Date of Approval: July 1, 2008

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-288

EXCENEL RTU EZ Sterile Suspension

Ceftiofur hydrochloride
Sterile suspension for injection
Swine and cattle (beef, non-lactating dairy, and lactating dairy)

For treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella* Choleraesuis, and *Streptococcus suis*.

For treatment of the following bacterial diseases in cattle: 1) bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*; 2) acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*; and 3) acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.

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

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I. GENERAL INFORMATION:

A. File Number: NADA 141-288

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(s): EXCENEL RTU EZ Sterile Suspension

D. Established Name(s): Ceftiofur hydrochloride

E. Pharmacological Category: Antimicrobial

F. Dosage Form(s): Sterile suspension for injection

G. Amount of Active Ingredient(s): 50 mg ceftiofur equivalents (CE)/mL

H. How Supplied: 100 mL vial

I. How Dispensed: Rx

J. Dosage(s): Swine: 1.36 to 2.27 mg CE/lb (3.0 to 5.0 mg CE/kg) body weight (BW) (1 mL per 22 to 37 lb BW), repeated at 24-hour intervals for a total of three consecutive days. Do not inject more than 5 mL per injection site.

Cattle: For bovine respiratory disease (BRD) and acute bovine interdigital necrobacillosis, 0.5 to 1.0 mg CE/lb (1.1 to 2.2 mg CE/kg) BW (1 to 2 mL per 100 lb BW), repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be administered on Days 4 and 5 to animals which do not show a satisfactory response (not recovered) after the initial three treatments. In addition, for BRD only, 1.0 mg CE/lb (2.2 mg CE/kg) BW every other day on Days 1 and 3 (48-hour interval). For acute post-partum metritis, 1.0 mg CE/lb (2.2 mg CE/kg) BW (2 mL per 100 lb BW), administered at 24-hour intervals for five

consecutive days. Do not inject more than 15 mL per injection site.

K. Route(s) of Administration: Intramuscular (swine); subcutaneous (cattle)

L. Species/Class(es): Swine; cattle (beef, non-lactating dairy, and lactating dairy)

M. Indication(s): Swine: For treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella* Choleraesuis and *Streptococcus suis.*

Cattle: For treatment of the following bacterial diseases:

– Bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*.

– Acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

– Acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.

II. EFFECTIVENESS:

A. Dosage Characterization:

EXCENEL RTU EZ Sterile Suspension is a reformulation of the currently approved ceftiofur hydrochloride injectable product, EXCENEL RTU Sterile Suspension (NADA 140-890).

The dosage regimen for EXCENEL RTU EZ Sterile Suspension in swine is identical to the dosage regimen for EXCENEL RTU Sterile Suspension. The FOI Summary for the original approval of NADA 140-890 dated April 1996, contains dosage characterization information for swine.

The dosage regimens for EXCENEL RTU EZ Sterile Suspension in cattle are identical to the subcutaneous dosage regimens for EXCENEL RTU Sterile Suspension. The FOI Summary for the supplemental approval of NADA 140-890 dated July 26, 1998, contains dosage characterization information for cattle.

B. Substantial Evidence:

Effectiveness of EXCENEL RTU EZ Sterile Suspension was confirmed using a plasma bioequivalence approach, comparing EXCENEL RTU EZ Sterile Suspension to EXCENEL RTU Sterile Suspension.

1. Pharmacokinetic (PK) Study - Swine

a. Title: "Pharmacokinetic Comparison of EXCENEL RTU (Ceftiofur Hydrochloride) Sterile Suspension and the Revised Formulation of Ceftiofur Hydrochloride Administered to Swine by Intramuscular Injection at a Dose Rate of 5 mg Ceftiofur Equivalents/kg Body Weight." Study Number 1520N-60-04-232. December 2004 to April 2005.

b. Investigator: Dawn A. Merritt, Ph.D., Pfizer Animal Health, Kalamazoo, MI

c. Study Design:

1) *Objective*: To assess plasma bioequivalence of the reformulated product (EXCENEL RTU EZ Sterile Suspension) compared to the approved product (EXCENEL RTU Sterile Suspension, NADA 140-890).

2) *Animals*: 16 Landrace/Duroc mixed-breed healthy swine (8 castrated males, 8 females) weighing 49.0 to 57.1 kg at the beginning of the study.

3) *Experimental Design*: This study was designed as a three-period, two-treatment crossover PK study with a 28-day washout time between each study period. In each of the three study periods, blood samples were collected from each animal before treatment administration, at 20 and 40 minutes after treatment administration, and at 1, 1.5, 2, 3, 4, 8, 12, 16, 24, 36, 48, 60, 72, and 96 hours after treatment administration.

4) *Test Article Administration*: In each of the three study periods, each animal was administered either EXCENEL RTU Sterile Suspension (reference article) or EXCENEL RTU EZ Sterile Suspension (test article) as a single intramuscular (IM) injection in the neck at a dose level of 2.27 mg CE/lb (5 mg CE/kg) BW.

5) *Measurements and Observations*: The concentrations of ceftiofur and desfuroylceftiofur-related metabolites in plasma were measured using a validated high performance liquid chromatography-desfuroylceftiofur acetamide (HPLC-DCA) assay. PK parameters were determined for each animal individually in each period. General health observations of each animal were made once daily throughout the study.

d. Statistical Analysis: The plasma concentration data for ceftiofur and desfuroylceftiofur-related metabolites were analyzed using a

non-compartmental PK analysis. PK parameters were determined using Non-compartmental Analysis Model 200 (extravascular dosing, Linear/Log Trapezoidal Method, 1/y weighting) in WinNonlin™ software, Enterprise Edition, Version 3.2 Build 278 (Pharsight Corporation).

The log-transformed PK parameters were analyzed using a linear mixed model. The 90% confidence intervals (CIs) were constructed for the differences in the treatment means using the least squares means and their standard errors. The resulting CIs were exponentiated and expressed in a percent form. Geometric means were calculated by exponentiating the least squares.

e. Results: A significant period effect was noted for the plasma concentration data and for all PK parameters; however it should be noted that this study took place over a two-month time interval in rapidly growing swine. A significant carryover effect was also noted for T_{max} ($p = 0.0018$). However, because the three-period crossover design allows for the statistical separation of the treatment and carryover effects, and because T_{max} is a secondary parameter, it was concluded that the statistically significant carryover effect did not impact the bioequivalence determination of EXCENEL RTU EZ Sterile Suspension. No significant sex or treatment-by-sex effects were detected for any of the PK parameters tested. Further, no significant differences were detected between formulations for any of the PK parameters tested.

Table 1. Comparative average plasma PK parameters of ceftiofur and desfuroylceftiofur metabolites in swine following an IM administration of 2.27 mg CE/lb (5 mg CE/kg) BW, as either EXCENEL RTU Sterile Suspension (reference article) or EXCENEL RTU EZ Sterile Suspension (test article).

Comparative Bioavailability in Swine (Average ± SD) After IM Administration		
PK Parameter	Ceftiofur hydrochloride (HCl) (EXCENEL RTU EZ) (test article)	Ceftiofur HCl (EXCENEL RTU) (reference article)
C_{max} (µg/mL)	26 ± 3.95	23.7 ± 4.10
$AUC_{0\text{-}LOQ}$ (hr*µg/mL)	395 ± 99.4	377 ± 79.9
T_{max} (hr)	2.38 ± 0.979	2.83 ± 1.07
$T_{>0.2}$ (hr)	104 ± 15.3	101 ± 14.8
$T_{1/2\ \lambda z}$ (hr)	19.2 ± 2.56	18.7 ± 3.26
Definitions: C_{max} – maximum plasma concentration. $AUC_{0\text{-}LOQ}$ – the area under the plasma concentration vs. time curve from time of injection to the limit of quantitation of the assay (0.15 µg/mL). T_{max} – the time after initial injection to when C_{max} occurs. $T_{>0.2}$ – the time plasma concentrations remain above 0.2 µg/mL. $T_{1/2\ \lambda z}$ – the elimination-phase plasma half-life of the drug.		

Bioequivalence of EXCENEL RTU EZ Sterile Suspension compared to EXCENEL RTU Sterile Suspension was determined using the bioequivalence criteria set forth in the Center for Veterinary Medicine's bioequivalence guidelines. $AUC_{0\text{-}LOQ}$, C_{max}, and $T_{> 0.2}$ for EXCENEL RTU Sterile Suspension and EXCENEL RTU EZ Sterile Suspension were found to be bioequivalent (Table 2). The upper and lower bounds for the 90% CIs for these parameters were contained within -20% to +25% of the least squares means for EXCENEL RTU Sterile Suspension.

Table 2. Bioequivalence analysis for EXCENEL RTU EZ Sterile Suspension (test article) compared to EXCENEL RTU Sterile Suspension (reference article) following IM injection to swine at a dose rate of 5 mg CE/kg BW.

Parameter	Least Squares Means		CI Lower Bound (%)	CI Upper Bound (%)
	EXCENEL RTU EZ	EXCENEL RTU		
$AUC_{0\text{-}LOQ}$ (µg*h/mL)	379.2	364.8	96.3	112
C_{max} (µg/mL)	25.85	23.37	98.9	121
$T_{>0.2}$ (hr)	102.6	99.08	99.6	108

f. Adverse Events: There were no adverse events in the study that were attributed to ceftiofur hydrochloride administration.

g. Conclusion: EXCENEL RTU EZ Sterile Suspension was bioequivalent to EXCENEL RTU Sterile Suspension for $AUC_{0\text{-}LOQ}$, C_{max}, and $T_{>0.2}$ when administered by IM injection to swine at a dose rate of 5 mg CE/kg BW.

2. Pharmacokinetic Study - Cattle

a. Title: "Pharmacokinetic Comparison of EXCENEL RTU (Ceftiofur Hydrochloride) Sterile Suspension and Reformulated EXCENEL RTU Sterile Suspension Administered Once to Cattle Subcutaneously at a Dose Rate of 2.2 mg Ceftiofur Equivalents (CE)/kg Body Weight." Study Number 1530N-60-04-457. January to August 2005.

b. Investigator: Y.C. Anderson, Ph.D., Pfizer Animal Health, Kalamazoo, MI

c. Study Design:

1) *Objective*: To assess plasma bioequivalence of the reformulated product (EXCENEL RTU EZ Sterile Suspension) compared to the approved product (EXCENEL RTU Sterile Suspension, NADA 140-890).

2) *Animals*: 16 mixed-breed healthy beef cattle (8 males, 8 females) weighing 283 to 357.81 kg at the beginning of the study.

3) *Experimental Design*: This study was designed as a three-period, two-treatment crossover PK study with a 14-day washout time between each study period. In each of the three study periods, blood samples were collected from each animal before treatment administration, at 20 and 40 minutes after treatment administration, and at 1, 1.5, 2, 3, 4, 8, 12, 16, 24, 36, 48, 60, 72, and 96 hours after treatment administration.

4) *Test Article Administration*: In each of the three study periods, each animal was administered either EXCENEL RTU Sterile Suspension (reference article) or EXCENEL RTU EZ Sterile Suspension (test article) as a single subcutaneous (SC) injection in the neck at a dose level of 1 mg CE/lb (2.2 mg CE/kg) BW.

5) *Measurements and Observations*: The concentrations of ceftiofur and desfuroylceftiofur-related metabolites in plasma were measured using a validated HPLC-DCA assay. PK parameters were determined for each animal individually in each period. General health observations of each animal were made once daily throughout the study.

d. Statistical Analysis: The plasma concentration data for ceftiofur and desfuroylceftiofur-related metabolites were analyzed using non-compartmental PK analysis. PK parameters were determined using Non-compartmental Analysis Model 200 (extravascular dosing, Linear/Log Trapezoidal Method, 1/y weighting) in WinNonlin™ software, Enterprise Edition, Version 3.2 Build 278 (Pharsight Corporation).

The log-transformed PK parameters were analyzed using a linear mixed model. The 90% CIs were constructed for the differences in the treatment means using the least squares means and their standard errors. The resulting CIs were exponentiated and expressed in a percent form. Geometric means were calculated by exponentiating the least squares.

e. Results: The maximum concentration (C_{max}) of ceftiofur and metabolites was 11.1 µg/mL and was observed at 1.7 hours (T_{max}) following a SC administration of EXCENEL RTU Sterile Suspension (reference article). The C_{max} for cattle receiving EXCENEL RTU EZ Sterile Suspension (test article) was 12.7 µg/mL, and it occurred at 1.1 hours after dosing. No significant differences were detected between the two formulations for any of the PK parameters. There was no significant carryover, period, or sex effect.

Table 3. Comparative average plasma PK parameters of ceftiofur and desfuroylceftiofur metabolites in cattle following a SC administration of 1 mg CE/lb (2.2 mg CE/kg) BW, as either EXCENEL RTU Sterile Suspension (reference article) or EXCENEL RTU EZ Sterile Suspension (test article).

Comparative Bioavailability in Cattle (Average ± SD) After SC Administration		
PK Parameter	Ceftiofur HCl (EXCENEL RTU EZ) (test article)	Ceftiofur HCl (EXCENEL RTU) (reference article)
C_{max} (µg/mL)	11.7 ± 4.01	13.8 ± 6.77
$AUC_{0\text{-}LOQ}$ (hr*µg/mL)	94.9 ± 23.9	101 ± 25.3
T_{max} (hr)	1.99 ± 1.02	1.42 ± 0.99
$T_{>0.2}$ (hr)	43.1 ± 6.69	44.3 ± 5.48
$T_{1/2\ \lambda z}$ (hr)	9.32 ± 1.75	9.38 ± 1.58
Definitions: C_{max} – maximum plasma concentration. $AUC_{0\text{-}LOQ}$ – the area under the plasma concentration vs. time curve from time of injection to the limit of quantitation of the assay (0.15 µg/mL). T_{max} – the time after initial injection to when C_{max} occurs. $T_{>0.2}$ – the time plasma concentrations remain above 0.2 µg/mL. $T_{1/2\ \lambda z}$ – the elimination-phase plasma half-life of the drug.		

Bioequivalence of EXCENEL RTU EZ Sterile Suspension compared to EXCENEL RTU Sterile Suspension was determined using the bioequivalence

criteria set forth in the Center for Veterinary Medicine's bioequivalence guidelines. Although the results of the bioequivalence study indicated the two products were not bioequivalent for the C_{max} parameter, they are considered therapeutically equivalent, due to the established safety margin of ceftiofur in cattle and the bioequivalence of the two pivotal parameters, $AUC_{0\text{-}LOQ}$ and $T_{>0.2}$.

Table 4. Bioequivalence analysis for EXCENEL RTU EZ Sterile Suspension (test article) compared to EXCENEL RTU Sterile Suspension (reference article) following SC injection to cattle at a dose rate of 2.2 mg CE/kg BW.

Parameter	Least Squares Means		CI Lower Bound (%)	CI Upper Bound (%)
	EXCENEL RTU EZ	EXCENEL RTU		
$AUC_{0\text{-}LOQ}$ (µg*h/mL)	96.8	93.0	93.6	114.0
C_{max} (µg/mL)	12.7	11.1	90.5	139.0
$T_{>0.2}$ (hr)	43.4	43.7	96.1	106.6

f. Adverse Events: There were no adverse events in the study that were attributed to ceftiofur hydrochloride administration.

g. Conclusion: EXCENEL RTU EZ Sterile Suspension is bioequivalent to EXCENEL RTU Sterile Suspension for the $AUC_{0\text{-}LOQ}$ and $T_{>0.2}$ when administered by SC injection to cattle at a dose rate of 2.2 mg CE/kg BW. Therefore, EXCENEL RTU EZ Sterile Suspension and EXCENEL RTU Sterile Suspension are considered therapeutically equivalent when used in cattle.

III. TARGET ANIMAL SAFETY:

A. Systemic Safety:

1. Swine

Ceftiofur administered as EXCENEL RTU EZ Sterile Suspension was demonstrated to be bioequivalent to EXCENEL RTU Sterile Suspension for $AUC_{0\text{-}LOQ}$, C_{max}, and $T_{>0.2}$ (see EFFECTIVENESS above). The safety of EXCENEL RTU Sterile Suspension in swine was demonstrated via comparability to ceftiofur sodium (as NAXCEL Sterile Powder), and is described in the FOI Summary for NADA 140-890 dated April 1996. After parenteral administration, both ceftiofur sodium and ceftiofur hydrochloride are rapidly metabolized to desfuroylceftiofur.

Studies conducted with ceftiofur sodium are adequate for determining the systemic safety of EXCENEL RTU EZ Sterile Suspension. The FOI Summary for the supplemental approval of NADA 140-338 dated August 4, 1992, contains systemic target animal safety information for ceftiofur sodium in swine. Results

from a tolerance study (57 mg CE/lb BW per day for five consecutive days) and a toxicity study (2.27, 6.81, or 11.36 mg CE/lb BW per day for 15 consecutive days) conducted with ceftiofur sodium in healthy feeder pigs indicated that ceftiofur was safe.

2. Cattle

Ceftiofur administered as EXCENEL RTU EZ Sterile Suspension was demonstrated to be bioequivalent to EXCENEL RTU Sterile Suspension for $AUC_{0\text{-}LOQ}$ and $T_{>0.2}$ (see EFFECTIVENESS above). Mean plasma C_{max} concentrations in the pivotal bioequivalence study (Number 1530N-60-04-457) were slightly higher in the EXCENEL RTU EZ Sterile Suspension group compared to the EXCENEL RTU Sterile Suspension group (12.7 µg/mL vs. 11.1 µg/mL). However, the maximum plasma concentrations of EXCENEL RTU EZ Sterile Suspension were lower than those previously observed for ceftiofur sodium (as NAXCEL Sterile Powder). Therefore, EXCENEL RTU EZ Sterile Suspension is considered safe. The safety of EXCENEL RTU Sterile Suspension in cattle was demonstrated via comparability to ceftiofur sodium, and is described in the FOI Summary for NADA 140-890 dated July 26, 1998. After parenteral administration, both ceftiofur sodium and ceftiofur hydrochloride are rapidly metabolized to desfuroylceftiofur.

Studies conducted with ceftiofur sodium are adequate for determining the systemic safety of EXCENEL RTU EZ Sterile Suspension. The FOI Summaries for the original approval of NADA 140-338 dated January 25, 1988, and for the supplemental approval of NADA 140-338 dated April 5, 1990, contain systemic target animal safety information for ceftiofur sodium in cattle. Results from a tolerance study (25 mg CE/lb BW per day for five consecutive days) and a toxicity study (1, 3, 5, or 10 mg CE/lb BW per day for 15 consecutive days) conducted with ceftiofur sodium in healthy feeder calves indicated that ceftiofur was safe.

B. Injection Site Irritation Study – Swine:

1. Title: "Injection Site Tolerance of a Revised Formulation of EXCENEL RTU Sterile Suspension for Swine." Study Number 1423N-60-07-286. July 2007 to August 2007.

2. Study Director: Devendra Kumar, B.V.Sc. & A.H., M.S., Ph.D., Pfizer Animal Health, Kalamazoo, MI.

3. Study Design:

   a. *Objective:* To characterize the injection site tolerance of EXCENEL RTU EZ Sterile Suspension for swine when administered IM to growing pigs at the maximum proposed dose (5 mg CE/kg BW) once daily for three consecutive days. The study was conducted in compliance with FDA Good Laboratory Practice (GLP) regulations.

b. *Test Animals:* Twelve healthy crossbred (Yorkshire-Landrace-Duroc) swine (6 females, 6 castrated males), 10 weeks old and weighing 39.5 to 51.5 kg at arrival, were enrolled in the study. All pigs received the identical treatment and dosage regimen. A control group was not included.

c. *Test Article Administration:* The test article was ceftiofur hydrochloride as EXCENEL RTU EZ Sterile Suspension (50 mg CE/mL). Pigs were injected with 5 mg CE/kg BW once daily for three consecutive days, beginning on Day 0. Injections were given IM in three separate sites (cranial left neck on Day 0, right neck on Day 1, and caudal left neck on Day 2). Prior to injection, vials were vigorously shaken for at least 60 seconds or until the test article was visibly suspended.

d. *Measurements and Observations:* General health observations were conducted once daily from Days -7 to 16. Clinical and injection site observations were conducted on Day -7 and then once daily from Days -1 to 16. Injection sites were evaluated for the presence of erythema, heat, necrosis, drainage, and sensitivity or firmness by visual observation and palpation, and swelling dimensions were measured.

4. Statistical Analysis: None.

5. Results:

a. *Mortalities:* There were no mortalities during the study.

b. *General Health Observations:* Ten of the 12 enrolled animals did not have any abnormal general health observations. Coughing and loose stool were recorded, but were not considered to be test-article related.

c. *Clinical Observations:* Most observations were normal, and none of the abnormal post-treatment observations were considered test-article related. Coughing and sneezing were the most frequent observations noted. There were also some observations of abrasions and erythema, but not at the injection sites.

d. *Injection Site Observations:* Erythema, heat, sensitivity, necrosis, and drainage were not observed at any injection site on any study day. Swelling was present in all animals one day after injection. Firmness (associated with swelling) was also reported in most early post-treatment observations. By the end of the study, only 3 of the 36 injection sites had visible swelling or firmness noted.

6. Conclusion: Administration of ceftiofur hydrochloride as EXCENEL RTU EZ Sterile Suspension at 5 mg CE/kg BW by IM injection once daily for three consecutive days resulted in moderate swelling and firmness at the injection sites which showed signs of regression over the 14-day post-treatment period.

Injection site irritation extended beyond the assigned 4-day pre-slaughter withdrawal period.

C. Injection Site Irritation Study - Cattle

1. Title: "Injection Site Tolerance of EXCENEL RTU EZ Sterile Suspension for Cattle." Study No. 1433N-60-07-584. March 2007 to August 2007.

2. Study Director: Devendra Kumar, B.V.Sc. & A.H., M.S., Ph.D., Pfizer Animal Health, Kalamazoo, MI

3. Study Design:

   a. *Objective:* To characterize the injection site tolerance of EXCENEL RTU EZ Sterile Suspension for cattle when injected SC at the maximum proposed dose of 2.2 mg CE/kg BW once daily for five consecutive days. The study was conducted in compliance with FDA GLP regulations.

   b. *Test Animals:* Twelve healthy crossbred beef cattle (6 females, 6 castrated males), 10 to 14 months of age on Day -14 and weighing 280 to 363 kg on Day -1, were enrolled in the study. All cattle received the identical treatment and dosage regimen. A control group was not included.

   c. *Experimental Design:* The study animals were acclimated for two weeks beginning on Day -14. Twelve animals in good health were randomly selected by gender from the 16 animals available for enrollment. A control group was not used. Day 0 was defined as the day of first injection. Because there was only one treatment group, study personnel were not masked. Four animals were randomly assigned to each of three pens.

   d. *Test Article Administration:* The test article was EXCENEL RTU EZ Sterile Suspension containing 50 mg CE/mL. Animals were injected SC in the neck with 2.2 mg CE/kg BW once daily for five consecutive days beginning on Day 0. Each injection was given at a different location in the neck, and daily injection sites alternated between the left and right sides. Prior to dosing, the test article was vigorously shaken for at least 60 seconds or until the test article was visibly suspended.

Table 5. Injection site location by day.

Day	Injection Site Location
0	Cranial left side of neck (Left Cranial; LN1)
1	Cranial right side of neck (Right Cranial; RN1)
2	Middle of left side of neck (Left Middle; LN2)
3	Caudal right side of neck (Right Caudal; RN2)
4	Caudal left side of neck (Left Caudal; LN3)

e. *Measurements and Observations:* General health observations were conducted once daily from Day -14 to Day 33. Clinical and injection site observations were conducted on Day -14 and once daily from Day -1 to Day 33. Injection sites were evaluated for the presence of erythema, heat, sensitivity, firmness, swelling, necrosis, and draining by visual observation and palpation, and swelling dimensions were measured.

f. *Statistical Methods:* None.

4. Results:

a. *Mortalities:* There were no mortalities during the study.

b. *General Health Observations:* Only 1.4% (8/568) of the general health observations were abnormal, and none were considered to be test article-related. Abnormal observations included nasal discharge, watery eye, and a small cut on the nose.

c. *Clinical Observations:* Abnormal clinical signs were present in 31.3% (135/432) of the clinical observations, and none were considered to be test article-related. Abnormal observations included ocular discharge, nasal discharge, and cough.

d. *Injection Site Observations:* Erythema, heat, sensitivity, necrosis, and drainage were not observed at any injection site on any study day.

Firmness was present at most injection sites throughout the study.

Swelling was present at all injection sites on the first day after injection. Mean swelling volumes at each injection site were highest on the first day after injection and decreased rapidly within one week (Table 6). By Day 33, mean swelling volumes for most of the injection sites had decreased by more than 90% (Table 6). For most animals, swelling and firmness were still present at all injection sites on Day 33 (Table 7).

Table 6. Mean swelling volume (cm^3) per injection site.

	1 Day Post-Injection	7 Days Post-Injection	Day 33
LN1	47.6	14.6	0.6
RN1	62.5	15.1	0.8
LN2	50.7	15.8	1.2
RN2	43.9	8.5	2.6
LN3	21.3	8.5	2.0

Table 7. Number of animals with swelling and firmness present per injection site on the final day of the study.

	Day 33
LN1	6 (50%)
RN1	9 (75%)
LN2	8 (66.7%)
RN2	11 (91.7%)
LN3	11 (91.7%)

5. Conclusion: EXCENEL RTU EZ Sterile Suspension is well tolerated when administered SC in the neck in cattle at the maximum proposed dose of 2.2 mg CE/kg BW once daily for five consecutive days. Injection site reactions consisted mainly of detectable to moderate swelling which was most prominent the day after injection but showed substantial regression by the following week. Injection site irritation extended beyond the assigned 3-day pre-slaughter withdrawal period.

IV. HUMAN FOOD SAFETY:

A. Toxicology:

CVM did not require toxicology studies for this approval. The FOI Summaries for the original approval of NADA 140-338 (NAXCEL Sterile Powder, ceftiofur sodium) dated January 25, 1988; the original approval of NADA 140-890 (EXCENEL RTU Sterile Suspension, ceftiofur hydrochloride) dated April 1996; and the original approval of NADA 141-235 (EXCEDE for Swine, ceftiofur crystalline free acid) dated June 18, 2004, contain a summary of all toxicology studies for ceftiofur in cattle and swine.

B. Residue Chemistry:

1. Summary of Residue Chemistry Studies

a. Tissue Residue Study - Swine

A pivotal GLP tissue residue study in swine was conducted evaluating ceftiofur and desfuroylceftiofur-related residues (the marker residue) at the injection site and in kidney (target tissue) after administration of EXCENEL RTU EZ Sterile Suspension (5 mg CE/kg BW) for three consecutive days.

1) Title: "Decline of Ceftiofur and Desfuroylceftiofur-Related Residues in Injection Site and Kidneys of Swine Following Intramuscular Injection of the Revised Formulation of Ceftiofur Hydrochloride Sterile Suspension (5 mg Ceftiofur Equivalents/kg Body Weight)." Study Number 1521N-60-04-233. July 2005.

2) Investigator: Dawn A. Merritt, Ph.D., Pfizer Animal Health, Kalamazoo, MI

3) Test Animals: Thirty-two clinically healthy Landrace/Duroc mixed breed swine (16 males, 16 females), weighing 49.0 to 58.1 kg, were enrolled in the study. Of these, 30 (15M, 15F) were treated and 2 (1M, 1F) were non-treated.

4) Test Article Administration: The test article was administered at 5 mg CE/kg BW by IM injection once daily for three consecutive days.

5) Assay Methodology: The concentration of ceftiofur and desfuroylceftiofur-related metabolites in injection sites and kidney samples was measured using the HPLC-DCA assay. The assay measures ceftiofur and all desfuroylceftiofur metabolites (desfuroylceftiofur, desfuroylceftiofur cysteine disulfide, desfuroylceftiofur glutathione disulfide, and desfuroylceftiofur covalently bound to amino acids and proteins) without distinction. The limit of quantitation (LOQ) and limit of detection (LOD) for this assay are 0.1 µg/g and 0.05 µg/g, respectively.

   Kidney tissue samples and the third (final) injection site sample from each treated animal were analyzed in duplicate. Specifically, each of the two 10 g tissue subsamples was analyzed as a single replicate. The mean value from duplicate analyses of each sample was determined and used in statistical analyses.

6) Results: Mean residue concentrations (least squares means) in kidney tissue were 1.31, 0.296, and 0.120 µg/g at 24, 48, and 72 hours after the last dose, respectively. Residue concentrations in kidney tissue from all animals were below the assay LOQ by 96 hours post-treatment and below the assay LOD by 120 hours post-treatment.

   Mean residue concentrations (least squares means) in the final injection site were 1.68, 0.342, 0.160, and 0.121 µg/g at 24, 48, 72, and 96 hours after the last dose, respectively. Residue concentrations in the final injection site were below the LOQ by 120 hours post-treatment in all animals.

7) Conclusions: Residue decline profiles were established in kidney and the final injection site of grower swine receiving IM doses of EXCENEL RTU EZ Sterile Suspension. As expected, the highest residue levels were observed at 24 hours after the last dose. Residue levels in both tissues decreased at subsequent time points.

b. Tissue Residue Study - Cattle

A pivotal GLP tissue residue study in cattle was conducted evaluating ceftiofur and desfuroylceftiofur-related residues (the marker residue) at the injection site and in kidney (target tissue) after administration of EXCENEL RTU EZ Sterile Suspension (2.2 mg CE/kg BW) for five consecutive days.

1) Title: "Decline of Ceftiofur and Desfuroylceftiofur-related Residues in Injection Site and Kidneys of Cattle Following Subcutaneous Administration of the Revised Formulation of Ceftiofur Hydrochloride Sterile Suspension at a Dose of 2.2 mg Ceftiofur Equivalents/kg Body Weight Once Daily for Five Consecutive Days." Study Number 1531N-60-04-456. August 2005.

2) Investigators: Y.C. Anderson, Ph.D., Pfizer Animal Health, Kalamazoo, MI, and C. Heird, Southwest Bio-Labs, Las Cruces, NM

3) Test Animals: Thirty-two clinically healthy mixed breed beef cattle (16 males, 16 females), weighing 237.6 to 322.9 kg, were enrolled in the study. Of these, 30 (15M, 15F) were treated and 2 (1M, 1F) were non-treated.

4) Test Article Administration: The test article was administered at 2.2 mg CE/kg BW by SC injection once daily for five consecutive days.

5) Assay Methodology: The concentration of ceftiofur and desfuroylceftiofur-related metabolites in injection sites and kidney samples was measured using the HPLC-DCA assay. The assay measures ceftiofur and all desfuroylceftiofur metabolites (desfuroylceftiofur, desfuroylceftiofur cysteine disulfide, desfuroylceftiofur glutathione disulfide, and desfuroylceftiofur covalently bound to amino acids and proteins) without distinction. The LOQ and LOD for this assay are 0.1 μg/g and 0.05 μg/g, respectively.

   Kidney tissue samples and the fifth (final) injection site sample from each treated animal were analyzed in duplicate. The mean value from duplicate analyses of each sample was determined and used in statistical analyses.

6) Results: Mean residue concentrations in kidney tissue were 0.96, 0.34, 0.14, and 0.09 μg/g at 24, 48, 72, and 96 hours after the last dose, respectively. Residue concentrations in kidney tissue from animals were below the LOQ (one sample) or the LOD at 120 hours post-treatment.

   Mean residue concentrations in the final injection site were 5.4, 2.0, 1.2, 0.85, and 0.43 μg/g at 24, 48, 72, 96, and 120 hours after the last dose, respectively.

7) Conclusions: Residue decline profiles were established in kidney and the final injection site of cattle receiving SC doses of EXCENEL RTU EZ Sterile Suspension. As expected, highest residue levels were observed at 24 hours after the last dose. Residue levels in both tissues decreased at subsequent time points.

b. Milk Residue Study - Cattle

The use of EXCENEL RTU Sterile Suspension (NADA 140-890) does not require a milk discard time and supporting data have been summarized in the FOI Summary for NADA 140-890 dated July 26, 1998. The following milk-out study was conducted for the revised formulation, EXCENEL RTU EZ Sterile Suspension.

1) Title: "Determination of Ceftiofur and Desfuroylceftiofur-related Residues in Milk of Lactating Dairy Cattle Receiving SC Injections of the Revised Formulation of EXCENEL RTU for Five Consecutive Days." Study Number 1531N-60-06-528. July 2007.

2) Study Director: Pamela L. Boner, Pfizer Animal Health, Richland, MI

3) Study Design: Twenty lactating Holstein dairy cows were administered a revised formulation of ceftiofur hydrochloride sterile suspension at a dose of 2.2 mg CE/kg BW by SC injection once daily for five consecutive days. Milk from the cows was collected twice daily at approximately 10- to 14-hour intervals for 10 days (2 days prior to treatment, each day of treatment, and 3 days following last treatment).

4) Assay Methodology: Milk was assayed in triplicate for ceftiofur-related residue using the sponsor's HPLC-DCA procedure. The assay has an LOQ in milk of 0.05 μg/mL (ppm).

5) Results: The results of this study are summarized in Table 8. For ease of comparison, Table 8 also includes the data for milk that are summarized in the FOI Summary for NADA 140-890 (EXCENEL RTU Sterile Suspension) dated July 26, 1998 (animals treated with five IM doses of 2.2 mg CE/kg BW).

Table 8. Results of assays for milk after administration of EXCENEL RTU EZ Sterile Suspension (Study Number 1531N-60-06-528) and for EXCENEL RTU Sterile Suspension (NADA 140-890, FOI Summary dated July 26, 1998).

	EXCENEL RTU EZ Sterile Suspension		EXCENEL RTU Sterile Suspension	
Time after 1st dose (hours)	No. of animals with mean value ≥ the LOQ	Mean concentration (μg/mL)	No. of animals with mean value ≥ the LOQ	Mean concentration (μg/mL)
-36	0	0.015	---	---
12	0	0.030	---	---
24	0	0.025	---	---
36	5	0.040	1	0.058
48	1	0.029	0	NA
60	5	0.044	---	---
72	1	0.032	---	---
84	5	0.041	---	---
96 (0)*	0	0.031	---	---
108 (12)	7	0.048	7	0.063
120 (24)	0	0.030	0	NA
132 (36)	0	0.020	0	NA

*Numbers in parentheses represent the milk discard time, in hours.

Following five doses, all milk samples from all animals contained ceftiofur free acid equivalents as desfuroylceftiofur acetamide (DCA) residues below 0.1 μg/mL. The group mean values of all animals at each time point were below the LOQ. These data demonstrate that EXCENEL RTU EZ Sterile Suspension did not produce concentrations greater than 0.1 μg/mL when administered as five SC injections at 2.2 mg CE/kg BW approximately 24 hours apart.

2. Target Tissue and Marker Residue Assignment

The target tissue for residue monitoring in both swine and cattle is kidney. The marker residue in edible tissues, including cattle milk, is the sum of ceftiofur and desfuroylceftiofur-related metabolites, measured by HPLC as the stable derivative DCA.

3. Tolerance Assignments

Swine tolerances are 0.25 ppm DCA in kidney, 3 ppm DCA in liver, and 2 ppm DCA in muscle. For research purposes a value of 80 ppm DCA has been established for making decisions regarding the safety of the injection site (see the FOI Summary for NADA 141-235 [EXCEDE for Swine, ceftiofur crystalline free acid] dated June 18, 2004).

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. For research purposes a value of

95 ppm DCA has been established for making decisions regarding the safety of the injection site (see the FOI Summary for NADA 141-209 [EXCEDE Sterile Suspension, ceftiofur crystalline free acid] dated June 2, 2006).

4. Withdrawal Times and Milk Discard Time

a. Swine

The residue depletion data demonstrate that injection site does not impact the withdrawal period. The values observed in the above study were significantly less than 80 ppm.

The data provided by the above study were statistically analyzed to calculate the upper 95% confidence limits on the 99th percentile for the kidney tissue residues. The analysis demonstrated that the upper tolerance limit falls below the kidney tolerance of 0.25 ppm between 3 and 4 days. Therefore, the data support assignment of a 96-hour (4-day) pre-slaughter withdrawal period for EXCENEL RTU EZ Sterile Suspension when administered intramuscularly to swine.

b. Cattle

The residue depletion data demonstrate that the injection site does not impact the withdrawal period. The values observed in the above study were significantly less than 95 ppm.

The data provided by the above study were statistically analyzed to calculate the upper 95% confidence limits on the 99th percentile for the kidney tissue residues. The analysis demonstrated that the upper tolerance limit falls below the kidney tolerance of 0.4 ppm between 2 and 3 days. Therefore, the data support assignment of a 72-hour (3-day) pre-slaughter withdrawal period for EXCENEL RTU EZ Sterile Suspension when administered subcutaneously to cattle.

The information described in this FOI Summary demonstrates that EXCENEL RTU EZ Sterile Suspension is bioequivalent to EXCENEL RTU Sterile Suspension for the $AUC_{0\text{-}LOQ}$ and $T_{>0.2}$ in cattle. Therefore, no milk discard time, based on a tolerance of 100 ppb, is required when this product is used according to label directions.

C. Microbial Food Safety:

1. Swine

The Agency considered the impact of the formulation change from the current excipients in EXCENEL RTU Sterile Suspension (NADA 140-890) to miglyol in

EXCENEL RTU EZ Sterile Suspension, indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella* Choleraesuis, and *Streptococcus suis*, on the emergence or selection of antimicrobial resistant bacteria of public health concern in or on treated swine. The Agency determined that a microbial food safety assessment was not necessary at this time.

2. Cattle

This approval allows for use of a reformulated ceftiofur hydrochloride sterile suspension in cattle. EXCENEL RTU Sterile Suspension (NADA 140-890) currently is approved for the treatment of 1) bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*; 2) acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*; and 3) acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur. The only change involved a reformulation of the product. Conditions of use remain unchanged (including dose, duration, target animal species) with the exception of the route of administration (the reformulated product is for subcutaneous injection only).

The sponsor provided a hazard characterization addressing potential human illness caused by ceftiofur-resistant *Salmonella* attributable to cattle-derived food commodities, and treated with a third generation cephalosporin. The dose evaluated was 2.2 mg CE/kg BW administered once daily for five consecutive days. In addition, in their hazard characterization the sponsor also addressed β-lactamase resistance in commensal *Escherichia coli* associated with cattle. The hazard characterization assessed whether differences observed between the currently marketed and the reformulated products would have any impact on antimicrobial resistance, by either promoting resistance or creating favorable selection conditions for bacteria of public health concern.

Based upon the Agency's evaluation of the information submitted by the sponsor, and in consideration of the currently approved ceftiofur hydrochloride products for cattle (beef and dairy), and taking into consideration the proposed use conditions of EXCENEL RTU EZ Sterile Suspension, it was determined that the reformulated product is unlikely to exert any additional antimicrobial selection pressures on organisms of human health concern.

Because third-generation cephalosporins in human medicine are 1) used for treatment of enteric pathogens responsible for food borne diseases; 2) a sole/limited therapy or essential therapy for serious disease; and 3) used to treat enteric pathogens in non-food borne diseases, such as meningitis and necrotizing enterocolitis, the drug currently is ranked as **critically important** to human medicine. The proposed use of ceftiofur in cattle is adequately addressed

by the Agency's Category 1 risk management strategies, which include prescription only marketing status, injectable, limited number of animals – treated individually, and monitoring by the National Antimicrobial Resistance Monitoring System.

D. Analytical Method 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.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to EXCENEL RTU EZ Sterile Suspension:

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.

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.

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 EXCENEL RTU EZ Sterile Suspension, when used according to the label, is safe and effective for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella* Choleraesuis, and *Streptococcus suis*; and for treatment of the following bacterial diseases in cattle: 1) bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*; 2) acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*; and

3) acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur. Additionally, data demonstrate that residues in food products derived from swine and cattle treated with EXCENEL RTU EZ Sterile Suspension will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

Labeling restricts this drug to use by or on the order of a licensed veterinarian. This decision was based on the following factors: 1) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product to treat swine respiratory disease, bovine respiratory disease, bovine foot rot, or acute metritis; and 2) 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.

B. Exclusivity:

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval.

C. Patent Information:

EXCENEL RTU EZ Sterile Suspension is under the following U.S. patent number:

U.S. Patent Number	Date of Expiration
5,736,151	December 9, 2016

VII. ATTACHMENTS:

Facsimile Labeling:

A. EXCENEL RTU EZ Sterile Suspension - 100 mL vial label
B. EXCENEL RTU EZ Sterile Suspension - package insert
C. EXCENEL RTU EZ Sterile Suspension - shipping carton