Date of Approval Letter: June 18, 2004

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 140-338

NAXCEL Sterile Powder
(ceftiofur sodium)

To establish a 4-day pre-slaughter withdrawal time for swine

Sponsored by:
Pharmacia & Upjohn Company
A Division of Pfizer Inc

1. GENERAL INFORMATION:

a. File Number:	NADA 140-338
b. Sponsor:	Pharmacia & Upjohn Co. 7000 Portage Road Kalamazoo, MI 49001-0199 Drug Labeler Code: 000009
c. Established Name:	Ceftiofur sodium
d. Proprietary Name:	NAXCEL Sterile Powder
e. Dosage Form:	Sterile powder for reconstitution to injectable solution
f. How Supplied:	1 and 4 g glass vial
g. How Dispensed:	Rx
h. Amount of Active Ingredients:	50 mg ceftiofur equivalents (CE) per mL of reconstituted solution
i. Route of Administration:	Intramuscular (IM) injection
j. Species/Class:	Swine
k. Recommended Dosage:	1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) of body weight (1 mL of reconstituted sterile solution per 22 to 37 lb of body weight). Treatment should be repeated at 24 h intervals for a total of three consecutive days.
l. Pharmacological Category:	Antimicrobial
m. Indications:	NAXCEL Sterile Powder is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae*, *Pasteurella multocida*, *Salmonella choleraesuis*, and *Streptococcus suis* type 2.
n. Effect of Supplement:	To establish a 4-day pre-slaughter withdrawal time for swine

2. EFFECTIVENESS:

This supplement to NADA 140-338 does not change the effectiveness data for this product.

3. TARGET ANIMAL SAFETY:

This supplement to NADA 140-338 does not change the target animal safety data for this product.

4. HUMAN FOOD SAFETY:

A. Toxicology

Complete summaries of all pivotal toxicology studies of ceftiofur pertaining to human food safety are found in the original Human Safety Section of the Freedom of Information Summaries for NADA 140-338 and NADA 141-235 (ceftiofur crystalline free acid, EXCEDE for Swine Sterile Suspension). As described in the Freedom of Information Summary for NADA 141-235, CVM interpreted the results of the Acute Single Dose Intake (ASDI) study summarized in NADA 140-338 to establish a safe concentration of 166 ppm for injection site muscle.

B. Residue Chemistry

The total residue depletion and metabolism data in the target species and comparative metabolism data in the toxicological species for ceftiofur are summarized in the FOI Summaries for NADA 140-338 and NADA 140-890 (ceftiofur hydrochloride, EXCENEL RTU Sterile Suspension). The marker residue in edible tissues is the sum of ceftiofur and desfuroylceftiofur-related metabolites, measured by HPLC as the stable derivative desfuroylceftiofur acetamide (DCA). The target tissue for residue monitoring is kidney and the tolerance is 0.25 ppm. The following pivotal study was conducted to determine the withdrawal period.

1) **Title:** Decline of ceftiofur and desfuroylceftiofur-related residues in swine tissues after intramuscular administration of ceftiofur sodium (NAXCEL Sterile Powder) to swine at a rate of 5 mg ceftiofur equivalents/kg body weight for three consecutive days (Study Report No. a0100487, 12 March 2002).

   Principal Investigators: D.A. Merritt & M.J. Prough, Pharmacia Animal Health, Kalamazoo, MI.

   Animal Species: swine.

   Breed/Sex: Yorkshire mixed-breed/male and female in equal numbers.

   Number of Animals: 36.

Health Status: clinically healthy.

Route of Administration: intramuscular (IM).

Dose Rate: 5 mg of ceftiofur equivalents/kg body weight.

Duration of Dosing: 1 treatment per day at approximately 24-hour intervals for three consecutive days.

Marker Residue Depletion Data: Kidney tissues were collected from six animals at each time point of 3, 24, 48, 72, 96, and 120 hours after the three-day treatment period and were assayed for desfuroylceftiofur-related residue by the HPLC-DCA regulatory assay. This provided kidney residue concentration information as summarized in the following table.

Concentration of Desfuroylceftiofur-related Residue by the HPLC-DCA Assay in Swine Following 3 Days of IM Treatment of NAXCEL Sterile Powder at 5 mg ceftiofur/kg/day

Slaughter Interval, (hours)	**Concentration, μg/g * (Mean ± SD)**
	Kidney
3	5.4 ± 1.1
24	1.1 ± 0.2
48	0.38 ± 0.09
72	0.18 ± 0.06
96	(0.073) ± 0.012
120	(<LOD-0.067)

* LOQ = 0.10 μg/g, LOD = 0.050 μg/g. Values <LOQ but >LOD are listed in parentheses.

2) Withdrawal Period

The data from the study above were analyzed by a statistical method which determines the statistical tolerance limit for the 99th percentile of the population with a 95% confidence. At 4 days, the upper 95 percent confidence limit on the 99^{th} percentile for kidney residues was less than the kidney tolerance (0.25 ppm). These data support a 4-day pre-slaughter withdrawal period after intramuscular administration of NAXCEL Sterile Powder in swine when used according to label directions.

C. Microbial Food Safety

This NADA supplement establishes a 4-day pre-slaughter withdrawal period for swine. Because this change to NADA 140-338 does not change the product indication, dose, dose duration, or other conditions of use beyond the addition of a withdrawal period, an evaluation of Microbial Food Safety was determined not to be necessary at this time for the supplemental approval to this product.

D. Regulatory Method for Residues

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

5. USER SAFETY:

Studies to evaluate the safety of ceftiofur to users are discussed in detail in the original FOI Summary for NADA 140-338.

Human Warnings are provided on the product labeling as follows:

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 report adverse effects in users, to obtain more information or obtain a material safety data sheet, call 1-800-253-8600.

6. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that NAXCEL Sterile Powder, when administered according to the label directions, is safe and effective 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.

Labeling restricts this drug to use by or on order of a licensed veterinarian. This decision was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product to treat swine respiratory disease, (b) restricting this drug to use by or on order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues, and (c) the rate of emergence of ceftiofur-resistant organisms may be reduced by the involvement of veterinarians in product use.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

In accordance with the Center's supplemental approval policy 21 CFR 514.106(b)(2)(x), this is a Category II change which did not require a reevaluation of safety and effectiveness data in the parent application.

No patents were submitted with this application.

7. ATTACHMENTS:

Facsimile labeling is attached as indicated below.

A. NAXCEL Sterile Powder - 1 g vial and shipper carton label
B. NAXCEL Sterile Powder - 4 g vial and shipper carton label
C. NAXCEL Sterile Powder - package insert