SECTION 10. ENVIRONMENTAL ASSESSMENT

An Environmental Assessment describing the impact of the addition of turkey claim on the environment is provided.

Reference 14-8 in the Environmental Assessment is a tabular summary from Upjohn Technical Report 812-7926-94-001, titled "A ^{14}C-ceftiofur sodium (U-64279E) residue depletion study in turkey poults." Authors Hoffman GA, Nappier JL, Ho C, Gilbertson TJ, Travis MA, Arnold TS, Janose RL, Cox TD, Flook TF, Lewis VR. Dated 11 May 1995. The full technical report is included in Section 7 of this Supplement to NADA 140-338.

Ceftiofur Sodium Sterile Powder
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NAXCEL® STERILE POWDER (CEFTIOFUR SODIUM)

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

1. DATE

24 August 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 the supplemental New Animal Drug Application (NADA) #140-338 for NAXCEL Sterile Powder (ceftiofur sodium) for control of colibacillosis infections in day-old turkeys (early poult mortality) associated with *Escherichia coli*.

Colibacillosis is an important cause of early (first 14 days of life) turkey poult mortality, and *E. coli* is the major pathogenic species associated with this disease. Ceftiofur has demonstrated *in vitro* and *in vivo* activity against *E. coli*. Ceftiofur Sodium Sterile Powder will be used to treat colibacillosis in day-old turkey poults.

The population of turkeys raised for meat in the United States (U.S.) is estimated to be 300 million birds (9). Based on treatment rates and market penetration, it is estimated that approximately 70 kg of ceftiofur sodium will be used to control colibacillosis in turkey poults following market introduction (see Section 6.5).

4.2 Location Where the Product Will be Produced

4.2.1 Drug Substance

The drug substance, ceftiofur sodium (a cephalosporin analogue), will be produced at The Upjohn Company's (Upjohn) main pharmaceutical and chemical manufacturing complex in Portage, Michigan.

4.2.2 Drug Product

The drug product, Ceftiofur Sodium Sterile Powder, will be manufactured at SmithKline Beecham-U.S.'s (SKB) Anti-Infective Manufacturing facility. This is SKB's main antibiotic manufacturing facility, located in Conshohocken, Pennsylvania. The drug product will be for prescription use only.

4.3 Locations Where the Product Will be Used

Finished products will be stored in distribution centers prior to transportation to veterinarians. The use of the finished product will be in poult hatcheries, where it will be injected subcutaneously into the necks of turkey poults. The drug will be used in this manner throughout the United States (U.S.). Poult hatcheries are generally located in rural areas in the U.S.

4.4 Locations Where the Product Will be Disposed

Disposal of drug substance or drug product may result from the processing of off-specification lots, from returned goods, or from end-user disposal of empty or partly empty 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 Drug Substance

Off-specification lots of ceftiofur sodium, manufactured by Upjohn, 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 SKB's pharmaceutical 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 or from end-user disposal of individual units of empty or partly empty product containers 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 *Upjohn 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 by Upjohn 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 permits are in place for Upjohn to serve 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 Upjohn'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 manufacturing 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 manufacturing facility consists of approximately 80 buildings including chemical and pharmaceutical manufacturing operations, offices, laboratories, utility operations, and various other support buildings (see Appendix 15-1 tab). 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. SKB's facility is located in Upper Merion Township, Pennsylvania on a five-acre site. The facility is 184,080 square feet in size 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. Product manufacturing (solution preparation) is performed on the fourth floor of the manufacturing facility.

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

5.1 Chemical Process

The chemical structure for ceftiofur sodium is shown below. The material safety data sheet (MSDS) is enclosed (see Appendix 15-2 tab) and Chemical Abstracts Service (CAS) No., molecular weight (MW), molecular formula, and physical description of materials used in the manufacture of ceftiofur sodium are provided in Table 1.

Figure 1: Chemical Structure

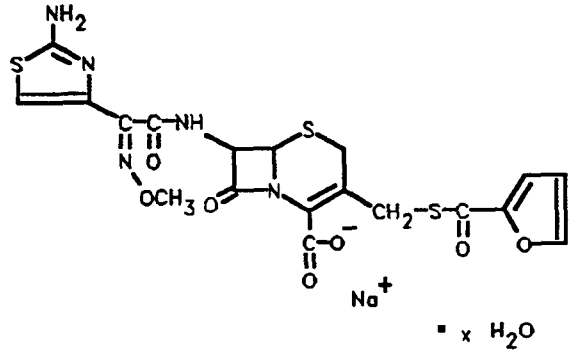

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Table 1: Ceftiofur Sodium: Materials Used in Manufacture

CEFTIOFUR SODIUM MATERIALS USED IN MANUFACTURE				
Material	CAS No.	MW	Formula	Description
2-Ethyl hexanoic acid	149-57-5	144.2	$C_9H_{18}O_2$	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	$C_{10}H_{11}N_2O_5S$	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				
Material	CAS No.	MW	Formula	Description
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 main properties of the ingredients used in the formulation of the drug product, Ceftiofur Sodium Sterile Powder, including CAS No., molecular weight, molecular formula, and descriptions are provided in Table 2.

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

CEFTIOFUR SODIUM STERILE POWDER INGREDIENTS USED IN FORMULATION				
Material	CAS No.	MW	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	545.55	$C_{19}H_{16}N_3NaO_7S_3$. 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) 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

6.1.1 Air/Solvent Emissions

Upjohn 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 Upjohn 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 decree); and a
- scrubber (98% efficiency, permitted under consent decree).

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

LAER controls must be installed on the VOC portion of the process by December 31, 1995. The ceftiofur production facility at Upjohn is part of Region IV in the Chemical Division. New equipment currently being engineered will be included in the Air Permit Application (submitted October 1, 1992).

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 (UIC) 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 UIC permit Nos. MI-077-1W-0001 and MI-077-1W-0002 granted by Region 5 of the U.S. Environmental Protection Agency (U.S. EPA), pursuant to the Safe Drinking Water Act.

With respect to Upjohn's permits to dispose of liquid waste by the CPWM system, the Federal UIC 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 Upjohn's 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 U.S. EPA, 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 added to the CPWM to further reduce contaminants in the injected fluid. Volatile contaminants are removed from this waste stream by steam stripping and recovered by Upjohn's 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, Upjohn wells are identified as "class 1" by U.S. EPA. 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 of 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 include residue wastewaters from sanitary use and washing operations. These wastewaters 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 - Recycling through Solvent Recycling and Distribution (SRD).* Used solvent mixtures are either directed to the 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 facility, or sent to an approved off-site facility as part of a waste-derived fuels program where the waste is blended at permitted facilities with other solvents for incineration or directly injected for incineration.

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 Upjohn manufacturing facility.

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 (see Section 4.4.3.1).

6.1.3.2.1 *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 U.S. EPA 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 the ceftiofur sodium manufacturing process:

Table 3: Spent Solvent Disposition

Solvent Disposition from Ceftiofur Sodium Manufacturing Process Through SRD				
Solvent	% SRD Recovers	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

6.2.1 Air Emissions

Particulate air emissions are filtered by dust collectors. Used dust collectors are disposed of as pharmaceutical waste (see 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 SKB's Industrial Wastewater Discharge Permit and Monitoring Requirements at Appendix 15-3 tab).

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.

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 Upjohn's main pharmaceutical and chemical manufacturing facility, including permit numbers and expiration dates where applicable, are identified at Appendix 15-4 tab.

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 Modification of Existing Facilities

Approval of the proposed action will not result in the modification of buildings and facilities at the Upjohn Portage manufacturing site.

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/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 ceftiofur sodium will not generate any new hazardous wastes as defined in 40 CFR 261.4, nor will it generate any of the priority pollutants listed in the Clean Water Act PL 95-217, as amended, nor 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 Appendix 15-5 tab).

6.4.3 Modification of Existing Facilities

Approval of the proposed action will not result in additional equipment or new construction to accommodate manufacture of drug product (Ceftiofur Sodium Sterile Powder).

6.5 Use and Disposal of Products

Colibacillosis is an important cause of early (first 14 days of life) turkey poult mortality, and *E. coli* is the major pathogenic species associated with this disease. Ceftiofur has demonstrated *in vitro* and *in vivo* activity against *E. coli*. Ceftiofur Sodium Sterile Powder will be used to control colibacillosis in day-old turkey poults. The product will be administered to poults by subcutaneous injection in the neck at 0.17 to 0.5 mg ceftiofur/poult. Each 1-gram or 4-gram (g) vial of ceftiofur will be reconstituted according to package instructions. One mL of the reconstituted solution (50 mg ceftiofur/mL) will be sufficient for the control of colibacillosis infections in 100 (0.5 mg/poult) to 294 (0.17 mg/poult) day-old poults.

Approximately 300 million turkeys are raised for meat annually in the U.S. (9). Of these, 95% are treated with an antibiotic the first day of life. At the maximum dose of ceftiofur of 0.5 mg/poult and assuming a market penetration of 50%, approximately 70 kg of ceftiofur would be used to control *E. coli*-associated colibacillosis in poults following market introduction.

The amount of ceftiofur used to treat colibacillosis in turkeys is small compared to the use of ceftiofur for control and treatment of bovine respiratory disease (BRD). In the Environmental Assessment (EA) report for BRD, the initial market volume of ceftiofur was predicted to be 1.2×10^5 kg (4). This amount of ceftiofur is approximately 20-fold greater than the kg of ceftiofur predicted to be used for the control of colibacillosis in turkeys. This additional incremental increase in ceftiofur use is not anticipated to have an adverse environmental impact.

Syringes and needles, used to administer the product to turkey poults, will be handled by the community's solid waste management system. The disposal of these items is not expected to have a significant negative impact on the environment.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

The fate of substances emitted into the environment resulting from the use of ceftiofur sodium in large animals (beef cattle and non-lactating dairy cattle in NADA 140-338; and lactating dairy cattle in Supplemental NADA 140-338), swine (NADA 140-338) and chickens (NADA 140-338) was addressed in previous EA reports. The fate of ceftiofur, from its use in turkeys, will be similar to that resulting from its use in chickens, cattle and swine.

7.1 Target Animal Metabolism

The results of a residue depletion study (8) with turkey poults predicts that the environment will be exposed to negligible ceftiofur parent and ceftiofur-related metabolites. Twenty-four turkey poults (12 males and 12 females) were injected subcutaneously in the neck with ^{14}C-ceftiofur sodium at 0.91 mg of ceftiofur free acid equivalents per poult. Excreta was collected daily from the poults starting just prior to the injection of radiolabeled drug up until 21 days post injection. Approximately 80% of the administered dose was found in the excreta. From day three on, no parent ceftiofur was detected in the poult excreta using HPLC/RAM (8). A microbiological assay was used to quantitate metabolites with antimicrobial activity and/or parent in the excreta. No microbiologically active metabolites or parent ceftiofur were detected in the excreta from day three on (8). Therefore, the target animal metabolism data support that the environment will be exposed to negligible quantities of parent ceftiofur (or ceftiofur-equivalent metabolites with antimicrobial activity), resulting from the use of ceftiofur sodium for the control of early turkey poult mortality. Notwithstanding this fact, it will be conservatively assumed for this EA, that all of the ceftiofur injected into poults will enter the environment by way of excretion.

7.2 Physical/Chemical Properties and Partitioning

The physicochemical properties of ceftiofur, and the effects of these properties on the partitioning of ceftiofur in the environment, were provided in a previously approved EA report (4). In brief, ceftiofur and ceftiofur-equivalent metabolites are soluble in water, expected to partition between aquatic and terrestrial compartments and not expected to bioconcentrate in fish or mammals (4).

7.3 Hydrolytic and Photolytic Degradation

Data on ceftiofur hydrolysis and photolysis were provided in a previously approved EA report (4). At pH 7 and 22°C, the $t_{½}$ (half-life) for hydrolysis of ceftiofur was eight days (4). The $t_{½}$ for photolysis at 22°C was 30 days (4). Both of these degradative mechanisms will contribute to the breakdown of ceftiofur-equivalent residues entering the environment.

7.4 Biodegradability of Ceftiofur

The biodegradability of ceftiofur and active metabolites of ceftiofur was addressed in previously approved EA reports (4,5,6). Ceftiofur and ceftiofur-equivalent metabolites can be degraded in cattle, poultry and swine excreta and soils. Disappearance of ceftiofur in soils, incubated aerobically at 22°C, had $t_{½}$ values of 22, 41 and greater than 49 days for three soils (4,5,6). In poultry excreta, the estimated $t_{½}$ for loss of ceftiofur was 25 hours (5). Results of the experiments support the interpretation that ceftiofur and ceftiofur-equivalent metabolites will not accumulate in the environment. There is no reason to expect ceftiofur (and its related metabolites) to be recalcitrant in turkey poult excreta.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1. Effects on Mammalian Species

The toxicity of ceftiofur and ceftiofur metabolites is low. Previously approved EA reports support this claim, based on data obtained using rats and beagle dogs (4,5,6).

Other effect data ?!

8.2 Effects on Microbial Species

The effects of ceftiofur on representative species of soil fungi were given in previously approved EA reports (4,5,6). In brief, available ceftiofur concentrations in soil or water would have to be on the order of 1000 ppm or more to inhibit fungal growth (4,5,6).

8.3. Estimation of Expected Environmental Concentrations (EECs)

EEC estimates for treatment of early poult mortality in turkeys using ceftiofur sodium are based on a set of assumptions and standard turkey rearing practices identified in the following table. Included in these estimates is the assumption that ceftiofur as parent is excreted at 100% of the injected dose. This assumption is exceptionally conservative given that parent ceftiofur (and ceftiofur-related metabolites having antimicrobial activity) cannot be found in turkey poult excreta three days after a single subcutaneous (SC) injection (8).

Table 4: Assumptions for EEC Calculations for a Turkey Confinement Facility with a 16,000 Bird Capacity

Item	Detail	Reference
Size of facility	16,000 turkeys	Present document
Stages in growing cycle	Brooder (day 0 to 6 weeks) and growout (6 weeks to market weight at 9 weeks)	2,11
Body weight of turkeys at 3 weeks	Toms = 0.508 kg; hens = 0.477 kg; average poult = 0.493 kg	10
Weight of turkeys at finish	12.5 kg at 123 days for toms; 6.67 kg at 97.6 days for hens	10
Treatment rate and period	0.17-0.5 mg ceftiofur/poult injected SC for 1 day at start of brooder period; 0.5 mg used in calculations; all poults treated	Present document
Percent excreted as ceftiofur parent	100% in manure	Present document
Manure storage conditions	Held in storage barn up to 12 months prior to disposal	3
Manure production rate	47 kg/1000 kg poult body weight/day	1
Manure disposal method	Plowed into soil to a depth of 6 inches	Present document
Manure application rate	10 tons/acre soil (= 9080 kg/acre) maximum	3
Soil bulk density	1.2 g/cm^3	7
Depths of one-acre ponds exposed	6 and 36 inches	Present document
Runoff scenario for rainfall event	Two-inch rainfall; 100% loss of ceftiofur from 10 ton/acre manure application draining into a one acre x 36 inch deep pond	Present document
Estimated $t_{1/2}$ for hydrolysis	8 days	4
Estimated $t_{1/2}$ for loss in soils	50 days	4,5,6
Estimated $t_{1/2}$ for loss in poultry manure	25 hours	5

Using the assumptions in Table 4, the calculated maximum amount of ceftiofur excreted from the 16,000 turkey poults during the one-day treatment period would be:

16,000 poults x (0.5 mg ceftiofur/poult) x 100% excreted
= 8.000×10^3 mg ceftiofur

The amount of manure produced by the 16,000 poults during the brooder stage (zero to six weeks), can be estimated by using the average weight of the turkeys at the mid-point (three weeks) of the brooder stage as follows:

[16,000 poults x (0.493 kg body weight/average poult)]
x (47 kg manure/1000 kg poult body weight/day) x 42
days = 1.557×10^4 kg manure

Manure from the brooder stage would normally be stored with manure from the growout stage, along with discarded litter, for up to 12 months prior to disposal. This would result in a dilution of the total quantity of ceftiofur and related residues that theoretically might be present in the manure. Here, it is conservatively assumed that the manure from the brooder stage is not diluted with manure from the growout stage or with litter from the entire turkey growing cycle, but instead is stored separately prior to land disposal. Under these conditions, the calculated maximum concentration of ceftiofur in the manure would be 8.000×10^3 mg ÷ $(1.557 \times 10^4$ kg) = 0.514 mg ceftiofur/kg manure (0.514 ppm).

Two sets of environmental exposure scenarios are considered next: first terrestrial and then aquatic. These are based on the assumptions and values listed in Table 4. The land disposal rate for poultry manure of 10 tons/acre (Table 4) is based on recommendations presented at the 1990 National Poultry Waste Management Symposium. According to Cullen (3), 10 tons of poultry manure per acre is approximately twice that needed for corn. Given a 10 ton/acre application rate and assuming the poultry manure is plowed uniformly into soil to a depth of six inches, the calculated maximum concentration of ceftiofur in soil would be:

[(0.514 mg ceftiofur/kg manure) x (2000 lb/ton) x 10 tons manure
x (0.454 kg/lb)] ÷ [(0.405 Ha/acre) x 1 acre x (10^4 m^2/Ha)
x (10^4 cm^2/m^2) x (30.5 cm/12 in) x 6 in soil x (1.2 g soil/cm^3 soil) x (1 kg/10^3 g)]
= 6.297×10^{-3} mg ceftiofur/kg soil (ppm)

Ceftiofur is a water soluble compound. It is thus possible that ceftiofur could partition into aquatic ecosystems. An extremely conservative scenario is one in which all of the ceftiofur in the 10 tons of applied poultry manure, [(0.514 mg ceftiofur/kg manure) x (2000 lb/ton) x 10 tons x (0.454 kg/lb)] = 4.67 g, entered a one-acre pond that is six inches deep. The concentration of ceftiofur in the water would be:

[(0.514 mg ceftiofur/kg manure) x (2000 lb/ton) x 10 tons x (0.454 kg/lb)]
÷ [(0.405 Ha/acre) x 1 acre x (10^4 m^2/Ha) x (10^4 cm^2/m^2) x (30.5 cm/12 in)
x 6 in water x (1.0 g water/cm^3 water) x (1 L/10^3 g)]
= 7.557×10^{-3} mg ceftiofur/L water (ppm)

A more realistic aquatic exposure scenario, but still conservative, is one that assumes ceftiofur is transported into aquatic ecosystems due to runoff occurring after a rainfall event. Assume 100% of the ceftiofur in a one-acre field, to which 10 tons of ceftiofur-containing turkey manure has been applied, dissolves into two inches of rain water. If all of this water flows (runoff) into a one-acre pond that is 36 inches deep, the concentration would be:

[(0.514 mg ceftiofur/kg manure) x (2000 lb/ton) x 10 tons x (0.454 kg/lb)]
÷ [(0.405 Ha/acre) x 1 acre x (10^4 m^2/Ha) x (10^4 cm^2/m^2)
x (30.5 cm/12 in) x (2 in rainfall + 36 in pond depth)
x (1.0 g water/cm^3 water) x (1 L/10^3 g)]
= 1.193×10^{-3} mg ceftiofur/L water (ppm)

The exposure scenarios considered above assume all ceftiofur injected into poults for the control of colibacillosis is excreted as ceftiofur-equivalent residues. Given the turkey metabolism data (see Section 7.1), the maximum ceftiofur concentration in the aquatic exposure scenario above (7.557 ppb) is extremely conservative.

None of the above EEC calculations take into account the removal mechanisms of hydrolysis, photodegradation and/or biodegradation for ceftiofur. All of these removal mechanisms will reduce the concentration of ceftiofur and related metabolites that might be plowed into soil and/or partition into aquatic ecosystems. Photodegradation is not likely to be an important removal mechanism in soil, but hydrolysis and degradation in poultry manure and in soils would be expected to substantially lower the EEC for ceftiofur, given the $t_{1/2}$ values for these processes (Table 4). These processes would be expected to reduce the concentration of any ceftiofur-related compounds (assuming they were present) by at least an order of magnitude prior to land disposal.

The following calculation demonstrates the impact degradation would have on ceftiofur-related residues assumed to enter the environment, following the use of ceftiofur sodium for treatment of early poult mortality. First, assume the $t_{1/2}$ for disappearance of ceftiofur in stored turkey manure is as slow as disappearance of ceftiofur in soils ($t_{1/2}$ = 50 days; Table 4). Second, assume the manure from turkey poults is stored for six months rather than 12 months prior to land disposal (Table 4). Third, assume the initial ceftiofur concentration is the calculated maximum ceftiofur concentration in turkey manure, 0.514 ppm (see above). The ceftiofur concentration in the manure, at the end of the storage period, can then be calculated according to the following exponential decay equation:

$$\text{Ceftiofur}_{6\ \text{months}} = 0.514\ \text{ppm} \times \text{EXP-}\{[(\log_e 2)/50\ \text{days}] \times 180\ \text{days}\} = 4.239 \times 10^{-2}\ \text{ppm}$$

Thus this single degradation mechanism alone would presumably reduce by more than a factor of 10, the maximum ceftiofur concentration calculated in the three exposure scenarios presented above. Hydrolysis would have an even greater effect given the shorter $t_{1/2}$ for this process (Table 4). In short, degradation mechanisms would be expected to reduce the ppb concentrations (calculated maximum values) to ppt concentrations once the practice of storage of poult manure is taken into account.

8.4 Risk Assessment

Possible residues entering the environment from the use of ceftiofur sodium for treatment of early turkey poult mortality should be safe environmentally for the following reasons:

- negligible concentrations of ceftiofur and ceftiofur-related metabolites are excreted;
- ceftiofur exhibits low toxicity in mammals;
- ceftiofur does not bioconcentrate in fish or mammals;
- ceftiofur and related metabolites are degraded in diverse ecosystems;
- expected environmental concentrations (EECs) are in the ppb range based on very conservative assumptions; and
- the amount of ceftiofur to be marketed for control of turkey poult mortality is small compared to ceftiofur sodium marketed for other purposes (such as control and treatment of bacterial respiratory disease in cattle).

9. USE OF RESOURCES AND ENERGY

9.1 Energy Usage

9.1.1 The Upjohn Company

The manufacture of ceftiofur sodium represents less than 5% 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 Upjohn. The use of natural resources and energy for the chemical processing of ceftiofur sodium will be much less than 1% 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 Pharmaceuticals

Energy usage for manufacture of Ceftiofur Sodium Sterile Powder at SKB will be approximately 25% 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, Upjohn 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 buildings or any earth-disturbing projects, historic property determination is not required (see Appendix 15-6 tab).

The emissions resulting from the manufacture by Upjohn of ceftiofur sodium will be controlled in accordance with Federal, State and local standards in order to prevent adverse effects on any endangered or threatened species.

9.2.2 SKB Pharmaceuticals

The property at SKB's manufacturing facility is not eligible for noting in the National Register of Historic Places.

The emissions resulting from the manufacture by SKB of Ceftiofur Sodium Sterile Powder will be controlled in accordance with Federal, State and local standards in order to prevent adverse effects on any endangered or threatened species.

10. MITIGATION MEASURES

10.1 The Upjohn Company

10.1.1 MSDSs

MSDSs for hazardous or potentially hazardous materials are made available to employees of Upjohn. These documents provide information on potential hazards, personal protective equipment, safe handling practices, and emergency procedures. The MSDS for ceftiofur sodium (see Appendix 14-2 tab) provides a warning that hypersensitivity to cephalosporins or penicillins may be aggravated by exposure to ceftiofur sodium.

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 an 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 internal label signifies that the material may cause irritation and/or allergic reactions and provides a statement of hazard/risk phrase and precautionary measures (see Appendix 15-2 tab).

10.1.4 Personal Protective Equipment

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

Upjohn has a comprehensive occupational health and safety program. This includes 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 firm does not conduct patch tests to detect antibiotic sensitization since this technique can contribute to sensitization.

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 6);
- Tote handling of bulk purchased raw materials instead of disposable drums (A tote is a reusable container, usually 200-300 gallons capacity, typically stainless steel or polypropylene, with a built-in bottom rack to facilitate movement by vehicles. Totes are filled by the vendor, shipped to Upjohn, discharged by chemical operators, then shipped back empty to the vendor for refilling with the same material. Totes are dedicated to a given material and labeled accordingly. A sample of the contents is assayed to confirm the material ID before use. Each tote holds from four

to six 55-gallon drums of raw material. Upjohn uses totes because they significantly reduce labor in material handling, reduce the risk of accidental releases and the number of containers disposed.); and

- Scrubbing of off gases.

10.1.7 Spill Procedures

Standard operating procedures for spills are in place at Upjohn.

10.2 SKB Pharmaceuticals

10.2.1 Waste Minimization

All raw material and finished drug product are shipped back to Upjohn. Only broken vials of drug product or off-specification drug product is incinerated as pharmaceutical waste. These materials are not amenable to recovery and/or reuse.

10.2.2 Spill Procedures

Spill procedures at SKB include containment of the spill, use of absorbent material for trapping the spill and placement of used absorbent material in plastic bags. All materials used for cleanup are discarded as pharmaceutical wastes.

10.2.3 Toxic/Hazardous Substances

No toxic or hazardous substances will need to be disposed of for the proposed action.

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 control of colibacillosis in turkey poults 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
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13. CERTIFICATION

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

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14. REFERENCES

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15. APPENDICES