FREEDOM OF INFORMATION SUMMARY

EXCENEL® Sterile Suspension

(ceftiofur hydrochloride)

"…for the treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis* and *Streptococcus suis* Type 2."

ORIGINAL NEW ANIMAL DRUG APPLICATION

Sponsored by:

THE UPJOHN COMPANY

April 1996

Table of Contents

I. GENERAL INFORMATION

NADA Number: 140-890

Sponsor: The Upjohn Company
7000 Portage Road
Kalamazoo, Michigan, 49001

Accepted Name: ceftiofur hydrochloride sterile suspension

Trade Name: EXCENEL® Sterile Suspension*

Marketing Status: This is a prescription product and will include the caution statement as follows: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

II. INDICATIONS FOR USE

EXCENEL® Sterile Suspension is indicated for the treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis* and *Streptococcus suis* Type 2.

*EXCENEL® Sterile Suspension contains the hydrochloride salt of ceftiofur, which is the active component of the approved product, NAXCEL® Sterile Powder (ceftiofur sodium). Indications for the use of EXCENEL® Sterile Suspension in swine are identical to those of NAXCEL® Sterile Powder, and the dose range for EXCENEL® Sterile Suspension is the same as the dose range recommended for NAXCEL® Sterile Powder. Ceftiofur administered as either salt, sodium or hydrochloride is rapidly metabolized to desfuroylceftiofur, the principal active moiety. The hydrochloride salt formulation is a sterile suspension. The sodium salt formulation requires reconstitution prior to use.

Only data unique to the hydrochloride salt formulation or data which addresses residues in edible tissues, bioavailability, clinical efficacy and tissue tolerance are included in this summary. Other relevant data are included in the NAXCEL® Sterile Powder Freedom of Information (FOI) Summary (NADA 140-338, approved by FDA August 1992) for swine respiratory disease and in the approval of NAXCEL® Sterile Powder for Bovine Respiratory Disease and associated FOI and FOI supplements (initial approval January 1988 with supplements January 1990, June 1992, and August 1993).

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

A. *Dosage Form:* EXCENEL® Sterile Suspension is available in 100-mL glass vials. Each mL contains ceftiofur hydrochloride equivalent to 50 mg ceftiofur.

EXCENEL® Sterile Suspension should be stored at controlled room temperature (15 to 30 °C or 59 to 86 °F). Protect from freezing. Shake well before using.

B. *Route of Administration:* EXCENEL® Sterile Suspension should be administered by intramuscular injection.

C. *Approved Dose Range:* EXCENEL® Sterile Suspension should be administered to swine at a dosage of 1.36 to 2.27 mg ceftiofur/lb (3.0 to 5.0 mg/kg) body weight (1 mL of sterile suspension per 22 to 37 lb (10 to 17 kg) body weight). Treatment should be repeated at 24-hour intervals for a total of 3 consecutive days.

IV. EFFECTIVENESS

A. Dose Determination

1. Overview of Dose Determination:

Ceftiofur, administered as either the hydrochloride or sodium salt, is rapidly metabolized to desfuroylceftiofur, the primary metabolite and principal active moiety for both salts. The similar metabolism of both salts and the 1992 supplemental approval of ceftiofur sodium (NAXCEL® Sterile Powder, NADA 140-338) for swine bacterial respiratory disease are the basis for dose determination of ceftiofur hydrochloride using swine plasma pharmacokinetic (PK) data and *in vitro* susceptibility data for bacteria isolated from cases of swine respiratory disease.

An initial PK study characterized the concentration of ceftiofur and desfuroylceftiofur metabolites in swine plasma over the dosing interval established for ceftiofur sodium (24 hours) when administered at 1.36 mg ceftiofur equivalents/lb (3.0 mg/kg) body weight. These data were compared to the minimum inhibitory concentrations (MIC) for the swine pathogens for NAXCEL® Sterile Powder (ceftiofur sodium), *Pasteurella multocida, Actinobacillus pleuropneumoniae, Salmonella choleraesuis,* and *Streptococcus suis* Type 2.

In a comparative bioavailability PK study, ceftiofur hydrochloride sterile suspension (EXCENEL® Sterile Suspension) demonstrated equivalent relative bioavailability to, and provided therapeutic concentrations for at least as long as, ceftiofur sodium sterile powder (NAXCEL® Sterile Powder) when each product was administered intramuscularly at the upper end of the label dose range [2.27 mg ceftiofur equivalents/lb (5.0 mg/kg) body weight]. Administration of either salt resulted in similar plasma concentrations of ceftiofur and desfuroylceftiofur metabolites at 24 hours, which corresponds to the dosing interval.

2. Plasma Disposition and Pharmacokinetics Study: TR 796-7926-91-002. Determination of Pharmacokinetic Parameters of Ceftiofur Given at 3 mg/kg to Pigs; A. Banting, A. Mignot, M.A. LeFebvre, L. Millerioux, and M.J. Douin.

   a. Purpose: The purpose of this study was to determine the pharmacokinetics of ceftiofur and desfuroylceftiofur metabolites after a single intramuscular (IM) or intravenous (IV) injection of ceftiofur as ceftiofur sodium at 1.36 mg ceftiofur equivalents/lb (3.0 mg/kg) body weight and after daily intramuscular injections of ceftiofur sodium at 1.36 mg ceftiofur equivalents/lb body weight for 3 days. This pivotal study serves as part of the requirement for dose determination.

   b. Investigators: A. Banting, A. Mignot, M.A. LeFebvre, L. Millerioux, and M.J. Douin, Cephac Research Center, Saint Benoit, France.

c. General Design

1) Experimental Animals: Three male and three female pigs, weighing approximately 20 kg.

2) Dosage Form: Ceftiofur sodium sterile powder reconstituted with sterile water. This dosage form is the approved and marketed product, NAXCEL® Sterile Powder for Injection (Lot #19532).

3) Experimental Design: Pigs were randomly divided into two groups of three animals (Groups A and B).

- Sequence 1: Group A received a single intravenous (IV) injection of 1.36 mg ceftiofur equivalents/lb (3.0 mg/kg) body weight. Group B received single intramuscular (IM) injection of 1.36 mg ceftiofur equivalents/lb body weight.

- Sequence 2: Following a 7-day washout period, Group B received drug administered IV and Group A received drug administered IM.

- Sequence 3: Following a second 7-day washout period, the 3-day multiple IM administration phase was initiated in all six pigs.

4) Sampling: Following single administration (IV or IM), blood samples were taken before dosing and at 0.25, 0.5, 1, 2, 4, 8, 16, 24, 36, 48, 60 and 72 hours. Additional samples at 2, 5, 10, and 90 minutes were collected after IV administration. For the multiple IM dosing study, blood samples were taken before dosing and at 0.5, 1, 2, 4, 8, 16, 24 and 48 hours after each injection.

5) Assay Method: HPLC for ceftiofur and desfuroylceftiofur metabolites, LOD 0.1 mg/mL. Each sample was analyzed with a single determination.

6) Pharmacokinetic Analysis Method: Main pharmacokinetic parameters were calculated according to standard methods using the SIPHER program.

d. Results:

Mean (± standard deviation) for the pharmacokinetic parameters after multiple intramuscular administration (3 administrations at 24-hour intervals) of 1.36 mg ceftiofur equivalents/lb (3 mg/kg) body weight are presented in Figure 4.1 and Table 4.1. Mean (± SD) for a single administration of 1.36 mg ceftiofur equivalents/lb (3.0 mg/kg) body weight are also presented in Table 4.1. After the single administration, C_{MAX} was 19.23 (±7.88) μg/mL and $AUC_{0\text{-}LOD}$ was 198.3 (±119.8) μg•h/mL. Mean plasma ceftiofur and desfuroylceftiofur metabolite concentrations at 24 hours after the single IM dose (the dosing interval) were 2.02 (±1.53) μg/mL.

Figure 4.1. Plasma concentration of ceftiofur and desfuroylceftiofur metabolites in swine following repeated intramuscularly administration at 1.36 mg ceftiofur equivalents/lb (3.0 mg/kg) body weight. The higher of the two horizontal lines on the graph represents the 1.0 µg/mL MIC_{90} value for *Salmonella choleraesuis,* whereas the lower line represents the 0.0078 µg/mL MIC_{90} value for *Actinobacillus pleuropneumoniae*.

Table 4.1. Mean (SD) ceftiofur and desfuroylceftiofur metabolite pharmacokinetic parameters after a single intramuscular (IM) or multiple-day (3) IM administrations of ceftiofur sodium at 1.36 mg ceftiofur equivalents/lb (3.0 mg/kg) body weight to pigs.

			Multiple Day IM	
	Single IM	Day 1	Day 2	Day 3
C_{MAX} (µg/mL)	19.23 (7.88)	13.97 (2.45)	9.47 (3.29)	11.04 (2.85)
t_{MAX} (hr)	0.58 (0.20)	0.67 (0.26)	2.33 (0.82)	1.08 (0.49)
$AUC_{0\text{-}LOD}$ (µg•h/mL)	198.3 (119.8)	ND	ND	ND
$AUC_{0\text{-}\infty}$ (µg•h/mL)	203.16 (121.06)	ND	ND	ND
$t_{1/2}$ (hr)	13.46 (2.61)	ND	ND	ND
MRT (hr)	15.68 (2.63)	ND	ND	ND
C_{24} (µg/mL)	2.02 (1.53)	1.28 (0.47)	1.58 (0.60)	1.29 (0.40)
$AUC_{0\text{-}24}$ (µg•h/mL)	ND	97.32 (20.28)	93.52 (23.82)	104.3 (26.57)

*ND=Not determined.

e. Conclusions:

Pharmacokinetic data from both the single-day and multiple-day administration phases of the study indicated that plasma ceftiofur and desfuroylceftiofur metabolites achieved peak concentrations within 1 to 2 hours. Data from the single administration phase indicated that the plasma half-life was approximately 13.5 hours, and that concentrations of ceftiofur and desfuroylceftiofur metabolites at the dosing interval of 24 hours averaged 2.02 μg/mL. These data support dose determination when compared with the minimum inhibitory concentration (MIC) data for swine respiratory disease (SRD) bacteria in the following studies.

3. Microbiological survey #1: TR 705-7923-93-010. Minimum inhibitory concentrations for ceftiofur and desfuroylceftiofur with bacterial isolates from porcine and bovine sources. S.A. Salmon, J.L. Watts, R.J. Yancey, Jr., C.A. Case, A.R. Cazers, C.L. Gatchell.

a. Purpose: This study tested the susceptibility of bacteria isolated from cases of swine respiratory disease to ceftiofur.

b. Investigators: S.A. Salmon, J.L. Watts, R.J. Yancey, Jr., C.A. Case, A.R. Cazers, C.L. Gatchell, The Upjohn Company, Kalamazoo, Michigan 49001

c. General Design

- Bacteria: Isolates used in this study were obtained from The Upjohn Company culture collections. All isolates (*Pasteurella multocida, P. haemolytica, Salmonella choleraesuis*, and *Streptococcus suis*) were from cases of respiratory disease in swine. In addition to clinical isolates, the following American Type Culture Collection (ATCC) isolates were included as quality control strains, as recommended by National Committee on Clinical Laboratory Standards (NCCLS): *E. coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 29213 and *Pseudomonas aeruginosa* ATCC 27853.

- Antibiotics: Ceftiofur sodium and desfuroylceftiofur were tested. Both compounds were dissolved in 10% ethanol and sterile distilled water.

- Minimum Inhibitory Concentrations (MICs): All isolates were tested using the NCCLS microdilution broth method. Mueller-Hinton broth (Sensititre™, Westlake, Ohio) was used as the growth medium. Due to the instability of desfuroylceftiofur, all microdilution broth panels containing this compound were prepared and inoculated on the same day.

d. Results: Both ceftiofur and desfuroylceftiofur exhibited activity against all of the gram-negative organisms tested. Results are summarized in Table 4.2.

Table 4.2. Summary of minimum inhibitory concentrations (µg/mL) for isolates from clinical cases of swine respiratory disease.

Organism	Number Tested	Ceftiofur	Desfuroylceftiofur
P. multocida (SRD)	50		
MIC_{50}		$\leq$ 0.003	$\leq$ 0.003
MIC_{90}		$\leq$ 0.003	0.0078
Range		NR*	$\leq$ 0.003-0.015
Mode		$\leq$ 0.003	$\leq$ 0.003
Salmonella choleraesuis	48		
MIC_{50}		0.5	0.25
MIC_{90}		1.0	1.0
Range		0.5-2.0	0.13-1.0
Mode		0.5	0.25
Streptococcus suis	49		
MIC_{50}		0.0078	0.015
MIC_{90}		0.13	0.25
Range		$\leq$ 0.003-0.25	0.03-2.0
Mode		0.0078	0.03

*NR = no range

e. Conclusion: MIC_{50} obtained for *P. multocida , Salmonella choleraesuis* and *Streptococcus suis* were within two dilutions for ceftiofur and desfuroylceftiofur. The larger differences in MIC values against the streptococci were only detected when isolates were tested at concentrations well below the recommended dilutions for MIC testing (0.06 µg/mL).

4. Microbiological survey #2: TR 705-7923-93-007. Minimum inhibitory concentrations for ceftiofur and desfuroylceftiofur with isolates of veterinary importance; S.A. Salmon, J.L. Watts, R.J. Yancey, Jr., and C.A. Case.

a. Purpose: This study tested the susceptibility of bacteria isolated from cases of swine respiratory disease to ceftiofur.

b. Investigators: S.A. Salmon, J.L. Watts, R.J. Yancey, Jr., C.A. Case, The Upjohn Company, Kalamazoo, Michigan 49001

c. General Design

- Isolates: *Actinobacillus pleuropneumoniae* isolates were evaluated for *in vitro* activity using ceftiofur sodium and its primary metabolite,

desfuroylceftiofur. The isolates were obtained from The Upjohn Company culture collection and were from cases of respiratory disease in swine. In addition, the following NCCLS recommended ATCC isolates were included as quality control strains: *E. coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 29213 and *Pseudomonas aeruginosa* ATCC 27853.

- Antibiotics: Ceftiofur sodium and desfuroylceftiofur were tested. Both compounds were dissolved in 10% ethanol and sterile distilled water.

- Minimum Inhibitory Concentrations (MICs): All isolates were tested using the NCCLS microdilution broth method. Mueller-Hinton broth (Sensititre™, Westlake, Ohio) was used as the growth medium. Due to the instability of desfuroylceftiofur, all microdilution broth panels containing this compound were prepared and inoculated on the same day.

d. Results: Both ceftiofur and desfuroylceftiofur exhibited activity against all of the gram-negative organisms tested. Results are summarized in Table 4.3.

Table 4.3. Summary of minimum inhibitory concentration (MIC) data for *Actinobacillus pleuropneumoniae* (µg/mL) isolated from cases of swine respiratory disease.

Organism	No. Tested	Ceftiofur	Desfuroylceftiofur
A. pleuropneumoniae	50		
MIC_{50}		= 0.0039	0.0078
MIC_{90}		0.0078	0.015
Range		= 0.0039-0.015	= 0.0039-0.03
Mode		= 0.0039	0.0078

e. Conclusion: MIC_{50} values obtained for *A. pleuropneumoniae* are within one dilution for ceftiofur and desfuroylceftiofur.

5. Comparative bioavailability of ceftiofur sodium and ceftiofur hydrochloride: TR 796-7926-94-001. Pharmacokinetic comparison of ceftiofur hydrochloride sterile suspension and ceftiofur sodium sterile powder administered once to swine intramuscularly at a dose of 2.27 mg ceftiofur equivalents/lb (5.0 mg/kg) body weight; S.A. Brown, P.J. Hamlow, A.K. Speedy, V.L. Hubbard, J.K. Callahan, M. Al-Adhami, B.J. Hanson, T.S. Arnold, T.D. Cox, T.F. Flook, R.L. Janose, V.R. Lewis, and D.L. Kiefer.

a. Purpose: This study compared absolute plasma bioavailability and plasma ceftiofur and desfuroylceftiofur metabolite concentrations at 24 and 72 hours after equivalent doses of ceftiofur were administered as either ceftiofur hydrochloride sterile suspension or ceftiofur sodium sterile powder in swine.

b. Investigators: S.A. Brown, P.J. Hamlow, A.K. Speedy, V.L. Hubbard, J.K. Callahan, M. Al-Adhami, B.J. Hanson, T.S. Arnold, T.D. Cox, T.F. Flook, R.L. Janose, V.R. Lewis, and D.L. Kiefer, The Upjohn Company, Kalamazoo, Michigan 49001

c. General Design

1) Experimental Animals: Yorkshire crossbred pigs, seven gilts and seven barrows, weighing 28 to 37 kg.

2) Dosage Form: Ceftiofur sodium (NAXCEL⌈ Sterile Powder; Production Lot No. 663 HX). Ceftiofur hydrochloride (EXCENEL⌈ Sterile Suspension; Formulation Lot No. 40,583).

3) Route of Administration: Both drug products were administered once intramuscularly at a dose of 2.27 mg ceftiofur equivalents/lb (5.0 mg/kg) body weight.

4) Experimental Design: Two-period, two-treatment crossover design. There was a two-week washout period between doses.

5) Sampling: Blood samples were obtained by venipuncture from each pig before drug administration and at 20 and 40 minutes and 1, 1.5, 2, 3, 5, 8, 12, 16, 24, 36, 48, 60, 72, and 96 hours after drug administration.

6) Assay Method: Blood plasma concentrations of ceftiofur and desfuroylceftiofur metabolites were measured as derivatized desfuroylceftiofur acetamide by high-performance liquid chromatography. The limit of quantitation (LOQ) for the assay was 0.15 mg ceftiofur free acid equivalents/mL of plasma.

7) Pharmacokinetic Analysis: The trapezoidal rule was used to determine the area under the concentration-time curve from time of injection (Time 0) to the limit of quantification (LOQ), denoted as $AUC_{0\text{-}LOQ}$. Terminal half-life ($t_{1/2}$) and $t_{>0.2}$ were determined by linear regression of the logarithm of the last few quantifiable concentrations over time. These values were not determined from a predictive pharmacokinetic model. In addition, observed maximum concentrations (C_{MAX}) and concentrations at 24 and 72 hours (C_{24}, C_{72}, respectively) were tabulated.

8) Decision Criteria: To establish equal relative bioavailability, the following criteria were defined.

- The 90% confidence interval for the $AUC_{0\text{-}LOQ}$ for ceftiofur hydrochloride was contained within the 80 to 120% interval of the mean $AUC_{0\text{-}LOQ}$ for ceftiofur sodium.

- The 90% confidence interval for the time plasma concentrations remained above 0.2 µg/mL ($t_{>0.2}$) for ceftiofur hydrochloride was not less than 80% of that for ceftiofur sodium.

- The upper end of the 90% confidence interval for C_{MAX} for ceftiofur hydrochloride was less than 120% of the mean C_{MAX} for ceftiofur sodium.

- Statistical Analysis: The $AUC_{0\text{-}LOQ}$, C_{MAX} and $t_{>0.2}$ were analyzed on an experimental unit basis using Type III sums of square from the GLM procedure of SAS® (SAS Institute, Cary, NC).

d. Results : Concentrations of ceftiofur and metabolites 72 hours after injection were 0.518 ± 0.126 µg/mL for ceftiofur hydrochloride and 0.407 ± 0.0675 µg/mL for ceftiofur sodium. Other results are summarized in Table 4.4.

Due to significant period and sequence effects in this study, only values from Period 1 were used to evaluate the pharmacokinetic parameters. For Period 1, the $AUC_{0\text{-}LOQ}$ for ceftiofur hydrochloride was 321 ±50.2 µg•h/mL, compared to an $AUC_{0\text{-}LOQ}$ for ceftiofur sodium of 314 ± 55.1 µg•h/mL. The 90% confidence interval for the difference between the $AUC_{0\text{-}LOQ}$ after ceftiofur hydrochloride and after ceftiofur sodium (-43.3 to +57.3 µg•h/mL) was completely contained within the -20 to +20% interval of the mean $AUC_{0\text{-}LOQ}$ after ceftiofur sodium, namely -62.7 to +62.7 µg•h/mL.

Table 4.4. Plasma concentrations and related parameters* of ceftiofur and desfuroylceftiofur metabolites after EXCENEL⌈ Sterile Suspension (ceftiofur hydrochloride sterile suspension (50 mg/mL)) or NAXCEL⌈ Sterile Powder (ceftiofur sodium sterile powder (50 mg/mL)) administered intramuscularly at 2.27 mg/lb ceftiofur equivalents/lb (5.0 mg/kg body weight).

	Ceftiofur HCl	Ceftiofur Na
C_{max} <µg/mL>:	26.1 ± 5.02	29.2 ± 5.01
t_{max} <h>:	0.66-2.0 (range)	0.33-2.0 (range)
$AUC_{0\text{-}LOQ}$ <µg•h/mL>:	321± 50.2	314 ± 55.1
C_{24} h <µg/mL>:	3.45 ± 0.431	3.53 ± 0.791
C_{72} h <µg/mL>:	0.518 ± 0.126	0.407 ± 0.0675
¶$t_{1/2}$ <h>:	16.2 ± 1.55	14.0 ± 1.23
$t_{>0.2}$ <h>:	93.8 ± 7.98	85.0 ± 7.71

¶$t_{1/2}$ determined by linear regression of the logarithm of the last few quantifiable concentrations over time. These values were not determined from a predictive pharmacokinetic model.

*Due to significant period and sequence effects in this study, only values from Period 1 were used to evaluate these parameters.

e. Conclusions:

Ceftiofur hydrochloride sterile suspension provides equal relative bioavailability compared to ceftiofur sodium sterile powder when the products are administered intramuscularly to pigs. This conclusion was based upon three criteria:

1) $AUC_{0\text{-}LOQ}$ for ceftiofur hydrochloride was equivalent to the mean $AUC_{0\text{-}LOQ}$ for ceftiofur sodium,
2) C_{MAX} (C_{MAX} for ceftiofur hydrochloride was less than 120% of the mean C_{MAX} after ceftiofur sodium), and
3) $t_{>0.2}$ ($t_{>0.2}$ for ceftiofur hydrochloride was greater than $t_{>0.2}$ for ceftiofur sodium).

These results and the time plasma concentrations remained above 0.2 µg/mL ($t_{>0.2}$), indicating that comparable doses of ceftiofur hydrochloride administered to swine provided comparable drug exposure and comparable duration of therapeutic concentrations as ceftiofur sodium.

6. Conclusions for dose determination based on the relationship of pharmacokinetic and *in vitro* minimum inhibitory concentration (PK/MIC) data:

   The plasma concentrations of ceftiofur and metabolites in swine at the label dosing interval (24 hours) are compared in Table 4.5.

   Table 4.5. Concentration of ceftiofur and metabolites in swine plasma 24 hours after administration of ceftiofur as either the hydrochloride or sodium salt

	Dose/Body Weight		
Salt	(mg/lb)	(mg/kg)	C_{24} (µg/mL)
ceftiofur sodium	1.36	3.0	2.02 ± 1.53
ceftiofur sodium	2.27	5.0	3.53 ± 0.79
ceftiofur hydrochloride	2.27	5.0	3.45 ± 0.43

   At 1.36 mg/lb (3.0 mg/kg) body weight, plasma concentrations of ceftiofur and desfuroylceftiofur metabolites (2.02 µg/mL for ceftiofur sodium) are greater than the MIC_{90} for *A. pleuropneumoniae* (0.0078 µg/mL), *P. multocida* (=0.003 µg/mL), and *Streptococcus suis* (0.13 µg/mL) for the entire dosing interval of 24 hours. At 2.27 mg/lb (5.0 mg/kg) body weight, plasma concentrations exceed the MIC_{90} for *Salmonella choleraesuis* (1.0 µg/mL) for the entire dosing interval of 24 hours.

   Since ceftiofur sodium sterile powder and ceftiofur hydrochloride sterile suspension demonstrated equal relative bioavailability in pigs when administered intramuscularly at equal doses, it is reasonable to conclude that doses determined to be effective for ceftiofur sodium are effective for ceftiofur hydrochloride.

B. Field Investigation

   The requirement for field investigation of the safety and effectiveness of EXCENEL® Sterile Suspension (ceftiofur hydrochloride) for swine bacterial respiratory disease was satisfied by the pivotal, natural-infection, multi-location field trial which supported the supplemental approval of ceftiofur sodium for swine bacterial respiratory disease [*see* FOI Summary for NADA 140-338 (NAXCEL® Sterile Powder) dated August 4, 1992].

   To establish the relevance of the pathogens isolated from the field trial which supported NADA 140-338 to current swine respiratory disease, a comparison was made of *in vitro* susceptibility of bacterial isolates obtained from the lungs of control pigs and from isolates obtained in the mid-1980s with those of current field isolates for the microorganisms included on product labeling of both ceftiofur products. Current isolates from clinical swine respiratory disease are similar to historical isolates in their sensitivity to ceftiofur. The results are summarized in Table 4.6.

Table 4.6. Comparison of historical and contemporary data bases of ceftiofur MIC (µg/mL) for swine respiratory disease pathogens. All values are MIC_{90} or a range, except values marked by *, which are MIC_{50}.

	Historical			Contemporary
Organism	AJVR[a]	705-7922-89-017[b]	796-9690-91-003[c]	705-7923-94-020[d]
A. pleuropneumoniae	= 0.06 (9)[e]	--	0.0078-0.03 (179)	= 0.03 (83)
P. multocida	= 0.06 (27)	= 0.06 (11)	0.0019-0.03 (33)	= 0.03 (74)
Salmonella choleraesuis	1.0-2.0 (2)	--	--	1.0 (50)
Streptococcus suis	= 0.06 (26)	= 0.06* (8)	0.015-0.03 (39)	0.25 (94)

[a]R.J. Yancey, Jr., et. al., *Am. J. Vet. Res.* 48:1050-1053, 1987.

[b]TR 705-7922-89-017. Minimum inhibitory concentration. Determinations of ceftiofur and twelve comparator antibiotics for bacteria isolated from swine respiratory disease. R.J. Yancey, Jr., C.A. Case, and R.A. Evans.

[c]TR 796-9690-91-003. European review of *in vitro* data for activity of ceftiofur sodium against recent field isolates with respiratory problems. S.T. Lens.

[d]TR 705-7923-94-020. Minimum inhibitory concentrations for ceftiofur and comparator antimicrobial agents against bacterial pathogens of swine from the United States, Canada and Denmark. S.A. Salmon, J.L. Watts, C.A. Case, and R.J. Yancey, Jr.

[e]Number of isolates tested.

Pharmacokinetic studies previously summarized in this document (*see* Dose Determination, pages 7-10) provided evidence that the two salts are comparably bioavailable at label dosages of their respective formulated products, NAXCEL® Sterile Powder (ceftiofur sodium) and EXCENEL® Sterile Suspension (ceftiofur hydrochloride). Therefore, the multi-location field trial for ceftiofur as the sodium salt suffices for the field investigation of ceftiofur hydrochloride for the same label claim and dose regimen, i.e., for the treatment/control of swine bacterial respiratory disease associated with *A. pleuropneumoniae, P. multocida, Salmonella choleraesuis*, and *Streptococcus suis* Type 2 at 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) body weight administered intramuscularly at 24-hour intervals for 3 days.

V. ANIMAL SAFETY

Ceftiofur hydrochloride administered intramuscularly to swine at levels of 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) body weight has equal relative bioavailability to ceftiofur sodium. This comparability was demonstrated in a study which compared ceftiofur hydrochloride sterile suspension and ceftiofur sodium sterile powder administered intramuscularly to swine at a dose of 2.27 mg ceftiofur equivalents/lb (5.0 mg/kg) body weight.

The safety of ceftiofur sodium has been demonstrated in safety, efficacy, and field trials, which are discussed in the FOI Summary for NADA 140-338. (53 FR 5369, February 24, 1988, as amended at 55 FR 13768, April 12, 1990; FR 12119, March 22, 1991; 57 FR 41862, September 14, 1992). Two studies were designed and conducted to specifically address target animal safety when ceftiofur (as ceftiofur sodium) was administered intramuscularly to swine. These included a tolerance study in which exaggerated doses of ceftiofur were administered to swine, and a safety/toxicity study in which multiples of the dose and duration were administered. The results of these studies demonstrate that ceftiofur is safe when administered intramuscularly to swine at doses up to 2.27 mg per lb of (5.0 mg/kg) body weight for 3 consecutive days.

In addition to the previously submitted studies with the sodium salt solution, an injection site irritation study was conducted using the proposed formulation, a hydrochloride salt suspension in oil.

A. Pivotal Study

Injection Site Tolerance Study: TR 7220-94-029. U-64279A: Injection Site Irritation Study of Ceftiofur Hydrochloride in Swine When Administered by Intramuscular Injection at Three Times Varying From 12 Hours to 25 Days Before Necropsy. W.J. Seaman and J.M. Marcek.

1. Purpose: To define tissue reaction and resolution following administration of EXCENEL⌈ ceftiofur hydrochloride sterile suspension.

2. Study Director: W.J. Seaman, D.V.M.
   Senior Veterinary Pathologist/Toxicologist
   Study Director, Unit 7220-300-1
   The Upjohn Company, Kalamazoo, Michigan 49001

3. General Design

   a. Test Animals: Twelve (12) crossbred swine approximately 3 to 4 months of age, and weighing 25.4 to 33.8 kg at the start of the study, were assigned to three groups of 2 barrows and 2 gilts.

   b. Dosage Form and Route of Administration: EXCENEL⌈, ceftiofur hydrochloride sterile suspension (50 mg/mL; Lot #40583) was administered intramuscularly using a 16 gauge 1.5 inch sterile needle in either the right or left neck region.

c. Dosage: Each pig received an injection of 1.36 mg ceftiofur equivalents/kg (3.0 mg/kg) body weight in the left side of the neck and an injection of 2.27 mg ceftiofur equivalents/lb (5.0 mg/kg) body weight in the right side of the neck on each of the 3 dosing days.

d. Test Duration: Each group of pigs was dosed on 3 days during the study as follows.

Group 1 was dosed at 15, 20 and 25 days before necropsy.

Group 2 was dosed at 7, 9 and 11 days before necropsy.

Group 3 was dosed at 12 hours, 3 and 5 days before necropsy.

e. Pertinent Parameters Measured: Injection sites were monitored daily for clinical signs of swelling and other reactions. At necropsy, injection sites were excised and examined grossly. Body weights were obtained during the pre-test period and prior to necropsy.

4. Results

a. Clinical Observations: Minor swelling at the injection site was noted in two sites injected with 2.27 mg ceftiofur equivalents/lb and one site injected with 1.36 mg ceftiofur equivalents/lb at approximately 12 hours after administration. No swelling or other signs of inflammation were observed throughout the remainder of the study. By 11 days after the last injection, the injection sites were grossly normal for a majority of animals.

b. Body Weight: All animals gained weight throughout the study period.

c. Gross Injection Site Observation:

Oily material was present at all injection sites for both doses at 12 hours post-injection. Injection sites were characterized by discoloration in the fat or muscle. Needle tracts, cavities at the injection site (thought to represent a residual drug depot), and a firm area below the skin were also observed.

Three (3) days after injection, oily material was still present at all injection sites for both doses and the main observation was again discoloration of the muscle or fat. Needle tracts, discolored dermis or superficial skin, and hemorrhage at the injection site were evident in most animals 5 days after injection. A needle tract, cavities at the injection site and foci in the dermis or superficial skin were also observed.

Oily material at the injection site was evident in half of the animals for either dose at 7 days after injection. Discoloration in the fat, muscle or fascia and cavities at the injection site were also present. Nine (9) days after injection, discoloration at the injection site was evident in a majority of animals for

either dose. Other observations included oily material and cavities at the injection site.

Sites were normal for a majority of animals at 11 days after injection. Discoloration of the injection site was evident in one animal. Injection sites were normal in three of the four animals for each dose at both 15 and 20 days after injection. Discoloration and cavities at the injection site were observed both 15 and 20 days after injection. Injection sites were normal in all animals for either dose by 25 days after injection.

5. Conclusions:

The absence of clinical reactions to injection as indicated by injection site scores indicates little muscle irritation following injection of either 1.36 or 2.27 mg ceftiofur equivalents/lb (3.0 or 5.0 mg/kg) body weight as ceftiofur hydrochloride sterile suspension in the neck of swine. Similarly, gross examination at necropsy revealed that reactions to injection of either dose were mild and were limited to discoloration of the fat and fascia present at the injection site. Gross lesions were not evident in the majority of injection sites 11 days or longer after injection, and no consistent differences in injection site reactions were observed between the two doses tested.

VI. HUMAN SAFETY

All issues concerning toxicity testing of ceftiofur are addressed in a previous FOI Summary for the New Animal Drug Application (NADA) for NAXCEL® Sterile Powder (ceftiofur sodium), NADA 140-338, the approval notice for which appeared in the FEDERAL REGISTER on April 12, 1990 (55 FR 13768). This summary was updated in June 1992. One additional study assessed the acute toxicity of ceftiofur hydrochloride.

A. Toxicity Study and Comparative Metabolism Study

1. Acute Intraperitoneal Single-Dose Study in the Rat

a. Technical Report No. 7263/87/022

b. Starting Date: April 2, 1986

c. Termination Date: April 16, 1986

d. Study Director: T.J. Kakuk

e. Location of Study: The Upjohn Company, Kalamazoo, Michigan

f. Identification of Substance and Dosage Form: ceftiofur sodium and ceftiofur hydrochloride, control article sterile vehicle 122 (methylcellulose 0.25 %)

g. Species and Strain: Sprauge-Dawley Rats

h. Number of Animals Per Sex Per Treatment Group: There were 120 rats in 11 treatment groups of 5 males and 5 females. Control group of 5 male and 5 female rats.

i. Drug Levels Tested and Duration of Dosing: 0 mg/kg (Vehicle) Ceftiofur Na, 250, 500, 1000, 1500, 2000, and 2500. mg/kg. Ceftiofur HCl 250, 500, 1000, 1500, and 2000 mg/kg body weight one day dosing followed by a 15-day observation interval. Dosing was intraperitoneal administered once.

j. Route of Administration: intraperitoneal

k. Parameters Tested: Survival and Clinical Signs recorded daily, body weight changes weekly. Necropsied examination was performed on all dead rats.

l. Significant Toxicology Observed: No deaths occurred from intraperitoneal injections of dose levels 250 or 500 mg/kg for either salt of ceftiofur. There was no significant difference in weight gain between salts at any dose or between treated and control groups for either salt except in the single surviving male at 2000 mg/kg dose level for ceftiofur sodium. The most frequently noted gross abnormality in animals which died on study were

prominent blood vessels in the large and small intestines, and hemorrhagic areas in the abdominal muscle wall and area on the urinary bladder. The Spearman-Karber Method was used to calculate the acute toxicity values and 95 % confidence limits for single dose intraperitoneal injection of each salt. The values for ceftiofur hydrochloride were 983 (809-1194) mg/kg for males, 789(673-925) mg/kg for females and 881 (774-1003) mg/kg for both sexes combined. Those for ceftiofur sodium were 1155 (963-1385) mg/kg for males and 744 (682-812) mg/kg for females and 927 (804-1069) mg/kg for the sexes combined.

m. Statistical Analysis: The Spearman-Karber Method was used to calculate the acute toxicity values and 95 % confidence limits for single-dose intraperitoneal injection of each salt.

o. Conclusions: The acute toxicities are similar for the two ceftiofur salts (sodium and hydrochloride).

2. Oral Bioavailability of Ceftiofur Hydrochloride and Ceftiofur Sodium

a. Technical Report Nos. 788-9760-86-009 - Study J-379, 788-9760-86-001 and 002 - Study J-080, and 796-7926-95-005

b. The metabolism of radiolabeled ceftiofur hydrochloride after a single oral dose of 200 mg ceftiofur equivalents/kg body weight was characterized in urine, plasma and tissues in rats. Metabolites and residue concentrations were characterized at 6 and 12 hours post-treatment. Metabolites and residue concentrations in this study (TR 788-9760-86-009 - Study J-379) were compared to a similar study conducted in rats using the sodium salt. In the sodium salt studies, rats received ceftiofur orally at a rate of 240 mg ceftiofur equivalents/kg body weight (TRs 788-9760-86-001 and 002 - Study J-080) and tissue samples were obtained at 6 or 12 hours post-treatment.

c. Results: Dose recoveries in feces, and gastrointestinal track are summarized in TR 796-7926-95-005. There was no difference in metabolism of the ^{14}C ceftiofur hydrochloride compared to ^{14}C-ceftiofur sodium, in either male or female rats. Absorption, excretion in urine, and residue concentrations in tissues and plasma and the nature and concentration of metabolites were similar following oral administration of either salt to rats and are summarized in Table 6.1.

Table 6.1. Dose accountability in GI tract and excreta of rats 6 and 12 hr after a single oral dose of either ceftiofur hydrochloride or ceftiofur sodium at approximately 200 mg CFAE/kg body weight. Data are reported as means (s.d.).

	Time (h)	Mean Percent (s.d.) Recovered			
Ceftiofur Salt	post-slaughter	GI tract	Urine	Feces	Total
Na	6	64.7 (3.4)	0.9 (0.2)	10.7 (0.7)	64.7 (3.4)
Na	12	64.8 (6.3)	1.3 (0.2)	0.4 (0.7)	64.8 (6.3)
HCl	6	77.4 (6.1)	0.6 (0.1)	0.0 (0.1)	78.0 (6.1)
HCl	12	74.9 (9.2)	0.8 (0.2)	2.34 (5.12)	77.6 (5.3)

d. Conclusions: The oral bioavailability and metabolism of ceftiofur hydrochloride in rats is similar to the oral bioavailability and metabolism of ceftiofur sodium in rats.

When rats were administered ceftiofur sodium or ceftiofur hydrochloride orally, most of the dose remained in the gastrointestinal tract to be excreted in the feces, (>60% for rats administered ceftiofur sodium, and >75% for rats administered ceftiofur hydrochloride), indicating that it was not available to the animal. Dose recovery in urine and feces up to 12 hours after dosing, was small for both ceftiofur salts (<2.5%). The distribution of the drug in tissues follows the same pattern regardless of the species, dose level, route of administration of ceftiofur salt administered. Highest residue concentrations are consistently found in kidneys, followed by liver, fat and muscle. Residue concentrations were similar in rat tissues after oral administration of either ceftiofur salt for the same tissue type and slaughter time, suggesting similar availability of the drug. The type of metabolites present in the urine of rats was similar for both ceftiofur salts.

These studies established that the Allowable Daily Intake (ADI) and Safe Concentration (SC) determined for ceftiofur sodium are applicable to ceftiofur HCl.

B. Safe Concentration of Total Residues

1. No Observed Effect Level (NOEL):

Germane toxicologic investigations included mutagenicity, oral feeding, and hypersensitivity studies. The lowest no observed effect level (NOEL) from the 90-day oral feeding studies in both dogs and rats was 30 mg ceftiofur per kg body weight (bw). Since the drug is considered a Low Use Drug intended for therapeutic use in specific animals and because it has undergone extensive safety testing, chronic toxicity studies were not required. Thus, the ADI was based, without the 25 µg/kg bw/day limitation, on the 90-day studies; a safety factor of 1000 is used in the safe concentration calculations.

2. Calculation of Allowable Daily Intake (ADI):

Allowable Daily Intake (ADI) =	$\frac{\text{Lowest NOEL}}{\text{Safety Factor}}$

A safety factor (SF) of 1000 is used because the ADI is based on 90-day feeding study data.

The lowest NOEL is 30 mg/kg, so ADI =	$\frac{30 \text{ mg/kg}}{1000}$
=	0.03 mg/kg or 1.8 mg/adult/day.

3. Allocation of ADI:

The revised General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals (FDA-CVM July 1994) provides for the reservation of a portion of the ADI for milk. Since 1) ceftiofur sodium is approved for parenteral use in lactating dairy cattle, 2) both salts, hydrochloride and sodium, accede to the same primary metabolite, and 3) total residues are indistinguishable quantitatively or qualitatively, the ADI for both salts is the same.

The portion of the ceftiofur ADI reserved for milk is 27%.

ADI for milk = 27% x total ADI
= 0.27 x 0.03 mg/kg body weight (bw)/day
= 008 mg/kg body weight/day

ADI for edible tissues = total ADI - ADI for milk
= 0.030 mg/kg bw/day - 0.008 mg/kg body weight//day
= 0.022 mg/kg bw/day

4. Safe Concentration (SC) Calculations: The following are the new SC for ceftiofur in edible tissues of swine using an allocation of ADI that includes milk:

Safe Concentration (SC) =	$\frac{\text{Acceptable Daily Intake (ADI) x Human Weight}}{\text{Consumption Factor}}$

The average human weight is approximated as 60 kg. The daily consumption values of tissues are approximated as 300 g muscle, 100 g liver, 50 g kidney, and 50 g skin/fat.

SC (muscle)	=	$\frac{0.022 \text{ mg/kg bw/day x } 60 \text{ kg}}{300 \text{ g/day}}$	= 4.40 mg/kg = 4.40 ppm
SC (liver)	=	$\frac{0.022 \text{ mg/kg bw/day x } 60 \text{ kg}}{100 \text{ g/day}}$	= 13.20 mg/kg = 13.20 ppm
SC (kidney or fat)	=	$\frac{0.022 \text{ mg/kg bw/day x } 60 \text{ kg}}{50 \text{ g/day}}$	= 26.40 mg/kg = 26.40 ppm

Using the revised food consumption factors, the permitted Safe Concentrations for total residues in edible tissues from swine are as summarized in Table 6.2.

Table 6.2. Safe Concentrations For Total Residues In Edible Tissues From Swine

Tissue	Daily Consumption (grams)	Safe Concentration (ppm)
Muscle (non-injection)	300	4.4
Liver	100	13.2
Kidney	50	26.4
Fat	50	26.4

5. Threshold Assessment: This compound is a Category A compound as determined by the Threshold Assessment considerations. Based on a Structural Activity Assessment, it was assigned to Category C (non-carcinogen). Subsequent to this, the 90-day feeding studies allowed it to be classified as Category A. Because the drug is intended for therapeutic use on specific animals, it is considered a Low Use Drug. Accordingly, chronic studies were not required and, based on 90-day studies, a Safety Factor of 1000 is used in the Safe Concentration calculations.

C. Total Residue Depletion and Metabolism Study

1. Purpose: The purpose of this study was to quantify and characterize ^{14}C ceftiofur total residue concentrations in tissue, plasma and excreta from swine administered either 2.27 or 3.41 mg ceftiofur equivalents/lb (5.0 or 7.5 mg/kg) body weight radiolabeled ceftiofur hydrochloride intramuscularly 12 hours after the last of three injections administered at 24 hours intervals (TR 796-7926-94-006).

2. Study Directors: Maria G. Beconi-Barker, Ph.D., and
Terry Gilbertson (investigator), Ph.D.
Animal Health Drug Metabolism, Unit 7926
The Upjohn Company, Kalamazoo, Michigan 49001

3. General Design:

   a. Test Animals: Twenty-four (24) animals; crossbred swine (12 gilts and 12 barrows); approximately 25 to 40 kg and 3 to 6 months of age at the start of the study.

   b. Dosage Form and Route of Administration: All injections of the ^{14}C-ceftiofur hydrochloride sterile suspension were administered intramuscularly.

   c. Dosage: The dose level administered was 2.27 or 3.41 mg radiolabeled ceftiofur equivalents/lb body weight (i.e., 5.0 or 7.5 mg/kg) as 3 intramuscular injections at 24-hour intervals.

4. Results - Total Residues (based on total radioactivity)

   All total residue levels were less than the Safe Concentration at 12 hours after the last dose. Data are summarized and compared to Safe Concentrations in Table 6.3.

   Table 6.3. Mean concentrations of ^{14}C-ceftiofur hydrochloride 12 hours after the last of 3 intramuscularly doses of 3.41 mg/lb (7.5 mg/kg) body weight administered at 24-hour intervals compared to Safe Concentrations for edible tissues of swine.

Tissue	Safe Concentration (ppm)	Mean Concentration (ppm)
Muscle	4.4	1.07
Liver	13.2	2.64
Kidney	26.4	10.68
Fat	26.4	2.45
Injection Site 1	--	8.62
Injection Site 2	--	8.71
Injection Site 3	--	11.45

5. Conclusions for Total Residue in Edible Tissues:

   Since this residue study was conducted at 1.5 times the approved dosage level and total residue levels for edible tissues at 12 hours after the last dose were less than the Safe Concentration, this study supports zero-day withdrawal.

6. Results - Metabolism [based on swine administered 2.27 mg ceftiofur equivalents/lb (5.0 mg/kg) body weight for 3 days]

   a. Plasma: For swine dosed with either ceftiofur hydrochloride or ceftiofur sodium, desfuroylceftiofur (DFC)-cysteine was the only free ^{14}C-metabolite found in plasma. The remaining ^{14}C-residues were associated with

macromolecules. Following incubation of the macromolecule associated fraction with dithioerythritol, DFC was the only ^{14}C-residue released.

b. Urine: Urine accounted for >60% of the dose. DFC-cysteine was the most abundant metabolite in the urine of swine administered ceftiofur hydrochloride, representing 33.57, 38.29 and 32.31% of the total radioactivity in urine collected from the initial dose to the second dose (0 to 24 hours), from the second dose to the third dose (24 to 48 hours), and from the third dose until euthanatized (48 to 60 hours), respectively. Minor components included DFC-dimer and parent ceftiofur. Polar metabolites represented less than 20% of the residue, with four ceftiofur-related residues with an intact ß-lactam ring accounting for the remainder (<5%). DFC-cysteine was also one of the two most abundant metabolites in the urine of swine dosed with ceftiofur sodium, representing 22.11% of total radioactivity. The other major component was DFC-dimer (23.66%). Minor components included parent ceftiofur (14.63%) and Polar A (7.70%).

DFC-cysteine, DFC-dimer, parent ceftiofur and polar metabolites were found in urine of swine dosed with either ceftiofur hydrochloride or ceftiofur sodium. The type and proportion of ceftiofur-related residues are summarized in Table 6.4. Therefore, there was a qualitative match of characterized metabolites in swine when comparing profiles after the administration of either ceftiofur salt.

Table 6.4. Type and proportion of ceftiofur-related residues found in swine urine from 0 to 12 hours after the last of 3 intramuscular injections of ceftiofur hydrochloride at 6.76 and 4.41 mg CFAE/kg body weight, and of ceftiofur sodium at 5.18 mg CFAE/kg body weight.

	Dose	Mean Percent (s.d.) of Total Eluted from HPLC				
Ceftiofur salt	(mg/kg)	polar	unknown	DFC-cysteine	DFC-dimer	ceftiofur
HCl	6.76	3.5 (2.6)	5.7 (2.8)	27.0 (3.7)	40.9 (8.3)	22.9 (5.7)
HCl	4.41	6.9 (2.4)	5.4 (1.6)	32.3 (6.9)	27.1 (7.8)	28.3 (4.5)
Na	5.18	9.9 (4.4)	<5%	30.7 (10.0)	32.1 (13.8)	18.3 (10.7

c. Tissues: In swine administered ceftiofur hydrochloride, an average of 3.64, 0.92, 0.36, 1.22, and 0.45 µg ceftiofur equivalent/g tissue were extracted from swine kidney, liver, muscle, last injection site, and fat, respectively, using the extracting conditions previously used for rat tissues. These values represent 59.88, 52.81, 43.96, 26.80, and 33.99% of the concentration of ceftiofur-related residues found by combustion for kidney, liver, muscle, last injection site, and fat, respectively. These values indicate that a fraction of the residues was not removed from the matrix under the extracting conditions used in this study. Of the residues recovered in the homogenate, averages of 0.71, 0.13, 0.04, 0.11, and 0.08 µg ceftiofur equivalents/g tissue were free, while averages of 2.46, 0.69, 0.32, 1.11, and 0.38 µg ceftiofur equivalents/g tissue were associated with

macromolecules for kidney, liver, muscle, last injection site, and fat, respectively.

In swine dosed with ceftiofur hydrochloride, an average of 22.22% of kidney residues were free, while the remaining 77.78% were bound to macromolecules. DFC-cysteine was the only free metabolite observed in kidney, representing, 28% of the total residues. In swine dosed with ceftiofur sodium, an average of 37.4% of kidney residues were free, while the remaining 62.6% were bound to macromolecules. In the free kidney residues of the swine administered ceftiofur sodium, the major metabolite containing an intact ß-lactam ring was DFC-cysteine, representing 12.3% of the total residues. The remaining 23.2% of the free residues corresponded to unidentified polar metabolites. Therefore, in kidney extracts from swine administered either ceftiofur hydrochloride or ceftiofur sodium, a large proportion of residues were bound to macromolecules, and the most abundant free metabolite containing an intact ß-lactam ring was DFC-cysteine for both salts.

Table 6.5. Total residue concentration in swine tissues 12 hours after the last of 3 intramuscular injections of ceftiofur hydrochloride at 6.76 and 4.41 mg CFAE/kg body weight, and of ceftiofur sodium at 5.18 mg CFAE/kg body weight. (Data are reported as mean and s.d).

	Dose	Micrograms (µg) CFAE/g tissue			
Ceftiofur Salt	(mg/kg)	Kidney	Liver	Muscle	Fat
HCl	6.76	10.68 (2.68)	2.64 (0.46)	1.07 (0.15)	2.45 (0.63)
HCl	4.41	6.33 (1.75)	1.79 (0.35)	0.80 (0.20)	1.35 (0.40)
Na	5.18	4.47 (0.81)	1.55 (0.18)	0.76 (0.24)	1.49 (0.54)

7. Conclusions for Metabolism:

Quantitative and qualitative assessments of residue levels and profiles in swine tissues, plasma, and urine demonstrate the similarity in metabolism of ceftiofur administered as either ceftiofur sodium or ceftiofur hydrochloride.

D. Comparative Metabolism of Ceftiofur in Swine and Rats

The metabolic profiles of ceftiofur in the urine and kidney extracts of rats treated orally with doses of about 700 mg/kg body weight - ^{14}C ceftiofur sodium were compared to the urine and kidney extracts of pigs dosed intramuscularly for 3 days with 2.27 mg/lb body weight ^{14}C ceftiofur hydrochloride (5.0 mg/kg). This rat dose approximates the highest NOEL (1000 mg/kg) observed in any of the oral rat feeding studies. Kidney is the limiting tissue because observed concentrations of total residues were highest in this tissue relative to the calculated Safe Concentration.

1. Urine: The most abundant metabolite in the urine of rats at 8 and 24 hours after dosing was ceftiofur sulfoxide cysteine ester (31 and 37%, respectively). Other significant metabolites were polar ones devoid of a ß-lactam ring (27 and 24%, for 8 and 24 hours, respectively) and DFC-dimer (11 and 10%, for 8 and 24 hours, respectively). Parent ceftiofur and DFC-cysteine were found as minor components (<5%). The most abundant metabolite in swine urine collected from the time the last dose was administered until 12 hours after last dose was DFC-cysteine (32%). Parent ceftiofur (28.34%), DFC-dimer (27.14%) and polar metabolites (6.86%) were also significant components of swine urine collected during this period. The ceftiofur sulfoxide cysteine ester metabolite found in rat urine was not observed in swine urine.

2. Kidney: In swine, approximately 78% of the kidney metabolites were conjugated to macromolecules with the remainder free. DFC-cysteine was the predominant component of the fraction not conjugated to macromolecules. In rats, 63.9 to 70.2 percent of the kidney metabolites are found bound to macromolecules, with the remainder free. The free kidney metabolites in rats were DFC-cysteine and polar metabolites.

3. Plasma: In swine plasma 92.63 to 96.63% of the ceftiofur related residues are found conjugated to macromolecules with the remainder free. DFC-cysteine was the predominant component of the fraction not conjugated to macromolecules. In rat plasma approximately 72% of the ceftiofur related residues found were conjugated with proteins with the remainder free. In rat plasma there was no consistent major free metabolites. In most animals, Polar A was the main free metabolite, and in one animal, DFC-cysteine was the main metabolite found.

4. Conclusion: These data support the contention that the rat was autoexposed to metabolites to which humans would be exposed as a result of eating pork from ceftiofur treated pigs. Therefore, the toxicology studies in the rat accurately reflect the toxicity of the metabolites to which humans would be exposed.

E. Withdrawal Time

The total residue data showed that the mean concentrations of total ceftiofur residues at 12 hours after the last injection ("zero-day withdrawal") were well below the permitted Safe Concentration in edible tissues of swine treated with a 1.5 overdose. Therefore, a withdrawal period will not be required for this use of the drug in swine, and a target tissue, marker residue and tolerance have not been assigned.

F. Regulatory Method

An official regulatory method is not required, because the residue and toxicology data support a zero-day withdrawal.

G. User Safety

Studies used to evaluate the safety of ceftiofur to users are discussed in detail in the FOI Summary for NADA 140-338 (NAXCEL® Sterile Powder).

VII. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that ceftiofur hydrochloride injectable suspension is effective against swine pneumonia when administered intramuscularly for 3 to 5 days at a dose of 3.0 to 5.0 mg ceftiofur per kilogram body weight.

Labeling restricts this drug to use by or on order of a licensed veterinarian. This decision was based on the following factors: (a) the product contains a new antimicrobial entity intended only for therapeutic purposes, (b) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product to treat swine bacterial pneumonia, and (c) the frequency of violative tissue residues and rate of emergence of resistant organisms will be reduced by the involvement of veterinarians in product use.

A withdrawal period of zero days was calculated from a residue depletion study of ceftiofur residues in swine, following the administration of EXCENEL⊂ injectable suspension.

The agency has carefully considered the potential environmental effects of this action and has concluded that the action is categorically excluded under 21 CFR 25.24(d)(1)(iii) from the requirement to prepare an environmental assessment (EA). The categorical exclusion applies to this action because ceftiofur HCl will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect for ceftiofur sodium. The data available to the Agency do not establish that, at the expected exposure level, the substance may be toxic to organisms in the environment.

Under Section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval for food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the application contains reports of new clinical or field investigations and new human food safety studies essential to the approval of the application and conducted or sponsored by the applicant. EXCENEL⊂ is under patent number U.S. # 4902683; expiring February 20, 2007.

VIII. APPROVED PRODUCT LABELING

A copy of the draft facsimile labeling is attached to this document.

A. EXCENEL® INJECTION Master Shipper (Case) Label

B. EXCENEL® INJECTION Carton Label

C. EXCENEL® INJECTION Bottle Label

D. EXCENEL® INJECTION Package Insert