Date of Approval: September 13, 2013

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-288

EXCENEL RTU EZ

Ceftiofur Hydrochloride

Sterile Suspension

Swine and cattle (beef, non-lactating dairy, and lactating dairy)

This supplement provides for a reformulated product for use in swine and cattle, addition of a new route of administration (intramuscular injection) in cattle, change of withdrawal period in cattle, and a 250 mL vial size.

Sponsored by:

Zoetis Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-288

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

EXCENEL RTU EZ

D. Established Name

Ceftiofur hydrochloride

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Sterile suspension for injection

G. Amount of Active Ingredient

50 mg ceftiofur equivalents (CE)/mL

H. How Supplied

100 mL and 250 mL vials

I. Dispensing Status

Rx

J. Dosage Regimen

Swine: Administer intramuscularly at a dosage of 1.36 to 2.27 mg ceftiofur equivalents (CE)/lb (3 to 5 mg CE/kg) body weight (BW) (1 mL of sterile suspension per 22 to 37 lb BW). Treatment should be 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 and acute bovine interdigital necrobacillosis: administer by intramuscular or subcutaneous administration at the dosage of 0.5 to 1 mg CE/lb (1.1 to 2.2 mg CE/kg) BW (1 to 2 mL sterile suspension per 100 lb BW). Administer daily at 24 hour intervals for a total of three consecutive days.

Additional treatments may be administered on Days 4 and 5 for animals which do not show a satisfactory response (not recovered) after the initial three treatments. In addition, for BRD only, administer intramuscularly or subcutaneously 1 mg CE/lb (2.2 mg CE/kg) BW every other day on Days 1 and 3 (48-hour interval). Do not inject more than 15 mL per injection site.
Selection of dosage level (0.5 to 1 mg CE/lb) and regimen/duration (daily or every other day for BRD only) should be based on an assessment of the severity of disease, pathogen susceptibility and clinical response.
— For acute post-partum metritis, administer by intramuscular or subcutaneous administration at the dosage of 1 mg CE/lb (2.2 mg CE/kg) BW (2 mL sterile suspension per 100 lb BW). Administer at 24 hour intervals for five consecutive days. Do not inject more than 15 mL per injection site.

K. Route of Administration

Intramuscular (swine and cattle); subcutaneous (cattle)

L. Species/Class

Swine; cattle (beef, non-lactating dairy, and lactating dairy)

M. Indication

Swine: EXCENEL RTU EZ Sterile Suspension is indicated for treatment/ control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella* Choleraesuis and *Streptococcus suis*.

Cattle: EXCENEL RTU EZ Sterile Suspension is indicated 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.

N. Effect of Supplement

This supplement provides for a reformulated product for use in swine and cattle, addition of a new route of administration (intramuscular injection) in cattle, change of withdrawal period in cattle, and a 250 mL vial size.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the original approval of EXCENEL RTU Sterile Suspension (NADA 140-890) dated April 1996 contains dosage characterization information for swine. The FOI Summary for the supplemental approval of EXCENEL RTU Sterile Suspension (NADA 140-890) dated July 26, 1998, contains dosage characterization information for cattle.

B. Substantial Evidence

This supplemental approval provides for a reformulation of EXCENEL RTU EZ Sterile Suspension. The previously approved EXCENEL RTU EZ product was a reformulation of another ceftiofur hydrochloride injectable product, EXCENEL RTU Sterile Suspension (NADA 140-890). Effectiveness of the reformulated EXCENEL RTU EZ Sterile Suspension was confirmed using a plasma bioequivalence approach, comparing the reformulated EXCENEL RTU EZ Sterile Suspension to EXCENEL RTU Sterile Suspension.

1. Pharmacokinetic (PK) Study – Swine (Intramuscular)

a. Title: Pharmacokinetic Comparison of EXCENEL RTU (Ceftiofur Hydrochloride) Sterile Suspension and Reformulated EXCENEL RTU-EZ Administered to Swine at 5 mg Ceftiofur Equivalents/kg Body Weight. Study Report: 1521N-60-11-377. April 2011 to November 2011.

b. Study Director: Steven P. Lesman; Pfizer Animal Health, Kalamazoo, MI

c. Study Design:

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

2) *Animals*: 24 healthy commercial breed swine (12 barrows, 12 gilts) weighing 15.8 to 23.6 kg at the beginning of the study.

3) *Experimental Design*: This study was designed as a two-period, two-treatment crossover pharmacokinetic study with a two-week washout time between study periods. In each of the two study periods, blood samples were collected from each animal before treatment administration, at 20 and 40 minutes, and at 1, 1.5, 2, 3, 4, 7, 10, 24, 48, 72, 96, 144, and 168 hours after treatment administration.

4) *Test Article Administration*: In each of the two 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 liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assay for desfuroylceftiofur acetamide (DCA). Pharmacokinetic (PK) parameters were determined for each animal individually in each period. General health observations of each animal were made once daily throughout the study. Injection sites were evaluated at 2, 24, and 48 hours after each injection.

d. Analysis: The plasma concentration data for total ceftiofur moiety (i.e., parent ceftiofur and its desfuroylceftiofur-related metabolites) were

analyzed using non-compartmental PK analysis with Watson (v 7.4 SP3, Thermo Fischer Scientific, Inc.). The time above 0.2 µg/mL was calculated in Microsoft Office Excel 2007 with the following equation:

$$T_{>0.2} = T_{last} + [\ln(0.2/C_{last})/\lambda_z]$$

where $T_{>0.2}$ is the time where drug concentrations are above the concentration of 0.2 µg/mL, T_{last} is the time to the last measured concentration exceeding 0.2 µg/mL, C_{last} is the last measured concentration exceeding 0.2 µg/mL, and λ_z is the slope of the terminal elimination phase based on the natural log of concentration.

The 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 (which translates into the ratio of the untransformed data) using the least squares (LS) means and their standard errors for $AUC_{0\text{-}LOQ}$ and C_{max}. The resulting CIs were exponentiated and expressed in a percent form. Geometric means were calculated by exponentiating the least squares.

e. Results: Summary statistics for pharmacokinetic parameters are shown in Table 1.

Table 1. Comparative treatment values (arithmetic mean ± standard deviation [SD]) for the plasma PK estimates of total ceftiofur (parent compound plus 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 as EXCENEL RTU EZ Sterile Suspension (test article).

PK parameter	EXCENEL RTU	EXCENEL RTU EZ
C_{max} (µg/mL)	18.2 ± 4.09	19.7 ± 3.39
$AUC_{0\text{-}LOQ}$ (µg*h/mL)	257 ± 57.1	263 ± 54.8
t_{max} (h)	1.5 ± 0.49	1.5 ± 0.73
$t_{1/2}$ (h)	20.0 ± 1.56	20.0 ± 1.82
$t_{>0.2}$ (h)	83.1 ± 10.3	82.5 ± 10.5

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 quantification of the assay
t_{max} - the time after initial injection to when C_{max} occurs
$t_{1/2}$ - the plasma half-life of the drug
$t_{>0.2}$ - the time plasma concentrations remain above 0.2 µg/mL

The standard bioequivalence (BE) criteria, based upon the exponentiated 90% confidence bounds about the ratio of treatment means, were met for the pivotal bioequivalence parameters, $AUC_{0\text{-}LOQ}$ and C_{max}, when each formulation was administered to swine IM at a dose rate of 2.27 mg CE/lb (5 mg CE/kg) BW (Table 2).

Bioequivalence of EXCENEL RTU EZ Sterile Suspension compared to EXCENEL RTU Sterile Suspension was determined using the bioequivalence criteria described in the Center for Veterinary Medicine's Guidance for

Industry #35, "Bioequivalence Guidance." $AUC_{0\text{-}LOQ}$ and C_{max} for EXCENEL RTU Sterile Suspension and EXCENEL RTU EZ Sterile Suspension were found to be bioequivalent (Table 2). The 90% CIs for the ratios of these parameters were contained within 80% to 125%.

Table 2. Back-transformed least squares means and 90% confidence interval (CI) for the two pivotal pharmacokinetic parameters, C_{max} and $AUC_{0\text{-}LOQ}$ in swine following an intramuscular (IM) administration of 2.27 mg CE/lb (5 mg CE/kg) BW, as either EXCENEL RTU Sterile Suspension (reference article) or as EXCENEL RTU EZ Sterile Suspension (test article).

PK Parameter	LS mean difference	90% CI	BE†
C_{max}	1.10	1.03 to 1.18	Yes
$AUC_{0\text{-}LOQ}$	1.03	0.99 to 1.06	Yes

† If the 90% CI of the LS mean difference is within the limits of 0.80 to 1.25, then the results support bioequivalence of treatment groups

f. Adverse Events: One animal that had received EXCENEL RTU Sterile Suspension (reference article) had a measurable swelling at 2 hours post-dose. The swelling resolved prior to the 24-hour observation period. No other injection site swellings were noted in this study.

Soft stools were noted in pigs from both treatment groups, starting on Day 9 of the study (Period 1). One animal with soft stools was removed from the study after the second treatment due to deteriorating body condition. There is no indication that the reformulated EXCENEL RTU EZ product has an increased risk of gastrointestinal disturbances when compared to EXCENEL RTU Sterile Suspension.

g. Conclusion: The reformulated EXCENEL RTU EZ Sterile Suspension was bioequivalent to EXCENEL RTU Sterile Suspension for $AUC_{0\text{-}t(last)}$ and C_{max} when administered by IM injection to swine at a dose rate of 5 mg CE/kg BW.

2. PK Study – Cattle (Intramuscular)

a. Title: Pharmacokinetic Comparison of EXCENEL RTU (Ceftiofur Hydrochloride) Sterile Suspension and Reformulated EXCENEL RTU-EZ Administered by Intramuscular Injection to Cattle at 2.2 mg Ceftiofur Equivalents/kg Body Weight. Study Report: 1532N-60-11-877. April 2011 to June 2011.

b. Study Director: Erin Ivey Weich, DVM, Southwest Bio-Labs

c. Study Design:

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

2) *Animals*: 24 healthy English Cross breed cattle (12 steers, 12 heifers) weighing 195.9 to 266.2 kg at the beginning of the study.

3) *Experimental Design*: This study was a two-period, two-treatment crossover PK study with a two-week washout time between study periods. In each of the two study periods, blood samples were collected from each animal before treatment administration, at 20 and 40 minutes, and at 1, 1.5, 2, 2.5, 3, 4, 7, 10, 24, 48, 72, 96, and 144 hours after treatment administration.

4) *Test Article Administration*: In each of the two study periods, each animal was administered either EXCENEL RTU Sterile Suspension (reference article) or EXCENEL RTU EZ Sterile Suspension (test article) as a single IM 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 LC-MS/MS assay for DCA. 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. Analysis: The concentrations of ceftiofur and desfuroylceftiofur-related metabolites in plasma were measured using a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assay for desfuroylceftiofur acetamide (DCA).

The log-transformed PK parameters were analyzed using a linear mixed model. The 90% CIs were constructed for the differences in the treatment means (which translates into the ratio of the untransformed data) using the LS means and their standard errors for $AUC_{0\text{-}LOQ}$ and C_{max}. The resulting CIs were exponentiated and expressed in a percent form. Geometric means were calculated by exponentiating the least square means.

e. Results: Summary statistics for PK parameters are shown in Table 3.

Table 3. Comparative treatment values (arithmetic mean ± SD) for the plasma PK estimates of total ceftiofur (parent compound plus desfuroylceftiofur metabolites) in cattle following an IM administration of 1 mg CE/lb (2.2 mg CE/kg) BW, as either EXCENEL RTU Sterile Suspension (reference article) or as EXCENEL RTU EZ Sterile Suspension (test article).

PK Parameter	EXCENEL RTU	EXCENEL RTU EZ
C_{max} (µg/mL)	8.58 ± 1.50	9.25 ± 1.73
$AUC_{0\text{-}LOQ}$ (µg*h/mL)	89.4 ± 13.8	88.5 ± 17.0
t_{max} (h)	1.71 ± 0.71	1.73 ± 0.49
$t_{1/2}$ (h)	32.0 ± 8.48	29.3 ± 7.35
$t_{>0.2}$ (h)	42.2 ± 6.20	41.2 ± 6.11

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 quantification of the assay
t_{max} - the time after initial injection to when C_{max} occurs
$t_{1/2}$ - the plasma half-life of the drug
$t_{>0.2}$ - the time plasma concentrations remain above 0.2 µg/mL

$AUC_{0\text{-}LOQ}$ and C_{max} for EXCENEL RTU Sterile Suspension and EXCENEL RTU EZ Sterile Suspension were found to be bioequivalent (Table 4). The 90% CIs for the ratios of these parameters were contained within 80% to 125%.

Table 4. Back-transformed LS means and 90% CI for the two pivotal PK parameters, C_{max} and $AUC_{0\text{-}LOQ}$ in cattle following an IM administration of 1 mg CE/lb (2.2 mg CE/kg) BW, as either EXCENEL RTU Sterile Suspension (reference article) or as EXCENEL RTU EZ Sterile Suspension (test article).

PK parameter	LS mean difference	90% CI
C_{max}	1.08	1.00 to 1.16
$AUC_{0\text{-}LOQ}$	0.984	0.94 to 1.03

f. Adverse Events: Except for injection site reactions, no other treatment-related adverse reactions were reported. At one day post-injection, one EXCENEL RTU-treated calf had a palpable, visible injection site swelling. Five other calves (three reformulated EXCENEL RTU EZ-treated calves and two EXCENEL RTU-treated calves) had palpable, non-visible injection site swellings at one day post-injection. All injection site swelling resolved by 3 days post-injection.

g. Conclusion: The reformulated EXCENEL RTU EZ Sterile Suspension was bioequivalent to EXCENEL RTU Sterile Suspension for $AUC_{0\text{-}LOQ}$ and C_{max} when administered by IM injection to cattle at a dose rate of 1 mg CE/lb BW.

3. PK Study – Cattle (Subcutaneous)

a. Title: Pharmacokinetic Comparison of EXCENEL RTU (Ceftiofur Hydrochloride) Sterile Suspension and Reformulated EXCENEL RTU-EZ Administered by Subcutaneous Injection to Cattle at 2.2 mg Ceftiofur

Equivalents/kg Body Weight. Study Report: 1532N-60-11-878. April 2011 to June 2011.

b. Study Director: Erin Ivey Weich, DVM, Southwest Bio-Labs

c. Study Design:

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

2) *Animals*: 24 healthy English cross breed cattle (12 steers, 12 heifers) weighing 179.1 to 256.2 kg at the beginning of the study.

3) *Experimental Design*: This study was a two-period, two-treatment crossover PK study with a two-week washout time between study periods. In each of the two study periods, blood samples were collected from each animal before treatment administration, at 20 and 40 minutes, and at 1, 1.5, 2, 2.5, 3, 4, 7, 10, 24, 48, 72, 96, 144, and 168 hours after treatment administration.

4) *Test Article Administration*: In each of the two 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 LC-MS/MS assay for DCA. 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. Analysis: The concentrations of ceftiofur and desfuroylceftiofur-related metabolites in plasma were measured using a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assay for desfuroylceftiofur acetamide (DCA).

The log-transformed PK parameters were analyzed using a linear mixed model. The 90% CIs were constructed for the differences in the treatment means (which translates into the ratio of the untransformed data) using the LS means and their standard errors for $AUC_{0\text{-}LOQ}$ and C_{max}. The resulting CIs were exponentiated and expressed in a percent form. Geometric means were calculated by exponentiating the least square means.

e. Results: Summary statistics for PK parameters are shown in Table 5.

Table 5. Comparative treatment values (arithmetic mean ± SD) for the plasma PK estimates of total ceftiofur (parent compound plus 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 as EXCENEL RTU EZ Sterile Suspension (test article).

PK parameter	EXCENEL RTU	EXCENEL RTU EZ
C_{max} (µg/mL)	8.40 ± 1.42	9.19 ± 1.65
$AUC_{0\text{-}LOQ}$ (µg*h/mL)	86.7 ± 20.3	91.0 ± 20.2
t_{max} (h)	2.08 ± 0.670	2.25 ± 0.872
$t_{1/2}$ (h)	34.0 ± 8.52	32.9 ± 6.91
$t_{>0.2}$ (h)	40.5 ± 5.28	41.5 ± 7.32

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 quantification of the assay
t_{max} - the time after initial injection to when C_{max} occurs
$t_{1/2}$ - the plasma half-life of the drug
$t_{>0.2}$ - the time plasma concentrations remain above 0.2 µg/mL

$AUC_{0\text{-}LOQ}$ and C_{max} for EXCENEL RTU Sterile Suspension and EXCENEL RTU EZ Sterile Suspension were found to be bioequivalent (Table 6). The 90% CIs for the ratios of these parameters were contained within 80% to 125%.

Table 6. Back-transformed LS means and 90% CI for the two pivotal PK parameters, C_{max} and $AUC_{0\text{-}LOQ}$ 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 as EXCENEL RTU EZ Sterile Suspension (test article).

PK parameter	LS mean difference	90% CI
C_{max}	1.09	1.02 to 1.18
$AUC_{0\text{-}LOQ}$	1.06	0.99 to 1.13

f. Adverse Events: Except for injection site reactions, no other treatment-related adverse reactions were reported. One reformulated EXCENEL RTU EZ-treated calf had redness and bruising at the injection site, which resolved by Day 3. Ten EXCENEL RTU-treated calves had palpable, either visible or non-visible injection site swellings at one day post-injection; with the exception of one calf, all swellings were resolved by 7 days post-injection. Ten reformulated EXCENEL RTU EZ-treated calves had palpable, either visible or non-visible injection site swellings at one day post-injection; swelling was still present on 7 days post-injection in three calves.

g. Conclusion: The reformulated EXCENEL RTU EZ Sterile Suspension was bioequivalent to EXCENEL RTU Sterile Suspension for $AUC_{0\text{-}LOQ}$ and C_{max} when administered by SC injection to cattle at a dose rate of 1 mg CE/lb BW.

III. TARGET ANIMAL SAFETY:

A. Systemic Safety

1. Swine

Evaluation of target animal safety in swine was based on a PK comparison between the reformulated EXCENEL RTU EZ Sterile Suspension and EXCENEL RTU Sterile Suspension. Ceftiofur administered to swine as the reformulated EXCENEL RTU EZ Sterile Suspension at a dose of 5 mg CE/kg BW by IM injection was demonstrated to be bioequivalent to a corresponding IM injection of EXCENEL RTU Sterile Suspension based upon comparability of their respective $AUC_{0\text{-}LOQ}$ and C_{max} values (see EFFECTIVENESS section above). Because of the demonstrated blood-level bioequivalence, this study confirms the systemic safety of the reformulated EXCENEL RTU EZ Sterile Suspension in swine when administered by IM injection at a dose of 5 mg CE/kg BW for three consecutive days.

The systemic safety of EXCENEL RTU Sterile Suspension in swine was previously demonstrated using a comparison between the total and peak systemic exposure of a single IM injection of 5 mg CE/kg BW EXCENEL RTU Sterile Suspension to a single IM injection of 5 mg CE/kg BW ceftiofur sodium (as NAXCEL Sterile Powder, NADA 140-338). The FOI summary for the original approval of NADA 140-890 dated April 1996, contains a summary of this comparison. The FOI Summary for the approval of NAXCEL Sterile Powder dated August 4, 1992, contains the results of the systemic target animal safety study confirming the safety of ceftiofur sodium when administered by IM injection at a dose of 5 mg CE/kg BW to healthy feeder pigs for three consecutive days.

2. Cattle

Evaluation of target animal safety in cattle was based on two PK studies comparing the reformulated EXCENEL RTU EZ Sterile Suspension and EXCENEL RTU Sterile Suspension (one study comparing IM administration and one study comparing SC administration). In both studies, ceftiofur, when administered to cattle at a dose of 2.2 mg CE/kg BW of the reformulated EXCENEL RTU EZ Sterile Suspension, was demonstrated to be bioequivalent to a 2.2 mg CE/kg BW dose of EXCENEL RTU Sterile Suspension (see EFFECTIVENESS section above). Because of the demonstrated blood-level bioequivalence, these studies confirm systemic safety of the reformulated EXCENEL RTU EZ Sterile Suspension when administered either IM or SC at a dose of 2.2 mg CE/kg BW for five consecutive days.

The systemic safety of EXCENEL RTU (ceftiofur hydrochloride) Sterile Suspension in cattle was previously demonstrated using a comparison between the total and peak systemic exposure of EXCENEL RTU Sterile Suspension (administered as a single IM injection) and a single 2.2 mg CE/kg BW IM dose of ceftiofur sodium (as NAXCEL Sterile Powder, NADA 140-338). The FOI summary for NADA 140-890 dated July 26, 1998, contains a summary of this comparison. For the same supplemental approval, administration of a single dose of EXCENEL RTU Sterile Suspension either by IM or SC injection resulted in comparable total and peak systemic exposure in

cattle. The FOI Summary for the approval of NAXCEL Sterile Powder dated April 5, 1990, contains results of the systemic target animal safety study confirming the safety of ceftiofur sodium when administered by IM injection at a dose of 2.2 mg CE/kg BW for five consecutive days.

B. Injection Site Safety - Swine

1. Title: "Injection Site Tolerance of a Revised Formulation of EXCENEL RTU EZ Sterile Suspension in Swine." Study Number 1423N-60-11-374. April 2011 to March 2012.

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

3. Study Design:

   a. *Objective:* To characterize the injection site tolerance of a revised formulation of EXCENEL RTU EZ Sterile Suspension when administered IM to growing pigs at the labeled maximum dose volume once daily for three consecutive days.

   b. *Test Animals:* Sixteen healthy, commercial crossbred, castrated male and female swine, weighing 58 to 72.5 lb at arrival, were enrolled in the study. Animals were housed individually in pens, and were randomly assigned to pen, treatment group, and necropsy day.

   c. *Test Article Administration:* The test article was ceftiofur hydrochloride as the reformulated EXCENEL RTU EZ Sterile Suspension (50 mg CE/mL). The control article was sterile saline injectable solution. Pigs were injected with 5 mL or 3 mg CE/kg BE (whichever resulted in a higher volume per injection site) once daily for three consecutive days. Each injection was given IM in a separate site in the neck.

   d. *Measurements and Observations:* General health observations were conducted at least once daily from Day -14 to the last day of the study. Clinical observations were conducted at least once daily on Days -14, -1, 0, 1, 2, 7, 14, 28, and 42. Injection site observations were conducted on Day -14 and once daily from Day -1 to the last day of the study. Injection sites were evaluated for the presence of erythema, heat, sensitivity, firmness, necrosis, and drainage by visual observation and palpation, and swelling dimensions were measured. Animals were euthanized on Day 7, 14, 28, or 42 (two saline-treated pigs and two EXCENEL RTU EZ-treated pigs at each time point).

4. Statistical Analysis: None.

5. Results:

   a. *General Health and Clinical Observations:* There were no abnormal clinical observations or general health observations related to test article administration. All treated animals completed the study.

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

and swelling were observed in one saline-treated pig and four EXCENEL RTU EZ-treated pigs. No swelling was observed at any injection site in any animal after Day 5 (three days after the last injection).

c. *Gross Necropsy and Histopathology:* Discoloration of one or more injection sites were observed in both EXCENEL RTU EZ-treated pigs necropsied on Day 7, and in both EXCENEL RTU EZ-treated pigs necropsied on Day 14. The discoloration was described as red, dark red and tan mottled, or tan. No grossly visible changes were observed for saline-treated pigs (any day), or for EXCENEL RTU EZ-treated pigs necropsied on Days 28 and 42.

Microscopic findings consistent with inflammation were seen in 5 injection sites in saline-treated pigs and 12 injection sites in EXCENEL RTU EZ-treated pigs. No test article-related microscopic findings were observed in pigs necropsied on Day 42.

6. Conclusion: Administration of ceftiofur hydrochloride as a revised formulation of EXCENEL RTU EZ Sterile Suspension at 5 mL or 3 mg CE/kg BE (whichever resulted in a higher volume) per injection site by IM injection once daily for three consecutive days was well tolerated in growing pigs. Injection site irritation (as evidenced by grossly visible lesions at necropsy) extended beyond the assigned pre-slaughter withdrawal period.

C. Injection Site Safety - Cattle

1. Title: "Injection Site Tolerance of a Revised Formulation of EXCENEL RTU EZ Sterile Suspension in Cattle." Study Number 1433N-60-11-866. April 2011 to March 2012.

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

3. Study Design:

a. *Objective:* To characterize the injection site tolerance of a revised formulation of EXCENEL RTU EZ Sterile Suspension when administered IM or SC to cattle at the labeled maximum dose volume once daily for five consecutive days.

b. *Test Animals:* Thirty-two healthy, castrated male, crossbred beef cattle, weighing 248 to 512 kg at arrival, were enrolled in the study. Animals were housed in pens, and were randomly assigned to pen, treatment group, and necropsy day.

c. *Test Article Administration:* The test article was ceftiofur hydrochloride as the reformulated EXCENEL RTU EZ Sterile Suspension (50 mg CE/mL). The control article was sterile saline injectable solution. Cattle were injected with their assigned treatment (eight animals in each group - saline SC, saline IM, EXCENEL RTU EZ [SC], or EXCENEL RTU EZ [IM]) at 15 mL once daily for five consecutive days (Days 0, 1, 2, 3, and 4). Each injection was given IM or SC in a separate site in the neck.

d. *Measurements and Observations:* General health observations were conducted at least once daily from Day -14 to the last day of the study.

Clinical observations were conducted at least once on Days -14, -1, 0 through 4, 7, 14, 28, and 42. Injection site observations were conducted on Day -14 and once daily from Day -1 to the last day of the study. Injection sites were evaluated for the presence of erythema, heat, sensitivity, firmness, necrosis, and drainage by visual observation and palpation, and swelling dimensions were measured. Animals were euthanized on Day 7, 14, 28, or 42 (two calves from each treatment group at each time point).

4. Statistical Analysis: None.

5. Results:

   a. *General Health and Clinical Observations:* There were no abnormal clinical observations or general health observations related to test article administration. All treated animals completed the study.

   b. *Injection Site Observations:* Erythema, heat, sensitivity, necrosis, and drainage were not observed at any injection site on any study day. Injection site reactions consisted of swelling and firmness (generally associated with swelling) at the injection sites. Swelling was observed in 4/1030 (0.4%) of IM injection site observations and in 606/1029 (58.9%) of SC injection site observations.

   c. *Gross Necropsy and Histopathology*: Gross necropsy observations revealed mild local inflammation at IM sites and mild to moderate inflammation at SC sites. Altered tissue (changes in color or consistency, and/or a nodular surface appearance) was grossly visible in 6 of 10 EXCENEL RTU EZ SC injection sites (and 0 of 10 saline SC injection sites) and 2 of 10 EXCENEL RTU EZ IM injection sites (and 2 of 10 saline IM injection sites) on Day 42.

   Microscopic findings consistent with resolving inflammation were visible in 9 of 10 EXCENEL RTU EZ SC injection sites (and 2 of 10 saline SC injection sites) and 5 of 10 EXCENEL RTU EZ IM injection sites (and 2 of 10 saline IM injection sites) on Day 42.

6. Conclusion: Administration of ceftiofur hydrochloride as a revised formulation of EXCENEL RTU EZ Sterile Suspension at 15 mL per injection site by SC or IM injection once daily for five consecutive days was well tolerated in cattle. Injection site irritation (as evidenced by grossly visible lesions at necropsy) extended beyond the assigned pre-slaughter withdrawal period.

IV. HUMAN FOOD SAFETY:

A. Antimicrobial Resistance:

The impact of the proposed changes in the formulation of EXCENEL RTU EZ Sterile Suspension (ceftiofur hydrochloride) to increase ease of resuspension and syringing on microbial food safety (antimicrobial resistance) was carefully considered by the Agency. The Agency determined that this supplemental action should not significantly impact public health with respect to antimicrobial resistance. This supplement includes no changes in dosage, route of administration, or duration of use, the changes in formulation are minor to allow for ease in use, and bioequivalence was demonstrated; therefore, further

evaluation of microbial food safety (antimicrobial resistance) was not necessary at this time.

B. Impact of Residues on Human Intestinal Flora:

1. Determination of the need for establishing a microbiological ADI (mADI)

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

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

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

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

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

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

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

Table 7. Study Title - "Anaerobic Degradation of Ceftiofur by Human GI Tract Microflora in Human Fecal Slurries"

Study No.	788-7926-I-REH-93-001
Study Period	Experimental work performed between 1993-1994 (final report was dated January 26, 1994)
Study Director	Susan Kotarski, Ph.D.
Study Location	Veterinary Research & Development, Pharmacia & Upjohn Co., Kalamazoo, MI

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

The study was conducted in three phases:

1) Phase I determined whether rapid loss of biological activity occurs during anaerobic incubation of ceftiofur (500 µg/mL) with fecal slurries (up to 24 hours) from 8 human volunteers. Loss of microbiological activity was

measured by a microbiological cylinder plate assay with a bacterial strain of *Micrococcus luteus*.

2) Phase II determined whether the microbiological activity of ceftiofur was stable in the fecal slurry. Fresh and autoclaved fecal samples were fortified with 0 and 833 µg/mL of ceftiofur, and incubated for 0 or 4 hours.

3) Phase III included a series of experiments designed to study the capacity of inactivation of ceftiofur in buffer-diluted fecal slurries. 500 µg/mL of ceftiofur were added to different dilutions of slurries and incubated for 0, 1, 2, and 4 hours.

Results and Conclusions: The three-phase study revealed the following:

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

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

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

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

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

Yes, based on results from the study described above, it was concluded that ceftiofur residues in feces are rapidly inactivated, and biologically active residues were very low. Ceftiofur residues would not produce changes in human intestinal flora. Therefore, testing of either endpoint of concern - colonization barrier disruption or resistance development - is not needed.

2. Determination of the final mADI

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

Final conclusion: Due to effective inactivation, under the proposed conditions of use, the amount of microbiologically active residues reaching the human colon is negligible, and would most likely not cause adverse effects on the intestinal flora of consumers.

C. Toxicology:

Reassessment of the toxicological acceptable daily intake (ADI) or acceptable single-dose intake (ASDI) was not needed for this supplemental approval. The FOI Summaries for the original approval of NADA 140-338 dated January 25, 1988, NADA 140-890 dated April 26, 1996, NADA 141-209 dated September 5, 2003, and NADA 141-235 dated June 18, 2004, contain summaries of all toxicology studies and information.

D. Assignment of the Final ADI:

The final ADI is the toxicological ADI of 0.03 mg/kg BW/day derived from 90-day oral studies in dogs and rats. The ASDI is 0.83 mg/kg BW determined from challenges of injection site muscle extract.

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

The safe concentration of total ceftiofur residues in each edible tissue of swine and cattle is 4.40 ppm for muscle, 13.20 ppm for liver, 26.40 ppm for kidney, 26.40 ppm for fat, 0.320 ppm for milk (cattle) and 166 ppm for the injection sites.

F. Residue Chemistry:

1. Summary of Residue Chemistry Studies

a. Total Residue and Metabolism Studies

CVM did not require total residue and metabolism studies for this supplemental approval. The FOI Summaries for the original approval of NADA 140-338 dated January 25, 1988, and the original approval of NADA 140-890 dated April 26, 1996, contain summaries of total residue and metabolism studies for ceftiofur hydrochloride in swine and cattle.

b. Comparative Metabolism Study

CVM did not require comparative metabolism studies for this supplemental approval. The FOI Summaries for the original approval of NADA 140-338 dated January 25, 1988, and the original approval of NADA 140-890 dated

April 26, 1996, contain summaries of comparative metabolism studies for ceftiofur hydrochloride in swine and cattle.

c. Tissue Residue Depletion Studies

1) Swine

Study Title – "Depletion of Ceftiofur and Desfuroylceftiofur-Related Residues in Kidney and Injection Site Tissues Following Three Daily Intramuscular Administrations of EXCENEL RTU-EZ Reformulation to Pigs at a Dose Rate of 5 mg/kg Bodyweight" Study No. 1521N-12-11-373

Study Director: Anne Larvor, Ph.D.

Study Location: Avogadro, Parc de Genibrat, France

Animals Species: Crossbred swine

Number of Animals/Sex: 24, 12 castrated males, 12 females (no control animals)

Weights of Animals: 54 kg to 67.2 kg

Health Status: Healthy

Route of Administration: Intramuscular (IM) injection

Dose Rate: 5.0 mg/kg body weight (BW)

Duration of Dosing: 3 consecutive days

The concentration of ceftiofur and desfuroylceftiofur-related residues, measured as the marker residue, desfuroylceftiofur acetamide (DCA), was determined in the kidney (target tissue) of treated swine. Samples of kidney were assayed by a validated HPLC-UV procedure. These data, in tabular form, are presented in Table 8.

Table 8. Mean residue concentrations in kidney tissue samples (Study No. 1521N-12-11-373).

Withdrawal Time (hours)	Mean Ceftiofur Residues in Kidney (ppb ± S.D.)
10 to 12	4,866 ± 408 (3,702 ± 2,047)#
24	1,386 ± 277
36	844* ± 302
48	340 ± 94
72	166* ± 28
120	<LOQ
LOQ (ppb)	100
LOD (ppb)	50

includes one sample measured at 210 ppb that was not included in the tissue withdrawal period calculation

* indicates one sample measured below LOQ and one sample below LOD

2) Cattle

Study Title – "Determination of Ceftiofur Concentrations in Tissues of Beef Cattle Following Five Intramuscular Injections of RTU-EZ Reformulation at a Dose of 2.2 mg Ceftiofur/kg Body Weight" Study No. 1531N-03-10-850

Study Director: Sian Roberts

Study Location:
In-life Facility: Charles River, Edinburgh, United Kingdom
Analytical Facility: Covance Laboratories, North Yorkshire, United Kingdom

Animals Species: Cross- and purebred cattle

Number of Animals/Sex: 28, 14 castrated males, 14 females (no control animals)

Weights of Animals: 258 kg to 362 kg

Health Status: Healthy

Route of Administration: Intramuscular (IM) injection

Dose Rate: 2.2 mg/kg body weight (BW)

Duration of Dosing: 5 consecutive days

The concentration of ceftiofur and desfuroylceftiofur-related residues, measured as the marker residue, desfuroylceftiofur acetamide (DCA), was determined in the kidney (target tissue) and injection site muscle of treated cattle. Samples of kidney and injection site muscle were

assayed by a validated HPLC-UV procedure. These data, in tabular form, are presented in Table 9.

Study Title – "Determination of Ceftiofur Concentrations in Tissues of Beef Cattle Following Five Subcutaneous Injections of RTU-EZ Reformulation at a Dose of 2.2 mg Ceftiofur/kg Body Weight" Study No. 1531N-03-10-851

Study Director: Amanda Walker

Study Location:
In-life Facility: Charles River, Edinburgh, United Kingdom
Analytical Facility: Covance Laboratories, North Yorkshire, United Kingdom

Animals Species: Cross- and purebred cattle

Number of Animals/Sex: 28, 14 castrated males, 14 females (no control animals)

Weights of Animals: 250 kg to 342 kg

Health Status: Healthy

Route of Administration: Subcutaneous (SC) injection

Dose Rate: 2.2 mg/kg body weight (BW)

Duration of Dosing: 5 consecutive days

The concentration of ceftiofur and desfuroylceftiofur-related residues, measured as the marker residue, desfuroylceftiofur acetamide (DCA), was determined in the kidney (target tissue), injection site muscle, and surrounding injection site muscle of treated cattle. Samples of kidney and injection site muscle were assayed by a validated HPLC-UV procedure. These data, in tabular form, are presented in Table 10.

Table 9. Mean residue concentrations in kidney, injection site muscle, and surrounding injection site muscle tissue samples following five intramuscular injections of RTU-EZ reformulation at a dose of 2.2 mg ceftiofur/kg body weight (Study No. 1531N-03-10-850)

Withdrawal Time (hours)	Mean Ceftiofur Residues in Kidney (ppb ± S.D.)	Mean Ceftiofur Residues in Injection Site Muscle (ppb ± S.D.)	Mean Ceftiofur Residues in Surrounding Injection Site Muscle (ppb ± S.D.)
10 to 12	3,552 ± 412	16,478 ± 10,944	2,598 ± 885
24	1,684 ± 336	2,430 ± 1,828	1,699 ± 508
48	453 ± 163	1,313 ± 657	293 ± 193
72	193 ± 47	943 ± 702	272* ± 80

Withdrawal Time (hours)	Mean Ceftiofur Residues in Kidney (ppb ± S.D.)	Mean Ceftiofur Residues in Injection Site Muscle (ppb ± S.D.)	Mean Ceftiofur Residues in Surrounding Injection Site Muscle (ppb ± S.D.)
96	127 ± 50	143 ± 84	78* ± 28
120	NA	NA	NA
168	NA	NA	NA
LOQ (ppb)	320	500	500
LOD (ppb)	33	33	33

* one sample measured below LOD
NA samples not analyzed

Table 10. Mean residue concentrations in kidney, injection site muscle, and surrounding injection site muscle tissue samples following five subcutaneous injections of RTU-EZ reformulation at a dose of 2.2 mg ceftiofur/kg body weight (Study No. 1531N-03-10-851).

Withdrawal Time (hours)	Mean Ceftiofur Residues in Kidney (ppb ± S.D.)	Mean Ceftiofur Residues in Injection Site Muscle (ppb ± S.D.)	Mean Ceftiofur Residues in Surrounding Injection Site Muscle (ppb ± S.D.)
10 to 12	5,380 ± 785	21,577 ± 18,241	615 ± 91
24	2,539 ± 1,075	3,796 ± 844	508 ± 270
48	870 ± 210	1,193 ± 554	169 ± 32
72	554 ± 203	654 ± 199	96 ± 20
96	239 ± 68	496 ± 125	62 ± 13
120	212 ± 76	372 ± 193	83 ± 51
168	NA	NA	NA
LOQ (ppb)	320	500	500
LOD (ppb)	33	33	33

NA samples not analyzed

2. Target Tissue and Marker Residue

No reassessment of target tissue and marker residue was needed for this supplemental approval. The FOI Summaries for the original approval of NADA 140-338 dated January 25, 1988, and the original approval of NADA 140-890 dated April 26, 1996, contain summaries of information used to determine the target tissue and marker residue for swine and cattle.

3. Tolerance(s)

Swine: The tolerances for desfuroylceftiofur (the marker residue) are 0.25 ppm in kidney, 3 ppm in liver, and 2 ppm in muscle (21 CFR 556.113).

Cattle: The tolerances for desfuroylceftiofur (the marker residue) are 0.4 ppm in kidney, 2 ppm in liver, 1 ppm in muscle, and 0.1 ppm in milk (21 CFR 556.113).

4. Withdrawal Period

Swine: The kidney residue depletion data (Section F1c, above) were analyzed using a statistical tolerance limit algorithm that determines the upper tolerance limit for the 99th percentile of the population with 95% confidence. The data support the assignment of a 3-day withdrawal period. However, at the request of the firm, a 4-day withdrawal period is assigned.

Cattle: The kidney residue depletion data (Section F1c, above) were analyzed using a statistical tolerance limit algorithm that determines the upper tolerance limit for the 99th percentile of the population with 95% confidence. The data support the assignment of a 3-day and 4-day withdrawal period for the intramuscular injection product and subcutaneous injection product, respectively. However, at the request of the firm, a 4-day withdrawal period is assigned to ceftiofur hydrochloride, in the newly reformulated EXCENEL RTU EZ Sterile Suspension, when administered by either the IM or SC routes of administration.

G. Analytical Method for Residues:

The FOI Summary for the original approval of NADA 141-288 dated July 1, 2008, contains the analytical method summaries for ceftiofur hydrochloride in swine and cattle.

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) or to report any adverse event please call 1-888-963-8471.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

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, 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 species treated with EXCENEL RTU EZ 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)(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 reformulated product for use in swine and cattle, addition of a new route of administration (intramuscular injection) in cattle, change of withdrawal period in cattle, and a 250 mL vial size for which this supplement is approved.

C. Supplemental Applications:

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

D. Patent Information:

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