Date of Approval: February 21, 2012

FREEDOM OF INFORMATION SUMMARY -

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-209

EXCEDE

Ceftiofur Crystalline Free Acid
Sterile Suspension
Cattle (Beef, Non-lactating, and Lactating Dairy) -

To add a new indication for the treatment of acute metritis (0 to 10 days postpartum) associated with bacterial organisms susceptible to ceftiofur in lactating dairy cattle; and to provide modified injection techniques for the base of the ear route of administration.

Sponsored by:

Pharmacia & Upjohn Co.,
a Division of Pfizer, Inc.

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I. GENERAL INFORMATION:

A. File Number: NADA 141-209

B. Sponsor: Pharmacia & Upjohn Co.
a Division of Pfizer, Inc.
235 East 42d St. -
New York, NY 10017 -

Drug Labeler Code: 000009

C. Proprietary Name: EXCEDE

D. Established Name: Ceftiofur Crystalline Free Acid

E. Pharmacological Category: Antimicrobial

F. Dosage Form: Sterile Suspension

G. Amount of Active Ingredient(s): 200 mg ceftiofur equivalents (CE) per mL

H. How Supplied: 100 mL and 250 mL vials

I. How Dispensed: Rx

J. Dosages: BRD and Foot Rot: Single injection of 6.6 mg CE/kg (3.0 mg CE/lb) body weight (BW) (1.5 mL sterile suspension per 100 lb BW).

Metritis: 6.6 mg CE/kg (3.0 mg CE/lb) body weight (BW) (1.5 mL sterile suspension per 100 lb BW), given as two injections approximately 72 hours apart.

K. Routes of Administration: For subcutaneous (SC) injection in the posterior aspect of the ear where it attaches to the head (base of the ear) in lactating dairy cattle. For SC injection in the middle third of the posterior aspect of the ear or in the base of the ear in beef and non-lactating dairy cattle.

L. Species/Classes: Cattle (beef, non-lactating dairy, and lactating dairy)

M. Indications: EXCEDE Sterile Suspension is indicated for treatment of bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia*

haemolytica, *Pasteurella multocida*, and *Histophilus somni* in beef, non- lactating dairy, and lactating dairy cattle.

EXCEDE Sterile Suspension is also indicated for the control of respiratory disease in beef and non-lactating dairy cattle which are at high risk of developing BRD associated with *M. haemolytica*, *P. multocida*, and *H. somni*.

EXCEDE Sterile Suspension is also indicated for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii* in beef, non-lactating dairy, and lactating dairy cattle.

EXCEDE Sterile Suspension is also indicated for treatment of acute metritis (0-10 days post-partum) associated with bacterial organisms susceptible to ceftiofur in lactating dairy cattle.

N. Effects of Supplement: This supplement provides for a new indication for the treatment of acute metritis (0 to 10 days postpartum) associated with bacterial organisms susceptible to ceftiofur in lactating dairy cattle; and to provide modified injection techniques for the base of the ear route of administration.

II. EFFECTIVENESS:

A. Dosage Characterization:

The Freedom of Information (FOI) Summary for the original approval of NADA 141-209 dated September 5, 2003, contains dosage characterization information for the single dosage regimen of ceftiofur crystalline free acid (CCFA) in beef and dairy cattle.

To establish an appropriate dose and dosing regimen for the treatment of metritis in cows, a pharmacokinetic (PK) study (Study Report 1535R-60-05-495) evaluated plasma and uterine tissue levels of ceftiofur and its metabolites following administration of various doses of EXCEDE (CCFA) Sterile Suspension or the labeled dose of EXCENEL RTU (ceftiofur hydrochloride) Sterile Suspension. The study demonstrated good correlation between plasma and tissue (caruncle, lochial fluid, and endometrium) concentrations of ceftiofur and its metabolites.

A second PK study (Study Report 1531R-60-06-514) was conducted to characterize the PK of EXCEDE Sterile Suspension when administered in lactating dairy cows at two, 6.6 mg ceftiofur equivalents (CE)/kg body weight (BW), subcutaneous injections in the base of the ear approximately 72 hours apart (see the Target Animal Safety section below for study details). The results demonstrated that plasma concentrations of ceftiofur and its metabolites were higher and were sustained

above therapeutic levels for a longer period of time when administered at this dose and dosing regimen compared to other dosing regimens of EXCEDE Sterile Suspension.

B. Substantial Evidence:

Dose Confirmation Study

1. - Title: "Evaluation of Field Efficacy of Ceftiofur Crystalline Free Acid Sterile Suspension for Treatment of Acute Metritis in Dairy Cows when Administered at the Base of the Ear with a Repeated Dose of 6.6 mg Ceftiofur Equivalents per Kg Body Weight". Study 1133C-60-06-509. June 2006 to November 2006.

2. - Investigators:
Paul Busman, DVM; Sparta Animal Clinic P.C., Sparta, MI
Geoffrey Dahl, PhD and Richard Wallace, DVM; University of Illinois, Urbana, IL
Robin Carlson, RN, DVM; New London, IA
Mike Bossom, DVM; DeWitt, IA
Michael Capel, DVM; Perry Veterinary Clinic, Perry, NY
John Lee, DVM; Atwater Veterinary Clinic, Merced, CA
Ken Mitchell, DVM; Valley Veterinarians, Inc., Tulare, CA
Breck Hunsaker, DVM, PhD; Horton Research Center, Preston, ID
Scott Abbott, DVM; Dairy Vet Management, Sunnyside, WA
Kevin Crandall, DVM; Shelley, ID
Greg Goodell, DVM; Greeley, CO
Niles Jennett, DVM; Dairy Vet Services, Chandler, AZ
Chad Wright, DVM; Vet Outlet, Bakersfield, CA
Ricardo Chebel, DVM; University of Idaho, Caldwell, ID
Jose Santos, DVM, PhD; University of California VMTRC, Tulare, CA

3. - Study Design:

a) - *Objective:* To evaluate the effectiveness of a two-dose regimen of CCFA for the treatment of acute metritis under clinical field conditions, compared with a vehicle control. The study was conducted in accordance with Good Clinical Practices.

b) - *Study Animals:* A total of 1,023 cows across 15 commercial dairy study sites were enrolled in the study. Cows were lactating dairy cattle, in their first or greater lactation. Cows were identified by a unique individual number. Cows were subjected to the normal husbandry, health, and management practices of the location, except where superseded by the study protocol.

c) - *Experimental Design:* The study was a randomized block design with cows blocked on order of entry within study sites without regard to parity. Cattle at each site were randomly assigned to treatment and ear for the first injection in the order of enrollment. The Investigator, Associate Investigator(s), and personnel performing daily observations were masked to treatment assignments.

d) - *Test Article Administration:* The test article was EXCEDE (CCFA) sterile suspension as the commercially available product, 200 mg CE/mL. The

negative control article was the EXCEDE product vehicle (Miglyol® 812 and cottonseed oil), provided as a sterile solution.

Cows received a two-dose regimen of either CCFA at 6.6 mg CE/kg BW (n = 509 cows) or vehicle control at 1.5 mL/100 lb BW (n = 514 cows). The first dose was administered at enrollment (Day 0) at the base of one ear and the second dose was administered approximately 72 hours later (Day 3) at the base of the opposite ear.

e) - *Measurements and Observations:* To be enrolled in the study, a cow had to be ≤ 10 days post-calving, have a rectal temperature ≥ 103 °F (39.5 °C), have a vaginal/uterine discharge score = 4 (using a scale of 0 to 4 where 0 = no discharge and 4 = fetid discharge), and have no exclusion criteria based on medical records or identified during the pre-enrollment physical examination. On Days 1 to 13, each enrolled cow was observed once daily for any abnormal clinical signs. Rectal temperature was determined and recorded on Days 1 to 4. On Day 5 or 6 each cow was examined and determined if she was to remain in the study or be removed due to severity of clinical signs associated with acute postpartum metritis. Cows removed from Days 1 to 14 for worsening metritis were classified as a treatment failure in the effectiveness analysis, and were administered alternate therapy. On Day 14, each cow remaining in the study was examined and rectal temperature and vaginal discharge score, which were used to determine success (cure) or failure, were recorded. The Investigator also evaluated the ears of cows for injection site problems at each treatment administration, and on Days 5 or 6, 14, and 57±3.

4. - Statistical Analysis: The primary variable was the Day 14 cure rate. Cure was defined as a cow with a non-fetid vaginal discharge score (< 4), and rectal temperature < 103 °F on Day 14, and had no escape therapy administered during the study period. The cure rate variable was analyzed using a generalized linear mixed model (GLIMMIX) with a binomial error and logit link. Treatment was the fixed effect, and Investigator, treatment by Investigator, and residual were random effects. A two-sided test was used at the significance level of 0.05.

   Animal restraint and post-injection problems (bleeding, leak-back, etc.), ear injection site irritation, and rectal temperatures were evaluated as ancillary variables.

5. - Results: Cure rate was statistically significantly greater ($p < 0.0001$) in cows that were administered CCFA (362/493, 74.3%) than in cows that were administered vehicle (271/489, 55.3%) using back-transformed least square means for cure rate.

   The rectal temperature of cows administered CCFA was lower than that of cows administered vehicle on each of Days 1 to 5 or 6. Immediately after injection, there were no post injection problems observed in ≥ 78.5% of doses administered. Normal restraint equipment was adequate for base of the ear injection for ≥ 97.8% of injections administered. Injection site irritation (mostly swelling) was observed in 40.4% (first injection site) to 49.7% (second injection site) of CCFA-treated cows on Day 5 or 6, and only 2.3% to 3.6% of CCFA-treated cows by Day 57±3.

6. - Adverse Events: One cow died 15 to 20 minutes after administration of CCFA on Day 3 using the base of the ear "towards the opposite eye" technique. Necropsy findings determined the probable cause of death to be intra-arterial injection of CCFA. No other test-article related adverse events were reported.

7. - Conclusion: This study demonstrates that CCFA administered as two doses of 6.6 mg CE/lb BW subcutaneously at the base of opposite ears 3 days (72 hours) apart, is effective for the treatment of acute metritis (0 to 10 days postpartum) associated with bacterial organisms susceptible to ceftiofur.

III. TARGET ANIMAL SAFETY:

Evaluation of target animal safety is based on a pharmacokinetic (PK) bridge between EXCEDE Sterile Suspension and NAXCEL (ceftiofur sodium, NADA 140-338) Sterile Powder in cattle. First a PK study (Study Report 1531N-60-06-514) was conducted to characterize the PK of EXCEDE Sterile Suspension when administered in lactating dairy cows at two subcutaneous injections of 6.6 mg ceftiofur equivalents (CE)/kg body weight (BW) in the base of the ear approximately 72 hours apart. The results of this pivotal PK study were then compared to the historical PK data from a single-dose PK study of NAXCEL vs. EXCENEL in cattle (described in the FOI Summary for EXCENEL RTU Sterile Suspension, NADA 140-890, dated July 26, 1998; study report 788-7926-95-007) projected to 5 daily doses of NAXCEL at a dose of 2.2 mg/kg BW (the maximum labeled NAXCEL dosage).

A. Systemic Target Animal Safety for the Two-Dose Regimen in Lactating Dairy Cattle:

1. - Title: "Pharmacokinetics of Desfuroylceftiofur-residues in the Plasma of Lactating Dairy Cows Following Two Subcutaneous Injections of EXCEDE (CCFA; 200 mg/mL) in the Base of the Ear 72 Hours Apart at a Dose of 6.6 mg/kg Bodyweight for Each Injection". Study 1531N-60-06-514. August 2006 to August 2007.

2. - Study Director: M.F. Yancey, Pfizer Animal Health, Kalamazoo, MI

3. - Study Design:

   a) - *Objective:* To characterize PK and determine C_{max} and AUC_{0-LOQ} for desfuroylceftiofur residues after two treatments with CCFA dosed approximately 72 hours apart.

   b) - *Study Animals:* Twelve lactating, multiparous Holstein dairy cows were used in this study. Body weights ranged from 522 kg to 811 kg.

   c) - *Test Article Administration:* The test article was EXCEDE (CCFA) sterile suspension as the commercially available product, 200 mg CE/mL. Cows received a dose of 6.6 mg CE/kg BW as a SC injection in the base of the ear. A second dose was administered in the base of the opposite ear approximately 72 hours after the first injection.

   d) - *Measurements and Observations:* Blood samples were obtained prior to the first injection and at specified time points up to 336 hours after the first injection. General health, behavior, and injection sites were monitored daily.

4. - Analytical Method: The concentration of ceftiofur and desfuroylceftiofur (DCA)-related metabolites in plasma was quantified using the validated HPLC-DCA assay with UV detection (Watson HPLC system, Thermo Electron Corporation, Version 7.2).

5. - Statistical Analysis: Values for C_{max}, AUC_{0-LOQ}, $AUC_{0-\infty}$, T_{max}, $T_{1/2\lambda z}$ and $T_{>0.2}$ were estimated for each animal individually. AUC_{0-LOQ} was calculated using the trapezoidal rule. Additionally, $T_{>0.2}$ was calculated using the equation $T_{>0.2} = T_{last} + [\ln(0.2/C_{last})/\lambda_z]$, where $T_{>0.2}$ is the time where drug concentrations are above the concentration of 0.2 µg/mL, T_{last} is the time to the last measured concentration exceeding 0.2 µg/mL, C_{last} is the last measured concentration exceeding 0.2 µg/mL, and λ_z is the slope of the terminal elimination phase based on the natural log of concentration.

   The DCA plasma concentration data were summarized using the MIXED procedure of SAS. The mixed model repeated measures analysis included the fixed effect of time and the random effect of animal and utilized the heterogeneous compound symmetry covariance structure. Prior to analysis, the concentrations were transformed using the natural logarithm. Least squares means and 95% confidence levels were reported along with back-transformed values. All reported parameters were transformed via the natural logarithm prior to summarization. The averages and ranges were reported along with back-transformed values. Additionally, arithmetic means and standard deviations were calculated in Watson or Microsoft Excel.

6. - Results: All animals remained generally healthy during the study and no concomitant medications were administered. Two animals developed a seroma on their necks, but in both cases, the body temperature was normal and the swelling was not warm to the touch. No other adverse findings were reported during the study.

   A summary of the PK data for EXCEDE in lactating dairy cattle when administered in two doses of 6.6 mg CE/kg BW 72 hours apart is included in Table 3.1 below.

Table 3.1. Summarized PK data of ceftiofur in cows when administered as EXCEDE in two doses of 6.6 mg CE/kg BW 72 hours apart.

	C_{max} (µg/mL)	AUC_{0-LOQ} (µg*hr/mL)	$AUC_{0-\infty}$ (µg*hr/mL)	T_{max} (hr)	$T_{1/2\lambda z}$ (hr)	$T_{>0.2}$ (hr)
Geometric Mean*	5.56	641	NC***	59.9	55.5	340
Lower CI**	4.31	570	NC	31.2	52.5	318
Upper CI**	7.16	722	NC	115	58.8	363
Arithmetic Mean	5.98	651	NC	77.1	55.7	341
Standard Deviation	2.51	119	NC	33.4	4.84	34.0

* Back-transformed geometric mean
** Back-transformed 95% confidence interval (CI)
*** Not calculated

7. - Conclusion: Results of this pivotal PK study provided information on ceftiofur plasma exposure in cows when administered as EXCEDE in two doses of 6.6 mg CE/kg BW 72 hours apart. The C_{max} and AUC_{0-LOQ} results from this study were used for establishing a PK bridge between EXCEDE and NAXCEL.

B. Inter-study Comparison of Exposure from the 2-dose Study of EXCEDE and a Single-dose PK Study of NAXCEL in Cattle:

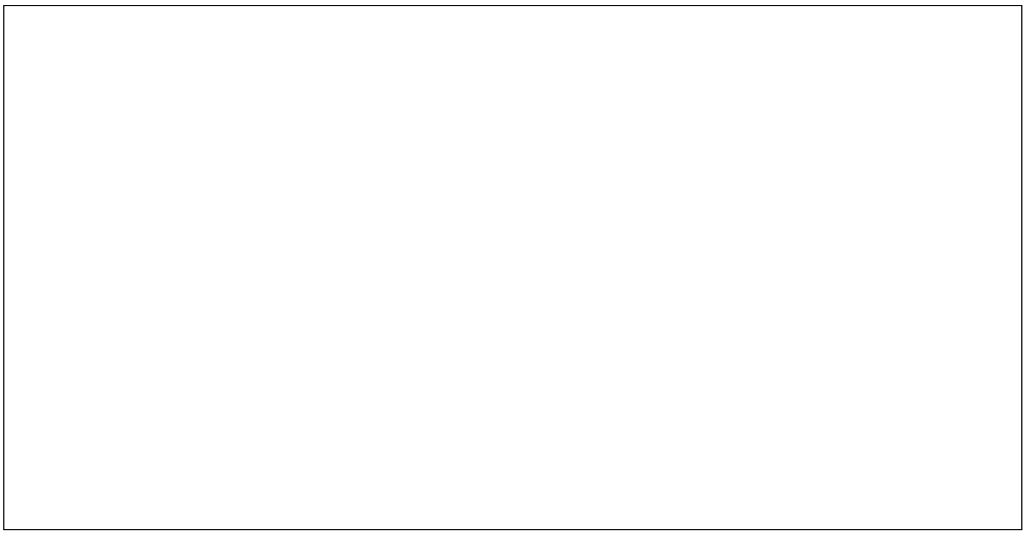
The PK data for EXCEDE administered twice 72 hours apart were compared to the projected plasma profile data of five doses of NAXCEL (ceftiofur sodium) administered at a dose of 2.2 mg CE/kg BW to establish a PK bridge between the two products. Projection of multiple-dose ceftiofur sodium C_{max} and AUC_{0-LOQ} data following five administrations of 2.2 mg CE/kg BW ceftiofur sodium was estimated from the historical single-dose PK data of NAXCEL vs. EXCENEL (described in the FOI summary for EXCENEL RTU Sterile Suspension, NADA 140-890, dated July 26, 1998; study report 788-7926-95-007). The C_{max} values from the multiple-dose regimen were assumed to be equal to the single dose data. The total AUC following 5 administrations was projected from the single dose data by multiplying the AUC_{0-LOQ} by 5.

When the individual animal C_{max} data for each treatment were compared across the treatment groups (as illustrated in Figure 3.1 below), it was demonstrated that the C_{max} after a 5-dose NAXCEL treatment exceeded the C_{max} after a 2-dose treatment with EXCEDE in all study animals.

Figure 3.1. Comparison of individual animal C_{max} values after a 5-dose NAXCEL treatment (2.2 mg CE/kg BW) and a 2-dose EXCEDE treatment (6.6 mg CE/kg BW) in cattle. C_{max} values after a 5-day treatment with NAXCEL ranged from approximately 12 to 26 µg/mL to approximately 2 to 12 µg/mL after a 2-dose EXCEDE treatment.

When the individual animal AUC_{0-LOQ} data were compared between the two treatments (as illustrated in Figure 3.2 below), the extent of exposure seemed to be more similar across the groups. However, on average the AUC_{0-LOQ} after a 5-dose NAXCEL treatment was still higher than after a 2-dose EXCEDE treatment.

Figure 3.2. Comparison of individual animal AUC_{0-LOQ} values after a 5-dose NAXCEL treatment (2.2 mg CE/kg BW) and a 2-dose EXCEDE treatment (6.6 mg CE/kg BW) in cattle. AUC_{0-LOQ} values after both treatments were in the range of 450 to 900 µg/mL.



Summary statistics for the C_{max} and AUC comparisons between the two treatment groups are provided in Table 3.2 and Table 3.3. The ratio of CCFA (EXCEDE) to ceftiofur sodium (NAXCEL) for AUC_{0-LOQ} was 0.94 with an upper confidence limit of 1.07. For C_{max}, the ratio was 0.34 with an upper confidence limit of 0.42.

Table 3.2. Summary statistics for the comparison of C_{max} after a 5-dose NAXCEL treatment (2.2 mg CE/kg BW) vs. a 2-dose EXCEDE treatment (6.6 mg CE/kg BW) in cattle

Statistic	Treatment	Parameter Estimate	95% Upper CL
LS-Mean	CCFA	5.56	6.49
LS-Mean	Ceftiofur sodium	16.3	18.82
Ratio	CCFA/sodium	0.34	0.42

Table 3.3. Summary statistics for the comparison of AUC_{0-LOQ} after a 5-dose NAXCEL treatment (2.2 mg CE/kg BW) vs. a 2-dose EXCEDE treatment (6.6 mg CE/kg BW) in cattle

Statistic	Treatment	Parameter Estimate	95% Upper CL
LS-Mean	CCFA	640	705
LS-Mean	Ceftiofur sodium	681	744
Ratio	CCFA/sodium	0.94	1.07

Based on these results, it was concluded that the ceftiofur exposure in cows following two 6.6 mg CE/kg BW doses of CCFA administered 72 hours apart is statistically no higher than the exposure following five daily 2.2 mg CE/kg BW doses of ceftiofur sodium. By establishing this PK bridge to the NAXCEL approval, the sponsor demonstrated the systemic target animal safety of EXCEDE Sterile

Suspension when administered SC as two 6.6 mg CE/kg BW doses 72 hours apart in the posterior aspect of the ear where it attaches to the head (base of the ear) in lactating dairy cattle.

C. Injection Site Tolerance for the Modified Base of the Ear Injection Techniques:

1. Dairy Conditions of Use Study

a. - Title: "Conditions of Use/Field Safety Study for Ceftiofur Crystalline Free Acid Sterile Suspension in Dairy Cows When Administered Subcutaneously Ventrally or Rostrally at the Base of the Ear". Study 1437C-60-09-768. January 2010 to March 2010.

b. - Investigators:
Paul Busman, DVM; Sparta Animal Clinic P.C., Sparta, MI
Keith Salmon, DVM; South Kent Veterinary Hospital, Caledonia, MI

c. - Study Design:

1) - *Objective:* To evaluate the injection site tolerance and field safety of EXCEDE Sterile Suspension when administered subcutaneously in the base of the ear of lactating dairy cattle.

2) - *Study Animals:* A total of 197 cows across two commercial dairy study sites were enrolled in the study. Cows were healthy lactating dairy cattle, greater than 21 days post-calving and not within 80 days of their expected calving date. Cows were subjected to the normal husbandry, health, and management practices of the location, except where superseded by the study protocol.

3) - *Experimental Design:* Within each site, cows were assigned randomly to one of two treatment techniques (defined in *Test Article Administration* below: rostral or opposite eye at Site A, and rostral or ventral at Site B) and one of four (Site A) or two (Site B) treatment administrators. In addition, at Site B, two different needle lengths (5/8" or 1") were evaluated.

4) - *Test Article Administration:* The test article was EXCEDE (CCFA) sterile suspension as the commercially available product, 200 mg CE/mL. Cows received a dose of 6.6 mg CE/kg BW as a single SC injection in the BOE using one of three injection techniques – 1) with the needle pointed in a rostral (anterior) direction (parallel with the saggital plane) towards the same eye ["rostral technique"]; 2) with the needle pointed ventrally (parallel with the saggital plane) ["ventral technique"] ; or 3) with the needle pointed toward the eye on the opposite side of the head ("opposite eye technique", the previously approved technique).

5) - *Measurements and Observations:* Immediately after injection an animal restraint score, an injection procedure score, and a post-injection problem score were recorded for each cow using the following scores.

Animal restraint index
0 = Normal, tolerate with restraint

1 = Additional restraint required
2 = Other

Injection procedure index
0 = Normal
1 = Required re-injection, due to animal movement and the needle needing to be reinserted into the ear

Post injection index
0 = None
1 = Excessive bleeding
2 = Excessive leak-back of injected material
3 = Other

Animals were observed on Days 0, 14, and 28 post-injection for abnormal clinical signs and injection site irritation. Ear carriage was recorded as either normal (N) or droopy (D). The following scores were used for ear injection site observations:

0 = Normal, no swelling or fluid
1 = Swelling or fluid, well defined, 1-2 inches in diameter
2 = Swelling or fluid, well defined, greater than 2 inches in diameter
3 = Diffuse swelling or fluid
4 = Ruptured, draining wound
5 = Other

d. - Statistical Analysis: Frequency distributions of animal restraint index, injection procedure index, post-injection index, ear injection site score, and ear carriage score were calculated for each treatment and time-point that data were collected.

e. - Results: There were few injection-related problems, and no relevant differences in restraint, re-injection, excessive bleeding, or excessive leak-back between the three techniques. Injection sites were normal in 32% of ears (average across sites) using the rostral technique on Day 14 after injection, compared to 46.9% using the ventral technique and 47.9% using the opposite eye technique. By Day 28, injection site scores were normal in 73% of ears (average across sites) using the rostral technique, compared to 87.8% using the ventral technique and 64.6% using the opposite eye technique. All ear carriage scores were normal at both sites on all days. Needle length did not affect distribution of injection site scores.

f. - Adverse Events: None.

g. - Conclusion: The study demonstrated that EXCEDE administered in the base of the ear of lactating dairy cows using a rostral or ventral injection technique is safe and was well-tolerated using normal equipment and restraint.

2. Beef Conditions of Use Study

a. - Title: "Conditions of Use/Field Safety Study for Ceftiofur Crystalline Free Acid Sterile Suspension in Beef Cattle When Administered Subcutaneously

Ventrally at the Base of the Ear". Study 1437C-60-09-769. January 2010 to March 2010.

b. - Investigator: Breck Hunsaker, DVM, PhD; Summit Research, Wellington, CO

c. - Study Design:

1) - *Objective:* To evaluate the injection site tolerance and field safety of EXCEDE Sterile Suspension when administered subcutaneously in the base of the ear of beef cattle.

2) - *Study Animals:* A total of 200 healthy beef heifers weighing approximately 750 lbs were enrolled in the study. Cattle were subjected to the normal husbandry, health, and management practices of the location, except where superseded by the study protocol.

3) - *Experimental Design:* Cattle were randomly assigned to needle length (5/8" or 1") and one of two treatment administrators.

4) - *Test Article Administration:* The test article was EXCEDE (CCFA) sterile suspension as the commercially available product, 200 mg CE/mL. Cattle received a dose of 6.6 mg CE/kg BW as a single SC injection in the base of the ear using the ventral injection technique (injection with the needle pointed in a ventral direction [parallel with the saggital plane] towards the same eye).

5) - *Measurements and Observations:* The measurements and observations were identical to those described for the dairy conditions of use study (Study 1437C-60-09-768) summarized above.

d. - Statistical Analysis: Frequency distributions of animal restraint index, injection procedure index, post-injection index, ear injection site score, and ear carriage score were calculated for each treatment and time-point that data were collected.

e. - Results: There were few injection-related problems, and no relevant differences in restraint, re-injection, excessive bleeding, or excessive leak-back between the two needle sizes. Injection sites were normal in 64.6% of animals injected with the 5/8" needle and 66.0% injected with the 1" needle on Day 14. By Day 28, injection site scores were normal in 87.9% of animals injected with the 5/8" needle and 97.0% injected with the 1" needle. All ear carriage scores were normal at both sites on all days.

f. - Adverse Events: One animal had an unusually large injection site swelling on Day 7 which reduced to a size comparable to other study animals by Day 14.

g. - Conclusion: The study demonstrated that EXCEDE administered in the base of the ear of beef cattle using a ventral injection technique is safe and was well-tolerated using normal equipment and restraint.

3. Injection Site Observations in Other Studies

Injection site information (post-injection problems and injection site evaluations) and an adverse reaction observed during the field effectiveness study (Study 1133C-60-06-509) are summarized in Section II (Effectiveness) above.

Injection site swelling was also evaluated in the residue study (Study 1531N-60-11-855) summarized in Section IV.B (Human Food Safety – Residue Chemistry) below. All 16 cows enrolled in the study had visible and palpable injection site swelling through at least 10 days and up to 19 days [the maximum study duration] after injection with EXCEDE at the base of the ear using the rostral injection technique described above.

IV. HUMAN FOOD SAFETY:

A. Microbial Food Safety:

Antimicrobial resistance:

The Agency evaluated a sponsor-produced microbial food safety risk assessment on the use of ceftiofur crystalline free acid (CCFA) for the treatment of acute metritis associated with bacterial organisms susceptible to ceftiofur in lactating dairy cattle (0 to 10 days postpartum). The product is administered as a subcutaneous injection in the base of the ear at a dosage of 3.0 mg ceftiofur equivalents/lb (6.6 mg CE/kg) body weight twice at a 72-hour interval.

The microbial food safety risk assessment included 1) a *release assessment,* describing the probability that the proposed use of CCFA for the treatment of acute postpartum metritis will result in the emergence of resistance or resistance determinants among bacteria in or on treated dairy cattle; 2) an *exposure assessment,* describing the probability of human exposure to bacteria from dairy foods; and 3) a *consequence assessment,* describing the probability that human exposure to resistant bacteria or resistant determinants results in an adverse health consequence. Outcomes of these assessments revealed that ceftiofur is a broad spectrum antibiotic with activity against a wide range of bacterial species. Transferable resistance mechanisms exist and are prevalent in bacteria from dairy cattle. Selection pressure from use of this antibiotic in dairy cattle could increase the amount of resistant *E. coli* and *Salmonella* entering the food chain. The risk of exposure to *Salmonella* and *E. coli* O157:H7 from consumption of ground beef is low, but the risk of exposure to *E. coli* is medium. Third generation cephalosporins are critically important in human medicine because they are used for treatment of enteric pathogens responsible for foodborne disease. They are a sole/limited therapy or essential therapy for serious disease, and are used to treat enteric pathogens in non-foodborne diseases, such as meningitis and necrotizing enterocolitis. These conclusions lead to an Agency determination that there is a high public health risk associated with this use of CCFA.

Decision Statement:

Prescription only (Rx) marketing status, parenteral injection only into individual animals with clinically recognizable symptoms of metritis, and continued monitoring in the National Antimicrobial Resistance Monitoring System (NARMS)

are among the appropriate risk mitigation strategies to manage the overall high risk estimation associated with this use of CCFA for the treatment of acute metritis associated with bacterial organisms susceptible to ceftiofur in lactating dairy cattle (0 to 10 days postpartum).

B. Impact of Residues on Human Intestinal Flora:

1. Determination of the need for establishing a microbiological ADI

A step-by-step approach was followed to determine whether there is a concern for effects of ceftiofur residues on human intestinal flora.

Step 1: Are residues of ceftiofur and/or its metabolites microbiologically active against representative human intestinal bacteria?

Yes, by default, ceftiofur has activity against representative human intestinal bacteria.

Step 2: Do residues of ceftiofur and/or its metabolites enter the human colon?

Yes, it is concluded that ceftiofur residues enter the human colon.

Step 3: Do residues of ceftiofur and/or its metabolites entering the colon remain microbiologically active?

Yes, ceftiofur residues remain microbiologically active in the colon, but their quantity is very low, as concluded from a comprehensive pivotal, multi-phased study that is summarized below.

Study Title: Anaerobic Degradation of Ceftiofur by Human GI Tract Microflora in Human Fecal Slurries.
Study No.: 788-7926-I-REH-93-001
Study Director: Susan Kotarski, PhD
Study Location: Veterinary Medicine Research & Development, Pharmacia & Upjohn Co., Kalamazoo, MI
Study Report Date: 26 January 1994 (Experimental work performed between 1993-1994)

Study Design: The objective of the study was to examine the degradation of ceftiofur in human fecal slurries and to identify degradation products. Fecal samples from 11 donors were collected, diluted 1:1 in anaerobic buffer, and ceftiofur added to the slurries at concentrations of 0, 10, 100, or 500 µg/mL. Untreated and autoclaved slurries were used in this experiment. Samples were incubated at 37 °C for up to 24 hours. Ceftiofur was used in the studies because its metabolites contain an intact β-lactam ring and any degradation detected for ceftiofur is very likely to apply also to metabolites.

The study was conducted in three phases:
1) Phase I was to determine whether rapid loss of biological activity occurs during anaerobic incubation of ceftiofur (500 µg/mL) with fecal slurries (up to 24 hours) from 8 human volunteers. Loss of microbiological activity was measured by a microbiological cylinder plate assay with a bacterial strain of *Micrococcus luteus*.

2) Phase II was to determine whether the microbiological activity of ceftiofur was stable in the fecal slurry. Fresh and autoclaved fecal samples were fortified with 0 and 833 µg/mL of ceftiofur, and incubated for 0 or 4 hours. 3) Phase III was a series of experiments designed to study the inactivation of ceftiofur in buffer-diluted fecal slurries. 500 µg/mL of ceftiofur were added to different dilutions of slurries and incubated for 0, 1, 2, and 4 hours.

Results and conclusions: -
The three-phase study revealed the following findings:
1. In Phase I, 1) ceftiofur immediately lost its activity in fecal slurries when fortified with low doses (1 and 10 µg/mL); 2) slurries from 7 of 8 donors fortified with 500 µg/ml immediately showed >90% loss of microbiological activity; 3) sterilized fecal slurries lost only 0 to 36% of the microbiological activity after 4 hours of anaerobic incubation at 37 °C, suggesting that part of the activity is due to chemical instability or degradation, binding, or both; 4) fresh and sterilized samples fortified with 100 and 500 µg/mL of ceftiofur also showed immediate and complete loss of activity at 100 µg/mL (fresh samples), and almost total loss at 500 µg/mL after 4 hours of incubation. Autoclaved samples had a small loss of activity at both concentrations of the drug; 5) fecal slurries, diluted and maintained under anaerobic conditions are capable of degrading ceftiofur to non-active products as concentrations as high of 500 µg/mL.

2. Phase II results showed that there might be some degradation of ceftiofur activity in the methanol diluted solutions, but its microbiological activity is largely retained, as confirmed by microbiological assay and HPLC methods. Because deactivating enzymes or other degrading factors are not present to degrade ceftiofur in the cylinders for in the microbiological assay *per se*, ceftiofur degradation or inactivation found in Phase I was not due to the processing method of the samples, but rather due to the incubation with fecal materials.

3. Phase III included three groups of experiments (i.e., degradative activity by dilution, protein binding experiment by ultrafiltration, and degradation profile), and demonstrated that ceftiofur in undiluted samples had a very high loss of activity at 0 hours. At 2 hours of incubation, all activity had been lost. The saturation point is reached between 50- and 250-fold dilutions dependent on individual feces used, which would indicate that 1 gram of undiluted fecal material would have the capacity to metabolize 22.5 to 112 mg ceftiofur within 5 minutes.

These results indicate the enormous capacity of undiluted fecal samples to metabolize ceftiofur. The fecal microbial flora had the capacity to inactivate ceftiofur. The loss of ceftiofur activity was not due to protein binding but was more likely due to ceftiofur inactivation by enzymatic action from the fecal environment.

Step 4: Is there any scientific justification to eliminate testing of either colonization barrier disruption or resistance development endpoints?

Yes, based on results from the study described above, it was concluded that ceftiofur residues in feces are rapidly inactivated, and biologically active residues are very low. Thus, ceftiofur residues would not produce changes in the human

intestinal flora. Therefore, testing of either endpoint of concerns - colonization barrier disruption or resistance development - is not needed.

2. Determination of the Final Microbiological ADI

There is no need to determine a microbiological ADI under the proposed application.

Final conclusion: As stated in the FOI Summary under NADA 141-235, dated June 18, 2004, the amount of microbiologically active residues of CCFA that reach the colon would most likely not cause adverse effects on the human intestinal flora of the consumer.

C. Toxicology:

CVM did not require toxicology studies for this supplemental approval. The FOI Summaries for the original approval of NADA 140-338 (NAXCEL Sterile Powder) dated January 25, 1988; for the supplemental approval of NADA 140-338 dated May 21, 1996; for the original approval of NADA 140-890 (EXCENEL RTU Sterile Suspension) dated April 1996; and for the original approval of NADA 141-235 (EXCEDE for Swine) dated June 18, 2004, contain summaries of all toxicology studies.

D. Assignment of the Final ADI and the Final ASDI:

No reassessment of the toxicological ADI, microbiological ADI, or toxicological ASDI was needed for this supplemental approval. The FOI Summary for the original approval of NADA 141-209 (EXCEDE Sterile Suspension) dated September 5, 2003, contains a summary of all toxicology studies and information used to assess the impact of residues on human intestinal flora.

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

No reassessment of the safe concentrations for total residues was needed for this supplemental approval. The FOI Summary for the original approval of NADA 140-338 (NAXCEL Sterile Powder) dated January 25, 1988; for the supplemental approval of NADA 140-338 dated May 21, 1996; for the original approval of NADA 140-890 (EXCENEL RTU Sterile Suspension) dated April 1996; and for the original approval of NADA 141-209 (EXCEDE Sterile Suspension) dated September 5, 2003, contain summaries of all toxicology studies and information used to assess the impact of residues on human intestinal flora.

F. Residue Chemistry:

1. Summary of Residue Chemistry Studies

The total residue depletion and metabolism in the target species and comparative metabolism in the toxicological species for ceftiofur are summarized in the FOI summaries for NADA 140-338 (NAXCEL Sterile Powder) and NADA 140-890 (EXCENEL RTU Sterile Suspension).

a. - Tissue Residue Depletion Study

1) **Determination of Ceftiofur and Desfuroylceftiofur-Related Residues in Kidneys of Dairy Cattle Receiving Two SC Injections of CCFA-SS (200 mg/mL) in the Base of the Ear at 6.6 mg/kg Body Weight. (Study 1531N-60-11-855)**

The purpose of this Good Laboratory Practice (GLP) study was to measure the concentration of ceftiofur and desfuroylceftiofur (DCA)-related residues in the kidneys of dairy cattle following two injections of CCFA (200 mg/mL) at a dose of 6.6 mg ceftiofur equivalents/kg body weight into the base of the ear.

Study Dates: January 28, 2011-May 12, 2011

Study Director: Pamela L. Boner, Ph.D., R.Ph.

Study Facility: Pfizer Animal Health, Richland, MI

Test Animals: Twenty lactating Holstein dairy cows (16 to be treated, 4 as back-up) weighing 442-720 kg at initiation of the study

Test Article Administration: Animals were randomly assigned to one of four treatment groups (n=4 animals/group) and received CCFA (200 mg/mL) as a subcutaneous injection at the base of the ear at a nominal concentration of 6.6 mg ceftiofur equivalents/kg body weight. The first dose (actual dose 6.6 ± 0.1 mg/kg) was administered subcutaneously at the base of the left ear, at the juncture of the auricular cartilage with the cranium, with the needle directed towards the same eye. The second dose (actual dose 6.9 ± 0.1 mg/kg) was administered subcutaneously at the base of the right ear approximately 72 hours later (3 days).

Sampling: Whole kidney samples were collected at withdrawal intervals of 4, 8, 12 and 16 days post second-dose.

Kidney Assay Results: The mean DCA residues were 1437.5 and 570 µg/kg at 4 and 8 days post second-dose, respectively. All values for DCA at 12 and 16 days post second-dose were below the limit of quantitation (LOQ, 200 µg/kg).

Table 4.1. Liquid Chromatography/Mass Spectrometry (LC/MS)-DCA Assay-Concentrations of ceftiofur free acid equivalents (as DCA) in Dairy Cattle Kidney Samples.

Treatment Group	Withdrawal Time (days)	Mean ± Standard Deviation (µg/kg)
T01	4	1437.5 ± 172.9
T02	8	570 ± 216.7
T03	12	BLQ[1]
T04	16	BLQ

[1]Below Limit of Quantitation (BLQ) of 200 µg/kg

2) Determination of Ceftiofur and Desfuroylceftiofur-Related Residues in Injection Sites of Non-Lactating Dairy Cattle Receiving Either a Single or Split SC Injection of CCFA-SS (200 mg/mL) in the Base of the Ear at 6.6 mg/kg Body Weight. (Study 1531N-60-08-705)

This GLP study was conducted to measure the concentration of ceftiofur and desfuroylceftiofur-related residue in the injection site tissue of non-lactating dairy cattle in two groups following injection of CCFA (200 mg/mL) at a dose of 6.6 mg ceftiofur equivalents/kg body weight into the base of the ear oriented towards the same eye.

Study Dates: November 20, 2008-June 10, 2009

Study Director: Pamela L. Boner, Ph.D., R.Ph.

Study Facility: Pfizer Animal Health, Richland, MI

Test Animals: Eighteen female Holstein non-lactating dairy cows (16 treated, 2 back-up) weighing 641-929 kg at the initiation of the study

Test Article Administration: Sixteen animals were randomly assigned to one of two treatment groups. Animals in Group 1 (T01) received a subcutaneous injection of CCFA (6.6 mg CE/kg BW) into the base of the left ear with the needle oriented towards the same eye. Animals in Group 2 (T02) received the subcutaneous dose of CCFA split into the base of both ears.

Sampling: T01 and T02 injection sites at the base of the left ear were collected (~ 500g). The right ear injection site for T02 animals was not evaluated or collected. All animals were slaughtered 13 days post-dose.

Analysis: T01 and T02 injection sites were analyzed by LC-MS method for ceftiofur free-acid equivalents (as DCA).

Muscle Assay Results: Mean concentrations of ceftiofur free-acid equivalents (as DCA) for each animal in T01 injection sites are shown in Table 4.2. Three of eight animals had mean DCA concentrations above the LOQ (250 µg/kg). Mean concentrations ranged from 279 ppb to 11 ppm, which is below the research tolerance of 95 ppm. Concentrations of ceftiofur free-acid equivalents (as DCA) in T02 injection sites all fell below LOQ (250 µg/kg).

Table 4.2. LC/MS-DCA Assay Concentrations of ceftiofur free-acid equivalents (as DCA) in T01 Injection Sites in µg/kg.

Animal #	Mean ± Standard Deviation (µg/kg)
569	BLQ*
570	BLQ
572	279
573	BLQ
574	342 ± 46
575	BLQ
580	11267 ± 1050
581	BLQ

*BLQ of 250 µg/kg

b. Milk Residue Depletion Study

Determination of Ceftiofur and Desfuroylceftiofur-Related Residues in Milk of Lactating Dairy Cattle Receiving Two SC Injections of High *In Vitro* Release Rate of CCFA-SS (200 mg/mL) in the Base of the Ear at 6.6 mg/kg Body Weight. (Study 1531M-60-06-515)

This GLP study was conducted to measure the concentration of ceftiofur and desfuroylceftiofur-related residue in the milk of lactating dairy cattle following two injections of ceftiofur crystalline free acid sterile suspension (200 mg/mL) at a dose-rate of 6.6 mg/kg of CCFA with a high *in vitro* drug release rate (≥ 80%) formulation into the base of the ear.

Study Dates: March 31, 2006-August 24, 2007

Study Director: Pamela L. Boner, Ph.D., R.Ph.

Study Facility: Halbert Dairy Farm, LLC, Battle Creek, MI

Test Animals: Forty-eight lactating Holsteins (40 treated, 8 as back-up) weighing 489-761 kg at initiation of the study.

Test Article Administration: Animals were assigned to two treatment groups (n=20 animals/group) and received CCFA (200 mg/mL) as a subcutaneous injection at the base of the ear at a nominal concentration of 6.6 mg ceftiofur equivalents/kg body weight. Animals in Group 1 were dosed with a subcutaneous injection of CFFA to the base of the left ear on Study Day 0 then again on Day 3 to the base of the right ear. Animals in Group 2 were dosed with a subcutaneous injection of CCFA to the base of the left ear on Study Day 0, three hours prior to milking, then dosed again with a subcutaneous injection to the base of the right ear on Day 3, six hours prior to milking.

Sampling: Within Group 1, milk was collected every 12 hours beginning 7 days prior to treatment (to measure milk production) through the morning milking of the 9th day post-first dose treatment (Study Day 9). In Group 2, milk was collected every twelve hours beginning 7 days prior to treatment through the 18-hour milking following the second dose. In addition, milk was collected three hours post first-dose and six hours post second-dose.

Test Article Release Rates: The mean release rates for Group 1 and Group 2 were 79 ± 4.19 and 77 ± 4.23%, respectively.

Milk Assay Results: The mean results for each time point for the HPLC-DCA assay are provided in Tables 4.3 and 4.4 for Groups 1 and 2, respectively. One animal in Group 1 had mean DCA concentrations that were above the codified milk tolerance of 0.1 ppm at four time points (96-132 hours post first dose).

Table 4.3. HPLC-DCA Assay- Dose Group 1- Mean Concentrations of ceftiofur free-acid equivalents (as DCA) for all animals (N=20) in Group 1 analyzed at each time point in µg/mL.

Time following 1st Dose (hours)	Mean ± Standard Deviation (ppm)
0	BLQ
12	.0286 ± .0157
24	.0303 ± .0210
36	.0324 ± .0181
48	.0316 ± .0196
60	.0260 ± .0119
72	.0224 ± .0102
84	.0376 ± .0170
96	.0424 ± .0231
108	.0433 ± .0271
120	.0400 ± .0296
132	.0380 ± .0294
144	.0299 ± .0149
156	.0260 ± .0094
168	.0223 ± .0062
180[1]	.0229 ± .0039
192[1]	.0197 ± .0040
204[1]	.0177 ± .0011
216[1]	.0207 ± .0040

[1]N=20, except for time-points noted, N=13. After completion of analysis for 13 animals, no values above the LOQ were found past 168 hours, therefore analysis of time-points past 168 hours for the remaining animals was discontinued.

Limit of Detection (LOD) = 0.015 µg/mL
LOQ = 0.050 µg/mL

Table 4.4. HPLC-DCA Assay-Dose Group 2-Mean Concentrations of ceftiofur free-acid equivalents (as DCA) for all animals (N=20) in Group 2 analyzed at each time point in µg/mL.

Time Following 1st Dose (hours)	Mean ± Standard Deviation (ppm)
-33	BLQ
3	BLQ
15	.0222 ± .0052
27	.0272 ± .0086
39	.0289 ± .0055
51	.0281 ± .0048
63	.0244 ± .0085
78	.0295 ± .0083
90	.0375 ± .0188

LOD = 0.015 µg/mL
LOQ = 0.050 µg/mL

2. Target Tissue and Marker Residue

The target tissue for residue monitoring is kidney. The marker residue in edible tissues, including milk, is the sum of ceftiofur and desfuroylceftiofur-related metabolites, measured by high performance liquid chromatography (HPLC) as the stable derivative desfuroylceftiofur acetamide (DCA). The studies supporting the target tissue and marker residue assignments can be found under NADA 140-338 FOI Summaries dated January 25, 1988, and March 15, 1991, and NADA 140-890 FOI Summary dated July 26, 1998.

3. Tolerance(s)

Cattle tolerances are 0.4 ppm DCA in kidney, 2 ppm DCA in liver, 1 ppm DCA in muscle and 0.1 ppm DCA in milk (21 CFR 556.113). For research purposes, a value of 95 ppm DCA has been established for making decisions regarding the safety of residues at the injection site. See the FOI Summary for the supplemental approvals of NADA 140-890 dated July 26, 1998, and NADA 141-209 dated June 2, 2006.

4. Withdrawal Period and Milk Discard Time

Tissue residue data from Study No. 1531N-60-11-855 support a 13-day withdrawal period for EXCEDE Sterile Suspension when used according to label directions as a 2-dose regimen in lactating dairy cattle.

Milk residue data from Study No. 1531N-60-06-515 were analyzed by a statistical method that determines the statistical tolerance limit for the 99th percentile of the population with 95% confidence. A bulk tank factor of one-third was applied to adjust for the whole herd not being treated at the same time. The data support assignment of a zero milk discard time as a 2-dose regimen in lactating dairy cattle.

G. Analytical Method for Residues:

The FOI Summary for the original approval of NADA 141-209 dated September 5, 2003, contains the analytical method summaries for EXCEDE Sterile Suspension (ceftiofur crystalline free acid) in cattle and swine.

V. USER SAFETY:

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

FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth and clothing. Sensitization of the skin may be avoided by wearing latex gloves.

Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

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. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention.

The material safety data sheet contains more detailed occupational safety information. To obtain a material safety data sheet please call 1-800-733-5500. To report any adverse event please call 1-800-366-5288.

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 EXCEDE, when used according to the label, is safe and effective for the treatment of acute metritis in lactating dairy cattle. Additionally, data demonstrate that residues in food products derived from cattle treated with EXCEDE will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). This decision was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product to treat acute metritis, and (b) 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:

EXCEDE qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the act. The three years of marketing exclusivity applies only to the indication

for the treatment of acute metritis indication and modified injection techniques for which this supplement is approved.

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.