

ENVIRONMENTAL ASSESSMENT REPORT (EA)

1. DATE

May 29, 1996

2. NAME OF APPLICANT

The Upjohn Company

3. ADDRESS

The mailing address and telephone number of The Upjohn Company's headquarters are:

7000 Portage Road
Kalamazoo, Michigan 49001
Corporate telephone number: (616) 323-4000

4. DESCRIPTION OF THE PROPOSED ACTION

4.1. Requested Approval

This environmental assessment (EA) report for Spectinomycin Sulfate Sterile Solution (U-18409E; ADSPEC™ Sterile Solution) is being submitted for phased review under INADA #2570. This document completely fulfills EA requirements for the New Animal Drug Application (NADA) for Spectinomycin Sulfate Sterile Solution, as defined in 21 CFR 25.31a(b)(4) (Reference 1).

4.2. Need for the Action

Spectinomycin Sulfate Sterile Solution will be used in cattle (not in lactating dairy cattle) for the treatment of bovine respiratory disease (pneumonia, shipping fever) associated with *Pasteurella haemolytica*, *Pasteurella multocida* and *Haemophilus somnus*.

Spectinomycin Sulfate Sterile Solution will be administered to cattle under a veterinarian's order by subcutaneous injection in the neck at a dosage of 10 to 15 mg spectinomycin per kg of body weight (4.5 to 6.8 mL per 100 lb body weight). Treatment will be administered at 24-hour intervals for 3 to 5 consecutive days. Selection of dosage (10 to 15 mg/kg) and duration of treatment (3 to 5 days) will be based on the veterinarian's

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judgment of severity of disease.

4.3. Production Locations

4.3.1. Drug Substance

Fermentation, crystallization and isolation of spectinomycin sulfate will be done at The Upjohn Company, 7171 Portage Road, Kalamazoo, Michigan 49001, 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. The Upjohn facility 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.

This complex consists of approximately 80 buildings including chemical and pharmaceutical manufacturing operations, offices, laboratories, utility operations, and various other support buildings (Appendix 1). 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.

4.3.2. Drug Product

Spectinomycin Sulfate Sterile Solution will be formulated and packaged at Upjohn S.A. de C.V., Calzada de Tlalpan 2962, 04870 Mexico, D.F., Mexico, located in the industrial block of pharmaceutical plants in southern Mexico City. The site occupies 28,528 m² of land, 12,028 of which are occupied by multiple buildings (sterile area, non-sterile area, warehouse, quality control, lunchroom and administrative offices). The buildings comprising the site are constructed of steel, bricks and concrete. Internal walls are made of glass framed with aluminum, sandwich panel or dry walls, and FRP walls. Except for the new sterile area, which was remodeled in 1993-94, most of the buildings are 35-40 years.

Sterile products are manufactured in a dedicated aseptic facility which includes components preparation, sterilization, drugs compounding, and aseptic filling areas.

The area in the immediate vicinity of the Upjohn site includes Mead-Johnson, Cyanamid, Ciba-Geigy, Columbia Laboratories, Kodak, and SERFIN facilities, a football

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training camp, and single- and multiple-family residences.

4.4. Locations of Use

The drug substance is the active ingredient in several of The Upjohn Company's drug products. Finished product will be stored in distribution centers prior to transportation for sale at veterinary clinics and animal health outlets. The primary end use will be in feed yards for beef cattle throughout the United States.

4.5. Disposal Sites

Disposal of drug substance does not normally occur as the material is reprocessed until it meets specifications. Disposal of drug product may result from processing or distribution activities in the form of off-specification lots, returned goods, or from end user disposal of individual units of empty or partly empty finished product containers. The present infrastructure at the proposed manufacturing sites provides for the following recovery and/or ultimate disposal mechanisms:

4.5.1. Off-Specification Lots of Drug Product

Off-specification formulated lots of the drug product at Upjohn S.A. de C.V. will be disposed of in a sanitary landfill site located at Camino antiguo a Chimalhuacán s/n, San José Chicoloapan Estado de México.

The permitting agency is Reind Química S.A. de C.V., and its permit number is SFDESOL 9596.

4.5.2. Returned Goods

Returned goods of the drug product to Upjohn's Kalamazoo, Michigan facility will be incinerated in an on-site incinerator (interim status treatment storage and disposal facility).

Please refer to format item 6.2. for specific disposal operations covering air, water, and solid waste streams.

4.5.3. Discarded Product

Any discarded product or product containers generated in veterinary clinics or animal health outlets would typically be disposed in accordance with applicable Federal, State and local regulations.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT

OF THE PROPOSED ACTION

The Material Safety Data Sheet (MSDS) for spectinomycin sulfate tetrahydrate is enclosed as Appendix 2 of this EA. The chemical structure and materials used in producing the bulk drug, spectinomycin sulfate tetrahydrate, are provided in Appendix 3. The list of ingredients used in formulating the drug product, Spectinomycin Sulfate Sterile Solution, is provided in Appendix 4.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

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. Spectinomycin sulfate tetrahydrate is not regulated as a hazardous material under current DOT regulations. Product ready for shipment will be stored in either the manufacturing facility or distribution centers. Both maintain security by limiting access.

6.1. Substances Expected to be Emitted

Portions of the ingredients used in manufacturing spectinomycin sulfate tetrahydrate (Appendix 3) may be released to the environment as a result of the proposed action. Specific disposal operations covering air, water, and solid waste streams are identified in 6.2.

Permits and other actions covering specific environmental regulations in force at Upjohn's chemical/fermentation processing complex, including permit numbers and expiration dates where applicable, are summarized in the Permits Chart enclosed as Appendix 5.

6.2. Controls Exercised

Fermentation Process

6.2.1. Air Emissions

The emissions from the fermentation process consist of off-gases from fermented beer. No other significant emissions will result from ion exchange treatment, evaporation, filtration, crystallization and purification operations. Fermentation emissions are essentially a large volume of water-saturated exhaust gas. Particulate matter is controlled through the use of wet rotoclones and baghouses with efficiencies in excess of 95%.

Solvent tanks and reactors are equipped with approved vent condensers with efficiencies in excess of 85%.

The Upjohn Company is operating under an air consent judgment with the Michigan Department of Environmental Quality. In compliance with the air consent judgment, an air permit application (No. 132-94) was submitted on March 23, 1994.

6.2.2. Spent Solvents

Used solvents at The Upjohn Company's fermentation production plant are received into tanks and then fed into 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 or virgin tank where they are then distributed to the various production areas located throughout the fermentation operations. Those portions of the fractionation process that do not result in a product that is usable in the fermentation 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, depending upon the chlorine and water content of an individual stream.

The solvent waste streams in this process consist of acetone and methanol which are processed through the fermentation facility's solvent recovery area where approximately 90-95% are recycled for reuse.

Aqueous waste streams resulting from the fermentation, filtration and partial purification process consist of residual wastewater from sanitary use, spent beer and process wastewater streams containing trace amounts of various impurities and will be discharged to the sanitary sewer under the City of Kalamazoo's Industrial Pretreatment Program (IPP).

6.2.3.1. *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, incorporated by reference are The City of Kalamazoo Sewer Use Ordinance and Sewer Use Regulations Nos.

- 1-89 (dated December 5, 1989), detailing violations and related penalties 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.

The above documents detail additional specific discharge requirements and regulations. Projecting to the fifth year of production, all discharges from the production of spectinomycin sulfate tetrahydrate are permitted and will not impact the limits imposed under the ICD and accompanying sewer use regulations.

6.2.4. Solid Wastes

Bags, boxes, and filter cartridges are disposed at an approved sanitary landfill along with the other solid wastes generated at the plant site. If the company were to dispose of such material at the present time, it would use the following facilities:

- Westside Landfill in Three Rivers, MI (Waste Management of Michigan, Inc.) operating under State of Michigan Solid Waste Disposal License No. 8147 for bulk, uncrushed material;
- Orchard Hills Landfill in Watervliet, MI, operating under State of Michigan Solid Waste Disposal License No. 8113 for any finished drug product; or
- a comparable facility.

Upjohn has contracts with each of these facilities that require the facility to be in compliance with all applicable laws and regulations. The underlying agreements with the sanitary landfills affirm compliance status. All facilities must be audited and approved for use by Upjohn environmental auditors prior to the first shipment of waste from Upjohn to the site. In addition, Upjohn personnel conduct periodic environmental audits of off-site disposal facilities during use of the facilities.

6.2.5. *Incinerator.* All unused, discarded, or returned product will be incinerated in an approved on-site incinerator. An on-site approved incinerator is being operated as a Resource Conservation and Recovery Act (RCRA) interim status treatment storage and disposal facility under #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 certain 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 a minimum of 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 451, Part 111 permit application has been submitted to the Waste Management Division of the Michigan Department of Natural Resources (now the Michigan Department of Environmental Quality, MDEQ) in Lansing, Michigan. The Upjohn facility is operating under interim status provisions until action is taken on the permit application. MDEQ action on the permit application is expected in 1996.

The MDEQ Air Quality Division air permit issued on July 15, 1980 (#242-80), revised to incorporate the Act 451, Part 111 requirements, was approved on May 26, 1993.

All necessary permits are in place for the manufacture of spectinomycin sulfate tetrahydrate to begin, as an existing interim status facility in accordance with Section 3005(e) of RCRA and Michigan Act 64 licensing requirements.

Ash generated as a result of the incineration process will be sent to a permitted hazardous waste landfill. At the present time, Upjohn uses the following facilities:

- Chemical Waste Management, Trade Waste Incinerator Division, 7 Mobile Avenue, Sauget, IL, operating under EPA ID No. ILD 098 642 424 and Illinois Environmental Protection Agency No. IEPA 1631210009;
- Systech Environmental Corporation in Alpena, MI, operating under EPA ID

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No. MID981200835 and State Air Permit No. 587-93; or in Paulding, OH, operating under EPA ID No. OHD005048947 and State Air Permit Nos. 0363000002P016 and 0363000002P017;

- Continental Cement in Hannibal, MO, operating under EPA ID No. MOD054018288 and Air Permit No. 1086-004A; or
- alternative facilities that are properly permitted.

Upjohn has identified hazardous waste as well as air permits provided to Upjohn by the above facilities; however, there may be other permits and licenses applicable which are currently held by these facilities. While Upjohn has contracts with each of these facilities that require compliance with all applicable laws and regulations, Upjohn does not own, operate, or control these facilities. The waste stream profiles established with the hazardous waste landfill sites contain an affirmation by the facility of its compliance status. All facilities are audited and approved for use by Upjohn environmental auditors prior to the first shipment of waste from Upjohn to the site.

Pharmaceutical Formulation

See Appendix 6 for a document dated March 7, 1996 from Upjohn S.A. de C.V. certifying the manufacturing facilities are:

- in compliance with all national and local environmental laws;
- in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and
- that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

6.3. Citation of and Statement of Compliance with Applicable Emission Requirements

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, including subsections 306(a) and (b) [debarment].
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 Waste water) 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.)

6.3.1. *Emission Requirements.* Upjohn 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 spectinomycin sulfate tetrahydrate 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 spectinomycin sulfate tetrahydrate at its facilities in Kalamazoo, Michigan.

6.3.2. *OSHA Requirements.* Upjohn certifies that it has comprehensive programs and practices in place addressing all applicable OSHA requirements.

6.4. Discussion of the Effect of Approval on Compliance with Current Emissions

Existing facilities with no new environmental control equipment are used for the entire fermentation, crystallization, and isolation process.

Projecting to the fifth year of production, all discharges from the production of spectinomycin sulfate tetrahydrate are permitted and will not affect compliance with current emission requirements. Waste water emission for this drug substance will be <1% of the permit limit.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

As cited at 21 CFR 25.31a(b)(4)(i) and (ii), documentation for format items 7 through 11 is not required in an EA for inclusion with an NADA intended to be approved for use under a prescription or veterinarian's order, and these items have therefore been excluded.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

As cited at 21 CFR 25.31a(b)(4)(i) and (ii), documentation for format items 7 through 11 is not required in an EA for inclusion with an NADA intended to be approved for use under a prescription or veterinarian's order, and these items have therefore been excluded.

9. USE OF RESOURCES AND ENERGY

As cited at 21 CFR 25.31a(b)(4)(i) and (ii), documentation for format items 7 through 11 is not required in an EA for inclusion with an NADA intended to be approved for use under a prescription or veterinarian's order, and these items have therefore been excluded.

10. MITIGATION MEASURES

As cited at 21 CFR 25.31a(b)(4)(i) and (ii), documentation for format items 7 through 11 is not required in an EA for inclusion with an NADA intended to be approved for use under a prescription or veterinarian's order, and these items have therefore been excluded.

11. ALTERNATIVES TO THE PROPOSED ACTION

As cited at 21 CFR 25.31a(b)(4)(i) and (ii), documentation for format items 7 through 11 is not required in an EA for inclusion with an NADA intended to be approved for use under a prescription or veterinarian's order, and these items have therefore been excluded.

12. LIST OF PREPARERS

Following is a listing of those persons, and corresponding qualifications, who 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.

Jeffrey S. Mehring	Environmental Quality and Safety Division Manager, Environmental Health Sciences Ph.D., Agriculture Professional experience: 25 years
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Susan I. Shedore	Environmental Quality and Safety Division Environmental Technician A.A., Liberal Arts Corporate experience: 25 years
Nicholas J. Tuit	Worldwide Pharm. Mfg. Operations Environmental & Safety Administrator B.S., Industrial Engineering Professional Experience: 20 years
Nancie L. Rolinski	Chemical Operations Environmental Contract Professional B.S., Resource Development Professional experience: 4 years
Joseph A. Robinson	Sr. Research Scientist Worldwide Animal Health Product Development Ph.D., Microbiology Professional experience: 14 years
B. Lamar Lee	Clinical Research Scientist III Worldwide Animal Health Clinical Research and Product Development Ph.D., Entomology Professional experience: 25 years
Stephen F. Sutherland	Director Worldwide Animal Health Regulatory Services B.S. & D.V.M. (Veterinary Medicine) Professional experience: 15 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, Manager
Corporate Environmental Affairs
(telephone 616/323-5341)

Date

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

Date

14. REFERENCES

1. 21 Code of Federal Regulations Part 25.31a(b)(4)(i) and (ii).

15. APPENDICES

- 1 Map of Upjohn's Kalamazoo Chemical/Fermentation Manufacturing Site Complex
- 2 MSDS for the Active Ingredient, Spectinomycin Sulfate Tetrahydrate
- 3 Spectinomycin Sulfate Tetrahydrate: Chemical Structure and List of Materials Used in the Fermentation/Bulk Drug Manufacturing Process
- 4 Spectinomycin Sulfate Sterile Solution(ADSPEC™): List of Ingredients Used in the Formulation
- 5 Permits Chart
- 6 Certification document: Upjohn S.A. de C.V.

APPENDIX 2

Material Safety Data Sheet

Revision Date: May 28, 1996
Agent Id#: 25019

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

COMMON NAME: SPECTINOMYCIN SULFATE TETRAHYDRATE

SYNONYMS: Alternate cas- 23312-56-3 (sulfate)

64058-48-6 - CAS NUMBER

4h-pyrano{2,3-b}{1,4}benzodioxin-4-one,decahydro-4a,7,9-
trihydroxy-2-methyl-6,8-bis(methylamino)-, {2r-(2.alpha.,4a.
beta.,5a.beta.,6.beta.,7.beta.,8.

beta.,9.alpha.,9a.alpha.,10a.beta.)}-, sulfate

273000 - EDP NUMBER

273010 - EDP NUMBER

U-18,409E - UPJOHN U#

MOLECULAR FORMULA: C14-H24-N2-O7.H2-S-O4.4H2-O

CHEMICAL FAMILY: Antibiotic

USE: Drug

MANUFACTURER/SUPPLIER: PHARMACIA & UPJOHN INC

7171 PORTAGE RD

KALAMAZOO, MI 49001-0199

DATA SOURCE: PHARMACIA & UPJOHN INC

7171 PORTAGE RD

KALAMAZOO, MI 49001-0199

TELEPHONE NUMBERS: (616) 833-5122 - (24 HOURS)

(616) 833-7555 - (8:00 a.m. - 4:30 p.m.)

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENT 1

COMMON NAME: Spectinomycin Sulfate Tetrahydrate

CHEMICAL NAME: 4h-pyrano{2,3-b}{1,4}benzodioxin-4-one,decahydro-4a,7,9-
trihydroxy-2-methyl-6,8-bis(methylamino)-, {2r-(2.alpha.,
4a.beta.,5a.beta.,6.beta.,7.beta.,8.

beta.,9.alpha.,9a.alpha.,10a.beta.)}-, sulfate

% BY WEIGHT: Main component.

CAS NUMBER: 64058-48-6

EXPOSURE LIMIT(S):

UPJOHN EXPOSURE LIMIT-TWA: 2 MG/M3

Value is for spectinomycin

3. HAZARDS IDENTIFICATION

EFFECTS OF OVEREXPOSURE: In general, spectinomycin sulfate tetrahydrate is of low toxicity. Irritation to the eyes and respiratory passages may occur. Other salts of spectinomycin have shown that in single doses, adverse effects including urticaria, transient rash, dizziness, headache, nausea, vomiting, chills, fever, nervousness, and insomnia have been reported. Hypersensitivity reactions may occur. Antibiotics have been reported to cause irritation to the airways. Some antibiotics are absorbable when inhaled and can have systemic effects.

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: Not established.

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: If serious allergic reactions occur, the usual agents (epinephrine, corticosteroids, and/or antihistamines) should be used as 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. Sulfur oxides. Nitrogen oxides.

6. ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED: Remove

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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: Avoid generating dust and contact with skin, eyes and clothing. Use with adequate ventilation. Wash thoroughly after handling. Launder contaminated clothing before reuse. Store at room temperature.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

RESPIRATORY PROTECTION: Approved respirator when levels exceed the exposure limit.

VENTILATION: Local exhaust at the point of dust generation.

PROTECTIVE GLOVES: Rubber.

EYE PROTECTION: Safety glasses with side shields.

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE/PHYSICAL STATE: White crystalline powder

BOILING POINT: No information found

EVAPORATION RATE: Not applicable.

FREEZING POINT: Not applicable.

MELTING POINT: 185 C (365 F)

MOLECULAR WEIGHT: 502.48

ODOR: No information found

ODOR THRESHOLD: No information found

PARTITION COEFFICIENT (n-OCTANOL/WATER): 0.0036 (at pH 7 (0.0033 and 0.0039 at pH 5 and 9, respectively))

PH: 3.8 - 5.6

SOLUBILITY IN SOLVENTS: 0.045 mg/ml diethyl ether and 0.020 mg/ml acetone

SOLUBILITY IN WATER: Soluble

SPECIFIC GRAVITY (WATER=1): No information found

VAPOR DENSITY (air = 1): Not applicable.

VAPOR PRESSURE: Not applicable.

VOLATILITY: Not applicable.

10. STABILITY AND REACTIVITY

STABILITY: Stable in water at pH less than or equal to 4. Degrades to

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spectanoic acid (no biological activity) at pH greater than or equal to 5.

PHYSICAL CONDITIONS TO AVOID: Avoid bases.

INCOMPATIBILITY WITH OTHER MATERIALS: None.

HAZARDOUS DECOMPOSITION PRODUCTS: None.

HAZARDOUS POLYMERIZATION: Does not occur.

11. TOXICOLOGICAL INFORMATION

ACUTE STUDIES:

EYE IRRITATION (RABBIT): Minimally irritating to eyes.

SKIN IRRITATION (RABBIT): Allergic skin reactions may occur.

SENSITIZATION: Hypersensitivity reactions may occur.

INTRAVENOUS LD50 (MOUSE): 1,022 MG/KG

ACUTE TOXICITY: (Based on studies on spectinomycin) Results of laboratory tests may be abnormal following multiple doses; decreased hemoglobin, hematocrit, and creatinine clearance and elevated alkaline phosphatase, blood urea nitrogen (bun), and serum glutamic pyruvic transaminase (alt) levels have been reported. A reduction in urine output has been reported in single and multiple dose studies.

Extensive renal function studies demonstrate no consistent changes indicative of renal toxicity.

ORAL TOXICITY (RAT): In a 13-week oral toxicity study in rats with doses of 0, 50, 400, and 3000 (free base equivalents) mg/kg/day, a NOEL (no-observed-effect level) was not determined because changes in the digestive system were present in the low-dose group. These changes were felt to be a result of an antibody effect on the intestinal microflora rather than a direct toxic effect from systemic exposure.

All dose levels were well tolerated.

ORAL LD50 (RAT): > 5,000 MG/KG

INTRAPERITONEAL LD50 (MOUSE): 3,577 MG/KG

OTHER STUDIES:

GENOTOXICITY: Mutagenicity studies, including the ames assay, showed no evidence of mutagenicity.

TERATOGENICITY: Animal tests showed no teratogenic effects and no evidence of toxic effect through placental or milk transfer.

CARCINOGENICITY: Not listed as a carcinogen by IARC, NTP or OSHA.

12. ECOLOGICAL INFORMATION

ENVIRONMENTAL FATE:

MOBILITY: Spectinomycin is a polar base. It readily forms salts with acids. The melting point of spectinomycin sulfate pentahydrate is 185 C and a similar reading may be expected for the tetrahydrate form. The salts of spectinomycin should have a low vapor pressure and should not

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enter the air. The octanol/water partition coefficient is 0.0033, 0.0036 and 0.0039 at pH values of 5, 7 and 9, respectively.

Spectinomycin sulfate has a water solubility of > 20 mg/ml in both 0.1N NaOH and 0.1N HCl. Based on these properties, spectinomycin sulfate tetrahydrate would be expected to be relatively mobile in the aquatic compartment with little or no sorbtion onto organic particles taking place.

PERSISTENCE/DEGRADABILITY: Spectinomycin is stable in water at pH's below 4. At pH's above 5 it degrades to spectanoic acid which has no biological activity. The degradation is readily measured at 70 C and 40 C but is much slower at room temperature. Thus in naturally occurring waters above pH 5 spectinomycin sulfate tetrahydrate would be expected to slowly degrade to the nonbiologically active spectanoic acid. Microorganisms in soil have the potential to degrade spectinomycin sulfate tetrahydrate to carbon dioxide.

BIOACCUMULATIVE POTENTIAL: Spectinomycin's partition coefficient should be greater than the value observed for the analog trospectomycin (0.000079), therefore it would not be expected to bioaccumulate. not

ABIOTIC POTENTIAL: No information found.

ECOTOXICITY: No information found.

13. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL METHOD: Dispose of by incineration in accordance with applicable international, national, state, and/or local waste disposal regulations.

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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. OTHER INFORMATION

REVIEWED BY: Kristin Jaeger. Environmental Health Sciences.

DISCLAIMER: The MSDS information is believed to be correct but should only be used as a guide. Pharmacia & Upjohn, Inc. 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.

16. LABELING

UPOJOHN 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.

EEC (EUROPE) HAZARD CLASS: HARMFUL.

EEC (EUROPE) STANDARD RISK PHRASE(S): R 42/43 May cause sensitization by inhalation and skin contact.

EEC (EUROPE) STANDARD SAFETY PHRASE(S): S 36/37/39 Wear suitable protective clothing, gloves and eye/face protection.

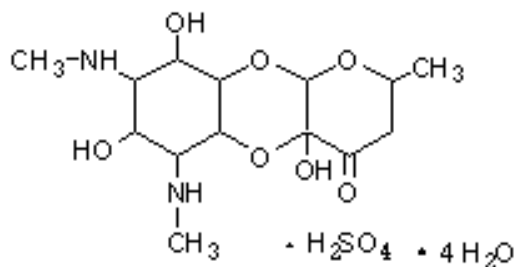
EEC (EUROPE) HAZARD SYMBOL: St. Andrew's Cross.

APPENDIX 3

Spectinomycin Sulfate Sterile Solution (ADSPEC™): Chemical Structure and List of Ingredients Used in the Fermentation/Bulk Drug Manufacturing Process

Generic Name: Spectinomycin sulfate tetrahydrate

Chemical Structure



Trademark: Spectinomycin Sulfate Sterile Solution (ADSPEC™)

CAS Nomenclature

and Number: 4h-pyrano{2,3-b}{1,4}benzodioxin-4-one, decahydro-4a,7,9-trihydroxy-2-methyl-6,8-bis(methylamino)-{2r-(2.alpha.,4a.beta.,5a.beta.,6.beta.,7.beta.,8.beta.,9.alpha.,9a.alpha.,10a.beta.)}-, sulfate

64058-48-6

Upjohn Number: 18,409E

Molecular

Formula: C₁₄H₂₄N₂O₇ · H₂SO₄ · 4H₂O

Molecular

weight: 502.48

Appearance: White crystalline powder

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Name	CAS No.	M.W.	Formula	Appearance
Acetone	67-64-1	58.08	C ₃ H ₆ O	Colorless liquid
Amylase (starch liquefying enzyme)	58-78-9	not provided	not provided	Liquid
Calcium chloride flake	10035-04-8	47.0	CaCl ₂	White powder
Celatom FW-40 (filter aid precoat)	Diatomaceous earth: 68855-54-9 Cristobalite: 14464-46-1	mixture	SiO ₂	Light pink to white powder
Corn flour	68525-86-0	not provided	unknown	Yellow powder
Dowex CCR-2 resin	not provided	not provided	not provided	Light yellow to amber solid (beads)
ECCO blend nonfat milk replacement	not provided	not available	not available	not provided
Ferric chloride lumped	7705-08-0	270.0	FeCl ₃	Yellow brown deliquescent crystals
Formaldehyde solution, 37%, 7% methanol	50-00-0	mixture	CH ₂ O	Colorless liquid
Lard oil	8016-28-2	not provided	unknown	White-yellow liquid
Magnesium sulfate	7487-88-9	246.0	MgSO ₄	White powder
Manganous chloride 4 hydrate	13446-34-9	198.0	MnCl ₂	Pink crystals
Monobasic sodium phosphate anhydrous	7558-80-7	119.98	NaH ₂ PO ₄	White granules or powder
Nuchar S-A (activated carbon)	7440-44-0	not available	C	Black, particulate solid
Polyalkylene glycol	51258-15-2	not provided	not provided	Clear, viscous liquid
Potassium sulfate industrial grade	7778-80-5	135.0	K ₂ SO ₄	White granular solid or powder
SAG 471	not provided	not provided	mixture	Opaque, viscous fluid
Sodium chloride; low calcium	7647-14-5	58.44	NaCl	White crystals
Sodium hydroxide, 50% solution	1310-73-2	40.0	NaOH	Clear liquid
Sodium acetate	127-09-3	82.03	NaC ₂ H ₄ O ₂	White crystalline

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Name	CAS No.	M.W.	Formula	Appearance
anhydrous				powder
Sonic dried brewers yeast	8013-01-2	not available	not available	Solid
Soybean flour - low NSI (20-25)	68513-95-1	not available	unknown	White lyophilized powder
Starch	9005-25-8	not available	(C ₆ H ₁₀ O ₅) _x	Pure powder
Sulframmin 90 flake	not provided	not provided	C ₈ H ₉ HO ₃ S	not provided
Sulfuric acid 48.5 BE	7664-93-9	98.0	H ₂ SO ₄	Clear to slightly cloudy, oily liquid
Zeolite (10N-SIV A 51)	Quarts: 14808-60-7 Sodium oxide: 1313-59-3	mixture	Al ₂ Na ₂ O ₆ Si	May appear as bead, pellet, mesh, cake, or powder
Zinc chloride USP granular	7646-85-7	136.0	ZnCl ₂	White crystals

APPENDIX 4

Spectinomycin Sulfate Sterile Solution: List of Ingredients Used in the Formulation

Name	CAS No.	M.W.	Formula	Appearance
Spectinomycin sulfate tetrahydrate injectable grade	64058-48-6	502.48	$C_{14}H_{24}N_2O_7 \cdot H_2SO_4 \cdot 4H_2O$	White crystalline powder
Benzyl alcohol NF	100-51-6	108.14	C_7H_8O	Colorless liquid
Sodium hydroxide reagent	1310-73-2	40.0	NaOH	Clear liquid
Hydrochloric acid reagent	7647-01-0	36.47	HCl	Corrosive, toxic, colorless liquid
Water for injection	7732-18-5	18.0	H_2O	Clear liquid

APPENDIX 5

The Upjohn Company: Permits Chart

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 reissued 12/1/95, effective 3/1/96	10/1/2000
RCRA/Michigan Hazardous Waste Management Act 451/Part 111 (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 Act 451/ Part 111 permit application.		
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	U.S. EPA, Region 5	MI-077-1W-0001	07/09/93	10/27/96

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PERMIT DESCRIPTION	REGULATORY AGENCY	PERMIT NO.	ISSUED	EXPIRES
(CPWM) Injection System (Class 1 wells) Underground Injection Control Permit	Safe Drinking Water Act	MI-077-1W-0002		

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APPENDIX 1

Map of Upjohn's Kalamazoo Chemical/Fermentation Manufacturing Site Complex

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APPENDIX 2

MSDS for the Active Ingredient, Spectinomycin Sulfate Tetrahydrate

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APPENDIX 3

Spectinomycin Sulfate Tetrahydrate: Chemical Structure and List of Materials Used in the Fermentation/Bulk Drug Manufacturing Process

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APPENDIX 4

Spectinomycin Sulfate Sterile Solution (ADSPEC™): List of Ingredients Used in the Formulation

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Permits Chart

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APPENDIX 6

Certification Document: Upjohn S.A. de C.V.