Approval Date: August 4, 1992

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-338

B. Sponsor

The Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

C. Proprietary Name

NAXCEL® Sterile Powder

D. Established Name

ceftiofur sodium sterile powder

E. Dosage Form

NAXCEL® Sterile Powder is available in two package sizes: 1 gram and 4 gram vials.

Reconstituted product should be used within 12 hours if stored at controlled room temperature 15° to 30° C (59° to 86° F) or within 7 days if stored in a refrigerator 2° to 8° C (36° to 46° F).

1 gram vial
Reconstitute with 20 mL Sterile water for injection or with bacteriostatic water for injection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

4 gram vial
Reconstitute with 80 mL sterile water for injection or with bacteriostatic water for injection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

F. Dosage Regimen

NAXCEL® Sterile Solution should be administered to swine at a dosage of 1.36 to 2.27 mg ceftiofur per pound of body weight (3.0 mg to 5 mg ceftiofur per kilogram of body weight). This translates to 1 mL reconstituted sterile solution per 37 to 22 pounds of body weight (17 to 10 kilograms of body weight).

G. Route of Administration

Intramuscular injection

H. Indication

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

I. Effect of Supplement

This supplement provides for an additional species, swine, to be added to the previously approved product, NAXCEL®.

II. EFFECTIVENESS

A. Pivotal Studies

1. Dose-Finding Study

   a. Type of Study - Experimental Challenge:
   This study is described as a dose-finding study to provide efficacy data at various doses of ceftiofur compared with that of the nontreated groups. Growing pigs were challenged intranasally with *A. pleuropneumoniae* organisms and were treated with either no drug or ceftiofur at 1, 3, or 5 mg per kilogram of body weight (.45, 1.36, or 2.27 mg/pound) as their rectal temperature reached 1.04°F after challenge. Drug and placebo treatments were administered at 24 hr intervals for 3 consecutive days.

   b. Investigator:
   E. K. Uhlenhopp, D.V.M., M.S.
   Section Head, Veterinary Field Services
   Iowa State University
   Ames, Iowa 50011

   c. General Design: The purpose of this study was to provide information about the effectiveness of ceftiofur at various doses in an attempt to describe an optimal dose for bacterial swine pneumonia.

   d. Animals:
   - 30 to 60 pound feeder pigs
   - free of *H.pp* antibodies
   - crossbred barrows and gilts
   - 30 pigs in each of 4 treatment groups for a total of 120 animals

   e. Control:
   The control or placebo was sterile saline which was injected intramuscularly at 1 mL per 5 kg of body weight (1 mL/11 pounds of body weight) as pigs' temperature reached 104°F and at 24 hour intervals until 3 doses were given.

   f. Diagnosis:
   After intranasal challenge with a serotype 5 strain of *A. pleuropneumoniae*, the pigs were observed for signs of pneumonia and their rectal temperatures were checked at 3-hour intervals. A sudden rise in body temperature was determined to be a good indication of the peracute nature of the disease. As the temperature of each pig reached 1.04°F after challenge, the first treatment was administered.

g. Dosage Form:
The dosage form of ceftiofur was a sterile powder reconstituted with sterile water for injection. This dosage is the marketed form of NAXCEL® Sterile Powder.

h. Route of Administration:
Route of administration was intramuscular injection into the neck region of each pig.

i. Dosages:
Dosages used were placebo (0), 1, 3 or 5 mg of ceftiofur equivalents per kilogram of body weight (0, .45, 1.36 or 2.27 mg per pound of body weight).

j. Test Duration:
The drug treatments and placebo were administered for 3 consecutive days. Fourteen days after challenge lung lesion scores and mortality were calculated.

k. Parameters of Measure:
- mortality
- lung lesion scores
- live pig days
- clinical signs of pneumonia

l. Results:
Compared with the negative controls, mortality was significantly reduced as a result of the 3 and the 5 mg ceftiofur (1.36 and the 2.27 mg/pound) dose but not the 1 mg (.45 mg/pound) dose. All three ceftiofur treatments significantly reduced lung lesion scores when compared with the scores of the nontreated pigs. Live pig days and clinical signs of pneumonia improved in a linear relationship with dose, but differences between doses of ceftiofur were not significant.

Table 1. Treatment Means for Pigs Treated with Ceftiofur

Dose mg/kg (mg/pound)	Percent Mortality	Lung Lesion Scores	Live Pig Days
0 (0.00)	59.17a	48.51a	27.19a
1(0.45)	35.83a	30.61b	40.81a
3 (1.36)	30.00b	27.59b	47.56b
5 (2.27)	13.33b	21.17b	55.40b

a,b Non-zero doses with different superscripts from control in the same column are significantly different at P<.05.

m. Statistical Analysis:
This study is described as a randomized complete block design with six blocks of four treatments with five pigs per pen. The following analysis of variance procedure was performed for all parameters of measure.

Table 2. Analysis of Variance Table

Code	Source	df	Test Term
S	Room	5	--
T	Dose	4	E(a)
T	Linear	(1)	E(b)
T	Quadratic	(1)	E(c)
T	REST	(2)	E
E	Error	20	--

(a) This design has a power of 80% to detect a 25% difference in mortality between any two dose groups at the .05 level of significance.

(b) Significance at .05 without significance in Quadratic or REST will indicate the optimal is outside the dose range.

(c) Significance at .05 without significance in REST will indicate the optimal is within the dose range.

n. Conclusions:
Based on the analysis of the data from the primary measures (mortality, lung lesion scores, and live pig days) there is a linear relationship with dose and effectiveness of the drug. The optimal effective dose of ceftiofur for the treatment of experimentally induced bacterial pneumonia caused by *A. pleuropneumoniae* was nearly reached at the 5 mg/kg dose administered daily for 3 consecutive days (2.27 mg/pound dose administered daily for 3 days).

o. Adverse Reactions:
Some animals showed signs of local transient pain as a result of the intramuscular injection, but no evidence of any adverse effects of ceftiofur was noted.

2. Clinical or Field Study

a. Type of Study - Natural Outbreaks:
This field study was an 11-location (10 in the USA and one in Canada) clinical trial in which pigs with natural occurrences of bacterial pneumonia were the subjects of treatment.

b. Names and Addresses of Investigators:
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c. General Design of the Investigation:
This study was a randomized complete block design at each location.

The purpose of this study was to evaluate the effectiveness of 3 mg and 5 mg ceftiofur equivalents per kg of body weight (1.36 mg and 2.27 mg/pound) when administered intramuscularly for three consecutive days to pigs experiencing natural occurrences of bacterial respiratory disease (bacterial pneumonia).

d. Animals:
A total of 1,762 feeder pigs were used in this clinical trial. Most of the pigs were crossbreds and ranged in weight from 32 pounds to 148 pounds at the time of the first treatment. Within a location, pigs were of similar age and weight.

e. Control:
The control of placebo was sterile saline for injection and was administered to the control pigs at the same volume as the NAXCEL® was administered. At each location separate controls within each pen were used for comparison to the 3 mg and 5 mg ceftiofur treated groups.

f. Diagnosis:
The investigator at each location (a veterinarian) made a clinical diagnosis prior to treatment. After treatment was initiated, the diagnosis was confirmed by laboratory diagnostic identification of the causative agent(s) recovered from lung tissue and adjacent lymph nodes from necropsied pigs.

g. Dosage Form:
The dosage form of ceftiofur was a sterile powder reconstituted with sterile water for injection. This dosage is the marketed form of NAXCEL® Sterile Powder.

h. Route of Administration:
Route of administration was intramuscular injection into the neck region of each pig.

i. Dosage:
Dosages tested were 3 mg and 5 mg ceftiofur equivalents per kg of body weight administered for 3 days. This equals 1.36 mg and 2.27 mg of ceftiofur equivalents per pound of body weight for 3 days.

j. Test Duration:
The drug treatments and placebo were administered for 3 consecutive days. On day 7 after first treatment two randomly selected pigs from each treatment group at each location were necropsied to evaluate lung lesions. On day 14 after first treatment the trials ended and all survivors were weighed to determine the number of pigs that had gained weight. An additional 14 day nonexperimental observation period followed the 14 days of the trial.

k. Parameters of Measure:
- mortality
- lung lesion scores
- gainers' (pigs that survived and gained 5 pounds in 14 days)

l. Results:
Based on the above parameters, both the 1.36 mg and the 2.27 mg ceftiofur per pound of body weight doses (3 and 5 mg/kg of body weight) were determined to be effective. The 1.36 mg/pound dose (3 mg/kg) significantly reduced mortality, lung lesion scores and improved gainers when compared with the pigs that received the placebo. The 2.27 mg/pound dose (5 mg/kg) produced non-significant reductions in mortality and lesion scores and significant improvement in gainers when compared with the non-antibiotic treated pigs.

Table 3. Least Square Means and Least Significant Difference (LSD, 1-sided, .05) for Parameters of Interest for Pneumonic Pigs Treated with Various Levels of Ceftiofur Free Acid Equivalents for 3 Days

Dose mg/kg (mg/pound)	No. of Pens[1]	Lung Lesion Score[2]	Percent Mortality	Mortality (degrees)[4]	Percent Gainers[3]	Gainers (degrees)[4]
0 (0 mg)	30	2.50	7.05	15.59	79.36	64.42
3 (1.36 mg)	30	1.10	1.92	10.54	86.17	69.11
0 (0 mg)	30	1.79	9.08	16.51	74.69	60.74
5 (2.27 mg)	30	1.50	3.91	13.26	83.65	66.08
LSD (0 vs 3, .05) (0 vs 1.36)		0.47	4.38	4.22	5.03	3.23
LSD (0 vs 5, .05) (0 vs 2.27)		0.52	4.95	3.76	6.11	4.43
LSD (3 vs 5, .05) (1.36 vs 2.27)		0.54	1.79	2.09	2.57	2.47

[1]Each pen had from 18 to 33 pigs.
[2]Lesion score expressed on scale 0 = no lesion, 10 = 100%.
[3]Gainers = pigs that survived for 14 days and gained > 5 pounds.
[4]Degrees (mortality/gainers) = transformed data to normalize percent mortality and percent gainers.

m. Statistical Analysis:

This study was a randomized complete block design at each location. The following analysis of variance was performed for all parameters of interest for both the 1.36 mg ceftiofur/pound dose (3.0 mg/kg) and the 2.27 mg ceftiofur/pound dose (5.0 mg/kg).

Table 4. Analysis

Code	Source	df	Test Term	Decision
L	Location	9	P	
P	Pen (L)	20	--	
T	Control vs Treatment	1	LT	3 day, treatment regime is efficacious*
LT		9	S	
S		20	--	

* Significance was tested at P =.05 (one-sided). This test has more than an 80% chance of detecting a 10% increase in efficacy. This test was performed for both levels of ceftiofur (3 mg and 5 mg/kg of body weight).

n. Conclusions:
Based on the analysis of the data from this 11 location field trial, it was concluded that ceftiofur administered as ceftiofur sodium (NAXCEL®) is an effective treatment for bacterial pneumonia of swine. Both the 1.36 mg/pound (3.0 mg/kg) and the 2.27 mg/pound (5.0 mg/kg) doses of ceftiofur were determined to be effective.

o. Incidence of Pathogens Cultured at the 11 Field Trial Locations:
Table 5. Incidence of Pathogens Cultured

Pathogens	Number of Isolates
Pasteurella multocida	95
Actinobacillus pleuropneumoniae	45
Salmonella choleraesuis	25
Streptococcus suis Type 2	26

Pigs which died on days one through seven were necropsied and lungs, tracheae and adjacent lymph nodes were cultured. Recovered pathogens were classified by genus and species. As listed above all four bacterial agents commonly associated with swine respiratory disease were isolated in a well controlled laboratory identification procedure. The pathogens were isolated in swine known to be infected in various stages and etiologies of the disease. The data illustrates that a well designed and controlled study verified the incidence and presence of bacterial swine respiratory disease in all the herds and locations tested.

p. Mean Inhibitory Concentration (MIC) Data
MIC data was collected from pathogens isolated from the lungs of control group pigs in the 11 location natural field infection trial. These pigs were sacrificed on day seven of the clinical field trial. Ceftiofur and twelve other antimicrobial compounds were tested against 31 clinical isolates, representing three genera and six species. Ceftiofur sodium was equally or more active than some of the other compounds tested against the common pathogens

found to cause swine bacterial respiratory disease. This study provided well controlled *in vitro* information about the effectiveness of NAXCEL® for the treatment and control of swine bacterial respiratory disease caused by *Actinobacillus pleuropneumoniae*, *Salmonella choleraesuis* and *Streptococcus suis* Type 2.

3. Drug Efficacy Summary:

Throughout the dose determination and field confirmation trials, all the pathogens claimed by labeling were evaluated at various stages of swine respiratory disease.

Pasteurella multocida was the most common opportunistic pathogen encountered in these trials and caused atrophic rhinitis and pneumonia. *Actinobacillus pleuropneumoniae* (artificial and natural infections) and *Salmonella chloeraesuis* were recognized as causing acute epizootic and chronic pneumonia. *Streptococcus suis* Type 2 was isolated from the respiratory tracts of pigs infected with the peracute and acute forms of the disease.

Investigators encountered the diseases in various stages of morbidity and mortality. Different rates of the spread of the disease was observed under standard swine management practices. Rapidly progressing, more advanced cases were treated successfully with the highest recommended dose of 5 mg/kg body weight repeated three times while cases detected early were treated successfully with the lower dose of 3 mg/kg body weight.

Pigs with chronic respiratory disease were also evaluated in these studies. Although mortality due to chronic pneumonia was usually low in the trials. It was considered important to evaluate the dose range in the presence of high herd morbidity. Control of the spread of the disease in all field trial herds was accomplished by the prophylactic treatment of all the swine in the infected pen with either the 3 or 5 mg/kg body weight repeated three times, depending on the severity and etiology and clinical presentation of the disease.

To conclude, the three major swine respiratory syndromes with specific bacterial etiologies were evaluated by their response to Ceftiofur in a dose determination and a confirmation trial. These syndromes (atropic rhinitis, enzootic pneumonia, and pleuropneumonia) were treated and controlled successfully with a 3 to 5 mg/kg body weight repeated three times. Because of these well designed trials, the dose in the field use will be determined by an accurate clinical diagnosis of swine respiratory disease in the affected herd. Severity of the disease syndrome was documented by voluminous clinical observations and necropsies.

From this adequate and well controlled drug efficacy study it can be concluded Ceftiofur Sodium is indicated for the treatment and control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae*, *Pasteurella multocida*, *Salmonella choleraesuis* and *Streptococcus suis*, Type 2.

III. TARGET ANIMAL SAFETY

Two studies were designed and conducted to specifically address target animal safety when ceftiofur 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 anticipated labeled use dose and regimen were administered. Additionally, an 11 location field trial was conducted in which 881 swine were administered ceftiofur at either 3 or 5 mg per kg of body weight (1.36 or 2.27 mg/pound of body weight) for three consecutive days.

Based on the results of these studies, it is concluded that ceftiofur has a wide margin of safety when administered intramuscularly to swine at doses up to 5 mg per kg of body weight (2.27 mg/pound) for three consecutive days. Local pain reactions were the observed effect, and this was transient and deemed not detrimental to the safety of the sick animals to which the drug was administered in the field trials.

B. Pivotal Study #1 (acute toxicity study)

1. Purpose:

   The purpose of this study was to determine the tolerance of feeder pigs for intramuscular ceftiofur sodium at an exaggerated dose.

2. Study Director and Pathologist:

   G.A. Elliott, DVM Senior Veterinary Pathologist/Toxicologist
   Unit 7220-209-2
   The Upjohn Company
   Kalamazoo, MI 49001

3. General Design of the Study:

   a. Test Animals:

      Four crossbred swine (2 barrows and 2 gilts) served as treated animals and four crossbred swine (2 barrows and 2 gilts) served as controls (received sterile water for injection). The pig weights ranged from 28.5 kg (62.7 pounds) to 53 kg (116.6 pounds). These pigs were about 4 months of age.

   b. Dosage Form and Route of Administration

      NAXCEL® Sterile Powder for injection following reconstitution, the same product that will be marketed for this claim was administered intramuscularly.

   c. Dosage:

      The dosage was 125 mg ceftiofur equivalents/kg of body weight (56.8 mg ceftiofur equivalents/pound of body weight) for 5 consecutive days. This dose is greater than 25 times the highest recommended use level.

   d. Test Duration:

      The pigs were treated with either NAXCEL® or sterile water for injection for 5 consecutive days. All pigs were necropsied and gross evaluations made 24 hours post last injection.

   e. Pertinent Parameters Measured:

Measures used to identify target organ and tissue toxicity were: clinical observations, blood and clinical chemistry parameters, body weights, weights of selected organs and gross and microscopic pathology observations of selected tissues.

f. Results:

Clinical observations: No overt clinical signs of toxicity were noted. Lameness and limping were noted in two pigs on Days 3 and 4 of treatment, but were no longer evident by the end of the study. Bleeding from the injection site occurred in two pigs on Day 3 of the study but did not cause complications.

Hematology and clinical chemistry values were obtained pretrial and on Day 6 of the study. One drug treated pig developed a marked anemia as shown by a 3-fold decrease in terminal red blood cell count, hemoglobin and hematocrit values in comparison to the other animals. This pig also had the lowest terminal leukocyte and platelet counts and, when calculated on an absolute basis, had the lowest neutrophil count of all of the pigs in the study. A control pig exhibited markedly elevated terminal leukocyte and neutrophil counts compared to the other nontreated pigs. The clinical chemistry and hematology values of the other three ceftiofur treated animals were within ranges considered to be normal.

Organ weights: There were no appreciable differences in organ weights from the treated versus nontreated pigs.

Gross and microscopic observations: The only gross changes were coloration changes and some hemorrhage at the injection site. Microscopically, the drug-treated animals exhibited more severe areas of muscle necrosis at the injection site than did the control animals (see Table 6). Under the conditions of this exaggerated dosage of ceftiofur and/or placebo, both groups showed evidence of resolution and muscle regeneration at the earlier injection sites when necropsied 24 hours after the last 5 daily injections. No other organs were affected as a result of the elevated dose of ceftiofur tested in this study.

Table 6. Numbers of Pigs per Treatment Group with Microscopic Observations in Skeletal Muscle

Tissue and Microscopic Observations	**Ceftiofur Treatment 0 mg/kg**	**Ceftiofur Treatment 124 mg/kg (56.8 mg/lb)**
Fibroblastic activity with some necrosis present	4/4	4/4
Hemorrhage at injection site	4/4	4/4
Amorphous, eosinophilic, anuclear muscle cells present	0/4	4/4
Undergoing cellular repair at earlier injection sites	4/4	4/4

g. Statistical Analysis: Does not apply.

h. Conclusions:

Results of this study indicate that the administration of ceftiofur sodium at exaggerated doses produced no overt clinical signs of toxicity. All animals gained weight from five days pre-trial through six of the study. the results of this study indicate that swine are very tolerant of intramuscular injections of ceftiofur sodium.

C. Pivotal Study #2 (safety/toxicity study)

4. Purpose of Study

The purpose of this study was to evaluate the toxic potential of NAXCEL® Sterile Powder (ceftiofur sodium) when administered intramuscularly to feeder pigs at multiples of the clinical use level.

5. Name and Address of Investigator:

Study Director and Pathologist:
G.A. Elliott, DVM, Senior Veterinary Pathologist/Toxicologist
Unit 7220-209-2
The Upjohn Company
Kalamazoo, MI 49001

6. General Design of the Study:

a. Test Animals:

Five barrows and five female pigs were tested in each treatment group. All pigs were crossbreds of Yorkshire, Hampshire and Duroc. The males weighed in a range of from 49.5 pounds (22.5 kg) to 104.5 pounds (47.5 kg) and the females ranged from 42.9 pounds (19.5 kg) to 92.4 pounds (42.0 kg).

b. Dosage From and Route of Administration:

NAXCEL® Sterile Powder for injection following reconstitution, the same product that will be marketed for this claim was administered intramuscularly.

c. Dosage:

Three dosages of ceftiofur sodium; 5, 15 and 25 mg free acid equivalents per kilogram of body weight (2.27, 6.82 and 11.36 mg/pound of body weight) were compared to a placebo (sterile water for injection) treated group.

d. Route of Administration:

Intramuscular injections.

e. Test Duration:

Treatments were administered once daily for 15 consecutive days. All pigs were necropsied and evaluations made 24 hours after the last injection.

f. Pertinent Parameters Measured:

Clinical observations, body weight changes, blood and clinical chemistry, weights of selected organs, gross and microscopic observations of selected issues.

g. Results:

Throughout the course of this study, all pigs survived and gained weight. There were no systemic effects attributable to formulated ceftiofur sodium based on the parameters measured.

Gross necropsy examination revealed only incidental changes in most tissues with some red to reddish-tan streaks at the injection site in all groups including the controls. The more prominent streaks were noted in the group of animals that received the two higher doses.

Microscopic evaluations of the injection sites revealed some degree of necrosis with frequently accompanying hemorrhages. This observation was made in some animals in all treated groups as well as the placebo treated controls. There was also evidence that tissue regeneration was taking place in animals from all groups which had experienced injections at 24 hours and longer prior to necropsy.

Table 7. Number of Pigs per Treatment Group with Histopathologic or Gross Pathologic Observations

Observations	**0 mg ceftiofur/kg of body wt/ day for 3 days**	**5 mg ceftiofur/kg of body wt/ day for 3 days (2.27 mg/lb)**	**15 mg ceftiofur/kg of body wt/ day for 3 days (6.82 mg/lb)**	**25 mg ceftiofur/kg of body wt/ day for 3 days (11.36 mg/lb)**
Microscopic Observations Transient necrosis with or without hemorrhage along needle marks at most recent injection sites (24 to 96 hours post injection)	10/10	10/10	10/10	10/10
Gross Observations Red coloration along needle marks at injection site	10/10	9/10	0/10	10/10
Reddish-brown to reddish-tan coloration along needle marks at injection sites	0/10	0/10	10/10	10/10

h. Statistical Method:

A two-way analysis of variance was used to test treatment, sex, treatment by sex interaction and effects for sexes combined. In the case of a significant treatment effect, the Least Significant Difference Method was used to make comparisons of the treated group with the control group. In the case of significant interaction, treatment to control comparisons were performed for each sex separately. Tests of statistical significance were made at the 0.05 level of probability.

i. Conclusions:

Formulated ceftiofur sodium (NAXCEL®) is safe when injected intramuscularly into swine. This formulation is deemed to be a slight muscle irritant.

IV. HUMAN FOOD SAFETY

A. Toxicity Tests

All issues concerning toxicity testing of ceftiofur are addressed in the previous Freedom of Information Summary for New Animal Drug Application 140-338, the approval notice for which appeared in the FEDERAL REGISTER Vol. 55, No. 71, 12 April 1990, page 13768: Freedom of Information Summary for NAXCEL® Sterile Powder (ceftiofur sodium) for Bovine Respiratory Disease. This Summary was updated in June 1992.

B. Safe Concentration of Total Residues

1. No Observed Effect Level (NOEL)

As referenced in the above-mentioned FOI Summary for NADA 140-338, the lowest no observed effect level from the 90-day oral feeding studies in both dogs and rats is 30 mg/kg of body weight.

2. Safe Concentrations (SC) Calculations

SC in Muscle = ADI X Human Weight / Daily Consumption of Meat

where:

Allowable Daily Intake (ADI) = Lowest NOEL / Safety Factor

and

- a safety factor (SF) of 1000 is used because the ADI is based on 90-day feeding study data.
- Daily Consumption of Meat is approximated as 500 g.
- Average Human Weight is approximated as 60 kg.

The lowest NOEL is 30 mg/kg, so

ADI = 30 mg/kg /1000 = 0.03 mg/kg;

therefore

SC in Muscle = 0.03 mg/kg x 60 kg / 0.5 kg = 3.6 mg/kg or 3.6 ppm

Present FDA policy limits the safe concentration in muscle to no more than 3.0 ppm unless chronic toxicity data were used for the SC calculations.

Using the consumption factors listed below and a SC of 3.0 ppm in muscle, the permitted safe concentrations for total residues in other edible tissues are as follows:

Table 8. Permitted Safe Concentrations for Total Residues in Other Edible Tissues

Tissue	Consumption Factor	Safe Concentration
Liver	3	9 ppm
Kidney	4	12 ppm
Fat	4	12 ppm

3. Threshold Assessment

   This compound is a Category A compound as derived from the Threshold Assessment considerations. Based on a Structural Activity Assessment it was assigned to Category C (noncarcinogen). 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

Investigator: F.S. Yein, Ph.D., Upjohn Residue Scientist and Study Director.

Test Animals: twelve (12) Yorkshire x Hampshire crossbred swine (6 male, 6 female), 34-47 kg, 3 to 4 months of age.

Treatment Regimen: intramuscular injection of 5 mg ceftiofur free acid equivalent per kg of body weight (2.27 mg ceftiofur free acid equivalents per pound of body weight), once daily for three consecutive days.

Radioisotope used: 14-C ceftiofur sodium labeled in the 2 position of the thiazole ring.

Withdrawal Schedule: all 12 animals were sacrificed 12 hours after the last dose ("zero-day withdrawal").

Blood samples were taken periodically throughout the dosing period and up to the time of slaughter. Blood and plasma levels of 14-C were found consistently to be highest at two hours after injection in all 12 pigs. The mean values for blood levels at two hours after each daily injection indicate that the drug does not accumulate in the pigs' system. Blood levels of 14-C 2 hours after Day 1, 2 and 3 injections were 11.9 ppm, 14.5 ppm and 15.4 ppm, respectively. Plasma levels of 14-C two hours after day 1, 2 and 3 injections were 19.2 ppm, 23.4 ppm and 23.1 ppm, respectively.

Total 14-C residues excreted in the urine and feces of all 12 animals ranged from 65.8% to 90.8% of the doses administered. The mean value for urine for all 12 pigs

was 61.8% while feces mean value was 10.75%. Therefore about 73% of the total 14-C-labeled ceftiofur dose was excreted by 12 hours after the last injection.

Samples of muscle, liver, kidney and fat from each animal were radioassayed by combustion of the sample, trapping the resulting 14-CO2, and liquid scintillation counting. Mean residues from the 12 animals are shown in the following table. Kidney is the tissue with the highest concentration of total residues followed by the injection site, liver, fat and non-injection site muscle.

Table 9. Total Radioactivity in Edible Tissues of Swine Given Intramuscular Injections of 14-C Ceftiofur at 5 mg/kg of Bodyweight Once Daily for Three Days (all values are in ppm).

Tissue	Safe Concentration	Mean Observed Concentration[1]	Highest Observed Observed Concentration[2]	Standard Deviation
Muscle	3	0.76	1.22	0.24
Liver	9	1.55	1.92	0.18
Kidney	12	4.47	6.73	0.81
Fat	12	1.49	2.47	0.54
Injection Site	30	2.90	6.39	1.28

[1] Mean values from 12 swine each measured at 12 hours after the last injection.

[2] Highest observed concentration from the 12 swine used in the study. Swine kidneys from the above described residue study were subjected to wet chemistry procedures to establish the profile of 14-C-ceftiofur metabolites. The approach involved protein precipitation and solvent extractions, followed high performance liquid chromatography (HPLC) of the free metabolites.

About 65% of the residue in kidney was bound to macromolecules (protein) and about 35% was freely extractable. The extraction and fractionism of kidney tissue demonstrated that there were four primary components of the residue. Desfuroylceftiofur cysteine disulfide (DCD) was the major metabolite, comprising approximately 12% of the total residue. An unidentified polar metabolite C, representing 11.3% of the total residue, was also found in the kidney extract. Two other unknown polar metabolites, A and B, were also present in amounts of less than 10% of the total residue.

D. Comparative Metabolism Study

The metabolic profiles of ceftiofur in the urine and kidney extracts of rats treated orally with high doses of (about 700 mg/kg body weight) 14-C labeled ceftiofur were compared to the urine and kidney extracts of pigs dosed intramuscularly for 3 days with 5 mg/kg body weight 14-C ceftiofur (2.27 mg/pound). 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 are highest in the tissue relative to the calculated safe concentration.

Kidney Metabolites: The bound and free metabolite profiles in the rat were compared to those found in the total residue study described in Part C. About 65% of the residue was bound and 35% was free in the kidneys of both species. Of the free

residues, all four metabolites found in swine were also found in the rat kidney extracts, as shown in the following table.

Table 10. Percentages (PPM 14-C-Ceftiofur Free Acid Equivalents) of Metabolites Found in the Kidneys of Rats from Multiple High Oral Doses Versus in Kidneys of Pigs from Intramuscular Doses

Metabolite Name (R.T. in minutes)	Rats (8 Hours) - Male	Rats (8 Hours) - Female	Rats (24 Hours) - Male	Rats (24 Hours) - Female	Pigs (12 hours)
Polar A (4)	17.5 (2.0)	12.3 (3.1)	27.5 (1.4)	27.1 (1.3)	7.6 ± 2.3 (0.3 ± 0.1)
Polar B (5)	0.9 (0.1)	0 (0)	0.9 (0)	0.7 (0)	4.3 ± 3.1 (0.2 ± 0.1)
Polar C (6)	2.2 (0.3)	2.2 (0.6)	1.2 (0.1)	1.9 (0.1)	11.3 ± 2.9 (0.5 ± 0.2)
DCD (11-12)	8.1 (0.9)	15.5 (3.9)	0.7 (0)	0 (0)	12.3 ± 4.1 (0.6 ± 0.2)

Urinary Metabolites: The metabolite profiles in the urine of rats and pigs showed unmetabolized ceftiofur, 3,3'-desfuroylceftiofur disulfide and unknown Polar A as significant metabolites. Desfuroylceftiofur cysteine disulfide (DCD), small amounts of unknown Polar B, and desfuroyl ceftiofur were present in both rats and pigs. Ceftiofur sulfoxide cysteine thioester was the major metabolite in urine from rats but only minor in urine from pigs. There is a very close qualitative match (89%) in urinary metabolite profiles of rats and pigs.

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 man 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 the edible tissues of swine treated with the maximum dose (intramuscular injection of 5 mg/kg of body weight once daily for three days). 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. The analytical method used by Upjohn to analyze for non-radiolabeled ceftiofur residues in their drug development work is described in Upjohn Technical Report 788-9760-88-010, titled "HPLC Method for the Analysis of Bound Desfuroylceftiofur Residues in Bovine Kidney Using Precolumn Derivatization and UV Detection," 1988. Upjohn used the same method for analysis of bovine and porcine kidney.

V. AGENCY CONCLUSIONS

The data in support of this NADA satisfy the requirements of Section 512 of the Food Drug and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that ceftiofur sodium (NAXCEL®), when administered to swine by a single intramuscular injection at a dose range of 3 to 5 mg/kg is safe and effective for the treatment of swine respiratory disease associated with the major porcine pathogens.

Total residues in the edible tissues at 12 hours post-treatment (0 day withdrawal), were less than half of the permitted safe concentration in each tissue. Therefore neither a marker compound nor a tolerance for a marker compound is required.

Labeling restricts this drug to use by or on the order of a licensed veterinarian. This decision was based on the following factors: (a) adequate directions can not be written to enable laypersons to appropriately diagnose and subsequently use this product to treat swine respiratory disease caused by a variety of porcine pathogens, and (b) a dose range is indicated and therefore requires a veterinary clinician to calculate a proper dose depending on the etiology of the disease.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(c)(2) (F)(iii), this approval qualifies for 3 years of marketing exclusivity because it contains reports of new clinical or field investigations and human food safety studies, other than bioequivalence or residue studies, essential to the approval and conducted or sponsored by the applicant. NAXCEL® is under patent number U.S.446437 expiring August 7, 2001.

VI. LABELING

1. Naxcel® 4 gram product label

2. Naxcel® package insert

Copies of these labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.