Date of Approval Letter: June 2, 2006

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 period for cattle

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

1. GENERAL INFORMATION:

a. File Number:	NADA 140-338
b. Sponsor:	Pharmacia & Upjohn Co. a Division of Pfizer, Inc. 235 East 42d St. New York, NY 10017 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) or subcutaneous (SC) injection
j. Species/Class:	Cattle; may be used in lactating dairy cattle
k. Recommended Dosage:	0.5 to 1.0 mg ceftiofur per pound of body weight (1-2 mL reconstituted sterile solution per 100 lb body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments.
l. Pharmacological Category:	Antimicrobial
m. Indications:	NAXCEL Sterile Powder is indicated for treatment of bovine respiratory disease (shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*. NAXCEL Sterile Powder is also indicated for treatment of acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

n. Effect of Supplement: To establish a 4-day pre-slaughter withdrawal period for cattle

2. EFFECTIVENESS:

CVM did not require effectiveness studies for this supplemental approval. The FOI Summaries for the original approval of NAXCEL Sterile Powder (NADA 140-338) dated January 25, 1988, and the supplemental approvals of NADA 140-338 dated April 5, 1990; August 24, 1995; and May 29, 2001, contain summaries of studies that demonstrate effectiveness of the drug for cattle.

3. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The FOI Summaries for the original approval of NAXCEL Sterile Powder (NADA 140-338) dated January 25, 1988, and the supplemental approvals of NADA 140-338 dated April 5, 1990, and May 29, 2001, contain summaries of target animal safety studies for cattle.

4. HUMAN FOOD SAFETY:

A. Toxicology

The toxicity testing of ceftiofur is summarized in the FOI Summary for the original approval of NAXCEL Sterile Powder (NADA 140-338) dated January 25, 1988, and in the FOI Summary dated April 1996, for the original approval of EXCENEL RTU (ceftiofur hydrochloride) Sterile Suspension (NADA 140-890) for use in swine. Tolerances for cattle are summarized in the FOI Summary for NAXCEL XT (now EXCEDE) Sterile Suspension (NADA 141-209) dated September 5, 2003.

Safe concentrations are established for cattle as follows:

Muscle:	4.4 ppm
Liver:	13.2 ppm
Kidney:	26.4 ppm
Fat:	26.4 ppm
Injection site:	166 ppm
Milk:	0.320 ppm

B. Residue Chemistry

The total residue depletion and metabolism in the target species and comparative metabolism in the toxicological species for ceftiofur are summarized in the FOI Summaries under NADA 140-338 and NADA 140-890. The following pivotal study was conducted to confirm applicable withdrawal periods in cattle.

1. Study

"Decline of ceftiofur and desfuroylceftiofur-related metabolites in bovine tissues after intramuscular administration of ceftiofur sodium (NAXCEL Sterile Powder) to cattle at a rate of 2.2 mg ceftiofur equivalents/kg body weight for five consecutive days". Study Number: 2000-0427. June 2001.

Principal Investigators: D.A. Merritt and M.J. Prough, Pfizer Animal Health, Kalamazoo, MI

Animal Species: Bovine

Breed: Mixed breed

Number of Animals/Sex: 38; 18 male and 18 female (plus 1 male and 1 female control animals)

Weights of Animals: 200 to 297 kg

Health Status: Clinically healthy

Route of Administration: Intramuscular (IM) injection

Dose Rate: 2.2 mg ceftiofur equivalents (CE)/kg body weight (actual dose 2.25 ± 0.03 mg CE/kg BW)

Duration of Dosing: one injection daily for five consecutive days

Marker Residue Depletion Data: Samples of kidney, liver, injection site, muscle, and fat were assayed for desfuroylceftiofur-related residue by the HPLC-DCA assay. The results of the assays are provided in Table 1. The limit of detection (LOD) of the assay was 0.05 ppm and the limit of quantification (LOQ) was 0.10 ppm.

Table 1. Mean Concentration of Ceftiofur and Desfuroylceftiofur-Related Residues (as DCA) in Bovine Tissues from Animals Receiving Five Doses of NAXCEL Sterile Powder (2.2 mg CE/kg BW)

Tissue	Mean ± S.D., ppm					
	3 hours	24 hours	48 hours	72 hours	96 hours	121 hours
Kidney	5.29 ± 0.79	1.00 ± 0.18	0.35 ± 0.08	0.20 ± 0.07	0.12 ± 0.02	< LOQ
Injection site	33 ± 18	0.94 ± 0.85	0.25 ± 0.07	0.15 ± 0.06	0.21 ± 0.13	< LOQ
Liver	1.60 ± 0.25	0.19 ± 0.06	0.44 ± 0.13	< LOQ	< LOQ	< LOQ
Muscle	0.36 ± 0.04	< LOQ	< LOD	< LOD	<LOD	NA
Fat	0.31 ± 0.15	< LOQ	< LOD	NA	NA	NA

NA = not assayed

By 3 hours after the last dose, all injection sites contained less than 95 ppm DCA.

2. Target Tissue and Marker Residue

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

3. Tolerances

   Cattle tolerances are: 0.4 ppm DCA in kidney, 2 ppm DCA in liver, 1 ppm DCA in muscle, and 0.1 ppm DCA in milk. For research purposes, a value of 95 ppm DCA has been established for making decisions regarding the safety of the injection site.

4. Withdrawal Period

   The kidney data were analyzed with a statistical method which determines the statistical tolerance limit for the 99^{th} percentile of the population with 95% confidence as outlined in FDA's *Guideline for Establishing a Withdrawal Period*. The tolerance limit falls below the kidney tolerance of 0.4 ppm at 93 hours after the last dose. The data support the assignment of a 96-hour (4-day) pre-slaughter withdrawal period for the IM treatment.

   Based on a comparison of residue data for the SC route of administration (FOI Summary for NADA 140-338 dated May 29, 2001) vs. that for the IM route, FDA also established a 4-day pre-slaughter withdrawal period for the SC treatment.

5. Milk Discard

   The milk tolerance has not changed. Consequently, no milk out data were required and the no discard can be maintained.

C. Microbial Food Safety

FDA concluded the impact of the proposed supplemental application on microbial food safety was not of a magnitude that required a hazard characterization or a full microbial food safety assessment.

D. Analytical Methods 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 NAXCEL Sterile Powder (NADA 140-338) dated January 25, 1988.

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 obtain a material safety data sheet (MSDS) please call 1-800-733-5500. To report any adverse event please call 1-800-366-5288.

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 of bovine respiratory disease (shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*; and for the treatment of acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

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 cannot be written to enable lay persons to appropriately diagnose and subsequently use this product to treat bovine respiratory disease or foot rot, and (b) restricting this drug to use by or on the order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues.

In accordance with 21 CFR 514.106(b)(2) this is a Category II change which did not require a reevaluation of safety and effectiveness data in the parent application.

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

No patent information was 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