 hours (± 15 min) after test article administration.
Day 2: 0 (pre-dose), 6, and 12 hours (± 15 min) after test article administration.
Day 3: 0 (pre-dose), 1, 2, 4, 6, 8, and 12 hours (± 15 min) after test article administration.
Day 4: 0 (pre-dose), 1, 2, 4, 6, 8, 12, 24, 30, 36, and 48 hours (± 15 min) after test article administration.

Measurements: Serum levels of florfenicol quantified by LC/MS/MS.

Pharmacokinetic Analysis: Pharmacokinetic parameter analysis was performed using non-compartmental modeling (NCA) via WinNonlin 4.0.1 (Pharsight Corporation, Mountain View, CA).

5) Results: Day 0 and Day 4 mean florfenicol pharmacokinetic parameters in swine after administration of florfenicol at a dose rate of 10 mg/kg orally once daily for 5 consecutive days are tabulated in Table 5.

Table 5: Day 0 and Day 4 Mean Florfenicol Pharmacokinetic Parameters (mean ±SD) at n=12

Parameter	Day 0 (1st dose)	Day 4 (5th dose)
T_{max} (hr)	4.67±0.98	5.17±2.31
C_{max} (μg/mL)	1.93±0.44	2.40±0.57
$T_{1/2}$ (hr)	14.37±12.04	7.27±3.16
AUC_{last} (hr*μg/mL)	26.54±5.87	26.12±6.32

*Pharmacokinetic parameters calculated for florfenicol included the apparent elimination half-life ($T_{1/2}$), peaking time (T_{max}), peak concentration (apparent "C_{max}"), and area under the swine serum concentration vs. time curve from time zero to the last quantifiable concentration time point (AUC_{last}).

It should be noted that one pig exhibited very poor food intake and consequently had substantially lower AUC and C_{max} values as compared to the other study subjects. This pig was included in the estimate of the mean pharmacokinetic parameter values.

6) Adverse Reactions: No adverse reactions occurred in this study.

7) Conclusions: Florfenicol administered in feed once daily for 5 consecutive days resulted in minimal drug accumulation in serum. Blood levels observed when administered in feed exhibited large inter- and intra-subject variation, which is attributable to variability in animal feeding behavior and thus drug intake. No obvious gender effect on pharmacokinetics was observed in this small study. Lower and slower drug absorption and slower drug elimination were observed when drug was given in feed versus oral gavage.

III. TARGET ANIMAL SAFETY:

A. Toxicity study:

1. Study Title: SCH 25298 (Florfenicol) Medicated Feed Premix: Oral Target Animal Safety Study in Swine: (Study No.: 00210)

2. Type of Study: Target Animal Safety Study

3. Study Director and Location: Terry TerHune, DVM, PhD, HMS Veterinary Development, Inc., Tulare, CA.

4. Study Design:

   Objective: To assess the safety of NUFLOR (florfenicol), An Antibiotic Type A medicated article for swine when administered to swine at concentrations of 0 (0 ppm), 1.5 (300 ppm), 4.5 (900 ppm), and 7.5 (1500 ppm) times the final recommended label concentration (200 ppm) for 15 days, and at 15 (3000 ppm) times the recommended label concentration for 5 days.

   Test Animals: 40 crossbred swine (20 castrated males, 20 females) approximately 3 months of age and weighing between 33 to 42 kg at initiation of dosing.

   Test and Control Articles: The test article was NUFLOR (florfenicol), An Antibiotic Type A medicated article for swine, administered orally in feed at concentrations of 300 (1.5X), 900 (4.5X), or 1500 (7.5X) ppm for 15 consecutive days; and one group received 3000 (15X) ppm for 5 days. A basal ration (porcine grower diet) was used as a placebo control.

   Measurements and Observations: The following measurements and observations were made at various time points throughout the study: Florfenicol dietary and serum concentration analysis, physical examination, clinical observations, body weights, food and water consumption, hematology, serum chemistry, urinalysis, fecal analysis, gross pathology, and histopathology.

   Statistical Methods: All continuous variables were analyzed using analysis of variance (ANOVA) models. Variables measured multiple times were analyzed using repeated measures analysis of covariance (RMANCOVA) 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.

5. Results:

Florfenicol Dietary Concentrations: Homogeneity and stability analysis showed that florfenicol concentrations ranged from 96 to 110% of the target concentrations.

Florfenicol Serum Concentrations: On the first day of dosing, the serum concentrations increased in a dose proportional manner, and tended to peak nine hours after feeding. There were no obvious sex differences or accumulation.

Clinical Observations: An increased incidence of feed spillage was noted in the 4.5X, 7.5X, and 15X ppm treatment groups.

Body Weights: Decreased weight gain was observed in the 4.5X, 7.5X, and 15X treatment groups as compared to the 1.5X and control groups.

Food and Water Consumption: A decrease in food consumption was observed in the 4.5X, 7.5X, and 15X groups. Decreased water consumption was noted starting on Day 5 in the 7.5X treatment group and starting on Day 6 in the 4.5X treatment group.

Hematology: A decrease in the number of reticulocytes was noted in the 4.5X, 7.5X, and 15X treatment groups. However, the changes noted were within the normal reference range.

Serum Chemistry: Increased serum calcium was noted in all treated groups (1.5X to 15X). Decreased serum phosphorus was noted in the 15X treatment group. Increased serum urea nitrogen and creatinine were noted in the 4.5X, 7.5X, and 15X treatment groups. These differences were small and within the normal reference range.

Urinalysis: No drug-related findings were observed.

Fecal Analysis: No drug-related findings were observed.

Gross and Microscopic Pathology: No test article-related gross abnormalities were observed. Decreased bone marrow cellularity was noted in the 4.5X and 7.5X treatment groups.

6. Conclusion:

This study demonstrated that NUFLOR (florfenicol), An Antibiotic Type A medicated article for swine can be safely administered in feed to swine at the recommended concentration of 200 ppm to deliver 10 mg/kg BW for five consecutive days**.**

IV. HUMAN FOOD SAFETY:

A. Toxicology:

Summaries of all toxicology studies supporting NUFLOR (florfenicol), An Antibiotic Type A medicated article for swine are incorporated by reference to approved NADA 141-063 for NUFLOR Injectable Solution.

An assessment was presented on the effects of florfenicol residues present in edible tissues of swine on human intestinal flora. It was concluded that the amount of active florfenicol residues reaching the human colon following a 13-day withdrawal period is probably too low to produce any adverse effect on the human intestinal flora.

B. Residue Chemistry:

1. Summary of Residue Chemistry Studies:

a. Study to Establish Withdrawal Time:

1) Study Title: "SCH 25298 (Florfenicol): A final residue depletion study of the marker residue, florfenicol amine, in swine following administration of florfenicol in feed"

2) Study No: 99390, Report No. 45913

3) Investigators:

Study Director:
Mohammad Mushtaq, Ph.D.
Schering-Plough Research Institute
Lafayette, NJ

In-Life Testing Facility:
Patrick Lockwood, DVM
Schering-Plough Animal Health Center
Terre Haute, IN

Analytical Facility:
Drug Safety and Metabolism- Animal Health Corp.
Schering-Plough Research Institute
Lafayette, NJ

4) Study Design:

Animals: Twenty two mixed breed swine (11 males and 11 females) were used in this GLP study. They were randomly selected for the study

and were divided into six groups. Treatment Groups I to V had four swine: two males and two females per group. The Control Group VI had one animal of each sex. The control animals (Group VI) were euthanized on the day before the medication period was started. The treated animals were euthanized at 3 (Group I), 6 (Group II), 9 (Group III), 12 (Group IV) and 15 (Group V) days post-treatment (time after withdrawal of medicated feed).

Route of Drug Administration and Time/Duration of Dosing: NUFLOR Type A medicated article was the premix formulation. The premix formulation was mixed with commercial swine feed to provide a nominal concentration of 200 mg florfenicol/kg (200 ppm). The medicated feed was fed to swine for 5 consecutive days with the expected feeding rate of 5% of the body weight per day to provide a nominal dose rate of 10 mg florfenicol/kg body weight/day.

Test Article: Florfenicol (premix) at the intended final concentration of 200 mg florfenicol per kg of finished feed.

5) Edible Tissue Residue Concentrations: At sacrifice time points of 3, 6, 9, 12, and 15 days post final dose, the following edible tissues were collected: liver, kidney, muscle, and skin with intact fat. Samples were assayed using the validated determinative method-"Florfenicol amine-method for the determination of residues in swine tissues using HPLC with UV detection (ISO 78/2 format)", except for liver. The determinative method required ethyl acetate (for liver and muscle) or methylene chloride (for kidney and skin/fat) as the eluant for solid phase extraction (SPE) of residues. However, for liver samples, methylene chloride was used as the eluant for SPE rather than ethyl acetate. The final extract was analyzed by HPLC-UV. The results are shown in Table 6.

Table 6: Marker residue (florfenicol amine) concentrations in the swine edible tissues following oral administration of florfenicol in feed for five consecutive days. Study No. 99390/ Report No. 45913

Group #	Sacrifice time, Post treatment		Liver (ppm)	Kidney (ppm)	Muscle (ppm)	Skin with Fat (ppm)
I	3 days	Mean	6.055	1.125	0.137	0.089
		Std. Dev.	0.679	0.237	0.028	0.018
II	6 days	Mean	4.475	0.736	0.120	0.071
		Std. Dev.	0.597	0.077	0.011	0.006
III	9 days	Mean	2.584	0.507	0.121	0.058
		Std. Dev.	0.396	0.117	0.015	0.016
IV	12 days	Mean	1.661	0.352	0.096	0.038
		Std. Dev.	0.160	0.040	0.029	0.012
V	15 days	Mean	1.041	0.249	0.094	0.032
		Std. Dev.	0.259	0.032	0.011	0.006
VI (Control)	Prior to Group I	Male Female	ND 0.041	0.019 ND	ND ND	0.009 ND

ND: None detected

2. Target Tissue and Marker Residue Assignments:

The marker residue for florfenicol in swine is parent florfenicol. The target tissue is liver. The marker residue and target tissue are codified under 21 CFR 556.283.

3. Tolerance Assignments:

The tolerance for the marker residue (parent florfenicol) is codified under 21 CFR 556.283.

4. Withdrawal Time:

Using a tolerance of 2.5 ppm for parent florfenicol in the target tissue (liver) and a statistical tolerance limit algorithm for the 99th percentile (95% confidence) data from "SCH 25298 (Florfenicol): A final residue depletion study of the marker residue, florfenicol amine, in swine following administration of florfenicol in feed," summarized in section B1a above, a withdrawal period of 13 days is calculated.

C. Microbial Food Safety:

Microbial food safety information for florfenicol was evaluated using a qualitative risk assessment procedure. The dosage regimen evaluated was 10 mg of florfenicol per kg of body weight or 200 mg per kg in complete swine feed (200 ppm). The

indication associated with the dosage regimen is "For the control of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Streptococcus suis*, and *Bordetella bronchiseptica* in groups of swine in buildings experiencing an outbreak of SRD."

The qualitative risk assessment procedure involved conducting: 1) a release assessment to describe the probability that florfenicol and its use in swine will result in the emergence of resistant bacteria or resistance determinants in treated swine under proposed conditions of use; 2) an exposure assessment to describe the likelihood of human exposure to resistant bacteria or resistance determinants through consumption of edible products from treated animals (in this case, swine); and 3) a consequence assessment to describe potential human health consequences arising from exposure to the defined resistant bacteria or resistance determinants by considering the human medical importance of phenicols used in the treatment of human infectious disease.

It was determined that the risk of development of transferable resistance elements from this use of florfenicol in swine is **medium**, leading to an overall risk estimation of **medium**. The proposed conditions of use are compatible with the Agency's risk management strategies associated with a product having an overall risk estimation of medium.

D. Analytical Method for Residues:

The validated regulatory method for detection and confirmation of residues of florfenicol is available from the Center for Veterinary Medicine, 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 (florfenicol), An Antibiotic Type A medicated article for swine.

Avoid inhalation, oral exposure, and direct contact with skin or eyes. Operators mixing and handling NUFLOR Type A Medicated Article for Swine should use protective clothing, gloves, goggles, and a NIOSH-approved dust mask. Wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water. If irritation persists, seek medical attention.

To request a material safety data sheet, call 1-800-211-2573.

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 (florfenicol), An Antibiotic Type A medicated article for swine when administered according to the label, is safe and effective for the control of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Streptococcus suis*, and *Bordetella bronchiseptica* in groups of swine in buildings experiencing an outbreak of SRD. Additionally, data demonstrate that residues in food products derived from pigs treated with NUFLOR (florfenicol), An Antibiotic Type A medicated article for swine will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

This drug may be dispensed only under a valid Veterinary Feed Directive (VFD). Any animal feed bearing or containing this VFD drug will be fed to animals only by or on a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice. In addition, veterinary feed directives issued for this drug are not refillable.

Labeling restricts this drug to use by or on the order of a licensed veterinarian. The decision to restrict this drug to use by or on the order of a licensed veterinarian was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product, (b) restricting this drug to use by or on the order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues, and (c) the rate of emergence of florfenicol-resistant organisms may be reduced by the involvement of veterinarians in product use. Because the drug will be administered in feed, the drug will be marketed as a Veterinary Feed Directive drug.

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 is attached as indicated below:

NUFLOR (florfenicol), An Antibiotic 50 lb bag label (front panel)
NUFLOR (florfenicol), An Antibiotic 50 lb bag label (back panel)
NUFLOR (florfenicol), An Antibiotic Type C medicated feed label
NUFLOR (florfenicol), An Antibiotic VFD form