Date of Approval: June 2, 2006

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-238

SPECTRAMAST LC Sterile Suspension
(ceftiofur hydrochloride)

To establish a 2-day pre-slaughter withdrawal period for cattle

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

1. GENERAL INFORMATION:

a. File Number:	NADA 141-238
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:	SPECTRAMAST LC Sterile Suspension
e. Dosage Form:	Sterile oil suspension
f. How Supplied:	10 mL plastic syringes (PLASTETS) with cannula
g. How Dispensed:	Rx
h. Amount of Active Ingredient:	Each PLASTET contains ceftiofur hydrochloride equivalent to 125.0 mg ceftiofur (12.5 mg/mL).
i. Route of Administration:	Intramammary infusion
j. Species/Class:	Bovine/lactating dairy cattle
k. Recommended Dosage:	Infuse one (1) syringe into each affected quarter. Repeat this treatment in 24 hours. For extended duration therapy, once daily treatment may be repeated for up to 8 consecutive days.
l. Pharmacological Category:	Antimicrobial
m. Indications:	SPECTRAMAST LC Sterile Suspension (ceftiofur hydrochloride) is indicated for the treatment of clinical mastitis in lactating dairy cattle associated with coagulase-negative staphylococci, *Streptococcus dysgalactiae*, and *Escherichia coli*. Cows with systemic clinical signs caused by mastitis should receive other appropriate therapy under the direction of a licensed veterinarian.
n. Effect of Supplement:	To establish a 2-day pre-slaughter withdrawal period for cattle

2. EFFECTIVENESS:

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the original approval of SPECTRAMAST LC Sterile Suspension (NADA 141-238) dated February 9, 2005, contains a summary 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 original approval of SPECTRAMAST LC Sterile Suspension (NADA 141-238) dated February 9, 2005, 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 applicable withdrawal periods in cattle.

1. Study

   "Concentration of Ceftiofur Residues in Tissues of Lactating Dairy Cows at Various Intervals Following the IMM Administration of 125 mg Ceftiofur HCl (PNU-64279A) per Quarter per Day into All 4 Quarters of the Udder for 8 Consecutive Days." Study Number: 2000-0431.

Principal Investigators: R.E. Hornish and M.J. Prough, Pfizer Animal Health, Kalamazoo, MI

Animal Species: Bovine

Breed: Holstein

Number of Animals/Sex: 25, all lactating female

Weights of Animals: 582-819 kg

Parity: 1st through 4th lactation

Health Status: Clinically healthy

Average Pre-Dose Milk Production: 32.3 ± 4.2 kg

Route of Administration: intramammary (IMM)

Dose Rate: 125 mg CE/quarter into all 4 quarters/day (total daily dose = 500 mg)

Duration of Dosing: one infusion into each quarter daily for eight consecutive days

Marker Residue Depletion Data: Samples of kidney, liver, muscle, and fat 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 0.030 ppm.

Table 1. Mean Concentration of Ceftiofur and Desfuroylceftiofur-related Residue (as DCA) in the Tissues of Lactating Dairy Cattle Following the Daily Intramammary Administration of 125 mg of Ceftiofur Hydrochloride Into All Four Quarters for Eight Consecutive Days

Slaughter Group	Mean Concentration of Ceftiofur Residue as DCA, ppm			
	Kidney	Liver	Muscle	Fat
12-hour Withdrawal	0.277 ± 0.049	<LOQ	< LOD	< LOD
24-hour Withdrawal	0.172 ± 0.056	<LOQ	< LOD	< LOD
36-hour Withdrawal	0.112 ± 0.001	<LOQ	< LOD	< LOD
48-hour Withdrawal	<LOQ	< LOD	< LOD	< LOD
72-hour Withdrawal	< LOD	< LOD	< LOD	< LOD

At all time points, kidney is the tissue with the highest relative residue concentration.

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 this study 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 at 25 hours after the last dose. The data support the assignment of a 48-hour (2-day) pre-slaughter withdrawal period for the IMM administration of SPECTRAMAST LC Sterile Suspension in lactating dairy cattle when used according to label directions.

5. Milk Discard

   The milk tolerance has not changed. Consequently, no milk out data were required and the 72-hour 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:

Discard empty container: Do not reuse. 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. Sensitization of the skin may be avoided by wearing latex gloves.

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 to obtain a material safety data sheet, 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 SPECTRAMAST LC Sterile Suspension, when administered according to the label directions, is safe and effective for the treatment of clinical mastitis in lactating dairy cattle associated with coagulase-negative staphylococci, *Streptococcus dysgalactiae*, and *Escherichia coli*.

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 clinical mastitis, 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. SPECTRAMAST LC Sterile Suspension - PLASTET Label
B. SPECTRAMAST LC Sterile Suspension – Carton Label
C. SPECTRAMAST LC Sterile Suspension - Package Insert