Date of Approval: June 2, 2006

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-209

EXCEDE Sterile Suspension

(ceftiofur crystalline free acid)

1. To add a new route of administration for injection in the posterior aspect of the ear where it attaches to the head (base of ear).

2. To add a new indication, "For the treatment of bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in lactating dairy cattle."

3. To establish a 13-day pre-slaughter withdrawal period for cattle.

Sponsored by:
Pharmacia & Upjohn Co.,
A Division of Pfizer, Inc.

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1. 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. Established Name:	Ceftiofur crystalline free acid
d. Proprietary Name:	EXCEDE Sterile Suspension
e. Dosage Form:	Sterile oil suspension for injection
f. How Supplied:	100 mL glass vial
g. How Dispensed:	Rx
h. Amount of Active Ingredients:	200 mg ceftiofur equivalents (CE) per mL
i. Route of Administration:	For subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) in lactating dairy cattle. For subcutaneous injection in the middle third of the posterior aspect of the ear or in the posterior aspect of the ear where it attaches to the head (base of the ear) in beef and non-lactating dairy cattle.
j. Species/Class:	Cattle/beef, non-lactating dairy, and lactating dairy
k. Recommended Dosage:	Single injection of 6.6 mg CE/kg (3.0 mg CE/lb) body weight (1.5 mL sterile suspension per 100 lb body weight)
l. Pharmacological Category:	Antimicrobial

m. Indications:	EXCEDE Sterile Suspension is indicated for the 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*.
n. Effects of Supplement:	1. To add a new route of administration for injection in the posterior aspect of the ear where it attaches to the head (base of ear). 2. To add a new indication, "For the treatment of bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in lactating dairy cattle." 3. To establish a 13-day pre-slaughter withdrawal period for cattle.

2. EFFECTIVENESS:

a. Dosage Characterization

The Center for Veterinary Medicine (CVM) did not require dosage characterization for this supplemental approval. The FOI Summary for the original approval of EXCEDE Sterile Suspension (NADA 141-209) dated September 5, 2003, contains dosage characterization information for ceftiofur crystalline free acid (CCFA) sterile suspension in cattle.

b. Substantial Evidence

1. Beef Cattle – New Route of Administration

Effectiveness for use of CCFA (as EXCEDE Sterile Suspension) for the treatment of BRD in beef and non-lactating cattle and control of BRD in high risk cattle when administered by subcutaneous (SC) injection in the middle third of the posterior aspect of the ear was demonstrated with the original approval of NADA 141-209, and is summarized in the FOI Summary dated September 5, 2003. The effectiveness for injection at the new SC injection site, the posterior aspect of the ear where it attaches to the head (base of the ear), is demonstrated by a statistical comparison of the existing pharmacokinetic data (Study Number 1999-0126, Study Report a0058859) summarized in the FOI Summary for the original approval, to data obtained following base of the ear administration in beef cattle (Study Report 1531N-60-03-397; 13397).

Pharmacokinetic Data for the Base of the Ear Injection Location:

"Determination of Ceftiofur and Desfuroylceftiofur-Related Residues in Plasma of Beef Cattle Receiving SC Injections of CCFA Sterile Suspension (200 mg/mL) in the Base of the Ear: Plasma Assays and Pharmacokinetic Analysis" (Study Report 1531N-60-03-397; 13397). September 2003 to May 2004.

a. Type of Study: Pharmacokinetic study. The study was conducted in accordance with Good Laboratory Practice (GLP) standards.

b. Study Director: D. A. Merritt, J. K. Callahan, Pfizer Animal Health, Kalamazoo, MI.

c. Study Design:

1. *Objective:* To characterize the plasma total ceftiofur concentrations following administration of CCFA sterile suspension (200 mg ceftiofur equivalents [CE]/mL) in the base of the ear of cattle.

2. *Animals*: Plasma samples for this study were obtained from 15 mixed breed beef cattle (6 steers and 9 heifers) concurrently enrolled in a separate residue study. Cattle were housed in individual tie stalls.

3. *Experimental Design:* For the purpose of conducting the residue study, animals were assigned to one of five groups, scheduled for slaughter at 5, 7, 9, 11, or 14 days post-injection.

4. *Test Article Administration:* CCFA sterile suspension (200 mg CE/mL), was administered SC in the base of the ear. Each animal received a single dose of CCFA at 3.0 mg CE/lb (6.6 mg CE/kg) body weight (BW).

5. *Measurements and Observations:* All animals had blood sampled over a course of 5 days; animals slaughtered after 5 days were sampled at additional intervals. Table 2.1 summarizes plasma collection intervals for each group.

Table 2.1. Slaughter Times and Plasma Collection Intervals

Slaughter time (days)	Animals per group	Target sample collection interval (days)
5	3	0 (predose), 0.25, 0.5, 1, 2, 3, 4, 5
7	3	0 (predose), 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7
9	3	0 (predose), 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9
11	3	0 (predose), 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
14	3	0 (predose), 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Plasma was harvested and frozen prior to analysis. The ceftiofur and desfuroylceftiofur-related residues in each plasma sample were determined using the validated HPLC-DCA method. The limit of quantitation (LOQ) for this assay was 0.150 µg/mL plasma. Each sample was analyzed as a single determination. C_{max} (observed), the area under the plasma concentration-time curve to the LOQ ($AUC_{0\text{-}LOQ}$), and the time plasma concentrations remained above 0.2 µg/mL ($t_{>0.2}$) were the decision variables for this study.

6. *Pharmacokinetic Analysis:* Trapezoidal summation was used to estimate the $AUC_{0\text{-}LOQ}$. The parameter, $t_{>0.2,}$ was estimated as follows:

$$T > MIC = T_1 + \left[\frac{Ln\left(\frac{MIC}{C_1}\right)}{\lambda_z} \right]$$

where T_1 is the time to the last concentration exceeding the MIC, C_1 is the last concentration exceeding the MIC, and λ_z is the slope of the terminal elimination phase estimated by WinNonlin.

d. Results:

1. *Plasma Concentration Data*: The plasma concentration data (µg/mL) obtained in the base of the ear study are given in Table 2.2.

Table 2.2. Mean Plasma Ceftiofur Concentrations (µg/mL)

	Hours												
	0	6	12	24	48	72	96	120	144	168	192	216	240
Mean	<LOQ	3.88	5.48	5.96	3.78	2.41	1.58	1.07	0.657	0.453	0.312	0.214	0.175
SD	<LOQ	1.48	1.76	1.46	0.693	0.542	0.440	0.387	0.217	<LOQ	<LOQ	<LOQ	–

2. *Pharmacokinetic Parameters:* Estimates of C_{max}, t_{max}, $AUC_{0\text{-}LOQ}$, λ_z, $t_{1/2}\lambda_z$, and $t_{>0.2}$ obtained from non-compartmental analysis of the base of the ear plasma concentration data are provided in Table 2.3.

Table 2.3. Summary of Pharmacokinetic Data, Study 13397

	$C_{max,obs}$ (µg/mL)	$t_{max,obs}$ (hr)	$AUC_{0\text{-}LOQ}$ (µg•hr/mL)	λ_z (hr^{-1})	$t_{1/2}\lambda_z$ (hr)	$t_{>0.2,nca}$ (hr)
Mean	6.39	19.9	412	0.0178	40.7	218
SD	1.9	5.81	67.1	0.00316	11.2	45.5
%CV	30	29.2	16.3	17.8	27.6	21.5
Median	6.0	24	414	0.0183	38.0	213
Minimum	4.0	12	281	0.0089	30.5	160
Maximum	10.0	24	536	0.0227	77.8	366

Statistical Analysis for Equivalence of the Two Subcutaneous Injection Locations:

Estimates of C_{max}, $AUC_{0\text{-}LOQ}$, and $t_{>0.2}$ obtained in Studies 1999-0126 and 13397 were analyzed statistically to determine therapeutic equivalence, consistent with FDA-CVM requirements. The results are shown in Table 2.4.

Table 2.4. Summary of Statistical Analysis

Base of the Ear (Study No. 13397)						
	Arithmetic Mean	**Back-transformed LS Mean**	**90% Lower**	**90% Upper**	**% of Reference Lower**	**% of Reference Upper**
C_{max} (µg/mL)	6.4	6.15	5.40	7.00	0.80	1.11
$AUC_{0\text{-}LOQ}$ (µg•h/mL)	412	406	377	438	1.00	1.21
$t_{>0.2}$ (h)	218	214	196	234	0.80	1.00
Middle Third of the Ear (Study No. 1999-0126)						
	Arithmetic Mean	**Back-transformed LS Mean**	**90% Lower**	**90% Upper**		
C_{max} (µg/mL)	6.90	6.53	5.89	7.24		
$AUC_{0\text{-}LOQ}$ (µg•h/mL)	376	370	349	393		
$t_{>0.2}$ (h)	246	239	223	257		

The pharmacokinetic data obtained for the study in which CCFA sterile suspension was administered at the base of the ear are consistent with the pharmacokinetic data used to support the effectiveness of CCFA sterile suspension when injected in the middle third of the ear for the original approval of NADA 141-209. Given the results of these analyses, the two routes of administration (base of the ear and middle third of the ear) of CCFA sterile suspension in beef and non-lactating dairy cattle are considered therapeutically equivalent.

2. Dairy Cattle – Treatment of BRD

Effectiveness of CCFA for the treatment of BRD in beef and non-lactating dairy cattle was previously demonstrated in the original approval of EXCEDE Sterile Suspension (NADA 141-209), and is summarized in the FOI Summary dated September 5, 2003. Effectiveness of CCFA for the treatment of BRD in lactating dairy cattle, when administered via subcutaneous (SC) injection in the posterior aspect of the ear where it attaches to the head (base of the ear) is demonstrated by a statistical comparison of the existing pharmacokinetic data (Study Number 1999-0126, Study Report a0058859), summarized in the FOI Summary for the original approval of EXCEDE Sterile Suspension, to data obtained following base of the ear administration in lactating dairy cattle (Study Report 1531N-60-03-413; 13413).

"Pharmacokinetics of Desfuroylceftiofur-related Residues in Plasma of Dairy Cows Following SC Injections of a High *In Vitro* Release Rate Formulation of CCFA-SS (200 mg/mL) in the Base and Middle of the Ear at 6.6 mg/kg Bodyweight". Study Number 1531N-60-03-413; 13413. January 2004 to October 2004.

a. Type of Study: Pharmacokinetic study. The study was conducted in accordance with Good Laboratory Practice (GLP) standards.

b. Study Director: J.L. Nappier, Ph.D., Pfizer Animal Health, Kalamazoo, MI.

c. Study Design:

1. *Objective:* To generate plasma concentration data for ceftiofur and desfuroylceftiofur-related metabolites in the plasma of lactating dairy cows following administration of CCFA sterile suspension (200 mg CE/mL) in the base of the ear, in the middle third of the posterior aspect of the ear (middle third of the ear) as a single injection, or in the middle third of the ear as two injections.

2. *Animals*: Thirty-six Holstein cows, approximately 525.5 to 871 kg BW, were used for the study. Cows were in their first, second, or third lactation, were greater than 40 days in milk, and had a minimum mean pre-treatment (Study Days -8 to -5) milk production of 22.7 kg/day.

3. *Experimental Design:* Twelve animals were randomly assigned to one of three treatment groups - base of the ear (BOE); middle third of the ear, single injection (MOE1); or middle third of the ear, split injection (MOE2).

4. *Test Article Administration:* CCFA sterile suspension (200 mg CE/mL), was administered SC at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) BW as a single injection in the base of the ear or in the middle third of the ear (as a single injection or as two divided injections).

5. *Measurements and Observations:* Blood samples were collected at 6, 12, 24, and 36 hours, then 2, 3, 4, 5, 6, 7, 8, 9, and 10 days following treatment administration. Plasma was harvested and frozen prior to analysis. Ceftiofur and desfuroylceftiofur-related residues in each plasma sample were determined using the validated HPLC-DCA method. The LOQ for this assay was 0.150 μg/mL plasma. Each sample was analyzed as a single determination. The area under the plasma concentration-time curve to the LOQ ($AUC_{0\text{-}LOQ}$), and the time plasma concentrations remained above 0.2 μg/mL ($t_{>0.2}$) were the decision variables for this study. C_{max} (observed) also was estimated for this study.

6. *Pharmacokinetic Analysis:* Trapezoidal summation was used to estimate the $AUC_{0\text{-}LOQ}$. The parameter $t_{>0.2}$ was estimated as follows:

$$T > MIC = T_1 + \left[\frac{Ln\left(\frac{MIC}{C_1}\right)}{\lambda_z} \right]$$

where T_1 is the time to the last concentration exceeding the MIC, C_1 is the last concentration exceeding the MIC, and λ_z is the slope of the terminal elimination phase estimated by WinNonlin.

d. Results:

The means for the pharmacokinetic parameters obtained for this study are provided in Table 2.5.

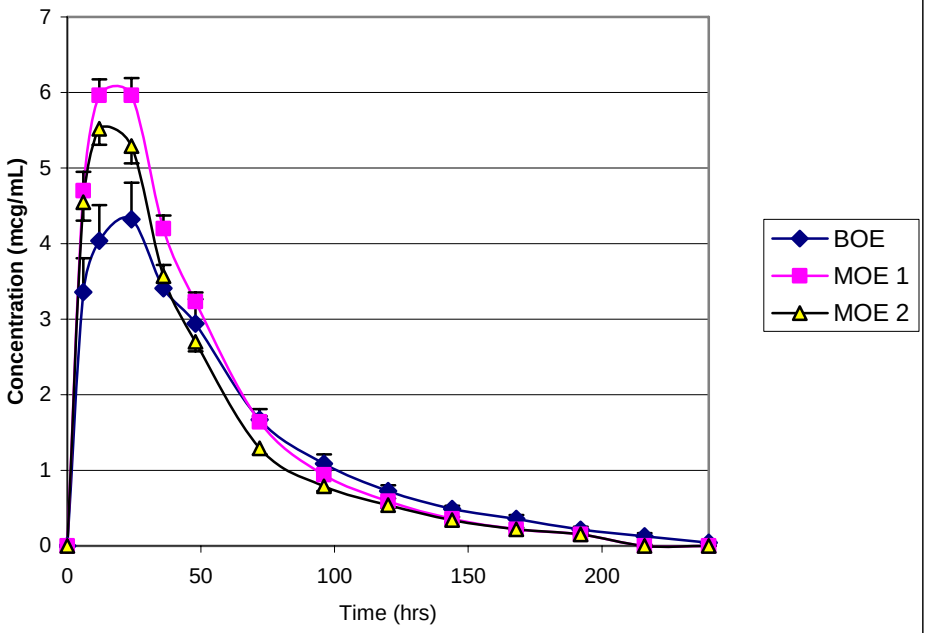
Table 2.5. Pharmacokinetic Parameter Estimates.

				Confidence limits*		
	BOE	**MOE1**	**MOE2**	**BOE vs. MOE1**	**BOE vs. MOE2**	**MOE1 vs. MOE2**
$AUC_{0\text{-}LOQ}$ (µg•hr/mL)	312.8	353.4	308.6	0.73 to 1.08	0.85 to 1.25	0.95 to 1.40
C_{max} (µg/mL)	4.44	6.13	5.67	0.55 to 0.83	0.61 to 0.93	0.90 to 1.37
t_{max} (day)	0.79	0.7	0.75	--	--	--
t_{half} (day)	1.67	1.53	1.57	--	--	--
$t_{>0.2}$ (days)	8.5 (205 hr)	7.3 (175 hr)	7.2 (172 hr)	1.06 to 1.27**	1.08 to 1.30**	0.93 to 1.12**

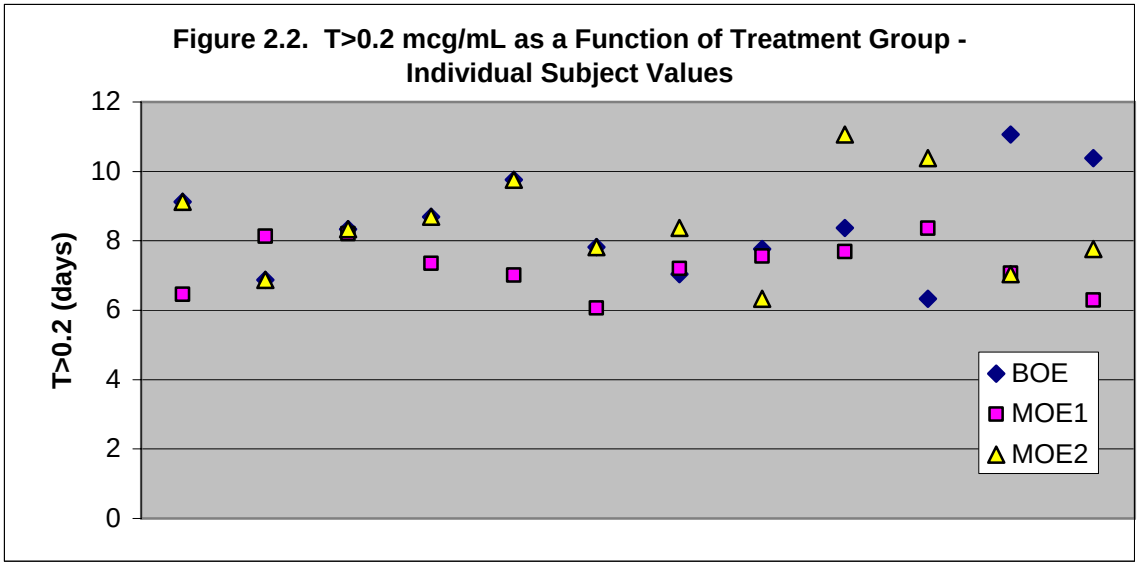
* based upon Ln-transformed data
** estimated using hourly values

The average concentrations seen after BOE, MOE1, and MOE2 administration are shown in Figure 2.1.

Figure 2.1. Mean Concentration vs. Time Profiles in Dairy Cattle after BOE, MOE1, or MOE2 Administration of CCFA



For effectiveness, the decision variable was the time that plasma concentrations remained above 0.2 µg/mL ($t_{>0.2}$). CVM and Pfizer previously agreed that effectiveness would be confirmed if each subject had a $t_{>0.2}$ of no less than 5 days and if the average $t_{>0.2}$ was no less than 7 days. The distribution of $t_{>0.2}$ (in days) is shown in Figure 2.2.



The data demonstrate that across all treatments, there was no subject with a $t_{>0.2}$ less than 5 days.

c. Microbiology

Based on pharmacokinetic and clinical studies of ceftiofur in cattle after a single administration of 6.6 mg CE/kg (3 mg CE/lb) BW and the minimum inhibitory concentration (MIC) and disk (30 µg) diffusion data, the following breakpoints are recommended by the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards) for ceftiofur against BRD pathogens.

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 21	≤ 2.0	(S) Susceptible
18-20	4.0	(I) Intermediate
≤ 17	≥ 8.0	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" is a technical buffer zone and isolates falling into this category should be retested. Alternatively the organism may be successfully treated if the infection is in a body site where drug is physiologically concentrated. A report of "Resistant" indicates that the achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms for both standardized diffusion techniques and standardized dilution techniques. The 30 µg ceftiofur sodium disk and the ceftiofur sodium standard reference powder (or disk) should provide MIC values and zone diameters for the reference strains as presented in Table 2.6. Ceftiofur sodium disks or powder reference standard are appropriate for all forms of ceftiofur (sodium, hydrochloride, and free acid).

Table 2.6. Acceptable Quality Control Ranges for Ceftiofur against Clinical and Laboratory Standards Institute Recommended American Type Culture Collection (ATCC) Reference Strains

Organism (ATCC No.)	MIC (µg/mL)	Zone Diameter (mm)
Escherichia coli (ATCC 25922)	0.25-1.0	26-31
Staphylococcus aureus (ATCC 29213)	0.25-1.0	-
S. aureus (ATCC 25923)	-	27-31
Pseudomonas aeroginosa (ATCC 27853)	16.0-64.0	14-18

3. TARGET ANIMAL SAFETY:

a. Beef Cattle

1. Systemic Target Animal Safety

Estimates of C_{max}, $AUC_{0\text{-}LOQ}$, and $t_{>0.2}$ obtained in studies SR a0058859 and 1531N-60-03-397 (discussed in the Effectiveness section above) were also analyzed to establish a pharmacokinetic bridge for target animal safety. In addition, CCFA C_{max} and $AUC_{0\text{-}LOQ}$ values were compared to ceftiofur sodium values after a single injection or five (projected) sequential daily doses.

The pharmacokinetic data from Study 13397 (base of the ear) are consistent with the pharmacokinetic data used to support the effectiveness of CCFA sterile suspension when injected in the middle third of the ear for the original approval of NADA 141-209. In addition, the peak concentrations observed following a single subcutaneous injection of ceftiofur sodium are higher than those associated with CCFA sterile suspension (base of the ear or middle third of the ear). The predicted $AUC_{0\text{-}LOQ}$ values following five sequential daily injections of ceftiofur sodium are higher than those associated with CCFA sterile suspension (base of the ear or middle third of the ear). These values are provided in Table 3.1.

Table 3.1. Summary of Pharmacokinetic Data Generated in Beef Cattle Using Ceftiofur Sodium or CCFA

	Mean ± stdev				
	C_{max} (µg/mL)	**t_{max} (hr)**	**$AUC_{0\text{-}LOQ}$ (µg•hr/mL)**	**$t_{1/2}$ (hr)**	**$t_{>0.2}$ (hr)**
Ceftiofur Sodium (IM, single dose)	16.5 ± 2.91	1.09 ± 0.44	142 ± 25.4	9.5 ± 1.15	50.9 ± 4.81
Ceftiofur Sodium (predicted values after IM injection for 5 consecutive days)	19.5	--	710	--	--
CCFA (middle third of the ear)	6.9 ± 2.7	12.0 ± 6.24	400 ± 69.6	62.3 ± 13.5	244 ± 48.9
CCFA (base of the ear)	6.39 ± 1.9	19.9 ± 5.81	412 ± 67.1	40.7 ± 11.2	218 ± 45.5

These data establish a pharmacokinetic bridge between the two injection site locations, supporting the systemic target animal safety of CCFA sterile suspension at the posterior aspect of the ear where it attaches to the head (base of the ear) location.

2. Injection Site Tolerance and Clinical Observations

"Multi-center Conditions of Use Field Safety Evaluation of Ceftiofur Crystalline Free Acid Sterile Suspension (200 mg ceftiofur equivalents [CE]/mL) Administered Subcutaneously In the Base of the Ear with 6.6 mg CE/kg Body Weight at Arrival in High Risk Feedlot Cattle" (Study Report 1437C-60-04-464). November 2003 to March 2004.

a. Type of Study: Ear injection site tolerance study. The study was conducted in accordance with Good Clinical Practices guidelines.

b. Study Investigators and Locations:
David Bechtol, DVM, Agri Research Center, Canyon, TX.
Shane Davis, PhD, Premiere Cattle Company, Syracuse, KS.
Jenifer Edmonds, DVM, PhD, Johnson Research, Parma, ID.
Mary Wray, PhD, Horton Feedlot & Research Center, Wellington, CO.

c. Study Design:

1. *Objective:* To evaluate the safety of administration of CCFA (200 mg CE/mL) by subcutaneous injection in the base of the ear under field conditions in beef cattle.

2. *Animals:* A total of 3658 female and castrated male beef crossbred or purebred cattle, weighing approximately 300 to 850 pounds, were enrolled in this study. Within 48 hours of arrival at the feedlot, each animal was assigned a unique identification number and processed according to feedlot practices.

3. *Experimental Design:* The study was conducted at four sites. At each site, calves were randomly assigned to treatment groups and allocated to pens. A positive control group (florfenicol) was also included in the study, but was not evaluated as a comparator for safety. A total of 2926 cattle were assigned to the CCFA group. Treatment groups were commingled in pens.

4. *Test Article Administration:* The test article was CCFA sterile suspension (200 mg CE/mL). The test article was administered on the day of enrollment (Day 0) as a subcutaneous injection at the base of the ear as a single injection of 6.6 mg CE/kg BW.

5. *Measurements and Observations:* The primary variables for the assessment of safety were ear tolerance and incidence of adverse events such as immediate death following CCFA administration. Immediately after injection, an animal restraint index (0 = normal, 1 = additional restraint needed, 2 = other), an injection procedure score (0 = normal, 1 = required re-injection due to animal movement), and a post-injection problem score (0 = normal, 1 = excessive bleeding, 2 = excessive leak back of injected material, 3 = other) were recorded for each animal.

Daily observations from Day 0 through Day 56 were made by pen riders to identify calves with symptoms of BRD and observe ear tolerance. Calves that developed BRD on Days 3 to 56 were administered standard feedlot therapy. On Days 28 and 56, all surviving calves were individually restrained using a head catch, both ears were evaluated, and ear examination scores were recorded using the following scales:

Ear Carriage Score: N = normal; D = droopy
Ear Injection Site Score: 0 = normal, no swelling detected; 1 = well defined swelling, 1-2 inches in diameter; 2 = well defined swelling, > 2 inches in diameter; 3 = diffuse swelling; 4 = ruptured draining wound; 5 = other.

Ancillary variables, including BRD morbidity rate, time to first pull, cumulative mortality, and average daily gain were also evaluated.

d. Statistical Methods: Results were summarized descriptively; no statistical analysis was conducted.

e. Results:

1. *Injection Procedure:* Normal restraint was adequate for administration of EXCEDE Sterile Suspension for 2914 (99.8%) of cattle treated with CCFA. A normal injection procedure index score was recorded for 2869 (98.2%) of cattle treated with CCFA. No post injection problems were observed in 2912 (99.8%) of cattle treated with CCFA. Excessive bleeding was observed in one CCFA-treated animal, and excessive leak back of injected material was observed in four CCFA-treated animals.

2. *Post-injection Observations:* By Day 28, 2843 (97.8%) of CCFA-treated animals had "normal" injected ears. On Day 56, 2847 (98.9%) of CCFA-treated animals had "normal" injected ears. No droopy ears were reported on Day 28. Two droopy ears were observed on Day 56. Four animals across the four locations were pulled by pen riders for further examination of ear injection site swelling. One CCFA-treated animal was diagnosed with anaphylactic shock after going down 30 minutes post-injection, but appeared normal several hours later. The animal was removed from the trial, but continued to be observed through the study period.

f. Conclusions: The results demonstrate that subcutaneous injection of EXCEDE Sterile Suspension into the base of the ear at 6.6 mg CE/kg BW was well tolerated and was achieved using facilities and equipment normally used for restraint of feedlot cattle.

"Determination of Ceftiofur Residues as Desfuroylceftiofur-Related Residues in Injection Sites and Kidneys of Beef Cattle Receiving SC Injections of Three Lots (*In Vitro* Release Rates Ranging from 60% to 70%) of CCFA-SS (200 mg/mL) in the Base of the Ear at 6.6 mg/kg Body Weight" (Study Report 1531N-60-03-416). January 2004 to February 2004.

a. Type of Study: Residue study. Only the parts of the study pertaining to clinical and necropsy injection site observations are included in this summary.

b. Study Director: J. L. Nappier, Ph.D., Pfizer Animal Health, Kalamazoo, MI.

c. Study Design:

   1. *Objective:* To evaluate local ear tolerance to CCFA administration in the base of the ear.

   2. *Animals:* Seventy-four mixed breed beef cattle ranging in weight from 173 to 288 kg were enrolled in the study.

   3. *Experimental Design:* Twenty-four cattle each were dosed with three lots of CCFA sterile suspension with different *in vitro* release rates. Two additional cattle served as untreated controls. Cattle were euthanized at 4, 7, 10, or 13 days post-injection.

   4. *Test Article Administration:* EXCEDE (CCFA) Sterile Suspension (200 mg CE/mL) was administered subcutaneously at the base of the ear at a dose rate of 6.6 mg CE/kg BW.

   5. *Measurements and Observations:* Injection sites were observed daily from treatment to necropsy for swelling and ear drooping. Injection sites and underlying tissues were also evaluated grossly at necropsy, following skinning and trimming procedures similar to slaughterhouse practices.

d. Statistical Methods: Results were summarized descriptively; no statistical analysis was conducted.

e. Results: All animals had injection site swelling during the study; swelling resolved prior to euthanasia in 23 of 72 animals. None of the animals showed ear drooping. At necropsy, signs of inflammation (hemorrhage, congestion, and firmness of tissue) and presence of drug material were seen in the area around the injection site and on the carcass. At 13 days post-injection, gross lesions were found in the inedible portions of the base of the ear in all 18 animals, and in the exposed carcass tissue in 11 of 18 animals. No drug-related adverse reactions were reported.

f. Conclusions: This study demonstrates that base of the ear injection of CCFA sterile suspension in beef cattle results in swelling at the injection site that persists through at least 13 days. In addition, the study demonstrates that injection site

lesions may be visible on the carcass after ear removal for at least 13 days post-injection.

b. Dairy Cattle

1. Systemic Target Animal Safety

To facilitate the comparison between CCFA (as EXCEDE Sterile Suspension) for lactating dairy cattle and ceftiofur sodium (NAXCEL), the NAXCEL AUC values were multiplied by a factor of 5, since a single dose of EXCEDE Sterile Suspension is intended to be comparable to five injections of NAXCEL. C_{max} values are also provided as single dose (observed) data and predicted steady state values (i.e., C_{max} * 1.21 is the extent to which ceftiofur moieties are expected to accumulate at steady state). The relative bioavailability of ceftiofur sodium (observed and predicted values) versus a single dose of EXCEDE Sterile Suspension administered in the middle third of the ear (one or two injection site locations) or at the posterior aspect of the ear where it attaches to the head (base of the ear) are provided in Table 3.2.

Table 3.2. Comparison of Pharmacokinetic Data Following Administration of Ceftiofur Sodium or CCFA

	C_{max} (µg/mL)	**$AUC_{0\text{-}LOQ}$ (µg•hr/mL)**
Ceftiofur Sodium (IM, single dose)	16.5 ± 2.91	142 ± 25.4
Ceftiofur Sodium (predicted values after IM injection for 5 consecutive days)	19.5	710
CCFA (middle third of the ear, one injection site)	6.13	353.4
CCFA (middle third of the ear, two injection sites)	5.67	308.6
CCFA (base of the ear)	4.43	312.8

Based upon these results, a single dose of EXCEDE Sterile Suspension provides lower AUC and C_{max} values as compared to that obtained from five NAXCEL injections. Accordingly, the systemic target animal safety data generated for ceftiofur sodium can be extrapolated to EXCEDE Sterile Suspension when administered as a single dosage of 6.6 mg CE/kg BW as a subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) in lactating dairy cattle.

2. Injection Site Tolerance and Clinical Observations

"Multi-Location Conditions of Use/Field Safety Study for Ceftiofur Crystalline Free Acid Sterile Suspension in Lactating Dairy Cows When Administered at 6.6 mg of Ceftiofur Equivalents per kg of Body Weight by Subcutaneous Injection Either at the Middle Third or Base of the Ear". Study Number 1433C-60-03-422. January 2004 to April 2004.

a. Type of Study: Conditions of use study. The study was performed in accordance with Good Clinical Practice standards.

b. Investigators:
Paul Busman, D.V.M., Meadow Rock Dairy, Greenville, MI.
Darrel Kesler, Ph.D., Stone Ridge Dairy, Mansfield, IL.
Jose Santos, D.V.M., Ph.D., River Ranch Dairy, Hanford, CA.
Keith Salmon, D.V.M., Swisslane Dairy, Alto, MI.
Kirk Smith, D.V.M., Jiminie Dairy, Sleepy Eye, MN.

c. Study Design:

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

2. *Animals:* A total of 342 clinically normal pregnant Holstein cows were enrolled at four large (>1000 cows) commercial dairies and one small (105 cows) dairy. Seventy five cows were enrolled at each of the large dairies and 42 cows were enrolled at the small dairy.

3. *Experimental Design:* Within each site cows were assigned randomly in replicates of three to one of three treatment groups - single administration in the middle third of the ear (MOE1, n = 113), split dose injected at two sites in the middle third of the same ear (MOE2, n = 115), or single injection at the base of the ear (BOE, n = 114).

4. *Test Article Administration:* EXCEDE (CCFA) Sterile Suspension (200 mg CE/mL) was injected subcutaneously at a dosage of 6.6 mg CE/ kg BW (1.5 mL /100 lb BW) on the day of enrollment (Day 0). Injection volumes ranged from 15 to 30 mL per cow.

5. *Measurements and Observations:* Dosing administrators were instructed to restrain cows using facilities and equipment normally used to inject into the jugular vein - use of head lock ups plus halters, nose tongs, etc. Immediately after injection an animal restraint score (0 = normal, 1 = additional restraint needed, 2 = other), an injection procedure score (0 = normal, 1 = required re-injection due to animal movement), and a post-injection problem score (0 = normal, 1 = excessive bleeding, 2 = excessive leak back of injected material, 3 = other) were recorded for each cow.

A veterinarian observed each cow 1, 3, 5, 7, 10, 14, 21, 28, and 56 days post-injection. Observations included clinical evaluation (normal or droopy), palpation of both ears, and assignment of ear injection scores (MOE: 0 = normal, no swelling detected; 1 = slight thickening detected by palpation; 2 = moderate thickening detected, no fluid; 3 = large thickening detected, small amount of fluid present; 4 = open, draining lesion. BOE: 0 = normal, no swelling or fluid observed; 1 = swelling or fluid, well defined, 1-2 inches in diameter; 2 = swelling or fluid, well defined, > 2 inches in diameter; 3 = diffuse swelling or fluid detected; 4 = ruptured, draining wound; 5 = other).

d. Statistical Methods: Results were summarized descriptively; no statistical analysis was conducted.

e. Results:

1. *Injection Procedure:* Normal restraint was adequate for administration of EXCEDE Sterile Suspension for 92.9, 84.3, and 97.4% of cows in treatment groups MOE1, MOE2, and BOE, respectively. A normal injection procedure index score was recorded for 90.2, 79.8, and 95.6% of cows in treatment groups MOE1, MOE2, and BOE, respectively. No post- injection problems were observed in 86.7, 72.8, and 99.1% of cows in treatment groups MOE1, MOE2, and BOE, respectively. Excessive bleeding was observed in 0, 2.6, and 0% of cows in treatment groups MOE1, MOE2, and BOE, respectively. Excessive leak back of injected material was observed in 10.6, 19.3, and 0.9% of cows in treatment groups MOE1, MOE2, and BOE, respectively.

2. *Post-injection Observations:* By Day 28, 31.0 and 27.0% of cows in the MOE1 and MOE2 treatment groups had "normal" injected ears, compared with 95.6% of cows in the BOE group. By Day 56, 61.9, and 62.6% of cows in the MOE1 and MOE2 treatment groups had "normal" injected ears, compared with 100% of cows in the BOE group. A total of nine cows (5 cows in the MOE1 group and 4 cows in the MOE2 group) had an injection site score of 4 (open, draining lesion) for the middle third of the injected ear documented on at least one day of observation. In these cows, injection volumes were greater than 19.5 mL. Other than injection site findings, no drug-related adverse reactions were reported.

f. Conclusions: Injection of EXCEDE Sterile Suspension, at the volumes needed for dairy cows (1.5 mL/100 lbs BW), into the base of the ear is safe and was achieved using facilities and equipment normally used for restraint of dairy cows for intravenous injections or infusions. Base of the ear administration was much better tolerated, resulting in fewer problems at injection, 95.6% "normal" ear scores on Day 28 compared to 31.0 and 27.0% "normal" ear scores following middle third of the ear administration, and 100% "normal" ear scores on Day 56 compared to 61.9 and 62.6% "normal" ear scores following middle third of the ear administration. Although both routes (base of the ear and middle third of the ear) were effective for the treatment of BRD, based on the results of this study, only base of the ear administration is approved for lactating dairy cattle.

"Determination of Ceftiofur and Desfuroylceftiofur-Related Residues in Injection Sites and Kidneys of Non-Lactating Dairy Cattle Receiving SC Injections of CCFA-SS (200 mg/mL) in the Base and Middle of the Ear at 6.6 mg/kg Body Weight". Study Report 1531N-60-03-414. May 2004 to July 2004.

1. Type of Study: Residue study. Only the parts of the study pertaining to clinical and necropsy injection site observations are included in this summary.

2. Study Director: J. L. Nappier, Ph.D., Pfizer Animal Health, Kalamazoo, MI.

3. Study Design:

   a. Objective: To evaluate local ear tolerance to CCFA administration.

   b. Animals: Twelve healthy non-lactating dairy cows ranging in weight from 688 to 1023 kg were enrolled in the study.

   c. Experimental Design: Cows were assigned to one of two treatment groups - single administration in the middle third of the ear (MOE, n = 6), or single injection at the base of the ear (BOE, n = 6).

   d. Test Article Administration: EXCEDE (CCFA) Sterile Suspension (200 mg CE/mL) was administered subcutaneously at the middle third of the ear or base of the ear at a dose rate of 6.6 mg CE/kg BW.

   e. Measurements and Observations: Injection sites were observed daily from treatment to 10 days post-injection for swelling and ear drooping. Injection sites and underlying tissues were also evaluated grossly at necropsy, following skinning and trimming procedures similar to slaughterhouse practices.

   f. Statistical Analysis: Results were summarized descriptively; no statistical analysis was conducted.

4. Results: All treated cows in both groups showed signs of swelling at the injection site at all observation times after dosing. In the BOE treatment group, no cows exhibited drooping ears at any time after treatment. At necropsy, evidence of CCFA injection was found in all cows. Areas of discoloration and signs of inflammation were seen at the injection site and tissues dorsal and posterior to the ear canal on the carcass.

   In the MOE treatment group, 3 to 5 out of 6 cows exhibited drooping ears at 1 to 6 days after dosing. By Day 10, only one cow had drooping ears. Areas of discoloration and inflammation were found on the ears, but not in the exposed tissue on the carcass after removal of ear.

   Other than injection site findings, no drug-related adverse reactions were reported.

5. Conclusions: This study demonstrates that both middle third of the ear and base of the ear administration of CCFA in dairy cows resulted in swelling at the injection site that persists at least 10 days. Ear drooping occurred following middle third of the ear injection. Base of the ear administration resulted in visible injection site lesions on the carcass after ear removal for at least 10 days post-injection.

"Pharmacokinetics of Desfuroylceftiofur-related Residues in Plasma of Dairy Cows Following SC Injections of a High *In Vitro* Release Rate Formulation of CCFA-SS (200 mg/mL) in the Base and Middle of the Ear at 6.6 mg/kg Bodyweight". Study Number 1531N-60-03-413. January 2004 to October 2004.

The pharmacokinetic portion of the study is summarized in the Effectiveness section above. Injection sites were observed daily from treatment to 10 days post-injection for swelling and ear drooping. All treated animals showed signs of swelling at the injection site at all observation times after dosing. In the BOE treatment group, no animals exhibited drooping ears at any time after treatment. Other than injection site findings, no drug-related adverse reactions were reported.

4. HUMAN FOOD SAFETY:

a. Toxicology

The toxicity testing of ceftiofur is summarized in the FOI Summary for NAXCEL (ceftiofur sodium) Sterile Powder (NADA 140-338) dated January 25, 1988; in the FOI Summary for the original approval of EXCENEL (ceftiofur hydrochloride) Sterile Suspension (NADA 140-890) dated April 1996, for use in swine; and in the FOI Summary for NAXCEL XT (now EXCEDE) Sterile Suspension (NADA 141-209) dated September 5, 2003, for use in cattle. The latter FOI Summary provides an acceptable daily intake (ADI) of 0.008 mg/kg BW per day for milk and 0.022 mg/kg BW per day for edible tissues. An acceptable single daily intake (ASDI) at the injection site of 0.830 mg/kg BW per day is also provided.

Safe concentrations have been previously established for cattle as follows:

Muscle:	4.4 ppm
Liver:	13.2 ppm
Kidney:	26.4 ppm
Fat:	26.4 ppm
Injection site:	166 ppm
Milk:	0.320 ppm

b. Residue Chemistry

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 and NADA 140-890 cited in 4.a. above.

1. Studies

The following pivotal studies were conducted to permit decisions on tolerances and the withdrawal period.

"Determination of Ceftiofur Residues in Injection Sites and Kidneys of Cattle at 7 and 10 Days After Injection of Ceftiofur Crystalline Free Acid (CCFA) Sterile Suspension Containing 14C-CCFA in the Base of the Ear"

a. Principal Investigators: D.A. Merritt and M.J. Prough, Pfizer Animal Health, Kalamazoo, MI

b. Test Animals: 12 mixed breed, clinically healthy cattle - 6 males (steers) and 6 females (heifers)

c. Test Article Administration: single injection of CCFA at 6.6 mg ceftiofur equivalents/kg body weight (actual dose 6.79 ± 0.06 mg CE/kg), administered as a subcutaneous injection in the base of the ear

d Radioisotope: ^{14}C located in the thiazole ring; specific activity 0.548 μCi/mg

e. Assay Methodology: The bovine tissues were assayed by combustion techniques to determine total ^{14}C-ceftiofur residues and by the HPLC-DCA assay that uses dithioerythritol to convert all desfuroylceftiofur metabolites that have an intact β-lactam ring to desfuroylceftiofur, which is then stabilized by derivatization to desfuroylceftiofur acetamide using iodoacetamide. This assay measures ceftiofur and all desfuroylceftiofur metabolites (both free desfuroylceftiofur and desfuroylceftiofur cysteine disulfide and desfuroylceftiofur covalently bound to amino acids and proteins) without distinction. Two detection techniques were used during the HPLC-DCA assays; namely UV analysis, which detects all ceftiofur and desfuroylceftiofur-related residues (both radiolabeled and nonradiolabeled), and RAM analysis, which detects ^{14}C-ceftiofur and ^{14}C-desfuroylceftiofur-related residues.

f. Results: The results of this study are summarized in Table 4.1 below. At the injection site 7 and 10 days after radiolabeled drug administration, the residues quantified using the regulatory method for the marker residue, desfuroylceftiofur acetamide (HPLC-DCA) were 57% of the total ceftiofur residues (as determined by radiolabeled ceftiofur). Although the mean at 10 days was less than the safe concentration of 166 ppm in the injection site, two of the six injection sites contained total residue exceeding the injection site safe concentration of 166 ppm.

Table 4.1. Mean Residue Concentrations of Ceftiofur in the Edible Tissues after Subcutaneous Administration of ^{14}C-CCFA-SS in the Base of the Ear

Tissue	Withdrawal Time	Total Residue (TR) ppm	HPLC-DCA UV ppm	HPLC-DCA RAM ppm	CCFA:Total Residue (RAM:TR) %
Kidney	7-day	3.94 ± 0.87	0.47 ± 0.24	ND	--
	10-day	2.96 ± 0.78	0.18 ± 0.07	ND	--
Injection Site	7-day	179.5 ± 172.4	107.0 ± 105.7	102.9 ± 99.5	57.4
	10-day	182.7 ± 95.6	89.2 ± 68.2	103.8 ± 55.0	56.8

g. Conclusions: The data of this study do not support the assignment of a 10-day withdrawal period. However, these data, taken together with those in the study described in 4.b.2. below, support the assignment of a 13-day withdrawal period.

Use of the ratio of 0.57 is considered appropriate for the 13-day withdrawal period. Thus, for research purposes a value of 95 ppm DCA (i.e., 166 ppm x 0.57, the ratio of DCA:total residue) has been established for making decisions regarding the safety of the injection site.

"Determination of Ceftiofur Residues as Desfuroylceftiofur-Related Residue in Injection-Sites and Kidneys of Beef Cattle Receiving SC Injections of Three Lots (*In Vitro* Release Rates Ranging from 60% to 70%) of CCFA-SS (200 mg/mL) in the Base of the Ear at 6.6 mg/kg Body Weight"

a. Principal Investigators: J.L. Nappier and M.J. Prough, Pfizer Animal Health, Kalamazoo, MI

b. Test Animals: 74 mixed breed, clinically healthy cattle - 30 males and 42 females, plus 2 male control animals, 173 to 288 kg

c. Test Article Administration: single injection of CCFA at 6.6 mg ceftiofur equivalents/kg body weight (actual dose 6.70 ± 0.10 mg CE/kg), administered as a subcutaneous injection in the base of the ear; 24 cattle each were dosed with three lots of EXCEDE Sterile Suspension with different *in vitro* release rates

d. Marker Residue Depletion Data: Samples of kidney and injection site were assayed for desfuroylceftiofur-related residue by the HPLC-DCA assay. The limit of detection (LOD) of the assay was 0.030 ppm (0.03 μg/g), and the limit of quantification (LOQ) was 0.100 ppm (0.1 μg/g).

   At 10 days withdrawal, the mean for injection site residues for the lowest *in vitro* release rate lot of material (which is expected to have the highest concentration of DCA at the injection site) was 21.6 ± 33.6 ppm (Table 4.2). Although the mean is below the research tolerance limit of 95 ppm, the 99% tolerance limit with 95% confidence exceeds 95 ppm.

Table 4.2. Concentration of Ceftiofur and Desfuroylceftiofur-Related Residues in Bovine Tissues from Beef Cattle Receiving 6.6 mg Ceftiofur Equivalents as CCFA/kg BW

Group	Animal #	Residue, μg/g		Group	Animal #	Residue, μg/g	
		Inj. Site	Kidney			Inj. Site	Kidney
Day 4	860	18.0	1.22	Day 7	870	98.1	0.445
	864	84.1	0.661		889	178	0.408
	893	206	1.36		904	61.6	0.192
	922	286	1.24		925	120	0.356
	928	1.16	0.604		927	140	0.214
	941	212	0.754		931	176	0.525
	Mean	**135**	**0.973**		**Mean**	**129**	**0.357**
	S.D.	**117**	**0.336**		**S.D.**	**45**	**0.131**
Day 10	869	0.954	0.124	Day 13	872	20.7	(0.055)
	908	(0.084)	(0.090)		894	0.384	(0.074)
	918	0.476	0.137		900	12.0	(0.098)
	930	0.298	(0.073)		903	0.142	(0.047)
	938	51.8	0.121		937	19.9	(0.047)
	942	75.8	0.100		940	0.104	< LOD
	Mean	**21.6**	**0.108**		**Mean**	**8.87**	**(0.056)**
	S.D.	**33.6**	**0.024**		**S.D.**	**9.96**	**0.028**
Control	877	< LOD	< LOD				
	907	< LOD	< LOD				

LOQ = 0.1 μg/g; LOD = 0.03 μg/g
S.D. = Standard Deviation

At 13 days withdrawal, the tolerance limits were well below 95 ppm for each of the three rates of release tested.

e. Conclusion: The injection site data support the assignment of a 13-day withdrawal period for cattle treated with ceftiofur crystalline free acid sterile solution at 6.6 mg CE/kg body weight at the base of the ear.

The following pivotal studies were conducted to confirm applicable withdrawal and milk discard times in dairy cattle.

"Determination of Ceftiofur and Desfuroylceftiofur-Related Residues in Injection Site and Kidneys of Non-Lactating Dairy Cows Receiving SC Injections of CCFA-SS (200 mg/mL) with a Low *In Vitro* Release Rate in the Base and Middle of the Ear at 6.6 mg/kg Body Weight"

a. Principal Investigators: J.L. Nappier and M.J. Prough, Pfizer Animal Health, Kalamazoo, MI

b. Test Animals: 13 Holstein, clinically healthy female cattle - 12 females (plus 1 female control animal); 688 to 1023 kg

c. Test Article Administration: single injection of CCFA at 6.6 mg ceftiofur equivalents/kg body weight (actual dose 6.45 ± 0.03 mg CE/kg), administered as a subcutaneous injection in the base of the ear

d. Marker Residue Depletion Data: Samples of kidney and injection site were assayed for desfuroylceftiofur-related residue by the HPLC-DCA assay. The LOD of the assay was 0.050 ppm and the LOQ was 0.100 ppm.

e. Conclusions: At 10 days withdrawal, the mean for injection site residues from the animals treated in the base of the ear and middle third of the ear were 0.168 ± 0.275 and 0.072 ± 0.098 ppm, respectively. In addition, all individual animals had injection site residues below 95 ppm DCA. The mean for residues of DCA in kidney from the animals treated in the base of the ear and middle third of the ear were 0.286 ± 0.084 and 0.268 ± 0.101 ppm, respectively. These data are consistent with the assigned 13-day withdrawal period.

"Determination of Ceftiofur and Desfuroylceftiofur-Related Residues in Milk of Lactating Dairy Cattle Receiving SC Injections of High *in Vitro* Release Rate of CCFA-SS (200 mg/mL) in the Base of the Ear and Middle of the Ear at 6.6 mg/kg Body Weight"

a. Principal Investigators: R.E. Hornish and M.J. Prough, Pfizer Animal Health, Kalamazoo, MI

b. Test Animals: 24 Holstein, clinically healthy female cattle; 606 to 811 kg

c. Test Article Administration: single injection of CCFA at 6.6 mg ceftiofur equivalents/kg body weight (actual dose 6.45 ± 0.03 mg CE/kg), administered as a subcutaneous injection in the base of the ear or middle third of the ear.

d. *In Vitro* Release Rates: ~90% at 60 minutes

e. Marker Residue Depletion Data: The highest ceftiofur residues in milk were observed in milkings 2, 3, and 4 for each of the injection sites (base of the ear, middle third of the ear). Table 4.3 gives the tolerance limits for each of milkings 2, 3, and 4, both for single and triplicate assays.

Table 4.3. Tolerance Limits (TL) for Milk

Milking No.	Base of the Ear		Middle Third of the Ear	
	TL (ppb) single assay	TL (ppb) triplicate assay	TL (ppb) single assay	TL (ppb) triplicate assay
2	111.3	105.7	108.5	114.2
3	102.6	82.8	108.7	81.1
4	83.2	72.4	73.5	71.2

f. Conclusions: The results for milk are comparable whether the drug is injected at the base of the ear or in the middle third of the ear. With the application of a

factor of one-third to adjust for the whole herd not being treated at the same time, the data support the assignment of a zero discard for milk.

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 HPLC as the stable derivative desfuroylceftiofur acetamide (DCA).

3. Tolerances

A tolerance of 0.4 ppm DCA in kidney is assigned based on the data provided in the studies described in sections 4.b.1. and 4.b.2.

Codified tolerances of 2 ppm DCA in liver, 1 ppm DCA in muscle, and 0.1 ppm DCA in milk remain unchanged.

As stated in 4.b.1., for research purposes a value of 95 ppm DCA (i.e., 166 ppm x 0.57, the ratio of DCA:total residue) has been established for making decisions regarding the safety of the injection site.

4. Milk Discard

The data support the assignment of a zero discard of milk.

c. Microbial Food Safety

The Agency evaluated microbial food safety information for the use of ceftiofur crystalline free acid for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida,* and *Histophilus somni* in beef, non-lactating dairy, and lactating dairy cattle when administered as a subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) body weight (1.5 mL sterile suspension per 100 lb body weight). This risk assessment procedure involved conducting: 1) a release assessment to describe the probability that the antimicrobial new animal drug and its use in animals will result in the emergence of resistant bacteria or resistance determinants in the food animal under proposed conditions of use; 2) an exposure assessment to describe the likelihood of human exposure to the resistant bacteria or resistance determinants through consumption of edible products from treated animals; and 3) a consequence assessment to describe the potential human health consequences of exposure to the defined resistant bacteria or resistance determinants by considering the human medical importance of third generation cephalosporins in the treatment of human infectious disease.

It was determined that the risk associated with the use of this product is High. The proposed conditions of use are compatible with the overall risk estimation of High: i.e., for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in beef, non-lactating dairy, and lactating dairy cattle when administered as a subcutaneous injection in the posterior

aspect of the ear where it attaches to the head (base of the ear) at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) body weight (1.5 mL sterile suspension per 100 lb body weight).

d. Analytical Methods for Residues

The regulatory method for determination of DCA in swine kidney and muscle, and bovine kidney, muscle, and milk is the HPLC-DCA assay which successfully completed a sponsor-monitored multi-laboratory method trial. The method is on file with the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

5. USER SAFETY:

Studies to evaluate the safety of ceftiofur to users are discussed in detail in the FOI Summary for NADA 140-338 (NAXCEL Sterile Powder, ceftiofur sodium), approved January 25, 1988.

Human Warnings are provided on the product labeling as follows:

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 (MSDS) please call 1-800-733-5500. To report any adverse event please call 1-800-366-5288.

6. 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 of the implementing regulations. The data demonstrate that EXCEDE Sterile Suspension (ceftiofur crystalline free acid), when administered as a subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) is safe and effective for the 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, and 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*.

Labeling restricts this drug to use by or on the order of a licensed veterinarian. 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 bovine respiratory disease and (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.

In accordance with 21 CFR 514.106(b)(2) this is a Category II change, that did not require a reevaluation of the safety or effectiveness data in the parent application.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the new route of administration (injection in the posterior aspect of the ear where it attaches to the head [base of the ear]) and new indication (treatment of BRD in lactating dairy cattle) for which this supplement is approved.

No patent information was submitted with this application.

7. ATTACHMENTS:

Facsimile labeling is attached as indicated below.

A. EXCEDE Sterile Suspension - Vial Label

B. EXCEDE Sterile Suspension – Carton Label

C. EXCEDE Sterile Suspension - Package Insert