TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

NAXCEL® STERILE POWDER (CEFTIOFUR SODIUM)

This Environmental Assessment (EA) is submitted in compliance with 21 CFR 25.31a to support the supplement to New Animal Drug Application (sNADA) #140-338 for NAXCEL Sterile Powder (ceftiofur sodium).

1. DATE

July 15, 1995

2. NAME OF APPLICANT

The Upjohn Company

3. ADDRESS

7000 Portage Road
Kalamazoo, MI 49001
telephone (616) 323-4000

4. DESCRIPTION OF THE PROPOSED ACTION

4.1 Requested Approval - Need for the Action

This environmental assessment is necessary for the approval of a Supplemental New Animal Drug Application (sNADA) which provides for the use of NAXCEL Sterile Powder (ceftiofur sodium) for the treatment of bovine interdigital necrobacillosis (foot rot, pododermatitis).

This product is approved for treatment of bovine respiratory disease (BRD) in beef cattle and lactating dairy cattle (see Federal Register of February 24, 1988 re: NADA 140-338 and Supplement to NADA 140-338, March 22, 1991).

4.2 Location Where the Product Will be Produced

4.2.1 Drug Substance

The drug substance, ceftiofur sodium, will be produced at The Upjohn Company's main pharmaceutical and chemical manufacturing complex in Kalamazoo, Michigan.

4.2.2 Drug Product

The drug product, Ceftiofur Sodium Sterile Powder, will be manufactured at SmithKline Beecham--U.S.'s Anti-Infective Manufacturing Plant; their main antibiotic manufacturing facility, located in Conshohocken, Pennsylvania.

4.3 Location Where the Product Will be Used

Drug product will be stored in distribution centers prior to transportation to veterinarians. The ultimate use of the finished product will be on dairy farms, beef farms and commercial feedlots, where it will be reconstituted and injected intramuscularly in cattle. The use potential of the drug is in all states in the U.S. However, there are 10 states which account for 68 percent of the U.S. milk production with 65 percent of the nation's dairy cattle. They are in descending order of milk production: Wisconsin, California, New York, Minnesota, Pennsylvania, Ohio, Michigan, Texas, Iowa and Washington. Beef cattle are concentrated in five states and account for 70 percent of the beef cattle. These states are: Colorado, Texas, Nebraska, Kansas and Iowa.

4.4 Locations Where the Product Will be Disposed

Disposal of drug substance or drug product may result from processing in the form of off-specification lots, from distribution activities in the form of returned goods, or from end user disposal of individual units of empty or partly empty finished product containers. Bulk quantities of material for disposal will be generated only at the manufacturing site and will be handled with other compatible waste materials resulting from current operations. The present infrastructure at the proposed manufacturing site provides for the recovery and/or ultimate disposal mechanisms identified below.

4.4.1 Off-Specification Lots of the Active Ingredient

Off-specification lots of the active ingredient, ceftiofur sodium, manufactured by The Upjohn Company, are reprocessed in accordance with procedures identical to those in the NADA for the drug product.

4.4.2 Off-Specification Lots of the Drug Product and Broken Vials

Off-specification lots of drug product and broken vials generated at SmithKline Beecham Pharmaceutical's facility are disposed of as pharmaceutical waste by incineration at Ogden Martin Systems in Alexandria, Virginia, or another previously audited (SKB) incineration facility.

4.4.3 Returned Goods

Drug product in the form of returned goods are received at the Upjohn Portage site facility where they are crushed, shredded, and placed in an approved sanitary landfill or incinerated in an on-site approved incinerator (see Section 4.4.3.1).

4.4.3.1 *Incinerator*. The incinerator is operated as a Resource Conservation and Recovery Act (RCRA) interim status treatment storage and disposal facility under license #MID000820381 in compliance with 40 CFR 264, Subpart O requirements. Additionally, 40 CFR 265.1(b) and Section 3005(e) of RCRA provide for the continued operation of an existing facility that meets defined conditions, until final administrative disposition of the owner's and operator's permit application is made.

The incinerator is a two-stage system: the primary chamber rotary kiln operates at a minimum of 700°F; the secondary chamber, where final destruction of the product and off-gasses occurs, operates at 1,904°F. The incinerator is equipped with a pollution control equipment train designed to remove gaseous and particulate pollutants. The pollution control equipment consists of: a quench section, an acid-gas pre-scrubber, a Venturi scrubber, an entrainment separator, an induced draft fan, and an exhaust stack.

A hazardous waste RCRA Part B/Act 64 permit application has been submitted to the Waste Management Division of the Michigan Department of Natural Resources (MDNR) in Lansing, Michigan. The Upjohn facility is operating under interim status until action is taken on the permit application. The State air permit issued on July 15, 1980 (#242-80), revised to incorporate the Act 64 requirements, was approved on May 26, 1993.

All necessary permits are in place for the manufacture of the product (Ceftiofur Sodium Sterile Powder), as an existing interim status facility in accordance with Section 3005(e) of RCRA and Michigan Act 64 licensing requirements.

4.4.4 Individual Empty or Partly Empty Vials

Individual empty or partly empty vials will be disposed of by veterinarians, and will likely be handled by the community's solid waste management system. Negligible amounts of the active ingredient, ceftiofur sodium, are expected to remain with empty product containers.

4.5 Type of Environment Present at and Adjacent to Manufacturing Locations

4.5.1 Drug Substance

The drug substance will be manufactured at the Upjohn Company's Portage site facility, located in the northern portion of the City of Portage in Kalamazoo County, Michigan. Kalamazoo County is in the southwest corner of the State, approximately 140 miles equidistant from Chicago and Detroit. The facility is 1.7 miles northeast of the center of the City of Portage, 5.4 miles south of the center of the City of Kalamazoo, and directly to the south of the Kalamazoo/Battle Creek International Airport.

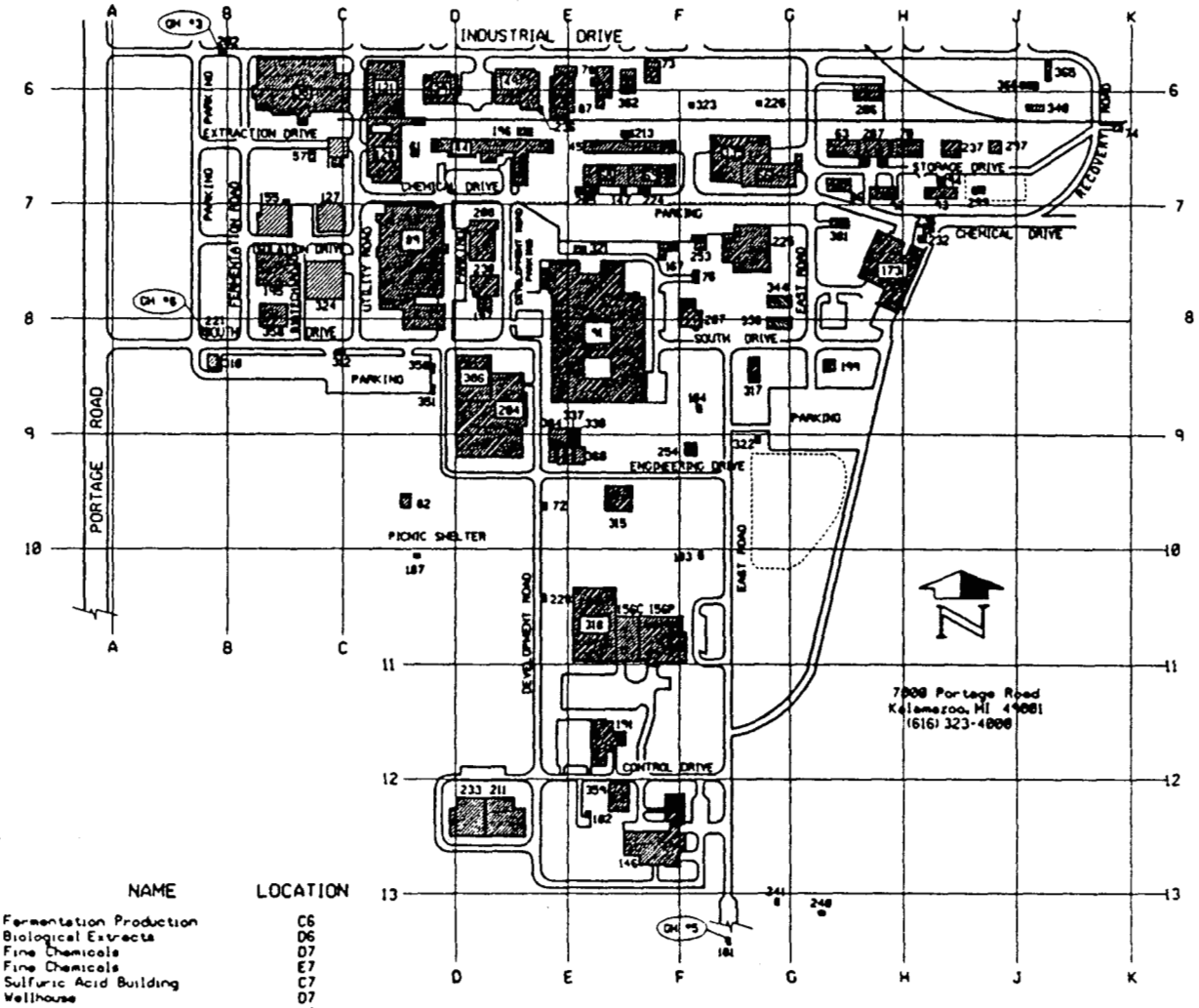
The area in the immediate vicinity of the Upjohn facility is a mix of zoning including heavy and light industry, general business, and single- and multiple-family residences. Upjohn is on land zoned for heavy industry. The site is directly bordered by airport property, residences, and undeveloped land. The climate is temperate. In terms of the Universal Transverse Mercator Coordinate System (UTM), the plant is located in Zone 16 at 619.1 Km east and 4674.1 Km north, which corresponds to latitude 42°12'42" north and longitude 85°33'25" west.

The Upjohn complex consists of approximately 80 buildings including chemical and pharmaceutical manufacturing operations, offices, laboratories, utility operations, and various other support buildings (see Item 14-1 at page 4A). The plant site occupies a portion of approximately 810 hectares lying south of Bishop Road, east of Portage Road, north of Centre Street, and west of Sprinkle Road in Portage, Michigan.

4.5.2 Drug Product

The drug product will be manufactured at SKB - U.S.'s main antibiotic manufacturing facility and is located in Upper Merion Township. The facility sits on a five-acre site. It is comprised of 184,080 square feet and is dedicated to the manufacturing and packaging of antibiotics for SKB and SKB's contract manufacturing customers. The SKB Anti-Infective Manufacturing facility is part of a complex which includes Research and Development facilities located to the west and south and River Road to the east of the complex. The Anti-Infective facility is bordered on the north by Swedeland Road and light industrial facilities. The manufacturing facility has its own shipping and receiving department, warehouse, and maintenance group. The manufacturing area consists of one bottle/vial preparation room, three sterile fill suites, six lyophilizers, three capping suites, and three packaging/labeling suites. The product manufacturing (solution preparation) is performed on the fourth floor.

PORTAGE ROAD BUILDINGS
EAST SIDE
South of Industrial Drive



BLDG.#	NAME	LOCATION
38	Fermentation Production	C6
39	Biological Extracts	D6
44	Fine Chemicals	D7
45	Fine Chemicals	E7
57	Sulfuric Acid Building	C7
61	Wellhouse	D7
63	Solvent Storage	G6
66	Specialty Chemical Production	G7
68	Fine Chemicals	E7
69	Fine Chemicals	F7
70	Solvent Storage	H7
72	Pumphouse Well #16	E10
73	Solvent Recovery	F6
74	Incinerator	K6
76	Fine Chemical Waste Disposal	F8
78	Fine Chemicals	E6
82	Picnic Shelter	D10
86	Chemical Dev. Storage Building	G7
87	Fine Chemicals	E6
89	Fermentation Development	D7
91	Chemical Development	E8
92	Chemical Storage	H7
93	Chemical Storage	H7
94	L.A.H. Storage	H7
182	Pumphouse Well #21	E12
183	Pumphouse Well #22	F10
184	Pumphouse Well #23	F9
120	Fermentation Warehouse	C7
121	Fermentation Structure	C6
127	Fermentation Production	C7
146	Animal Rearing Building	F13
147	Scale House-Dibal	E7
149	Fine Chemicals	E6
155	Ferm. Prod. Crystallization	B7
156c	Cephalosporin Processing	F11
156p	Penicillin Processing	F11
166	Rotary Filter Building	C7
167	Chlorine Storage	F7

BLDG.#	NAME	LOCATION
173	Specialty Chemical Production	H8
181	Guard House #5	F13
187	Picnic Area Rest Room	D10
191	Animal Quarantine Facilities	E12
195	Ferm. Prod. Crystallization	B8
196	Fine Chemicals Office	D6
199	Fire Reservoir #2 Pumphouse	G8
202	Guard House #3	B6
204	Welding Shop	D9
205	Fine Chem. Office & Classroom	E7
207	Chemical Production	F8
208	Pharmaceutical Chem. Cafeteria	D7
211	Chronic Toxicology Building	D12
213	Portable Office Unit	F6
221	Guard House #6	B8
224	Methanol Brine Chiller Bldg.	F7
225	Pharm. Chem. Prod. Facility	G7
226	Sodium Hydroxide Pumphouse	G6
228	Chlorinator House Well #18	E10
230	Analytical Laboratory Building	D8
232	Emergency Generator Building	H7
233	Biological Control Facilities	D12
236	Chiller Bldg. DPGII	E6
237	Cyanide Storage Building	H7
238	Acetylene Storage & Supply Bldg.	H7
240	Pumphouse Well #39	G13
241	Pumphouse Well #40	G13

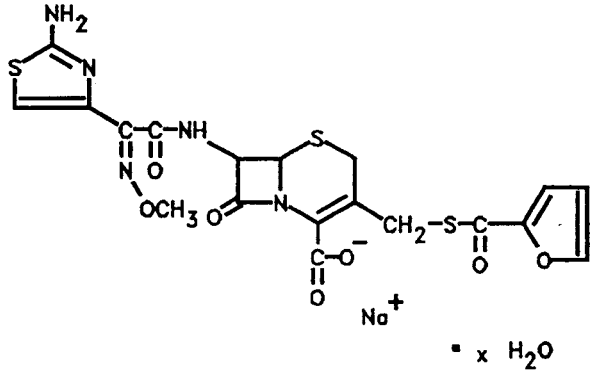
BLDG.#	NAME	LOCATION
253	Wellhouse for Disposal Well #3	F7
254	Wellhouse for Disposal Well #4	F9
287	Chemical Receiving Barn	H6
297	Cooler Bldg. for Minoxidil	J7
299	Freezer Building	J7
301	Maintenance Shop Building	G7
306	Chemical Engineering Building	D9
310	Backflow Preventer Bldg. #4	B8
312	Instrumentation Building	C8
315	Chilled Water General Facility	E10
317	Instrument Shop	G8
318	Cephalosporin Building	E11
321	Brine Building	E7
322	Instrumentation Building	G9
323	Motor Control Building	F6
324	RBST	C8
335	Office Trailer	F7
337	Office Trailer	E9
338	Office Trailer	G8
344	Office Trailer	G8
350	Office Trailer	D8
351	Office Trailer	D8
358	Refrigerated Equipment Building	B8
359	Airco Nitrogen Plant	E12
362	18/mcc Room	E6
368	Office Trailer	E9
384	Office Trailer	E9

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

5.1 Chemical Process

Ceftiofur sodium's chemical structure is shown below. The material safety data sheet (MSDS) is enclosed (see Item 14-2 on pages 5A through 5G) and Chemical Abstracts Service (CAS) No., molecular weight (M.W.), molecular formula, and physical description of materials used in its chemical process are presented beginning on page 6.

Figure 1: Chemical Structure



MATERIAL SAFETY DATA SHEET

UPJOHN

Print Date: January 11, 1995
Revision Date: December 08, 1992
Agent ID#: 28164

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

COMMON NAME: CEFTIOFUR SODIUM
SYNONYMS: 104010-37-9 - CAS NUMBER
5-thia-1-azabicyclo{4.2.0}oct-2-ene-2-carboxylic acid, 7-{{(2-amino-4-thiazolyl)(methoxyimino)acetyl}amino}-3-{{(2-furanylcarbonyl)thio}methyl}-8-oxo-, monosodium salt,{6r-{6.alpha.,7.beta.(z)}}
216040 - EDP NUMBER
216042 - EDP NUMBER
U-64,279E - UPJOHN U#
MOLECULAR FORMULA: C19-H16-N5-NA-O7-S3 .XH2-O
CHEMICAL FAMILY: Cephalosporin antibiotic
USE: Veterinary drug
MANUFACTURER/SUPPLIER: THE UPJOHN COMPANY
7171 PORTAGE RD.
KALAMAZOO, MI 49001-0199

TELEPHONE NUMBERS: (616) 323-5122 - (24 HOURS)
(616) 323-7555 - (8:00 a.m. - 4:30 p.m.)

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENT 1
COMMON NAME: Ceftiofur Sodium
CHEMICAL NAME: 5-thia-1-azabicyclo{4.2.0}oct-2-ene-2-carboxylic acid, 7-{{(2-amino-4-thiazolyl)(methoxyimino)acetyl}amino}-3-{{(2-furanylcarbonyl)thio}methyl}-8-oxo-, monosodium salt, {6r-{6.alpha.,7.beta.(z)}}
% BY WEIGHT: 98 - 100 %
CAS NUMBER: 104010-37-9
EXPOSURE LIMIT(S):
UPJOHN EXPOSURE LIMIT-TWA: 0.2 MG/M3

3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW: This off-white powder may cause allergic skin or respiratory reactions.
EFFECTS OF OVEREXPOSURE: The primary concern with inhalation or skin exposure to this agent would be the capability to elicit very mild to severe allergic reactions in some individuals. Repeated exposure may lead to sensitization.

Manifestations of an allergic response may include skin rash, fever, bronchospasm, angioedema (swelling of lips, tongue and face accompanied by asthmatic breathing and hives) and anaphylaxis. May also cause diarrhea, nausea and vomiting, and anemia.
TARGET ORGANS: Skin, respiratory tract, immune system, gastrointestinal tract, and blood.
MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: Hypersensitivity to ceftiofur sodium or the cephalosporin group of antibiotics. Persons with known sensitivity to other beta-lactam antibiotics such as penicillin may be at increased risk of developing hypersensitivity to ceftiofur sodium.

4. FIRST AID MEASURES

EYES: Flush with water for 15 minutes. Hold eyelids open to assure complete contact with water.
SKIN: Wash with soap and water. Remove contaminated clothing.
INHALATION: Remove from exposure.
INGESTION: Contact a physician or poison control center.
NOTES TO PHYSICIAN: Serious acute hypersensitivity reactions may require treatment with epinephrin and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management as clinically indicated.

5. FIRE FIGHTING MEASURES

FLASH POINT: Not applicable. (solid)
LOWER EXPLOSION LIMIT (LEL): Not applicable.
UPPER EXPLOSION LIMIT (UEL): Not applicable.
AUTOIGNITION TEMPERATURE: No information found
EXTINGUISHING MEDIA: Water, carbon dioxide, or dry chemical.
FIRE-FIGHTING PROCEDURES: Wear self-contained breathing apparatus and full body protective equipment.
UNUSUAL FIRE OR EXPLOSION HAZARDS: As with all finely divided organic powders, it is advisable to eliminate explosion hazards by methods such as grounding mechanical equipment in contact with the material to prevent the buildup of static electricity, inerting the atmosphere or controlling dust levels.
HAZARDOUS COMBUSTION PRODUCTS: Carbon monoxide, carbon dioxide, nitrogen and sulfur oxides.

6. ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED: Remove ignition sources; control the generation of dust/vapors; provide ventilation and respiratory, skin and eye protection to prevent overexposure. Keep out of drains; prevent entry to surface water, groundwater and soil. Vacuum (with HEPA-filtered and explosion-proof equipment) or scoop spilled material and place in container.

7. HANDLING AND STORAGE

PRECAUTIONS FOR HANDLING AND STORING: Follow good occupational hygiene practices. Avoid contact with skin, eyes and clothing. Avoid breathing dust. Wash thoroughly after handling. Launder contaminated clothing before reuse. Store in a cool dry place. Protect from light.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

RESPIRATORY PROTECTION: Approved respirator or dust mask.
VENTILATION: Local exhaust at point of manufacture or use.
PROTECTIVE GLOVES: Rubber.
EYE PROTECTION: Safety glasses with side shields.
OTHER PROTECTIVE EQUIPMENT: Protective covering for exposed areas of skin.

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE/PHYSICAL STATE: Beige to white amorphous powder
BOILING POINT: Decomposes
FREEZING POINT: Not applicable.
MELTING POINT: Decomposes above 190 C without melting
MOLECULAR WEIGHT: 545.55
ODOR: No information found
ODOR THRESHOLD: No information found
OPTICAL ROTATION: -67 degrees (c=1, H2O)
PARTITION COEFFICIENT (n-OCTANOL/WATER): 0.3 (at pH 5)
PH: No information found
SOLUBILITY IN SOLVENTS: Methanol: < 5 mg/ml; propylene glycol: 226 mg/ml; 2-Pyrrolidone: 302 mg/ml; THF: < 5 mg/ml.
SOLUBILITY IN WATER: > 400 MG/ML (Initially. Gels with time. No gelling or precipitation at 70 mg/ml.)

SPECIFIC GRAVITY (WATER=1): No information found
VAPOR DENSITY (air = 1): Negligible
VAPOR PRESSURE: Negligible
VOLATILITY: Negligible

10. STABILITY AND REACTIVITY

STABILITY: Stable from a safety point of view. Weakly hygroscopic.
PHYSICAL CONDITIONS TO AVOID: Slowly degrades on exposure to UV or fluorescent light, water or increases in temperature. The half-life at 70 C is 13 weeks; at 75% relative humidity is 13 weeks; with fluorescent irradiation is 4 weeks; and with UV irradiation is 16.5 weeks.
INCOMPATIBILITY WITH OTHER MATERIALS: Alkaline pH, oxidizing agents, and heavy metal ions.
HAZARDOUS DECOMPOSITION PRODUCTS: None.
HAZARDOUS POLYMERIZATION: Does not occur.

11. TOXICOLOGICAL INFORMATION

ACUTE STUDIES:
EYE IRRITATION (RABBIT): Minimally irritating but systemic absorption may occur via the ocular route.
SKIN IRRITATION (RABBIT): Practically non-irritating to intact skin.
SENSITIZATION: May cause hypersensitivity reactions.
INHALATION LC50 (RAT): > 8.3 MG/L
ORAL TOXICITY (DOG): The NOEL (no observable effect level) of 30 mg/kg/day was established in the dog as a result of a 90-day toxicity study.
LD50 (RAT): > 7,760 MG/KG (not acutely toxic)
INTRAPERITONEAL LD50 (RAT): 927 MG/KG
OTHER STUDIES:
GENOTOXICITY: Ceftiofur was negative in the Ames assay, micronucleus test, V79 mammalian cell mutation assay, and unscheduled DNA synthesis assay. In the in vitro chromosome aberration assay using CHO cells (in the absence of S9 metabolic activation), lengthy treatment with high doses of ceftiofur sodium resulted in increased frequency of aberrations. Aberrations were in the categories of chromatid breaks and gaps and isochromatid gaps. No evidence of the formation of rearrangements could be seen in these cells.
REPRODUCTION/FERTILITY: The reproduction NOEL in the rat is 1000 mg/kg/day orally. Oral administration at this level did not cause adverse effects upon fertility or reproductive performance of F0 and F1 generation animals. Likewise, no

adverse effects were observed in the growth and viability of the F2 litter through to the weaning period.
TERATOGENICITY: Not teratogenic in rats at oral doses up to 3200 mg/kg/day.
CARCINOGENICITY: Carcinogenicity studies have not been conducted on the compound.

12. ECOLOGICAL INFORMATION

ENVIRONMENTAL FATE:
MOBILITY: Ceftiofur sodium is very soluble in water, therefore, it is expected to be relatively mobile and migrate toward the aquatic compartment. Since ceftiofur sodium decomposes above 190 degrees C without melting and has no measurable vapor pressure, it is not expected to enter the air.
PERSISTENCE/DEGRADABILITY: In the aqueous environment, ceftiofur or its metabolites are subject to degradation by hydrolysis. At pH7 and 22 C, ceftiofur is 50% destroyed in 8 days and is completely destroyed in 80 days or less. Increases in temperature or pH, accelerate the rate of hydrolysis and destruction of antibacterial activity of ceftiofur and its metabolites. Degradation rate is also accelerated upon exposure to light or oxidizers. Ceftiofur sodium and its metabolites rapidly degrade in manure to 0 ppm bioactivity within 72 hours at ambient temperatures. Furthermore, a study of aerobic biodegradation in several soils showed that ceftiofur had no inhibitory effects on the soil organisms and readily biodegrades to carbon dioxide. It can be concluded that ceftiofur will not reach concentrations in soil at which adverse effects would occur.
BIOACCUMULATIVE POTENTIAL: Ceftiofur sodium has an octanol/water partition coefficient of 0.3 at pH5. Based on this value, it would be expected to migrate to the aqueous environment but it should not bioaccumulate in aquatic organisms. The biological concentration factor (BCF) is 0.235. Since all the metabolites are more polar and water soluble than ceftiofur, these compounds should also remain in the aqueous environment with no bioaccumulation.
ABIOTIC POTENTIAL: Based on its anticipated use and fate in the environment, and its decomposition rate in water, manure and soils, the concentration of ceftiofur and related metabolites in soil is expected to be below the MIC (minimal inhibitory concentration) of most bacteria and soil fungi. Therefore, no detrimental effects to these classes of organisms are expected. Small amounts released to sanitary sewerage should not adversely effect the biotic flora of sewage treatment facilities.
ECOTOXICITY: No information found.

13. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL METHOD: Dispose of by incineration in accordance with applicable European Economic Community (EEC), national and local waste disposal provisions. Stainless steel or glass equipment may be decontaminated with 5% sodium hydroxide solution, 5% ammonia solution or heating to 200 C for 5 hours to reduce microbiological activity.

14. SHIPPING REGULATIONS

Not regulated for transportation by the United States Department of Transportation (DOT), International Maritime Organization (IMO), or International Air Transport Association (IATA). May be subject to state and/or local transportation requirements.

15. REGULATORY INFORMATION

EMERGENCY PLANNING AND COMMUNITY RIGHT-TO-KNOW ACT (EPCRA): SARA SECTION 313: Ceftiofur sodium (EDP number 216040) contains the following toxic chemical, subject to the reporting requirements of section 313 of Title III of the Superfund Amendments and Reauthorization Act of 1986 and 40 CFR Part 372: acetone, CAS number 67-64-1, maximum weight 2.0%.

16. OTHER INFORMATION

REVIEWED BY: Environmental Health Sciences.
DISCLAIMER: The MSDS information is believed to be correct but should only be used as a guide. The Upjohn Company disclaims any express or implied warranty as to the accuracy of the MSDS information and shall not be held liable for any direct, incidental or consequential damages resulting from reliance on the information.

17. LABELING

UPJOHN PRECAUTIONARY LABEL CODE(S): K-2
HAZARD: SENSITIZER.
SIGNAL WORD: WARNING!
STATEMENT OF HAZARD/RISK PHRASE: May cause sensitization and/or allergic reactions.
PRECAUTIONARY MEASURES: Avoid contact with skin. Avoid breathing dust, vapor, mist or gas. Use with adequate ventilation. Wash thoroughly after handling.

Table 1: Ceftiofur Sodium: Materials Used in Manufacture

CEFTIOFUR SODIUM MATERIALS USED IN MANUFACTURE				
Material	**CAS No.**	**M.W.**	**Formula**	**Description**
2-ethyl haxanoic acid	149-57-5	144.2	$C_8H_{16}O_2$	Clear liquid
2-furoyl chloride	527-69-5	130.5	$C_5H_3ClO_2$	Light yellow liquid
7-amino-cephalosporanic acid	957-68-6	272.3	$C_{10}H_{11}N_2O_6S$	Tan amorphous powder
Acetone	67-64-1	58.08	C_3H_6O	Colorless liquid
Celite 545 or equivalent	61790-53-2	mixture	predominantly SIO_2	White to buff to pale-grey powder
Chloromethylene dimethyliminium chloride	3724-43-4	127.91	$C_3H_7Cl_2N$	White crystals
Dimethylformamide	68-12-2	73.10	C_3H_7NO	Clear, colorless liquid
Ethanol	64-17-5	46.07	C_2H_6O	Colorless liquid
Ethyl acetate	141-78-6	88.11	$C_4H_8O_2$	Colorless liquid
Ethyl-2-(2-amino-thiazol-4-yl)-2-methoxyimino-acetate	64485-82-1	229.2	$C_7H_9N_3O_3S$	Beige powder
Hydrochloric acid	7647-01-0	36.47	HCl	Corrosive, toxic, colorless liquid
Methanol	67-56-1	32.04	CH_4O	Clear, colorless liquid
Methylene chloride	75-09-2	84.94	CH_2Cl_2	Colorless liquid
n-Heptane	142-82-5	100.2	C_7H_{16}	Colorless liquid
n-Octane	111-65-9	114.22	C_8H_{18}	Colorless liquid
Oxalyl chloride	79-37-8	126.93	$C_2Cl_2O_2$	Colorless/yellow liquid
Phosphoric acid	7664-38-2	98.0	H_3O_4P	Water-white liquid
Polyvinylpyridine	9017-40-7	mixture	$(C_7H_7N)_n$	White to off-white powder
Pyridine	110-86-1	79.10	C_5H_5N	Clear, colorless to slightly yellow liquid
Sodium sulfide	1313-82-2	240.18	Na_2S	White crystals
Sodium hypochlorite	7681-52-9	74.44	NaOCl	Light straw color to greenish tint

CEFTIOFUR SODIUM MATERIALS USED IN MANUFACTURE				
Sodium hydroxide	1310-73-2	40.0	NaOH	Clear liquid
Tetrahydrofuran	109-99-9	72.11	C_4H_8O	Clear, colorless liquid
Toluene	108-88-3	92.13	C_7H_8	Colorless liquid
Triethylamine	121-44-8	101.19	$C_6H_{15}N$	Colorless liquid
Triphenyl methyl chloride	76-83-5	278.8	$C_{19}H_{15}Cl$	Tan solid

5.2 Pharmaceutical Formulation

The following summary describes the main properties of the ingredients used in the formulation of the drug product, Ceftiofur Sodium Sterile Powder. CAS No., molecular weight, molecular formula, and description are presented below.

Table 2: Ceftiofur Sodium Sterile Powder: Ingredients Used in Formulation

CEFTIOFUR SODIUM STERILE POWDER INGREDIENTS USED IN FORMULATION				
Material	**CAS No.**	**M.W.**	**Formula**	**Description**
Ceftiofur sodium Chemical name: Sodium (6R, 7R)-7-[[2-amino-4-thiazolyl)-z-(methroxyimino) acetyl] amino]-3-[(2-furanyl-carbonyl) thio] methyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0] oct-2-ene-2-carboxylate	104010-37-9	545.47	$C_{19}H_{16}N_6NaO_7S_3$. x H_2O	Beige to white amorphous powder
Sodium hydroxide	1310-73-2	40.0	NaOH	White deliquescent pellets
Nitrogen	7727-37-9	28.01	N_2	Colorless gas
Potassium phosphate monobasic	7778-77-0	136.09	H_2O_4PK	White to colorless, needle-like crystals
Water for injection, USP	7732-18-5	18.02	H_2O	Clear liquid

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT - CONTROL SYSTEMS

The drug substance and drug product are not expected to be introduced into the environment through transportation and storage. Product will be shipped in Department of Transportation (DOT) specification packaging. Ceftiofur sodium is not regulated as a hazardous material under current DOT regulations. Product ready for shipment will be stored in the manufacturing facility, which maintains security through limited access.

Portions of the materials listed in Section 5 may be released to the environment as a result of the proposed action. The manufacturing of the product may result in waste in the form of air emissions, liquid waste streams, and solid wastes.

6.1 Chemical Processing - Upjohn

6.1.1 Air/Solvent Emissions

The Upjohn Company is operating under an air consent judgment with the Michigan Department of Natural Resources (MDNR). This consent judgment was effective March 15, 1991, and all aspects of this consent judgment are scheduled to expire August 1, 1996. The air consent judgment required that an inventory be taken by July 1, 1991 of all equipment with either the potential to emit or to control an air contaminant. Further, permits are to be in place for this equipment in accordance with the schedule set forth in the consent judgment. That inventory was submitted to MDNR on July 1, 1991. Where applicable, lowest achievable emission rate (LAER) controls must be installed on the volatile organic compound (VOC) portion of the processes by September 1, 1995.

Particulate emissions in the ceftiofur production unit are controlled by use of the following:

- HEPA system, 98% efficiency, Permit No. 198-90C
- W-rotoclone, 98% efficiency, permitted under consent judgment (see below)
- Scrubber, 98% efficiency, permitted under consent judgment (see below)

Most of the processes and control devices in the Ceftiofur Production location are currently permitted under Michigan Department of Natural Resources (MDNR) Permit No. 198-90C.

LAER controls must be installed on the VOC (volatile organic compound) portion of the process by June 1, 1995. The Ceftiofur Production facility is part of Region IV in the Chemical Division. There is new equipment currently being engineered which will be included in the Air Permit Application (submitted October 1, 1992) for all subject equipment in this Region.

6.1.2 Aqueous Waste Streams

6.1.2.1 *Chemical Process Water Management (CPWM).* Aqueous waste streams resulting from chemical processes will be disposed of on-site by a chemical process water management (CPWM) injection system in accordance with this facility's Underground Injection Control permits granted pursuant to the Safe Drinking Water Act. Only those aqueous streams not allowed to be discharged to the sanitary sewer are sent to the CPWM. Upjohn's CPWM injection operations are conducted in accordance with this facility's Underground Injection Control permit Nos. MI-077-1W-0001 and MI-077-1W-0002 granted by Region 5 of the U.S. Environmental Protection Agency (USEPA) pursuant to the Safe Drinking Water Act.

With respect to Upjohn's permits to dispose of liquid waste by the CPWM system, the Federal Underground Injection Control Permits restrict the types and concentrations of contaminants in the injected fluid. The contaminants are the same contaminants which Upjohn is allowed to handle under our hazardous waste permit application. These permits require that the concentration and type of contaminants listed in the permits are to be monitored on a monthly basis and reported to the USEPA, Region 5. In addition, groundwater is protected through the construction and design of the CPWM injection system, the operating procedures employed and the continuous monitoring program, all of which are described in the permit. A steam stripper was recently added to the CPWM to further reduce contaminants in the injected fluid. Volatile contaminants are now removed from this waste stream by steam stripping and recovered by our solvent recovery and distribution process.

All chemicals listed in Section 5 may be expected to be included in the injected wastes either through direct discharge of spent materials or as trace contaminants in equipment washing.

With respect to the permit application terminology, The Upjohn Company wells are identified as "class 1" by USEPA. Class 1 wells are used to inject hazardous wastes below the deepest underground source of drinking water. A confining formation consisting of an impermeable geologic stratum prevents any upward migration of injected fluids into underground sources of drinking water. A containment system (pressurized annulus) prevents leakage of injected fluids from the injection wells into any aquifer outside the injection zone.

A further description of EPA's requirements for the issuance of UIC permits is contained in 40 CFR Part 144.

6.1.3 Liquid Process Waste Streams

Aqueous waste streams resulting from chemical processing will consist of residue wastewaters from sanitary use and washing operations which will be discharged into the municipal sewer system for biological treatment at the City of Kalamazoo Water Reclamation Plant.

6.1.3.1 *Industrial Pretreatment Program (IPP).* In response to Federal and State requirements governing the City of Kalamazoo's Industrial Pretreatment Program (IPP), The Upjohn Company has been issued a discharge permit in the form of an Industrial Control Document (ICD) dated March 25, 1994 through March 31, 1999. In addition, The City of Kalamazoo Sewer Use Ordinance and Sewer Use Regulations Nos. are incorporated by reference below:

- 1-89 (dated December 5, 1989), providing details for noncompliance;
- 91-1 (dated April 29, 1991), detailing pollutant discharge limits for metals;
- and 94-1 (dated February 9, 1994) detailing pollutant discharge limits for petroleum hydrocarbons.

These documents detail additional specific discharge requirements and regulations. All discharges from the production of ceftiofur sodium are permitted and, through the fifth year of production, will not impact the limits imposed under the ICD and accompanying Sewer Use Regulations.

6.1.3.2 Spent Solvents

Used solvent mixtures are either directed to the Solvent Recycling and Distribution (SRD) unit for recycle and reuse within the Portage manufacturing facility, used as a fuel in an on-site approved incinerator at the Portage manufacturing site, or are sent to an approved off-site facility as part of a waste-derived fuels program at permitted facilities where the waste is either blended with other solvents for incineration or directly injected for incineration.

6.1.3.2.1. *Recycling Solvents through SRD.* Used solvents at The Upjohn Company are collected at the production areas and conveyed via pipeline to a solvent recycling and distribution (SRD) facility within the plant site.

The SRD system receives the various solvents into dirty tanks and then feeds them into one of five distillation/reclamation columns that fractionate the constituents through the application of heat. At the different temperatures, various solvent species are recovered and sent to a clean tank where they are then distributed to the various production operations located throughout the plant site.

Those portions of the fractionation process that do not result in a product that is usable in Upjohn production operations are sent off-site for disposal. The vast majority of this material is used as a waste-derived fuel that replaces or enhances other fossil fuels burned for energy. Other disposal options are the local waste water treatment plant and high temperature incineration, dependent upon the chlorine and water content of an individual stream.

6.1.3.2.2 *On-Site Incinerator.* See Section 4.4.3.1.

6.1.3.2.3 *Off-site Disposal.* Waste spent solvents sent off-site are transported using the Uniform Hazardous Waste Manifest form. All facilities that receive the spent solvents are permitted by the USEPA and/or the state environmental agency where the facility is located. These facilities are audited periodically by Upjohn to verify compliance with State and Federal regulations.

The following table details the disposition of spent solvents for this process:

Table 3: Spent Solvent Disposition

Solvent Disposition from Chemical Process of Ceftiofur Sodium Through SRD				
Solvent	% SRD Recovery	Upgrading/ Distilling	Fuels Blending	Sanitary Sewer
Acetone	48	–	27	25
Heptane	50	41	9	–
Methylene chloride	88	12	--	--
Tetrahydrofuran	53	39	8	–
Toluene	69	9	22	–

6.1.4 Solid Waste

Ash generated as a result of the incineration process is sent to a permitted hazardous waste disposal facility.

6.2 Pharmaceutical Formulation - SKB

6.2.1 Air Emissions

Particulate air emissions are filtered by dust collectors. These are then disposed of as pharmaceutical waste as indicated in Sections 4.4.2 and 6.2.4. Manufacture of Ceftiofur Sodium Sterile Powder will not result in any solvent emissions.

6.2.2 Aqueous Waste Streams

Aqueous waste is sent to SKB's wastewater pretreatment facility where the wastewater is adjusted for pH. It is then disposed of in the sanitary sewer system (see Industrial Wastewater Discharge Permit and Monitoring Requirements, attached as Item 14-3 at pages 12A-12F).

6.2.3 Spent Solvents

Manufacture of Ceftiofur Sodium Sterile Powder will not result in any solvent waste.

6.2.4 Solid Waste

Pharmaceutical waste will be incinerated at Ogden Martin Systems in Alexandria, Virginia.

INDUSTRIAL WASTEWATER DISCHARGE PERMIT

Permit No. 94M-0011

UPPER MERION TOWNSHIP

INDUSTRIAL WASTEWATER DISCHARGE PERMIT

In accordance with the provisions of Upper Merion Township (hereafter, the Township) Ordinance No. 93-614, and 40 CFR 403.8 and 403.12,

SmithKline Beecham Pharmaceuticals, Inc.
709 Swedeland Road
King of Prussia, PA 19406

is hereby authorized to discharge industrial wastewater from the above identified facility and through the outfall(s) identified herein into the Township's sewer system in accordance with the conditions set forth in this permit. Compliance with this permit does not relieve the permittee of its obligation to comply with any or all applicable pretreatment regulations, standards or requirements under Local, State, and Federal laws, including any such regulations, standards, requirements, or laws that may become effective during the term of this permit.

Noncompliance with any term or condition of this permit shall constitute a violation of Township Ordinance No. 93-614.

The Township reserves the right to establish by Ordinance more stringent limitations or requirements on discharges to the wastewater disposal system if deemed necessary to comply with the objectives presented in Section 1.1 of Township Ordinance No. 93-614.

This permit is being issued temporarily by the Township. This temporary permit is in effect for the Fourth Quarter of 1994 only, beginning October 1, 1994, and expiring at midnight on December 31, 1994.

By: Edward J. O'Brien, Jr.
Assistant Director of Public Works

Issued this 29th day of September, 1994.

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UPPER MERION TOWNSHIP
INDUSTRIAL WASTEWATER DISCHARGE PERMIT
MONITORING REQUIREMENTS
PAGE 1

PERMIT NO. 94M-0011

COMPANY: SMITHKLINE BEECHAM PHARMACEUTICALS, INC.

ADDRESS: 709 Swedeland Road
King of Prussia, PA 19406

FACILITY: Corporate Campus

CLASSIFICATION: Categorical - 40 CFR 439 (D) - Mixing/Compounding and Formulation Subcategory

SAMPLING LOCATION: Manhole - Collection box where treated effluent leaves the treatment plant and enters the sanitary sewer

The above referenced permittee must comply with the following monitoring requirements:

1.

PARAMETER	LIMIT (mg/L)	SAMPLING FREQ.	SAMPLE TYPE
Arsenic	0.05	1/Month	24HC
BOD	250	1/Month	24HC
Beryllium	0.0002	1/Month	24HC
Benzene	0.002	1/Month	4 Grab Samples (A)
COD	500	1/Month	24HC
Copper	*	1/Month	24HC
Cadmium	0.010	1/Month	24HC

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PARAMETER	LIMIT (mg/L)	SAMPLING FREQ.	SAMPLE TYPE
Chloroform	0.020	1/Month	4 Grab Samples (A)
Total Cyanide	0.1	1/Month	4 Grab Samples (A)
Chromium (Hexavalent)	•	1/Month	24HC
Chromium (Trivalent)	•	1/Month	24HC
Lead	0.050	1/Month	24HC
Mercury	0.002	1/Month	24HC
Methylene Chloride	•	1/Month	4 Grab Samples (A)
Total Phenols	0.040	1/Month	4 Grab Samples (A)
pH	6.0-8.5	1/Month	Grab
Silver	0.006	1/Month	24HC
TSS	250	1/Month	24HC
TDS	2000	1/Month	24HC
Tin	0.034	1/Month	24HC
Toluene	0.660	1/Month	4 Grab Samples (A)

• = No set limit, monitor only
(A) = Monitoring Requirement No. 9 details the required sampling method.

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2. The permittee must submit reports consistent with the above monitoring requirements. Such reports must specify the following:

   (a) reporting unit
   (b) method detection limit
   (c) analytical Method and Method Number utilized for each parameter
   (d) sample times
   (e) sample dates
   (f) laboratory name
   (g) laboratory phone number
   (h) **chain of custody**
   (i) data and time laboratory received sample
   (j) **certification statement**
   (k) authorized signature

3. All testing analyses must be able to detect levels of the characteristic in question at or below the Township limits.

4. Monthly sampling analysis reports must be sent to the Township within fifteen (15) days after receipt of sampling results by permittee, but no later than the 15th of the following month.

5. If a permittee receives an analysis which exceeds the established permit limit, the Township requires that the permittee resample the parameter(s) which is in violation, during the same month. Permittee must submit all resample analyses, but they must be received by the Township by no later than the 15th of the following month.

6. A cover letter must accompany reports explaining the cause of any violations and supplying the Township with corrective and preventative measures taken by the permittee.

7. Permittees may not change any sampling, analysis, or reporting requirements without the advance written consent of the Township.

8. Twenty-four hour composite samples must comply with the following specifications:

   (a) sampling interval shall not be greater than twenty (20) minutes.

   (b) individual volume must be greater than one hundred (100) milliliters.

   (c) compatible preservatives shall be added for tested pollutants as stated for proper method of analysis.

9. Four (4) grab samples shall be taken during intervals throughout the sampling period, which provide a representative sample of the process wastestream generated during production shift(s). Volatile pollutant aliquots must be combined in the laboratory immediately before analysis.

10. All testing analyses shall be conducted in accordance with USEPA approved methods.

11. **Daily average flow (million gallons per day) shall be included for the day of sampling.**

12. All parameters reported by permittee shall conform with the units listed in this permit.

CONDITIONS

1. Upon providing proper identification, authorized Township personnel shall be permitted entry upon permittees' property for inspection and monitoring purposes.

2. All wastewater monitoring records (sampling analyses, permits, flows, incidents, etc.) must be kept for a minimum of three (3) years and must be available to Township personnel for review and copying.

3. This permit shall not be reassigned, transferred or sold to a new owner, new user, different premises or a new or changed operation without the approval of the Township.

4. Permittees must notify the Township immediately of any discharges which:
   (a) may be harmful or hazardous to personnel, the collection system, treatment system, treatment processes or receiving waters; or

   (b) are "slug" discharges as defined in Ordinance No. 93-614.

5. The permittee shall notify the Township in writing of any significant changes in the volume or characteristics of the wastewater.

6. Violators of the conditions of this permit shall be subject to the penalties of Township Ordinance No. 93-614, Section 10.

7. Violation of any condition of this permit may result in revocation of this permit.

8. Permittees are also reminded that if they generate, use, store, or dispose of toxic or hazardous material, they are subject to regulations in the Resource Conservation and Recovery Act. As such, they may be required to obtain permits from and file reports to the EPA.

6.3 Effect of the Approval of the Proposed Action - Upjohn

6.3.1 Regulations or Standards

The following regulations or standards are cited as applicable to the proposed action:

1. Federal Food, Drug and Cosmetic Act, PL 75-717, as amended.
2. Clean Air Act PL 91-604, as amended.
3. Clean Water Act PL 95-217, as amended.
4. Safe Drinking Water Act PL 93-523.
5. Resources Conservation and Recovery Act of 1976 PL 94-580, as amended.
6. Occupational Safety and Health Act of 1970, as amended.
7. Hazardous Materials Transportation Act of 1975, as amended.
8. Standards from the American National Standards Institute.
9. National Fire Protection Agency Standards.
   a. National Electrical Code Standards
   b. Life Safety Requirements
10. Act #348 of 1965, Michigan Air Pollution Act, as amended.
11. Act #245 of 1929, Michigan Water Resource Commission Act, as amended.
12. Act #399 of 1976, Michigan Safe Drinking Water Act, as amended.
13. Act #136 of 1969, Michigan Liquid Industrial Waste Disposal Act, as amended.
14. Act #315 of 1969, Michigan Mineral Well Act, as amended.
15. Act #641 of 1978, Michigan Solid Waste Management Act.
16. Act #64 of 1979, Michigan Hazardous Waste Management Act, as amended.
17. Act #368 of 1978, Public Health Code.
18. Chapter 28 of the Kalamazoo City Code (Services and Wastewater), as amended by ordinance No. 1190.
19. Michigan Occupational Safety and Health Act of 1970, as amended. (Local regulation applicable to the State of Michigan.)

Permits and other actions covering specific environmental regulations in force at The Upjohn Company's main pharmaceutical and chemical manufacturing complex in Kalamazoo, Michigan, including permit numbers and expiration dates where applicable, are summarized in the table attached (see Item 14-4 at p. 13A).

THE UPJOHN COMPANY: PERMIT INDEX

PERMIT DESCRIPTION	REGULATORY AGENCY	PERMIT NO.	ISSUED	EXPIRES
Air Consent Judgment	Michigan Department of Natural Resources, Air Quality Division		03/15/91	08/01/96
Air Use Permit	MDNR, Air Quality Division	923-92	03/29/94	
National Pollutant Discharge Elimination System (NPDES)	Michigan Department of Natural Resources Michigan Water Resources Commission	MI0002941	09/20/90	10/01/95
RCRA/Michigan Hazardous Waste Management Act 64 (On-site Incinerator)	Michigan Department of Natural Resources Waste Management Division	Incinerator operated as a RCRA Interim Status Treatment Storage and Disposal Facility under #MID 000820381 pending action on Part B/Act 64 permit app'n.		
Michigan Air Pollution Act 348 (On-site Incinerator)	Michigan Department of Natural Resources Air Quality Division	242-80	07/15/80 (revised to incorporate the Act 64 requirements) approved 05/26/93	non-expiring until modified
Wastewater Discharge Permit	City of Kalamazoo Industrial Pretreatment Program	The City of Kalamazoo Sewer Use Ordinance and Sewer Use Regulations/Industrial Control Document	03/25/94	03/31/99
Chemical Process Water Management (CPWM) Injection System (Class 1 wells) Underground Injection Control Permit	U.S. EPA, Region 5 Safe Drinking Water Act	MI-077-1W-0001 MI-077-1W-0002	07/09/93	10/27/96

6.3.2 Statement of Compliance

The Upjohn Company states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees or administrative orders applicable to the manufacture of ceftiofur sodium at its facilities in Kalamazoo, Michigan, as well as emission requirements set forth in applicable Federal, State, and local statutes and regulations applicable to the manufacture of ceftiofur sodium at its facilities in Kalamazoo, Michigan.

The Upjohn Company has comprehensive programs and practices in place addressing all applicable OSHA requirements.

6.3.3 Modifications of Existing Facilities

Approval of the proposed action will not result in the modification of the Upjohn Kalamazoo site existing facilities.

6.4 Effect of the Approval of the Proposed Action - Information Pertinent to and Supplied by the SKB Anti-Infective Manufacturing Facility

6.4.1 Regulations or Standards

The following regulations or standards are cited as applicable:

1. Occupational Safety and Health Act of 1970, as amended.
2. Standards from the American National Standards Institute.
3. National Fire Protection Agency Standards.
4. Pennsylvania Discharge Elimination System, Pennsylvania Code Title 25 Environmental Resources Chapter 92.
5. Pennsylvania Water Resources Regulation, Pennsylvania Code Title 25 Environmental Resources Part I Article 2.
6. Pennsylvania Air Pollution Control Regulation, Pennsylvania Code Title 25 Part I.
7. Pennsylvania Solid Waste Management Act, Pennsylvania Statutes Title 35 Health and Safety Chapters 29a and 75.

6.4.2 Statement of Compliance

The manufacture of this new compound will not generate any new hazardous wastes as defined in 40 CFR 261.4, priority pollutants listed in the Clean Water Act PL 95-217, as amended, or the Safe Drinking Act PL 93-523, as amended. There will be no discharge of VOCs or hazardous air pollutants as described in 40 CFR 61 of the regulations governing the National Emissions Systems for Hazardous Air Pollutants.

SKB's Environmental Protection Statement is included (see Item 14-5 at p. 15A).

6.4.3 Modifications of Existing Facilities

Approval of the proposed action will not result in additional equipment or new construction to accommodate this operation.

SmithKline Beecham
PHARMACEUTICALS

ENVIRONMENTAL PROTECTION STATEMENT

SmithKline Beecham Pharmaceuticals states that it is substantially in compliance with, or on an enforceable schedule to be substantially in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of cephalosporins at its Anti-Infective facility in Upper Merion, PA, as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of cephalosporins at its Anti-Infective facility in Upper Merion, PA.

Roberta O. Thompson 1/3/95

Roberta O. Thompson
Director - Anti-Infective Plant
Operations

THE UPJOHN COMPANY

7000 Portage Road
Kalamazoo, MI 49001-0199

WW Animal Product Development
Joseph A. Robinson, Ph.D.
7922-190-289
Telephone No. (616) 385-6752
FAX No. (616) 385-6769

July 20, 1995

On July 20, 1995, I, Joseph A. Robinson, contacted Ms. Roberta O. Thompson, Director of Anti-Infective Plant Operations at Smithkline Beecham Pharmaceuticals, regarding SKB's compliance with occupational worker safety requirements. Ms. Thompson assured me that SKB is in compliance with, or on an enforceable schedule to be in compliance with, all applicable occupational worker safety requirements.

Joseph A. Robinson 7/20/1995

Joseph A. Robinson

6.5 Use and Disposal of Products

It is estimated that the initial market volume for the treatment of acute bovine interdigital necrobacillosis (foot rot, pododermatitis) using ceftiofur sodium will be 70,000 4-gram (g) vials. Use of this volume of product will result in minute traces of drug residue to be disposed of in empty containers, thus having an insignificant impact on the environment.

The five-year domestic market forecast for Ceftiofur Sodium Sterile Powder for the treatment of interdigital necrobacillosis is shown below:

Table 4: Five-Year Domestic Market Forecast

YEAR	1	2	3	4	5
4 g Vials (000)	70	110	150	200	225
Active Ingredient (kg)	280	440	600	800	900

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

The environmental fate of ceftiofur sodium for treatment of acute interdigital necrobacillosis (bovine foot rot) is no different from the fate of this antibiotic when it is used in beef cattle and swine for treatment of respiratory disease. The fate of substances emitted into the environment resulting from the use of ceftiofur sodium in cattle (beef and non-lactating dairy cattle in NADA 140-338; and lactating dairy cattle in Supplemental NADA 140-338), horses (NADA 140-338), swine (NADA 140-338) and chickens (NADA 140-338) was addressed in previous EA documents. EAs for these previous indications and uses have concluded that ceftiofur sodium itself or its residues have no environmental impact. The same conclusion will hold for the use of ceftiofur sodium for the treatment of bovine foot rot.

The use of ceftiofur sodium for the treatment of foot rot is expected to minimally increase the amounts of ceftiofur and ceftiofur-related residues released into the environment. U.S. dairy farms average about 100 milking-age animals, but include as many as 9,000 or as few as 20 cows. Prevalence of foot rot in lactating dairy cattle is one percent or less. Assuming one percent incidence, there would be one animal suffering from foot rot per 100 cow herd. If the animal weighed 1200 lb (545 kg) and was treated with ceftiofur at 1 mg/lb body weight for five consecutive days (maximum label provisions), the farm and surrounding environment (aquatic and terrestrial ecosystems) would be exposed to at most 6 g of ceftiofur. This assumes conservatively that all of the ceftiofur injected into the animal is excreted into the environment. Furthermore, there are about 9.7×10^6 million dairy cattle in the U.S. or about 9.7×10^4 potential cattle to treat. There are approximately 3.3×10^7 million head of beef cattle in which the incidence of acute interdigital necrobacillosis (foot rot) is about one percent or 3.3×10^5 potential cattle to treat, for a total of 4.27×10^5 cattle. In contrast, the total potential cattle to be treated for bovine respiratory disease (BRD),

for which ceftiofur sodium has been approved previously, is $2x10^7$. This is based on an assumed incidence rate for respiratory disease of 50 percent and a total calf crop of $4x10^7$ calves. These values are taken from the EA prepared for use of ceftiofur sodium for the treatment of bovine respiratory disease (NADA 140-338). In summary, the use of ceftiofur sodium for the treatment of bovine foot rot would be expected to increase U.S. use of this product by two percent or less over its current usage for treatment of BRD. This minimal increase will not impact the environment.

7.1 Target Animal Metabolism

Metabolism of ceftiofur in the bovine has been previously addressed in an EA (NADA 140-338). In brief, lactating dairy cattle metabolize the product similarly to that of beef or non-lactating cattle. There are no metabolites present in milk not already present in urine or feces. The primary route of elimination of ceftiofur from cattle is through urinary and fecal excretion, with greatest radiolabel recoveries observed for urine. About 83 percent of ^{14}C-ceftiofur is excreted within 24 hours of the last dose. Approximately 60 percent is excreted via the urine, 25 percent in the feces and about 0.15 percent in milk. The major urinary excretion product is desfuroylceftiofur disulfide (7,8).

For this EA, it is conservatively assumed that 100 percent of ceftiofur as parent will be excreted from the comparatively small numbers of U.S. cattle injected IM with ceftiofur sodium for treatment of foot rot.

7.2 Physical/Chemical Properties and Partitioning

The water solubility of ceftiofur sodium and ceftiofur free acid are 400 mg/mL and 0.249 mg/mL, respectively (1). Ceftiofur sodium decomposes without melting at temperatures in excess of 190°C (1). The octanol/water partition coefficient (K_{ow}) for ceftiofur sodium and its free acid are 0.3 and 0.1, respectively (2). Ceftiofur sodium fluoresces in aqueous and ethanolic solutions. The following table provides values for the molar absorptivity of ceftiofur in water.

Table 5: Molar Absorptivity of Ceftiofur

UV Maximum (nm)	Molar Absorptivity (M-1 cm-1)
230	20,463
258	20,874
293	28,432

The water solubility data for ceftiofur predict that it would partition into the aqueous compartment, although partitioning of some ceftiofur and related metabolites of ceftiofur into the terrestrial compartment would be expected. The fact that ceftiofur decomposes above 190°C without melting indicates that this compound would not partition into the air.

The octanol/water coefficients for ceftiofur sodium and ceftiofur free acid can be used to predict bioconcentration factor (BCF = concentration of compound in fish/concentration of compound in water) values. For fish, Lyman et al. (13) cite the following equation:

$$\log_{10}BCF = (0.76 \times \log_{10}K_{ow}) - 0.23$$

Applying this expression yields BCF values for ceftiofur sodium and ceftiofur free acid of 0.2 and 0.1, respectively. These estimates support that significant partitioning of ceftiofur into the tissues of freshwater fish would not occur (13).

7.3 Hydrolytic Degradation

The hydrolysis of ceftiofur has been studied (12). Data in Table 6 show the temperature and pH dependence of hydrolysis of ceftiofur, as quantified by loss of antibacterial activity.

Table 6: Half-life ($t_{1/2}$) Estimates for Hydrolysis of Ceftiofur

pH	Temperature (°C)	$t_{1/2}$ (Days)
5	22	100
5	47	5.46
7	22	8.00
7	47	2.92
9	22	4.18

Representative environmental conditions for pH and temperature would be 7 and 22°C, respectively. Under these conditions, 50 percent of ceftiofur present initially in an aqueous system would have disappeared after 8 days. After 53 days, the loss of ceftiofur would be 99 percent complete under these conditions. Hydrolysis is thus an important removal mechanism for ceftiofur and related metabolites in aqueous ecosystems.

7.4 Photolytic Degradation

Ceftiofur would probably be exposed to sunlight, given that it would partition into aqueous ecosystems. An estimate of the photolysis half-life ($t_{1/2}$) for solid ceftiofur is 30 days at 22°C, based on loss of antibacterial activity (11). Extrapolating these solid state photolysis data to photolysis under aqueous conditions, this process would not be as rapid as hydrolysis (Table 6); however, it still represents a removal mechanism in aquatic ecosystems exposed to sunlight.

7.5. Biodegradability

Ceftiofur biodegradation has been studied in both aerobically incubated cattle excreta and soils (3,4,5). In cattle feces, the half-life ($t_{1/2}$) estimate for loss of activity is 2 hours. Loss in cattle urine is slower, but the $t_{1/2}$ for loss of antibacterial activity can be as short as 48 to 72 hours (3,4). Ceftiofur biodegradation with production of CO_2 (mineralization) has been shown in aerobically incubated soils (5). In this study, $t_{1/2}$ values ranged from 22 to > 49 days for the three soils tested (Table 7).

Table 7: Half-life ($t_{1/2}$) Estimates (Days) for Biodegradation of Ceftiofur Sodium

Soil Origin	California	Florida	Wisconsin
Soil Type	Clay Loam	Sand	Silty Clay Loam
$t_{1/2}$	22.2	> 49	41.4

In summary, the degradability of ceftiofur has been demonstrated in incubations of samples taken from habitats as diverse as cattle excreta and soils. These studies substantiate that ceftiofur can be degraded to compounds that lack antibacterial activity.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1. Mammalian Effects

The toxicity of ceftiofur in mammals is low. In the dog treated orally for 90 days, the no-observed-effect level (NOEL) is 30 mg/kg/day (6). The NOEL in rats dosed orally for 90 days is 30 mg/kg/day (10). The NOEL for reproduction in the rat is 1000 mg/kg/day (9). Therefore, at a recommended clinical dose of 1 mg/lb body weight (2.2 mg/kg) for cattle, no negative effects are expected.

8.2 Effects on Aquatic and Terrestrial Microbial Species

The effects of ceftiofur on representatives of terrestrial soil fungi have been investigated (14). Minimum inhibitory concentrations (MICs) for five fungi growing on three different media all exceeded 1000 ug/mL (Table 8).

Table 8: Minimum Inhibitory Concentration (MIC) of Ceftiofur Against Soil Fungi

	MIC (ug/mL or ppm) on Medium Type:		
Species	**CMA[a]**	**PDA[b]**	**SDA[c]**
Aspergillus carbonarius	> 1000	> 1000	> 1000
Chaetomium cochliodes	> 1000	> 1000	> 1000
Fusarium roseum	> 1000	> 1000	> 1000
Penicillium notatum	> 1000	> 1000	> 1000
Trichoderma viride	> 1000	> 1000	> 1000

a = corn meal agar; b = potato dextrose agar; c = Sabouraud dextrose agar

For the soil fungi tested, available ceftiofur concentrations in soil or water would have to be on the order of 1000 ppm to inhibit growth.

Ceftiofur and related metabolites (desfuroylceftiofur disulfide) found in the excreta of cattle treated for foot rot have also been tested against numerous species of bacteria including veterinary pathogens and those that can be isolated from soil, water and/or sediments (Table 9).

Table 9: Minimum Inhibitory Concentration (MIC) of Ceftiofur and Related Metabolites Against Select Bacterial Species

	MIC (ug/mL or ppm) for Ceftiofur or Related Metabolite[a]		
Species	**Ceftiofur**	**Desfuroylceftiofur**	**Desfuroylceftiofur Disulfide**
Escherichia coli	0.13 - 0.25	0.13 - 0.25	2
Micrococcus luteus	≤0.06	0.13	≤0.06
Pseudomonas aeruginosa	16	>32	>32

a Reported values and ranges are from Yancey et al. (15).
b ND = Not determined

The antibacterial activity of ceftiofur is generally greater than for either desfuroylceftiofur or desfuroylceftiofur disulfide (Table 9). Biological and chemical removal mechanisms are expected to reduce the negligible quantities of ceftiofur-related metabolites emitted into the environment, from the treatment of cattle with

foot rot using ceftiofur sodium, to values less than the MIC of bacteria even as sensitive as *Micrococcus luteus*.

8.3 Estimation of Expected Environmental Concentration (EEC)

In an Environmental Assessment submitted to FDA in October 1987 for Naxcel® (ceftiofur sodium) in cattle (NADA #140-338), the concentration of ceftiofur (and metabolites) in soil was calculated to be 0.013 µg/g soil under a worst case scenario. A 2% increase in the use of Naxcel in cattle is expected with the approval of the bovine foot rot claim. Based upon this increased use, the worst case soil concentration is calculated to be 0.01326 µg/g soil. This minor increase is not expected to affect the environment.

8.4 Risk Assessment

In the EA for Naxcel Sterile Powder (ceftiofur sodium) for treatment of bovine respiratory disease (NADA 140-338), it was concluded that ceftiofur-related metabolites would have no adverse effect on the environment. The same conclusion holds for the treatment of bovine foot root using ceftiofur sodium, for the following reasons: Negligible quantities of ceftiofur-related metabolites will accumulate in treated animals. Minute amounts of product will be released into the environment (maximum of 6 g per average dairy farm, for example). Ceftiofur has low mammalian toxicity and is not predicted to bioaccumulate in fish. The biological and chemical degradation of ceftiofur is so rapid and extensive that even the most sensitive microbial species tested will not be adversely affected. In short, the risk to the environment from metabolites released into the environment, due to this additional claim for ceftiofur sodium (foot rot), should be negligible.

9. USE OF RESOURCES AND ENERGY

Dairy and beef production will be more efficient and less costly to producers because of the reduction in morbidity of cattle suffering from acute interdigital necrobacillosis (foot rot). There are no increased demands on natural resources such as land, energy (fuel or feed stuffs) or water caused by the use of ceftiofur. The increased use of raw materials and utilities for the manufacture of ceftiofur for therapy of acute interdigital necrobacillosis (foot rot) should be only a small part of the millions of dollars this disease has been estimated to cost the cattle industry each year.

9.1 Energy Usage

9.1.1 *The Upjohn Company.* The manufacture of ceftiofur sodium represents less than five percent of the total chemical processing at the manufacturing facility. The proposed action will not alter land use since manufacture will take place on premises currently owned and occupied by The Upjohn Company. The use of natural resources and energy for the chemical processing of this product will be much less than one percent of present total plant usage and can be handled by the existing infrastructure.

The resources committed will be the materials listed in Section 5, the utilities used in manufacturing and minor miscellaneous support materials.

9.1.2 *SKB.* Energy usage at SKB will be approximately 25 percent of total production.

9.2 National Historic Preservation Act/Endangered Species:

9.2.1 *The Upjohn Company.* Under the authority of the National Historic Preservation Act of 1966, as amended, The Upjohn Company has received an opinion letter from the State Historic Preservation Officer. This letter states that, since this activity does not involve the alteration, demolition or construction of building or any earth-disturbing projects, historic property determination is not required (see Item 14-6 at page 22A). The amount of emissions from this formulation at the manufacturing site in Kalamazoo (Portage) will be controlled in accordance with Federal, State and local standards in order to prevent adverse effects on the environment or to any wild life.

9.2.2 *SKB.* SKB states there will be no impact on endangered or threatened species. The property is not eligible for noting in the National Register of Historic Places.

MICHIGAN DEPARTMENT OF STATE
RICHARD H. AUSTIN SECRETARY OF STATE
LANSING
MICHIGAN 48918

September 3, 1991

Ms. Susan I. Shedore
Environmental Technician
The Upjohn Company
Kalamazoo, MI 49007

RE: ER-910587 Environmental Assessment for the Formulation and Packaging of Drugs, Various Locations, Kalamazoo County (FDA)

Dear Ms. Shedore:

We have reviewed the above-cited project at the location noted above, under the authority of the National Historic Preservation Act of 1966, as amended. It is the opinion of the State Historic Preservation Officer (SHPO) that the project does not require a historic property determination since the activity does not involve the alteration, demolition or construction of buildings, or any earth disturbing projects.

Please maintain a copy of this letter with your environmental review record for this project. If you have any questions, please contact William Rutter, the Environmental Review Coordinator for the Bureau of History, at (517) 335-2721.

Thank you for this opportunity to review and comment.

Sincerely,

Kathryn B. Eckert
Acting State Historic Preservation Officer
Bureau of History

KBE:ER:br

10. MITIGATION MEASURES

10.1 The Upjohn Company

10.1.1 *MSDSs.* MSDSs for hazardous or potentially hazardous materials are made freely available to employees of The Upjohn Company. These documents provide information on potential hazards, personal protective equipment, safe handling practices, and emergency procedures. The MSDS for ceftiofur sodium provides an additional warning to the effect that hypersensitivity to cephalosporins or penicillins may be aggravated by exposure to ceftiofur sodium. The MSDS has been prepared for ceftiofur sodium and is included with this EA (see Item 14-2, pp. 5A-5G).

10.1.2 *Occupational Exposure.* There exists the possibility of occupational exposure during the manufacture of ceftiofur sodium from dermal or ocular contact and inhalation of dusts or aerosols containing ceftiofur sodium. Employees wear safety glasses with sideshields, protective gloves, protective coverings for other exposed areas of skin, and when there is a possibility for inhalation of dusts or aerosols containing ceftiofur sodium, an approved respirator such as M/8710 Dust and Mist Respirator. This particular respirator has been approved by the Mine Safety and Health Administration and the National Institute for Occupational Safety and Health for use with dusts and mists having permissible exposure limits of not less than 0.05 mg/m^3 of air.

10.1.3 *Precautionary Labeling.* Because ceftiofur sodium may have the potential to cause irritation, and/or allergic reactions, this material has been assigned an Upjohn K-2 precautionary label. This label signifies that the material may cause irritation and/or allergic reactions and provides a statement of hazard/risk phrase and precautionary measures (see Item 14-2, pp. 5A-5G).

10.1.4 *Personal protective equipment.* Additionally, the minimum level of personal protective equipment recommended for employees handling ceftiofur sodium includes safety glasses with side shields, protective gloves, and an approved respiratory protective device.

10.1.5 *Occupational health and safety.* The Upjohn Company has a comprehensive occupational health and safety program. This includes conduct of preplacement physical examinations of employees, and periodic health surveillance examinations of all employees in manufacturing areas. Additionally, the company operates a health clinic to address any employee illness and/or injury occurring during the course of employment. The above procedures will serve to monitor employees for the development of sensitization or other conditions attributable to ceftiofur sodium exposure.

The foregoing will assure protection for individuals handling ceftiofur sodium.

10.1.6 *Waste minimization.* Waste minimization measures taken during production of ceftiofur sodium are:

- Recycling of spent solvents (see Section 5);
- Tote handling of bulk purchased raw materials instead of disposable drums as much as possible;
- Scrubbing of off gases.

10.1.7 *Spill procedures.* Standard operating procedures for spills are in place.

10.2 SKB Pharmaceuticals

10.2.1 *Waste minimization.* SKB is not involved with waste minimization during formulation of Ceftiofur Sodium Sterile Powder. All raw material and product is shipped back to The Upjohn Company. Only broken vials of product or off-specification product is incinerated as pharmaceutical waste.

10.2.2 *Spill procedures.* Spill procedures include: containment of the spill, absorbent material applied to liquid, collection of absorbent material and product in a plastic bag, and disposal of all materials as pharmaceutical waste.

10.2.3 *Toxic/hazardous substances.* No toxic or hazardous substances will need to be disposed of for this work.

11. ALTERNATIVES TO THE PROPOSED ACTION

Resources and facilities are being used effectively to produce a quality product with minimal environmental impact. The alternative of no action resulting in deprivation of a beneficial therapy for the treatment of interdigital necrobacillosis (bovine foot rot) is not contemplated.

12. LIST OF PREPARERS

Following is a list of those persons, and corresponding qualifications, that participated in the preparation of this assessment. No government agency was consulted for this specific evaluation other than for routine implementation of ongoing environmental programs conducted at existing facilities.

Dan C. Wade	Project Management and Regulatory Affairs Project and Regulatory Affairs Manager B.S., Pharmacy; M.B.A., Economics Professional Experience: 21 years
Joseph A. Robinson	Research Scientist World-wide Animal Health Product Development Ph.D., Microbiology Professional experience: 12 years
Susan I. Shedore	Environmental Technician Environmental Affairs A.A. Corporate experience: 23 years
Raymond J. Sortman	Supervisor Chemical Production-Ceftiofur Production B.A., Biology/Chemistry Professional experience: 23 years
Jennifer A. Holcomb	Chemical Process R&D Process Engineer Professional experience: 4 years
Eileen D. Hotte	SmithKline Beecham Pharmaceuticals Manager, Radiation & Environmental Safety, Ph.D., CHP, Environmental Science Professional experience: 19 years

13. CERTIFICATION

The undersigned officials certify that the information presented is true, accurate, and complete to the best of their knowledge.

Randal S. Senger

July 17, 1995
Date

Randal S. Senger, Manager
Corporate Environmental Affairs
(telephone 616/323-5341)

Jeffrey Mehring

17 July 95
Date

Jeffrey S. Mehring, Manager
Environmental Health Services
(telephone 616/323-4746)

14. REFERENCES

The following Items are included as cited in Sections 4.5, 5.1, 6.2, 6.3, 6.4, and 9, respectively:

15. APPENDICES

References listed below were reviewed and accepted in Environmental Assessment Reports for NADA #140-338. Dates listed after each reference indicate the approval dates for new indications approved under NADA #140-338.

1. Barnes AC. Physical and chemical properties of U-64,279E. Upjohn Technical Report #7830/84/014. Sept. 25, 1984. Approval dates: Jan. 25, 1988; July 13, 1994.

2. Cazers AR, Koshy KT. Determination of octanol/water partition coefficients of U-64,279A (Ceftiofur, sodium salt) and U-64,279 (Ceftiofur,

3. Cazers AR, Stahl GL, Gilbertson TJ. The stability of ceftiofur sodium in bovine feces. Upjohn Technical Report #788-9760-87-013. June 15, 1987. Approval dates: Jan. 25, 1988; Jul. 13, 1994.

4. Gilbertson TJ, Stahl GL, Hubbard VL. The stability of ceftiofur urinary metabolites in urine and 1:1 urine/feces at room temperature. Upjohn Technical Report 788-9760-87-001. Jan. 12, 1987. Approval dates: Jan. 25, 1988; Jul. 13, 1994.

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6. Jackson TA, Brussee WM, Vrbancic JP, Mulholland MP. U-64,279E; 90-Day oral toxicology and drug safety study in the beagle dog. Upjohn Technical Report #7263/85/079. Dec. 11, 1985. Approval dates: Jan. 25, 1988; Aug. 4, 1992; Oct. 4, 1994.

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10. Kakuk TJ, Cole SL, Rop DA. 90-Day oral toxicity study in Sprague-Dawley rats with ceftiofur sodium (U-64279E). Upjohn Technical Report #7263/85/075. Dec. 17, 1985. Approval dates: Jan. 25, 1988; Jul. 4, 1992; Oct. 4, 1994.

11. Koshy KT, Stahl GL, Cazers AR. Correlation of the photolytic stability of ceftiofur sodium (U-64,279E) as determined by HPLC with antimicrobial activity as determined by the cylinder plate method. Upjohn Technical Report #788-9760-86-008. Dec. 19, 1986. Approval dates: Jan. 25, 1988; Aug. 4, 1992; Jul. 13, 1994.

12. Koshy KT, Stahl GL, Cazers AR, Paulissen JB. Correlation of hydrolytic stability of ceftiofur sodium with antimicrobial activity. Upjohn

Technical Report #788-9760-87-004. March 17, 1987. Approval dates: Jan. 25, 1988; Aug. 4, 1992; Jul. 13, 1994.

13. Lyman, WJ, Reehl, WF, Rosenblatt, DH. Environmental behavior of organic compounds. Handbook of chemical property estimation methods. McGraw-Hill: 1981. Approval dates: Jan. 25, 1988.

14. Yancey RJ, Jr., Kennedy MJ. *In vitro* effect of ceftiofur (U-64,279E) on mycelial fungi. Upjohn Technical Report #705-7922-86-016. Jan. 6, 1987. Approval dates: Jan. 25, 1988; Aug. 4, 1992.

15. Yancey RJ, Jr., Roberts BJ, Johnson DT, and Gatchell CL. *In vitro* evaluation of twelve disulfide analogs of desfuroylceftiofur. Upjohn Technical Report #705-7922-87-016. Dec. 30, 1987. Approval dates: Aug. 4, 1992.