Date of Approval Letter: June 2, 2006

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 140-890

EXCENEL RTU Sterile Suspension
(ceftiofur hydrochloride)

To establish a 3-day pre-slaughter withdrawal period for cattle

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

1. GENERAL INFORMATION:

a. File Number:	NADA 140-890
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 hydrochloride
d. Proprietary Name:	EXCENEL RTU Sterile Suspension
e. Dosage Form:	Sterile suspension for injection
f. How Supplied:	100 mL glass vial
g. How Dispensed:	Rx
h. Amount of Active Ingredients:	50 mg ceftiofur equivalents (CE) per mL
i. Route of Administration:	Intramuscular (IM) or subcutaneous (SC) injection
j. Species/Class:	Cattle; may be used in lactating dairy cattle
k. Recommended Dosage:	For bovine respiratory disease and acute bovine interdigital necrobacillosis: administer by IM or SC administration at the dosage of 0.5 to 1.0 mg CE/lb (1.1 to 2.2 mg/kg) body weight (BW) (1 to 2 mL sterile suspension per 100 lb BW). Administer daily at 24 hour intervals for a total of three consecutive days. Additional treatments may be administered on Days 4 and 5 for animals which do not show a satisfactory response (not recovered) after the initial three treatments. In addition, for BRD only, administer IM or SC 1.0 mg CE/lb (2.2 mg/kg) BW every other day on Days 1 and 3 (48 hour interval). Do not inject more than 15 mL per injection site.
l. Pharmacological Category:	Antimicrobial
m. Indications:	EXCENEL RTU Sterile Suspension is indicated for treatment of the following bacterial diseases: bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*; acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and

	Bacteroides melaninogenicus; and acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.
n. Effect of Supplement:	To establish a 3-day pre-slaughter withdrawal period for cattle

2. EFFECTIVENESS:

CVM did not require effectiveness studies for this supplemental approval. The FOI Summaries for the supplemental approvals of EXCENEL RTU Sterile Suspension (NADA 140-890) dated July 26, 1998, and February 8, 2002, 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 Summary for the supplemental approval of EXCENEL RTU Sterile Suspension (NADA 140-890) dated July 26, 1998, contains a summary 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 EXCEDE Sterile Suspension (NADA 141-209, approved 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 the applicable withdrawal period in cattle.

1. Study

"Determination of Desfuroylceftiofur-Related Residue in Injection Sites and Kidneys of Beef Cattle Receiving Subcutaneous Injections of EXCENEL RTU Sterile Suspension at 2.2 mg/kg of Body Weight/Day for Five Consecutive Days." Study Number 1531N-60-04-459.

Principal Investigators: R.E. Hornish, Pfizer Animal Health, Kalamazoo, MI, and C. Heird, Southwest Bio-Labs, Las Cruces, NM

Animal Species: Bovine

Breed: Mixed breed

Number of Animals/Sex: 32, 16 males, 16 females

Weights of Animals: 145-295 kg

Health Status: Clinically healthy

Route of Administration: Subcutaneous (SC)

Dose Rate: 2.2 mg CE/kg body weight

Duration of Dosing: one injection daily for five consecutive days

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

Table 1. Mean concentrations of ceftiofur and desfuroylceftiofur-related residue (as DCA) in the kidney and 5th injection site of cattle treated with 5 daily injections of 2.2 mg ceftiofur equivalents/kg body weight

Treatment Group	Sacrifice Interval	Kidney (µg/g)	5th Injection Site (µg/g)
T01	1 day	0.754 ± 0.245	2.47 ± 1.60
T02	2 days	0.244 ± 0.064	3.05 ± 3.90
T03	3 days	0.133 ± 0.027	0.556 ± 0.329
T04	4 days	<LOQ	0.875 ± 0.788
T05	5 days	<LOQ	1.32 ±1.06

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 residue data of Study Number 1531N-60-04-459 were analyzed by a statistical method which determines the statistical tolerance limit for the 99^{th} percentile of the population with a 95% confidence as outlined in the FDA's *Guideline for Establishing a Withdrawal Period*. The tolerance limit falls below the kidney tolerance of 0.4 ppm by 3 days after dosing. The data support the assignment of a 3-day pre-slaughter withdrawal period for the use of ceftiofur HCl, administered IM or SC at 1.1 to 2.2 mg/kg body weight for 3 to 5 days.

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 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 EXCENEL RTU Sterile Suspension, when administered according to the label directions, is safe and effective for the treatment of bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*; acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*; and acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.

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, foot rot, or acute metritis, 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. EXCENEL RTU Sterile Suspension - 100 mL vial label
B. EXCENEL RTU Sterile Suspension - package insert