Date of Approval: July 16, 2014

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-207

ADVOCIN Sterile Injectable Solution

Danofloxacin Injection

Beef Cattle

For the control of bovine respiratory disease (BRD) in beef cattle at high risk of developing BRD associated with *Mannheimia haemolytica* and *Pasteurella multocida*

Sponsored by:

Zoetis Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-207

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

ADVOCIN Sterile Injectable Solution

D. Established Name

Danofloxacin injection

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Injectable solution

G. Amount of Active Ingredient

180 mg/mL

H. How Supplied

100 mL and 250 mL bottles

I. Dispensing Status

Rx

J. Dosage Regimen

8 mg/kg body weight (BW), given once

K. Route of Administration

Subcutaneous injection

L. Species/Class

Beef Cattle

M. Indication

For the control of BRD in beef cattle at high risk of developing BRD associated with *Mannheimia haemolytica* and *Pasteurella multocida*

N. Effect of Supplement

This supplement provides for a new indication for the control of BRD in beef cattle at high risk of developing BRD associated with *M. haemolytica* and *P. multocida*.

II. EFFECTIVENESS

A. Dosage Characterization

The Freedom of Information (FOI) Summary for the original approval of NADA 141-207 dated September 20, 2002, and a supplemental approval dated December 16, 2011, contain dosage characterization information for cattle.

B. Substantial Evidence

1. Clinical Field Study

a. Title: "Evaluation of ADVOCIN for the Control of Naturally Occurring Bovine Respiratory Disease in Cattle at High Risk for BRD." Study Number A131C-US-12-128 (March 2013 to July 2013).

b. Investigators:

Site A: Kelly Lechtenberg, DVM, PhD. Midwest Veterinary Services, Inc. (MVS), Oakland, NE.

Site B: Jonathon R. Seagren, DVM. MVS, Oakland, NE.

Site C: Edward Johnson, DVM. Johnson Research, Parma, ID.

Site D: Matthew Edmonds, DVM, PhD. Johnson Research, Parma, ID.

Site E: David Bechtol, DVM. Agri Research Center, Canyon, TX.

Site F: Calvin Booker, DVM, M VetSc. Feedlot Health Management Service, Okotoks, Alberta, Canada.

Site G: Tye Perrett, DVM. Feedlot Health Management Service, Okotoks, Alberta, Canada.

c. Study Design:

1) Objective: To evaluate the effectiveness of ADVOCIN for the control of bovine respiratory disease (BRD) in cattle at high risk of developing BRD associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

2) Study Animals: Commercial beef-type calves were sourced from stockyards, auctions, and sale barns and transported to each study site. Calves were 4- to 10-month-old steers, with body weights ranging from 112 to 374 kg on the day of enrollment. Calves were

individually tagged with uniquely-numbered ear tags. Calves were housed in outdoor, dirt-floor pens with environmental management representative of industry standards (shading and/or wind breaks). A commercial-type feed ration appropriate for the calves' age and stage of production and without added antibiotics or growth promotants was provided *ad libitum* throughout the study. Non-medicated water was provided *ad libitum* in a manner consistent with commercial practice.

The calves were considered at high risk for developing BRD associated with *M. haemolytica* and *P. multocida* because they had experienced two or more of the following risk factors associated with naturally occurring BRD outbreaks:

- Stress associated with changes in feed and water.
- Crowding and handling associated with transport over long distances, (≥200 miles) with few to no rest stops.
- Increased exposure to different respiratory pathogens associated with the commingling of animals from multiple sources.
- Environmental temperature change of ≥30 °F from origin to study site.
- Environmental temperature change of ≥30 °F at a study site within a 24-hour time period.
- Exposure to wet or cold weather conditions.

Calves were enrolled if they had a Respiratory Score of ≤1 (see Table 1 below for scale) and an Attitude Score of 0 (see Table 2 below for scale) and a Rectal Temperature of <104.0 °F.

3) Treatment Groups: The test article was ADVOCIN Sterile Injectable Solution (180 mg danofloxacin as the mesylate salt per mL). Sterile saline solution was the control article. Calves were randomly assigned to receive either ADVOCIN once at 8 mg/kg BW by subcutaneous (SC) injection or saline once at 0.045 mL/kg BW by SC injecion. Across the study, 740 animals received ADVOCIN and 740 received saline. Treatment groups were commingled within each pen.

4) Drug Administration: ADVOCIN or saline were administered by SC injection in the left lateral neck at processing and enrollment (Day 0). The maximum volume allowed per injection site was 15 mL. Day 0 body weights were used to determine the amount administered.

5) Measurements and Observations: Animals were observed twice daily for signs of BRD from enrollment until Day 10. From Day 1 through Day 10, animals that had a Respiratory Score ≥2 or an Attitude Score ≥1 had their clinical scores recorded. The following scales were used to evaluate respiratory character (Table 1) and attitude (Table 2):

Table 1. Respiratory character clinical scoring scale

Clinical Score	Respiration
0	Normal: No abnormal respiratory symptoms present. Respiratory rate and effort were appropriate for the environment.
1	Mild Respiratory Distress: Serous nasal or ocular discharge and/or cough.

Clinical Score	Respiration
2	Moderate Respiratory Distress: Mucous or mucopurulent nasal or ocular discharge and/or increase in rate or effort.
3	Severe Respiratory Distress: Marked increase in rate or effort including one or more of the following: open-mouth breathing, abdominal breathing, or extended head.

Table 2. Attitude clinical scoring scale

Clinical Score	Attitude
0	Normal: Bright, alert, and responsive.
1	Mild Depression: May have stood isolated with its head down or ears drooping, but quickly responded to minimal stimulation.
2	Moderate Depression: May have stood isolated with its head down and/or shown signs of muscle weakness (standing cross-legged or knuckling when walking). Showed a delayed response to minimal stimulation or required greater stimulation before showing a response.
3	Severe Depression: May have been recumbent and reluctant to rise, or if standing isolated, was reluctant to move. Ataxia, knuckling, or swaying may have been evident when moving. Head carried low with eyes dull and ears drooping. Possible excess salivation and/or lacrimation.
4	Moribund: Unable to rise and get to feed or water.

Microbiologic samples were collected from all enrolled animals during incoming processing procedures (pre-treatment) and from all treatment failures (post-treatment) via a double-guarded, deep nasopharyngeal swab. The swabs were submitted to the diagnostic laboratory to determine the presence of *M. haemolytica* and *P. multocida*. Target pathogens were identified using biochemical methods.

d. Statistical Analysis: The primary variable for determining effectiveness was treatment success. Each calf was classified as a success or failure on Day 10. An animal was classified as a treatment failure if on any day from Day 1 through Day 10 it exhibited:

An Attitude Score = 1 or 2 and a Rectal Temperature ≥104°F.

OR

A Respiratory Score = 2 and a Rectal Temperature ≥104°F.

OR

A Respiratory Score = 3, regardless of Rectal Temperature,

OR

An Attitude Score = 3 or 4, regardless of Rectal Temperature.

An animal was classified as a Treatment Success on Day 10 if it met the following criteria:

1. It was alive.
2. It had not been identified as a treatment failure.
3. It had not been removed for non-BRD reasons.

Treatment success was analyzed as a binary variable (1=success, 0=failure) using a generalized linear mixed model with logit link and binomial error distribution. The statistical model included the fixed effect of treatment and random effects of study site, study site by treatment interaction, and pen within study site. The hypothesis test was a two-tailed test assessed at the 5% level of significance ($p \leq 0.05$).

e. Results: Four calves were removed from the study for non-BRD illness or protocol deviations and were excluded from the effectiveness analysis. A statistically significantly higher ($p = 0.0068$) success rate (based on back-transformed least squares means) was detected for the treated group (86.0%) compared to the control group (76.3%). Counting only a single isolate of a given pathogen from each enrolled calf, a total of 511 isolates of *M. haemolytica* and 330 isolates of *P. multocida* were recovered from the nasopharyngeal swab samples.

f. Adverse Reactions: No adverse reactions were reported in this study.

g. Conclusions: This study demonstrates that ADVOCIN Sterile Injectable Solution administered as a one-time SC injection at 8 mg/kg BW, is effective for the control of BRD in beef and non-lactating dairy cattle at high risk of developing BRD associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-207 dated September 20, 2002, contains a summary of target animal safety studies for beef cattle.

Reproductive safety has not been established for non-lactating dairy cattle; therefore, this approval does not include cattle intended for dairy production.

IV. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

A *hazard characterization* and *release assessment* were used to address FDA's concerns in the following areas: 1) current dairy farm management practices in the US, and their influence or lack thereof on the potential spread of antimicrobial resistance, 2) emerging multi-drug resistant, non-Typhimurium *Salmonella* serotypes, such as *S.* Newport and Dublin, 3) an update of NARMS information through 2010, specifically information on the impact of fluoroquinolone use in cattle on the emergence of *Salmonella* and *Escherichia coli* resistant to 3rd generation cephalosporins and fluoroquinolones, and 4) an update of any new pharmacokinetic or pharmacodynamic studies relevant to the proposed indications.

The microbial food safety of danofloxacin under the proposed conditions of use was assessed by the Agency on the sponsor's *hazard characterization*, *release assessment*, and data from studies provided to obtain Zoetis' supplemental approval (NADA 141-207) on December 16, 2011.

Decision Statement:
The Agency's evaluation of information in this submission, and additional consideration of the therapeutic use in beef cattle and non-lactating dairy cattle <20 months of age (excluding veal calves) for treating individual animals with a single dose, and an overall low extent of use, resulted in the Agency's individual rankings of medium for the release assessment, medium for the exposure assessment, and high for the consequence assessment. The Agency determined that the overall risk estimation associated with the use of the danofloxacin in beef cattle and non-lactating dairy cattle <20 months of age (excluding veal calves) under the proposed conditions is high, corresponding with mitigation strategies assigned to Category 1 antimicrobial drugs for food animal use. Risk management steps for a Category 1 antimicrobial drug include prescription (Rx) marketing status, extra-label use restriction, use in individual diseased animals, and continued monitoring by the National Antimicrobial Resistance Monitoring System (NARMS). These are all applicable to the use of danofloxacin in beef cattle and non-lactating dairy cattle <20 months of age (excluding veal calves) as described above.

B. Impact of Residues on Human Intestinal Flora

1. Determination of the need for establishing a microbiological ADI

a. Step 1: Are residues of the drug, and (or) its metabolites, microbiologically active against representatives of the human intestinal flora?

Yes, danofloxacin was active against representative bacterial human intestinal flora. The firm conducted a study and confirmed the above conclusion. The study is briefly summarized below.

Study title: Antibacterial activity of a fluoroquinolone against bacteria isolated from human gut flora: danofloxacin and its metabolite desmethyl danofloxacin (DMD).

Study No.	Not provided
Study Report	1993
Study Director	Prof. L. Dubreuil
Study Location	University of Lille, Cité Scientifique, 59100 Lille, France

Study objectives and procedures: The objective of the study was to determine the antimicrobial activity of danofloxacin and its metabolite (DMD) against human intestinal bacteria isolated in 1993, by determining MIC values using an agar dilution method. For quality control and assessment of reproducibility, four control reference strains were used in the testing (i.e., *Bacteroides fragilis* ATCC 25285, *B. thetaiotaomicron* ATCC 29741, *Clostridium perfringens* ATCC 13124, and *Eubacterium lentum* ATCC 43055). Representative bacterial groups (and numbers of isolates) obtained from human subjects included *B. fragilis* group (12),

Fusobacterium species (10), *Peptostreptococcus* sp (12), *Eubacterium* (10), *Clostridium* species (10), and *Bifidobacterium* species (10). MICs were determined by a reference agar dilution method according to methodology recommended by Clinical and Laboratory Standards Institute. MICs for the following aerobic bacteria were also determined following a similar methodology: *Proteus* spp. and *Morganella morganii* (11 isolates total), and *Lactobacillus* spp. (14 isolates). Strains were isolated from hospital patients. *E. coli* ATCC 25922 and *Enterococcus faecalis* ATCC 29242 were included as quality control organisms for testing of aerobic bacteria.

Results and conclusions: MICs of DMD for aerobic bacteria were similar and independent of the type of incubation (aerobic or anaerobic) and their MIC_{50} for danofloxacin was one dilution lower in anaerobes compared with aerobic bacteria. Danofloxacin and DMD were generally more active against aerobic bacteria than anaerobic bacteria. For aerobic bacteria, the average MIC was 0.25 µg/mL, while it was higher for anaerobic groups. The table below lists the MIC_{50} of danofloxacin against selected bacterial groups tested.

Table 3. Danofloxacin activity against selected group of representative bacteria of human intestinal flora

Organism/group	Number	MIC_{50} (µg/mL)
Bacteroides fragilis group	12	4
Fusobacterium species	10	4
Peptostreptococcus species	12	0.5
Eubacterium species	10	0.5
Clostridium species	10	2
Bifidobacterium Species	10	0.5
Lactobacillus species	14	16
Proteus species	11	0.25

(Note: MIC_{50} is the minimum inhibitory concentration that inhibits 50% of isolates tested for each group.)

b. Step 2: Do residues enter the human colon?

Yes, it was assumed that danofloxacin residues enter the human colon.

c. Step 3: Do the residues entering the human colon remain microbiologically active?

Based on the two studies described below, the amount of biologically active residues was too low to impact human intestinal flora. Therefore, the answer to the question is "No," and there is no concern for danofloxacin residue effects on human intestinal flora.

Study #1, title: Determination of *Kd* for [^{14}C] danofloxacin mesylate in human feces.

Study No.	53056.025
Study report	January 16, 2001
Study Director	Dr. Mark A. Moen

Study Location	Environmental Sciences Section, Chemical Research and Development, Pfizer Global Research & Development, Groton, CT

Study objectives and procedures: The study's objective was to characterize the sorption of [^{14}C] danofloxacin mesylate to human feces. The equilibrium constant was determined according to the modified FDA version of the Environmental Assessment Technical Assistance Document 3.08 (with modification of the protocol since the study was conducted in feces instead of secondary effluent or soil). Only sorption values were determined. Desorption values were not determined. Feces from 4 healthy male volunteers were pooled and made composite slurries by adding $CaCl_2$.

Preliminary and definitive experiments were performed with two different lots of [^{14}C] danofloxacin mesylate. The preliminary study was performed with the non-purified drug (radio-purity of 81.5%) and the definitive study with the purified drug (radiochemical purity of 99%). Unlabeled material was used as a standard. The purity was 75.6% of active ingredient.

Results and conclusions:
Preliminary experiments: studies were conducted to identify the appropriate solid levels (solids:solution ratio) and time required for reaching equilibrium. Solids:solution ratios of 1:50, 1:100, 1:200, and 1:500 were tested. No increase in sorption of [^{14}C] danofloxacin mesylate was seen from 48 to 72 hours in the 1:50 and 1:100 diluted samples. The sorption coefficients (*Kd*) in the 1:50 and 1:100 diluted feces remained constant, with no sorption occurring between 24 and 72 hours. The percent sorbed at the 1:200 dilution was similar to that seen at the 1:50 and 1:100 dilutions. Higher *Kd* values were seen at the 1:200 dilution. The *Kd* values seen at 1:500 dilution were similar to those seen at the 1:200 dilution. Higher dilutions did not affect the *Kd* values. It was concluded from the preliminary experiments that the 1:200 dilution represents a solids:solution ratio that gives an appropriate profile, and this dilution was selected for use in the definitive experiments.

Definitive experiments: Definitive experiments were conducted to determine the *Kd* at equilibrium using a concentration range of 0.1 to 5 mg/L of the mesylate salt and a solids:solution ratio of 1:200. Aliquots of fecal slurry were analyzed for solids concentration and it was determined to be 14.9%. Four concentrations of [^{14}C] danofloxacin mesylate (0.1, 0.5, 1, and 5 mg/L equivalent to 0.08, 0.81, and 4.1 mg/L of active ingredient, respectively) were tested in triplicate to determine the *Kd* at the solids:solution ratio of 1:200. Each drug concentration had triplicate control tubes without fecal material, and the experiments had triplicate controls of fecal material without danofloxacin. [^{14}C] Danofloxacin mesylate concentration for each dilution was determined by liquid scintillation counting. Tubes containing fecal slurry and the appropriate danofloxacin dose were incubated at 37^{0}C for 48 hours. After centrifugation of the samples, triplicate aliquots were assayed for radioactivity by liquid scintillation counting. Remaining fecal solids and sorbed drug from the glass tubes were also assayed for radioactivity.

Total mean recovery of radioactive drug ranged between 77.8% and 81.7% (mean: 79.6%) for samples with fecal material and from 100.4% to 105.9% for samples without fecal material (mean: 103.2%), which shows almost complete recovery of the drug from the experimental samples.

It was concluded that under the conditions of the study, with binding measured using a fecal dilution of 1:200, about 80% of radioactive danofloxacin was bound to fecal solids. Since human feces are composed of about 75% water and 25% solids, the solids:solution ratio is 0.33. Therefore, the binding of danofloxacin to normal feces would be more than 99%, leaving less than 1% of the drug to be biologically active.

Study # 2, title: Assessment of bioactivity of danofloxacin when bound to human feces.

Study No.	53560.022
Study Report	2001
Study Director	Catherine Reese, Ph.D.
Study Location	Pfizer Global Research and Development, Veterinary Medicine Safety & Metabolism, Groton, CT

Study objectives and procedures: The study was designed to determine the microbiological activity of danofloxacin bound residues by comparing danofloxacin activity, with and without human fecal slurries, against a danofloxacin-sensitive, streptomycin-resistant strain of *Salmonella typhimurium*.

Preliminary studies were conducted to determine the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of danofloxacin against the test strain under standard assay conditions, and confirm survival and recovery during incubation in human fecal slurry. The danofloxacin MIC for the *Salmonella* strain was 0.05 to 0.1 µg/mL, and MBC was 0.1 to 0.2 µg/mL.

Fecal slurries used in the sorption study summarized above were used in this study. The slurry was further diluted prior to use by adding an equal weight of distilled water. The estimated solid concentration was 7.45%. Different concentrations of danofloxacin were added to 2 g of fecal slurries to give final nominal concentrations of 25, 5, 2.5, 0.5, 0.25, 0.05, and 0.025 µg/g. Two fecal control tubes without danofloxacin were used as controls. A second test series was prepared without feces in which different dilutions of danofloxacin were added to a broth medium to give the same final concentrations as those in fecal slurries. A tube with only broth medium and without danofloxacin served as a control.

A culture inoculum of *S. typhimurium* (8.7×10^7 cfu/mL) was added to all tubes following the sorption step. One fecal control tube was left without inoculum. All tubes were incubated at 37^0 C with shaking, and samples taken after 3 and 6 hours of incubation for *S. typhimurium* viable counts (serial dilutions of samples with and without feces were plated in appropriate media). Samples were done in duplicate. As an alternative endpoint to monitor viable bacteria via colony counts, diluted and undiluted

samples were streaked on plates at 0, 3, 6, and 24 hours post inoculation. Fecal slurry samples without inoculation were also plated on selective agar, to determine if any other bacteria present in the fecal slurry could interfere with the results.

Results and conclusions: Bacterial counts of *S. typhimurium* from CAMH broth (no feces) assumed no interference from feces, and any reduction in counts can be attributed to the effects of the activity of biologically-available danofloxacin. In the presence of fecal material in the test system of otherwise equal conditions, changes in the counts may be due to the interference of feces.

Table 4. The counts of *S. typhimurium* at different incubation times in broth alone and in the presence of fecal slurry.

Danofloxacin concentration (μg/mL)	CAMH Broths (cfu/mL)	Fecal Slurries (cfu/mL)
0 hours		
2.5	9.65×10^5	4.45×10^6
0.05	5.25×10^6	3.80×10^6
0	5.05×10^6	3.75×10^6
Average:	5.15×10^6	3.78×10^6
3 hours		
25	$<3 \times 10^2$	$<3 \times 10^2$
5.0	$<3 \times 10^2$	6.65×10^6
2.5	$<3 \times 10^2$	1.55×10^7
0.5	3.45×10^2	2.04×10^7
0.25	1.97×10^3	1.95×10^7
0.05	5.70×10^4	2.55×10^7
0.025	2.48×10^7	2.15×10^7
0	3.32×10^8	4.10×10^7
6 hours		
25	$<3 \times 10^2$	$<3 \times 10^2$
5.0	$<3 \times 10^2$	4.55×10^5
2.5	$<3 \times 10^2$	7.77×10^7
0.5	$<3 \times 10^2$	1.02×10^8
0.25	1.26×10^3	1.61×10^8
0.05	1.83×10^4	2.31×10^8
0.025	1.98×10^8	1.54×10^8
0	1.79×10^9	4.05×10^8

At time 0, counts were performed in experiments in the presence of 0.05 and 0 μg/mL danofloxacin concentrations. In general, the average counts at 0 hours at each drug concentration were similar between the study group and broth control, which were consistent with the initial inoculum.

Counts of *Salmonella* in CAMH broth (no feces) at 3 hours of incubation decreased 99.9% at 0.25 μg/mL and higher, which demonstrate the high antibacterial activity of the drug. Even at 0.05 μg/mL, the activity was only 1% of that at 0 time. Counts were also lower at 0.025 μg/mL (1 log lower than those of the control no drug). The same pattern was observed

at 6 hours of incubation. Therefore, the MBC, based on the criteria of >99.9% kill, was 0.25 µg/mL. The lowest observed effect concentration (LOEC) is considered to be 0.05 µg/mL, and the no-observed effect concentration (NOEC) 0.025 µg/mL.

The counts of *Salmonella* in fecal slurries at 3 hours of incubation, except for drug concentration at 25 µg/mL, increased compared to those at 0 hours. The counts after 6 hours of incubation were similar, although the counts at 5 µg/mL decreased about 1 log (88% kill) compared to the 0 time sample. Based on these results, the MBC of danofloxacin in the presence of feces is 25 µg/mL, and the LOEC is 5 µg/mL, and the NOEC is 2.5 µg/mL.

The results of the non-quantitative tests for survival of *S. typhimurium* in CAMH broth (growth on plates inoculated from diluted and undiluted samples with different concentrations of danofloxacin) generally agree with the quantitative results discussed above. Tests conducted from fecal slurry samples also gave similar results. After 24 hours of incubation, both diluted and non-diluted samples from CAMH and fecal slurries gave results consistent with quantitative results presented above for samples after 3 and 6 hours of incubation. The MBC of 0.25 µg/mL (CAMH) and 25 µg/mL (fecal slurries) were confirmed. The purity test confirmed that only *S. typhimurium* strains grew on inoculated strains. No contamination was seen during the study.

It was concluded that the results of the study demonstrated that the presence of feces attenuates the activity of danofloxacin on *S. typhimurium*. The MBC of danofloxacin against the sensitive *S. typhimurium* strain is 100-fold higher in the presence of feces (25 µg/mL) than that measured in the absence of feces (0.25 µg/mL). The LOEC and NOEC are also 100-fold higher in the presence of feces than in the absence of feces. Results are consistent with those found in the binding study which demonstrated that danofloxacin binds to fecal material. Therefore, bound danofloxacin is no longer bioactive.

Decision Statement:

As previously stated in the FOI Summary for the original approval, the amount of microbiologically active residues of danofloxacin reaching the colon would likely not cause adverse effects on human intestinal microflora, due to inference by fecal materials. CVM did not require additional information for the impact of residues on human intestinal flora for this supplemental approval.

C. Toxicology

Reassessment of the toxicological ADI was not needed for this supplemental approval. The FOI Summary for the original approval of NADA 141-207 dated September 20, 2002, contains a summary of all toxicology studies and information.

D. Assignment of the Final ADI

The final ADI is the toxicological ADI of 2.4 µg/kg body weight per day, derived from a 3-month, subchronic, oral toxicity study in dogs. The codified ADI is listed under 21 CFR §556.169.

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

The safe concentrations of total danofloxacin residues in each edible tissue of beef and non-lactating dairy cattle are 0.48 ppm for muscle, 1.44 ppm for liver, 2.88 ppm for kidney, and 2.88 ppm for fat.

F. Residue Chemistry

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-207 dated September 20, 2002, contains a summary of residue chemistry studies for cattle.

G. Analytical Method for Residues

The FOI Summary for the original approval of NADA 141-207 dated September 20, 2002, contains the analytical method summaries for danofloxacin in cattle.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to ADVOCIN Sterile Injectable Solution:

For use in animals only. Keep out of reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following ocular or dermal exposures. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight.

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 ADVOCIN Sterile Injectable Solution, when administered subcutaneously at a dose of 8 mg/kg BW as a single injection, is safe and effective for the control of BRD in beef cattle at high risk of developing BRD associated with *M. haemolytica* and *P. multocida*. Additionally, data demonstrate that residues in food products derived from beef cattle treated with ADVOCIN Sterile 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 control BRD in beef cattle at high risk of developing BRD, and (2) restricting this drug to use by or on order of a licensed veterinarian should help prevent indiscriminate use that could result in violative tissue residues.

B. Exclusivity

This supplemental approval for ADVOCIN Sterile Injectable Solution qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the claim for control of bovine respiratory disease (BRD) in beef cattle at high risk of developing BRD associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information:

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