CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020926

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

RenaGel®

(sevelamer hydrochloride)

Capsules

NDA 20-926

Food And Drug Administration
Center For Drug Evaluation And Research
Division of Metobolic and Endocrine
Drug Products(HFD-510)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-926

RenaGel®

(sevelamer hydrochloride)

Capsules

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for RenaGel® (sevelamer hydrochloride) Capsules, GelTex Pharmaceuticals, Inc. has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal of the product.

Sevelamer hydrochloride is a chemically synthesized drug which is used treatment of hyperphosphatemia in end-stage renal failure patients without risk of hypercalcemia.

Sevelamer may enter the environment from patient use and disposal. It is expected to enter into the aquatic and terrestrial environment. As the drug is expected to persist in the environment for some time, the toxicity of sevelamer to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at the expected environmental introduction concentration.

At U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

5/11/98
DATE

/S/

PREPARED BY
Nancy B. Sager
Environmental Officer
Center for Drug Evaluation and Research

5/14/98
DATE

/S/ for

CONCURRED
Eric B. Sheinin, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

Note: Although the EA is marked "confidential" on each page, the applicant has confirmed in section 1.13 (page 32) that it can be released to the public.

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cc: Original to NDA 20-926 through PM JWeber/HFD-510
HFD-357/EA File
HFD-357/Docket File
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ENVIRONMENTAL ASSESSMENT

~~Confidential~~ See section 1.13, page 32
FDA 5/11/98

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1. ENVIRONMENTAL ASSESSMENT

1.1 DATE

November 3, 1997

1.2 NAME OF APPLICANT

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GelTex Pharmaceuticals, Inc.

1.3 ADDRESS

Nine Fourth Avenue
Waltham, MA 02154

1.4 DESCRIPTION OF PROPOSED ACTION

1.4.1 Requested Approval

GelTex Pharmaceuticals, Inc. has filed an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for RenaGel® Capsules (Sevelamer Hydrochloride), 403 mg (anhydrous), packaged in HDPE bottles. An EA has been submitted pursuant to 21 CFR § 25.31a(a).

1.4.2 Need for Action (Proposed Use)

RenaGel is indicated for the treatment of hyperphosphatemia in end-stage renal failure patients without the risk of hypercalcemia. The proposed method of administration of RenaGel is by oral ingestion of capsules with meals. The duration of use will be lifetime, from the onset of end-stage renal disease.

1.4.3 Production Locations

1.4.3.1 Manufacturing of the Drug Substance (Sevelamer Hydrochloride)

1.4.3.1.1 Dow Chemical Company

Sevelamer hydrochloride (HCl) is manufactured at The Dow Chemical facilities located in Midland, Michigan, in compliance with applicable state and federal environmental regulations.

Facility Address
The Dow Chemical Company
Michigan Division
Midland, MI 48667

Drug Establishment Registration No. 1810030

Description of Surrounding Environment
The Michigan Division of The Dow Chemical Company is situated on approximately 1900 acres in the Saginaw Valley of mid-Michigan. The Tittabawassee River runs through the Michigan Division site. The manufacturing site is adjacent to the city of Midland, Michigan which has a population of approximately 38,000.

Disposal Sites
Wastes from the manufacture of sevelamer hydrochloride will be treated at the Michigan Division site of The Dow Chemical Company in Midland, Michigan.

Rejected, expired, returned or waste drug substance or product (if not reprocessed) will be incinerated at The Dow Chemical Incineration Complex:

> The Dow Chemical Company, Building 703, Midland, Michigan 48667
> EPA ID No.: MID 000724724
> Permitted by: State of Michigan Department of Natural Resources
> Air Use Permit Nos.: 93-73, 471-79, 403-78, 403-78A, 678-83, 887-89, 441-88, 336-81A (no expiration)
> Hazardous Waste Facility Operating License #: Incinerator Complex, Act 64, Operating License (Expiration 9/27/94; license remains in effect due to submission of a complete reapplication in accordance with the appropriate license conditions and administrative rules)

1.4.3.1.2 Abbott Laboratories

Sevelamer hydrochloride is manufactured at Abbott Laboratories located in North Chicago, Illinois, in compliance with applicable state and federal environmental regulations.

Facility Address
Abbott Laboratories
Chemical & Agricultural Products Division
North Chicago Plant
1401 N. Sheridan Road
North Chicago, Illinois

Drug Establishment Registration No. 1411365

Description of Surrounding Environment

The Abbott Laboratories' North Chicago pharmaceutical manufacturing facility (NC Site) is approximately 220 acres in size. The NC Site is located in an industrial zoned area within the city of North Chicago, in Lake County, Illinois. The NC Site operations are 600 to 1,000 feet west of Lake Michigan, at an average elevation approximately fifty (50) feet above the 580 foot mean sea level elevation of the lake. Other than Lake Michigan, there are no significant geographic features, such as mountains or rivers, in close proximity to the NC Site. Area topography is fairly flat, sloping gently east toward Lake Michigan. Drainage is dominantly to the east-southeast, toward Lake Michigan.

NC Site geology consists of approximately 105 feet of unconsolidated Quaternary Age glacial deposits overlying much older Silurian Dolomite bedrock formations. The glacial deposits consist primarily of silty clay tills, sand and gravel outwash, and lake bottom silt and clay deposits. These materials were deposited during the Wisconsinan Age, which occurred from 75,000 to 7,000 years ago and was the last glaciation period for the region.

The area climate is characterized by warm summers (74 to 94°F) and cold winters (20 to 32°F). Average annual rainfall is 32 inches, and wind directions are primarily from the west and can be highly variable.

Disposal Sites

Certain spent manufacturing materials may be of sufficient purity or quality to be sold to another company for reuse or use as a secondary fuel source. Certain solid and liquid non-hazardous, pharmaceutical, and hazardous wastes generated during production are collected and shipped off-site to state and federal permitted commercial waste disposal facilities. These off-site waste disposal facilities are properly equipped and designed to securely treat or dispose of the wastes in an environmentally sound manner. Off-site commercial waste treatment is dependent upon the type of waste and may include incineration or distillation and recovery of valuable raw materials followed by incineration or secure landfilling of distillation residues. Of the facilities contracted by Abbott, incineration for energy recovery or disposal have typical waste destruction efficiencies in excess of 99.9%.

Off-site commercial disposal of industrial solid waste, certain pharmaceutical wastes, and certain hazardous wastes in secure, permitted landfills is performed for certain other generated wastes. Abbott Laboratories does not own or operate any solid waste landfills.

Several of the state and federal permitted off-site disposal, recycling or energy recovery facilities may include, but are not limited to:

Continental Cement, Inc.
Highway 79 South
Hannibal, MO 63401
USEPA Hazardous Waste Permit No. MOD054018288
Expiration Date: Interim Status

Safety Kleen Corporation
S.E. Highway 79 North
Clarksville, MO 63336
USEPA Hazardous Waste Permit No. MOD029729688
Expiration Date: Interim Status

Rhone-Poulenc
2000 Michigan Street
Hammond, IN 46320
USEPA Hazardous Waste Permit No. IND001859032
Expiration Date: Interim Status

Safety Kleen Corporation
633 East 138th Street
Dolton, IL 60419
USEPA Hazardous Waste Permit No. ILD980613913
Expiration Date: Interim Status

1.4.3.2 Manufacturing of the Drug Product (RenaGel Capsules)

Facility Address
Circa Pharmaceuticals, Inc.
33 Ralph Avenue
PO Box 30
Copiague, New York 11726

Drug Establishment Registration No. 2410284

Description of Surrounding Environment
The manufacturing site is located in a temperate region on flat land. The site is approximately 28,000 m^2 in size, surrounded by a mix of industrial, commercial and residential development. There are no significant water bodies (rivers, lakes or oceans) within one mile of the facility.

Disposal Sites

GelTex Pharmaceuticals, Inc. will request that all unsold or expired RenaGel Capsules be returned to GelTex or GelTex's distributor(s) for disposal. Returned or rejected drug product will be disposed of at a facility which is licensed by the EPA or an appropriate state authority to destroy materials.

At U.S. hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy or clinic procedures and/or that in the home, empty or partially empty containers will typically disposed of by a community's solid waste management system which may include landfills, incineration and recycling, although minimal quantities of unused drug may be disposed of in the sewer system.

1.4.4 LOCATIONS OF USE

RenaGel Capsules will be distributed by, or on behalf of, GelTex Pharmaceuticals, Inc. to hospitals and pharmacies throughout the United States, for prescription use by patients with end-stage renal disease.

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

1.5.1 Nomenclature

1.5.1.1 Established Name (U.S. Adopted Name- USAN)

Sevelamer Hydrochloride

1.5.1.2 Brand/Proprietary Name

RenaGel®

1.5.1.3 Chemical Names

Poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane), hydrochloride (CAS)
2-propen-1-amine, polymer with (chloromethyl)oxirane, hydrochloride (CAS)
Oxirane, (chloromethyl)-, polymer with 2-propen-1-amine, hydrochloride (CAS)
Allylamine polymer with 1-chloro-2,3-epoxypropane, hydrochloride (IUPAC)

1.5.2 Chemical Abstracts Service (CAS) registration number

182683-00-7

1.5.3 Molecular Formula

$(C_3H_7N \cdot nHCl)_{812z}(C_9H_{18}N_2O \cdot nHCl)_{94z}$ where z equals a large number

1.5.4 Molecular Weight

The equivalent molecular weight which corresponds to 1.0 allylamine unit, 0.094 hydroxypropyl units and 0.40 HCl is 77.1.

1.5.5 Structural (graphic) Formula

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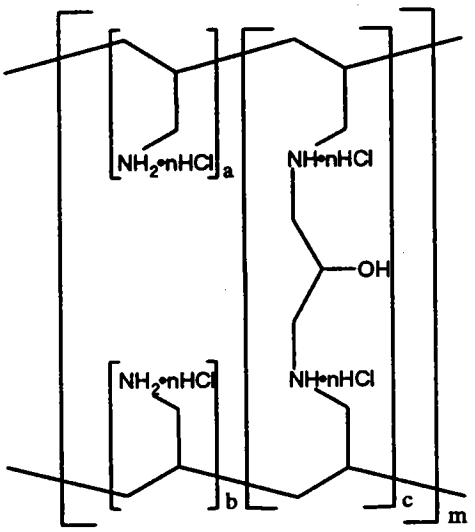

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Where:

a,b	= number of primary amine groups	a + b = 9
c	= number of crosslinking groups	c = 1
n	= fraction of protonated amines	n = 0.4
m	= large number to indicate extended polymer network	

The primary amine groups shown in the structure are derived directly from poly(allylamine hydrochloride). The crosslinking groups consist of two secondary amine groups derived from poly(allylamine hydrochloride) and one molecule of epichorohydrin.

1.5.6 Physical Description

White to off-white powder.

1.5.7 Additives

The drug product will be available in a capsule formulation containing 403 mg of sevelamer HCl. The composition is described in appendices

Appendix 1-1.

1.5.8 Impurities

There are no impurities in the drug substance at a level >1%.

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1.6 INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

1.6.1 Drug Substance- Sevelamer Hydrochloride

Appendix 1-2 describes the chemical synthesis for sevelamer hydrochloride. The following provides details of the emissions into the air, aquatic, and terrestrial compartments as a result of the manufacture, statement of controls exercised, citation of compliance with applicable emissions requirements, and effect of approval on compliance with current emission requirements.

1.6.1.1 Air Emissions

1.6.1.1.1 List of components of emitted streams:

Reference Waste Stream Nos. 1,2,3,5,6, and 7 on the Sevelamer Hydrochloride Block Flow Diagram (Appendix 1-3).

COMPONENT	CAS #	MAXIMUM YEARLY RATE (KG/YR)*
2-Propanol	67-63-0	
Acetonitrile	75-05-8	
Allylamine	107-11-9	
Epichlorohydrin	106-89-8	
* Quantities listed are after treatment and are based on 100,000 kg/yr production of sevelamer hydrochloride		

1.6.1.1.2 Statement of controls exercised:

Air emissions generated from the bulk drug production process are controlled using condensers, activated carbon bed adsorption systems, particle filters, scrubbers and combustion devices.

1.6.1.1.3 Citation of compliance with applicable emissions required at federal, state, and local levels:

An Air Use Permit will be obtained by The Dow Chemical Company, if required, from the State of Michigan Department of Natural Resources, before commercial manufacturing commences.

The Abbott Laboratories NC Site is in compliance with environmental laws and regulations, including the Illinois State Implementation Plan regarding ambient air quality as approved by the USEPA under 40 CFR Part 52, promulgated and enforced by the U.S. Environmental Protection Agency, the Illinois Environmental Protection Agency, the North Shore Sanitary District of Gurnee, Illinois and various local ordinances of the city of North Chicago and the country of Lake, Illinois.

1.6.1.1.4 Effect of approval on compliance with current emission requirements at production site:

Production of sevelamer hydrochloride at the Dow Chemical Company Midland, Michigan site and at the Abbott Laboratories NC site at the yearly production rates estimated in Appendix 1-4 will have no impact on compliance with current emission requirements.

1.6.1.2 Aquatic Emissions

1.6.1.2.1 List of components of emitted streams:

Reference Waste Stream Nos.1,2, and 4 on the Sevelamer Hydrochloride Block Flow Diagram (Appendix 1-3).

COMPONENT	CAS #	MAXIMUM YEARLY RATE (KG/YR)*
Acetonitrile	75-05-8	
Allylamine	107-11-9	
Sevelamer hydrochloride	182683-00-7	
Sodium chloride	7647-14-5	
*Quantities listed are before treatment at the Dow Chemical Waste Water or the POTW operated by North Shore Sanitary District (Abbott) and are based on 100,000 kg/yr production of sevelamer hydrochloride		

1.6.1.2.2 Statement of controls exercised:

The aqueous streams are discharged to The Dow Chemical Company Waste Water Treatment Plant (WWTP). Any acids and bases are subsequently neutralized and are discharged as dissolved solids from the WWTP to the Tittabawassee River.

At the Abbott Laboratories NC site, wastewater's are treated on-site in two stages: (1) physical and chemical treatment for pH control and solids removal, followed by (2) anaerobic and aerobic biologic treatment using the activated sludge process. In certain cases, additional wastewater treatment may be performed using distillation and stripping equipment to remove certain waste constituents from the wastewater prior to discharge into the Abbott NC Site activated sludge process wastewater treatment system. All Abbott NC Site wastewater is discharged to a Public Owned Treatment Works (POTW), operated by the North Shore Sanitary District, where it is again treated in an aerobic activated sludge wastewater treatment system.

1.6.1.2.3 Citation of compliance with applicable emissions required at federal, state, and local levels:

Aqueous discharge from The Dow Chemical Company Waste Water Treatment Plant is in compliance with the requirements set forth in the National Pollutants Discharge Elimination System (NPDES) Permit No. MI 40000868 for the Dow Chemical Waste Water Treatment Plant. Total dissolved solids daily maximum limit is and total maximum monthly average is

The Abbott Laboratories NC Site is in compliance with environmental laws and regulations, including wastewater Effluent Guidelines and Standards for Pharmaceutical Manufacturing defined in Title 40 of the Code of Federal Regulations (40 CFR) Pat 439, promulgated and enforced by the U.S. Environmental Protection Agency, the Illinois Environmental Protection Agency, the North Shore Sanitary District of Gurnee, Illinois and various local ordinances of the city of North Chicago and the country of Lake, Illinois.

1.6.1.2.4 Effect of approval on compliance with current emission requirements at production site:

Production of sevelamer hydrochloride at the Dow Chemical Company Midland, Michigan site and at the Abbott Laboratories NC site at the yearly production rates estimated in Appendix 1-4 will have no impact on compliance with current emission requirements.

1.6.1.3 Terrestrial Emissions

1.6.1.3.1 List of components of emitted streams:

Reference Waste Stream Nos. 3,5,6, and 7 on the Sevelamer Hydrochloride Block Flow Diagram (Appendix 1-3).

COMPONENT	CAS #	MAXIMUM YEARLY RATE (KG/YR)*
Acetonitrile	75-05-8	
Allylamine	107-11-1	
2- Propanol	67-63-0	
* Quantities listed are before treatment and are based on 100,000 kg/yr production of sevelamer hydrochloride.		

1.6.1.3.2 Statement of controls exercised:

These waste streams are incinerated at the Dow Chemical Incineration Complex. The thermal oxidizer operates at a minimum efficiency of 99.99%. Ash from the combustion process is disposed of in The Dow Chemical Company Salzburg Landfill, Midland, Michigan 48667.

At Abbott Laboratories, waste streams are shipped off-site to state and federal permitted comercial disposal facilities. These off-site facilities are properly equipped and designed to securely treat or dispose of wastes in an environmentally sound manner.

1.6.1.3.3 Citation of compliance with applicable emissions required at federal, state, and local levels:

The Dow Chemical Company Thermal Oxidation Unit permit is operated according to the requirements set forth by the State of Michigan Department of Natural Resources in the Dow Chemical Incineration Complex Air Use Permit Nos. 336-81A, 93-731, 471-79, 441-88 and State of Michigan Department of Natural Resources Hazardous Waste Facility Operating License EPA ID No. MID 000 724 724. The Dow Chemical Company Salzburg Landfill is operated according to the regulations set forth by the State of Michigan Department of Natural Resources, Hazardous Waste Facility Operating License EPA ID No. MID 890 617 435.

The Abbott Laboratories NC Site is in compliance with environmental laws and regulations, including the Federal and Illinois State Hazardous Waste Regulations defined in 40 CFR, promulgated and enforced by the U.S. Environmental Protection Agency, the Illinois Environmental Protection Agency, the North Shore Sanitary District of Gurnee, Illinois and various local ordinances of the city of North Chicago and the country of Lake, Illinois.

1.6.1.3.4 Effect of approval on compliance with current emission requirements at production site:

Production of sevelamer hydrochloride at the Dow Chemical Company Midland, Michigan site and at the Abbott Laboratories NC site at the yearly production rates estimated in Appendix 1-4 will have no impact on compliance with current emission requirements.

1.6.1.4 Employee Protection

Personnel in chemical production facilities are provided with appropriate personal protective equipment including safety glasses and goggles, safety shoes, protective gloves and clothing. Facilities and equipment are designed to minimize employee exposure to hazardous dusts, fumes, and vapors through engineering, work practices and administrative controls. Industrial hygiene monitoring of exposure to hazardous agents is routinely conducted at all production facilities. For certain non-routine or emergency situations, approved respiratory protection is provided to employees, and they are trained and fitted for use of the applicable respiratory protection device.

Employees are trained in the proper operation of equipment to minimize potential safety, health or environmental risks. Extensive training is mandated in all production facilities. Material Safety Data Sheets are available on-site for all chemicals handled in the production facilities.

1.6.1.5 Incinerator Emission Limits, The Dow Chemical Company, Midland, Michigan

The Michigan Division Incineration Complex consists of Buildings 703, 830, and 1078. Buildings 703 and 830 each house a rotary kiln incinerator and associated air pollution control equipment. Building 1078 serves as the control room and office complex for both incinerators.

The Building 703 incinerator consists of a rotary kiln and secondary combustion chamber. Air pollution control equipment for the Building 703 incinerator consists of a wet quench tower, a venturi scrubber, a demister, and an electrostatic precipitator.

The Building 830 incinerator consists of a rotary kiln and secondary combustion chamber. Air pollution control equipment for the Building 830 incinerator consists of a wet quench tower, a wet condensing tower, a venturi scrubber, a demister, and ionizing wet scrubbers.

The incinerators are licensed under Michigan's Hazardous Waste Management Act, 1979 PA 64, as Amended (Act 64). The license stipulates the following emission limits:

Pollutant	Emission Limit for Building 703 Incinerator	Emission Limit for Building 830 Incinerator
Particulate	15.1 lb/hr	3.26 lb/hr
HCl	3.4 grams/sec	3.4 grams/sec
CO	100 ppm	100 ppm
Opacity	20%	10%
Antimony	1.9 grams/sec	0.41 grams/sec
Arsenic	0.029 grams/sec	0.00013 grams/sec
Barium	0.45 grams/sec	0.41 grams/sec
Beryllium	0.022 grams/sec	$1x10^{-6}$ grams/sec
Cadmium	0.04 grams/sec	0.00039 grams/sec
Chromium	0.026 grams/sec	0.0035 grams/sec
Lead	0.61 grams/sec	0.014 grams/sec
Mercury	0.037 grams/sec	0.0025 grams/sec
Silver	0.09 grams/sec	0.41 grams/sec
Thallium	1.9 grams/sec	0.41 grams/sec

Both incinerators also have air permits issued under the Michigan Air Pollution Act, 1965 PA 348, as Amended (Act 348). Air permit numbers applicable to the incineration of solid wastes are 336-81A, 471-79, and 441-88. These permits have no expiration date.

Hazard communication information for wastes is filed with the applicable waste characterization form in Building 703. MSDS's for other materials used at the Incineration Complex are filed separately from the information on wastes, but also kept at Building 703.

Water used in the Incineration Complex air pollution control equipment is discharged to the Michigan Division Wastewater Treatment Plant (WWTP).

The WWTP operates under NPDES Permit No. MI 0000868, issued by the Surface Water Quality Division of the Michigan Department of Natural Resources. The permit has an

expiration date of October 1, 1993, and continues in effect due to timely reapplication. WWTP discharges are subject to regulation under the Michigan Water Resource Act, as Amended, (Act 245, Public Acts of 1929, as Amended, the "Michigan Act").

The WWTP discharges to the Tittabawassee River. The WWTP permit stipulates the following limits on the outfall:

pH 6.5 to 9.5
BOD <12 mg/L at 20 MGD; Actual limit is 2000 lb/day
Suspended Solids <30 mg/L at 20 MGD; Actual limit is 5000 lb/day
Flow <48 MGD
Fecal Coliform <400/100 MI
Phosphorus <1.0 mg/L
TDS Total River <500 mg/L

Salzburg Landfill is licensed under Michigan's Hazardous Waste Management Act, 1979 PA 64, and Amended (Act 64) and also under Michigan's Solid Waste Management Act 1978 PA 64, as Amended (Act 64).

Disposal of hazardous wastes (i.e., incineration residues) is performed according to Salzburg Landfill's Act 64 Operation License. The EPA I.D. Number for Salzburg Landfill is MID 980 617 435. Salzburg's Act 64 Operating License expiration date is January 12, 1992. The license continues in effect due to timely reapplication.

Disposal of non-hazardous wastes at Salzburg is performed according to the unit's Act 641 Operational License, License Number 8227.

1.6.2 Manufacture and Packaging of Drug product - RenaGel Capsules:

1.6.2.1 Substances Expected to be Emitted

The Circa Pharmaceuticals facility holds air permits which regulate emissions of volatile organic compounds (VOCs) and particulates. Appropriate controls are exercised to limit potential emissions to air and waste water and to limit occupational exposures to the drug substance and excipients. Because of the in-place emission controls, neither sevelamer HCl nor any other drug product or packaging components are expected to be released to air or water in sufficient quantities to have any significant environmental impact.

1.6.2.2 Controls Exercised

1.6.2.2.1 Air Handling and Treatment

All manufacturing and packaging areas are connected to a non-recirculating dust collection system. The system removes particles by vacuum action, controlling the amount of dust in manufacturing areas.

1.6.2.2.2 Wastewater Handling and Treatment

All manufacturing and packaging buildings are connected to the Suffolk County sewage collection system. All treatment of wastewater is performed by Suffolk County. A spill prevention plan is in place and responses are governed by a company Standard Operating Procedure (SOP). Depending on the type of spill (hazardous or non-hazardous), one of two waste disposal companies are asked to respond.

1.6.2.2.3 Disposal of Production Waste, and Non-usable Product

All significant production waste and non-usable product is collected for destruction by incineration by licensed disposal companies. This includes laboratory solvents, acids and bases.

For non-hazardous industrial waste, disposal is by:

SDS, Inc.
Specialty Disposal Services
115 Routs 46 West, Building A-1
Mountain Lakes, NY 07046
NYS Transporter License #PA-199
Solid Waste Transporter License #A90113-1E-126
New York Department of Conservation permit number for the facility at which incineration occurs is 1-2809-00088/00006-0

For hazardous liquids and solids, disposal is by:

Chemical Waste Disposal Corporation
42014 19th Avenue
Astoria, NY 11105-1082
EPA # NYD077444263, Transporter License #NY2A029

1.6.2.2.4 Occupational Exposure

Appropriate safety precautions are observed during all manufacturing operations to prevent occupational exposures. Employees are given instructions regarding safe product handling procedures and are provided with the proper safety clothing and protective equipment (e.g. masks, gloves, uniforms, etc.). Respirators are used during the manufacture of RenaGel® Capsules. These respirators are OSHA recommended, with filters appropriate for handling various solvents and acid/base materials. Material Safety Data Sheets are obtained and retained in the company files for each material handled at the facility. MSDSs are readily available and accessible to employees for their reference.

1.6.2.3 Citation of, and Statement of Compliance with Applicable Emission Requirements

The Circa Pharmaceuticals facility holds several "Permits to Operate' under Article 19 Air Pollution Control, form the New York Department of Environmental Conservation (see listing in the table below). These permits cover emissions of volatile organic compounds (VOC's) and particulate matter.

AIR POLLUTION PERMITS ISSUED BY THE NEW YORK STATE DEPARTMENT OF ENVIRONMENTAL CONSERVATION FOR CIRCA PHARMACEUTICALS, INC.

DEC Permit Number	Facility/Program Number	Expiration Date	Authorized Activity
1-4720-01137/00001-0	A4720005680	September 30, 1999	Operate emission points C0001 and C0002 (dust collection systems)
1-4720-01242/00001-0	A4720005679	September 30, 1999	Operate emission points B0001, B0002 and B0003 (dust collection systems)
1-4720-01241/00001-0	A4720000239	September 30, 1999	Operate emission point A0001 (dust collection)
1-4720-01241-00002-0	A4720000239	September 30, 1999	Operate emission point A0002 and A0003 & A0004

For wastewater handling and treatment, Circa Pharmaceuticals has a discharge certification, but not a specific discharge permit, from the Suffolk County Sewer District. Suffolk County monitors the effluent that leaves each building and has determined that the facility discharges do not exceed the relevant limits for pH, color, total suspended solids (TSS) and biochemical oxygen demand (BOD).

In addition to these permits and certifications, Circa Pharmaceuticals has EPA "Acknowledgment of Notification of Hazardous Waste Activity", EPA identification numbers NY0000187260 and NYD982540361.

The Circa Pharmaceuticals Inc. facility operates in compliance with all emission requirements, including occupational, set forth in applicable federal, state and local environmental laws, regulations and permits (see attached certified statement of compliance).

1.6.2.4 Effect of Approval on Compliance with Applicable Emission Requirements

The Circa Pharmaceuticals facility currently manufactures formulated drug products for itself and other companies. Approval of the proposed action and subsequent manufacture of production quantities RenaGel Capsules will not significantly increase facility production and therefore, is not expected to affect facility compliance with current discharge or emission requirements.

1.6.3 Expected Introduction Concentrations

The estimated annual production for the first five years following approval is described in Appendix 1-4.

1.6.3.1 Expected Introduction Concentration from Use

EIC-Aquatic or Terrestrial (ppm) = A x B x C x D

where A = kg/year production
B = _____ entering publicly owned treatment works (POTW's)
C = year/365 days
D = _____)

EIC = _____ x 1 year/365 days x _____

1.7 FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

1.7.1 Identification of Substance of Interest

Sevelamer hydrochloride

1.7.2 Physical/Chemical Characterization

1.7.2.1 Water Solubility

Sevelamer hydrochloride is not soluble in water.

1.7.2.2 Dissociation Constant(s)

Sevelamer hydrochloride is a polyelectrolyte, there is no discrete dissociation constant.

1.7.2.3 Octanol/Water Partition Coefficient

Sevelamer hydrochloride is not soluble in water or hydrocarbon solvents, therefore the octanol/water partition coefficient was not calculated.

1.7.2.4 Vapor Pressure

Sevelamer hydrochloride has no vapor pressure.

1.7.3 Environmental Depletion Mechanisms

Sevelamer hydrochloride was evaluated for ready biodegradability following the OECD Method 301F: Manometric Respirometry test guidelines. The final study report is included in Appendix 1-5. Oxygen consumption and CO_2 evolution as indicators for biodegradation were measured over a 28-day test period using a _____

_____

Sevelamer hydrochloride exhibited no net biodegradation based on O_2 consumption or CO_2 production after 28 days. The suitability of the test procedure and microbial inoculum were validated by rapid biodegradation of the control compound (sodium benzoate). Biodegradation of sodium benzoate averaged 60% after only 2.3 days and 111.8% after 28 days. A toxicity control reaction containing a mixture of sodium benzoate and sevelamer hydrochloride showed no evidence for inhibition of biodegradation. The observed O_2 consumption and CO_2 production in the biodegradtion reactions can be attributed solely to biological activity, as negligible O_2 consumption and CO_2 production were observed in a killed control reaction over the 28 day test period.

Results from this study indicate that sevelamer hydrochloride is **not** readily biodegradable.

1.7.4 Expected Environmental Concentration (EEC)

Since sevelamer hydrochloride is not readily biodegradable, the EEC will be similar to the EIC of 2.6 ppb.

1.7.5 Summary

Sevelamer hydrochloride is a crosslinked polymer of (poly)allylamine which is highly stable and does not appear to degrade biologically. Since it is possible that this compound could enter both the aquatic and terrestrial environments, the following section described studies performed to assess the potential effects of selevamer hydrochloride on the environment.

1.8 ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

1.8.1 Evaluation of the Acute Toxicity of Sevelamer Hydrochloride to *Daphnia magna* Straus

Objective

The objective of this study was to determine the acute toxicity of sevelamer hydrochloride to the daphnid, *Daphnia magna* Straus. These data will be used to calculate 48-hour LC50 and EC50 values and a no-observed-effect concentration, if possible. The final study report is included in Appendix 1-6.

Design

Definitive testing was conducted at nominal concentrations of 0 (water control), 62.5, 126, 250, 500, and 1000 mg/L with 20 instars per dose level (4 replicates per level; 5 instars per replicate). Test solutions were prepared by adding appropriate aliquots of test material to 1 L of daphnid water. Undissolved test material (increasing with test concentration) was readily visible in the test solutions after preparation and transfer to the test vessels.

Results

The 48-hour LC50 and EC50 for sevelamer hydrochloride with *Daphnia magna* Straus are greater than 1000 mg/L. After 48 hours of exposure, the mortality pattern was as follows: 0 mg/L (0/20 or 0%), 62.5 mg/L (0/20 or 0%), 126 mg/L (2/20 or 10%), 250 mg/L (1/20 or 5%), 500 mg/L (1/20 or 5%), and 1000 mg/L (2/20 or 10%). Some surviving organisms were coated with the test material in the 1000 mg/L test level, but were able to swim.

Conclusion

Based on mortality and sublethal effects (coating of test material on the test organisms), the no-observed-effect concentration for sevelamer hydrochloride in *Daphnia magna* was 62.5 mg/L.

1.8.2 Evaluation of the Acute Toxicity of Sevelamer Hydrochloride to the Rainbow Trout, *Oncorhynchus mykiss* Walbaum

Objective

The objective of this study was to determine the acute toxicity of sevelamer hydrochloride to the rainbow trout, *Oncorhynchus mykiss* Walbaum. These data will be used to calculate a 96-hour LC50 value and a no-observed effect concentration, if possible. The final study report is included in Appendix 1-7.

Design
Definitive testing was conducted for 96 hours at nominal concentrations of 0 (water control), 15.7, 31.3, 62.6, 125, 250, and 500 mg/L with 20 fish per dose level (2 replicates per level; 10 fish per replicate). Test concentrations were prepared by addition of appropriate aliquots of test material directly to the test vessels that contained 10 L of water. Undissolved test material (increasing with test concentration) was readily visible in the test solutions after preparation and throughout the study.

Results
The 96-hour LC50 for sevelamer hydrochloride with the rainbow trout is 82 mg/L, with a 95% confidence interval of 62.6-125 mg/L. After 96 hours of exposure, there was 100% mortality (20/20) at 125, 250, and 500 mg/L, 10% mortality (2/20) at 62.5 mg/L, and 0% mortality (0/20) at 31.3 mg/L and 15.6 mg/L. Sublethal effects, such as loss of equilibrium, erratic movement, lethargy, surface swimming, and/or melanosis were noted in surviving fish at dose levels down to 31.3 mg/L. Neither mortality or sublethal effects were observed in the laboratory water control.

Conclusion
Based on mortality and sublethal effects, the no-observed-effect concentration for sevelamer hydrochloride in the rainbow trout was 15.6 mg/L.

1.8.3 Evaluation of the Acute Toxicity of Sevelamer Hydrochloride to Selenastrum capricornutum Printz

Objective
Sevelamer hydrochloride was tested for its phytotoxicity to a freshwater green alga, Selenastrum capricomutum Printz. This test was conducted using methods formulated by the U.S. Environmental Protection Agency (U.S. EPA). The final study report is included in Appendix 1-8.

Design
The definitive test was set in a geometric series using a ratio of approximately two. The nominal range of sevelamer hydrochloride test concentrations used during this study was 1.5 to 96 mg/L, and a negative control group (algal assay medium and algae) was also set. This range of concentrations was selected based on the results of a range-finder test study. The ratio of two was selected based on the range of dose levels required to meet the testing guidelines under which this test was conducted. The algal toxicity endpoints were based on algal growth [effective concentration (EC), based on algal cell counts/mL] and percent inhibition of growth (inhibition concentration (EbC), based on area under the growth curves). The day 3 and day 4 EC90, EC50, and ECIO values for algal growth (the nominal test material concentrations which effect 90, 50, or 10% of the algal growth, compared to the control group, respectively) were determined using a least squares linear regression of the nominal test material concentration versus the mean total cell counts. The day 3 and day 4 EbCgo, EbC50, and EbCo values for percent inhibition of growth

(the nominal test material concentrations which inhibit 90, 50, or 10% of the algal growth, compared to the control group, respectively) were determined using a least squares linear regression of the log of the nominal test material concentration versus the area under the algal growth curve. The no-observed effect concentration (NOEC) was determined using the analysis of variance and Dunnett's test comparing each dose group to the control.

Results

The effects of sevelamer hydrochloride by day 4 on algal growth (cell counts), relative to the controls, ranged from growth stimulation of 3.6% at 3 mg/L to 96.3% growth inhibition at 48 mg/L. Data from the 96 mg/L exposure samples were excluded from analysis due to sevelamer hydrochloride particulate interference (i.e. negative counts after subtracting background). Treatments and control groups were set in triplicate with an initial algal cell density of approximately 10,000 cells/mL. The results were as follows:

		SEVELAMER HCL NOMINAL CONCENTRATIONS (MG/L)			
	Endpoint	**EC_{90}**	**EC_{50}**	**EC_{10}**	**NOEC**
Day 3	Algal growth	41 (28-54)	23 (10-35)	5 (-8-17)	6
Day 4	Algal growth	46 (36-56)	27 (17-36)	7 (-2-16)	6
		E_bC_{90}	**E_bC_{50}**	**E_bC_{10}**	**NOEC**
Day 3	% Inhibition	38 (3-470)	10 (1-81)	3 (0-23)	not determined
Day 4	% Inhibition	168 (4-8017)	25 (2-338)	4 (0-36)	not determined

Conclusion

Based on algal growth effects, the no-observed-effect concentration (NOEC) for sevelamer hydrochloride was 6 mg/L.

1.8.4 Evaluation of the Effects of Sevelamer Hydrochloride on Activated Sludge in a Watewater Treatment Plant.

Objective

Sevelamer hydrochloride is being developed for pharmaceutical applications. Following human use, the product may enter domestic sewage systems and ultimately wastewater treatment plants. The effects of sevelamer hydrochloride on activated sludge respiration, sewage treatment, and settling of sludge solids were assessed in laboratory screening experiments. The final study report is included in Appendix 1-9.

Design

The activated sludge mixed liquor was obtained from the Midland Municipal Wastewater

Treatment Plant (Midland, MI). The effect of sevelamer HCl on aerobic microbial treatment plants was assessed using the Activated Sludge, Respiration Inhibition Test, OECD 209. The effect of sevelamer HCL on the treatment of synthetic sewage by activated sludge was evaluated using a modification of the semi-continuous activated sludge (SCAS) procedure used to evaluate the biodegradability of surfactants. The effects of sevelamer HCl on the settling of activated sludge solids were determined in batch settling tests.

Results

Actual concentrations of sevelamer HCl used in the screening studies ranged from 100-fold to 200,000 fold higher than expected wastewater concentrations. Sevelamer hydrochloride did not inhibit activated sludge respiration at $\leq$ 2,000 mg/L, the highest concentration tested. During a 14-day simulation of sewage treatment using semi-continuous activated sludge units operated on a 48-hour treatment cycle, sevelamer hydrochloride (10 mg/L in synthetic sewage) had no effect on the ability of the activated sludge to remove dissolved organic carbon. Finally, sevelamer hydrochloride (1,000 mg/L added to activated sludge) had no adverse effect on either the settling rate of the sludge solids or the settled sludge volume. Thus, the laboratory screening tests indicate that the presence of sevelamer hydrochloride in sewage should have no adverse effect on the operation of a wastewater treatment plant.

Conclusion

Sevelamer HCl had no effect on activated sludge respiration at 2000 mg/L, no effect on the ability of activated sludge to remove dissolved organic carbon (10 mg/L) and no adverse effect on either settling rate of the sludge solids or the settled sludge volume (1000 mg/L). Thus, the presence of sevelamer HCl in sewage should have no adverse effects on the operation of a WWTP.

1.9 USE OF RESOURCES AND ENERGY

1.9.1 Natural Resources and Energy

There will not be a significant impact on total usage of energy or utilities by the Michigan Division site of The Dow Chemical Company, Midland, Michigan or by Abbott Laboratories NC site, North Chicago, Illinois. The total steam and electrical power consumption for this purpose is estimated to be less than 1% of the overall site usage. No new land use will be required for the proposed new action.

1.9.2 Effect on Endangered or Threatened Species

The Michigan Department of Natural Resource Wildlife Division was contacted to determine if endangered or threatened species inhabit the area of drug substance manufacture. A search of the Michigan Natural Features Inventory database (Natural Heritage Program, Wildlife division) was conducted. The database indicated there are

records of the threatened sedge *Carex serosa* in the Chippewa and Tittabawassee Rivers. The records documenting this species presence are very old, and the Department of Natural Resources assessment is that the plant should not be impacted by the manufacturing site. The manufacturing of sevelamer hydrochloride at Abbott Laboratories NC site will have no effect on endangered or threatened species.

1.9.3 Effect on Property Listed in or Eligible for Listing in the National Register of Historic Places

The National Register of Historic Places includes at least 17 listings of historical sites in Midland County, Michigan. Consultation with the Midland County Historical Society indicated the nearest historical site is approximately one mile from the manufacturing site property. The proposed action is not expected to have a significant impact on these historical sites, as the controls on the manufacturing process should prevent any adverse effects to these sites. The manufacturing of sevelamer hydrochloride at Abbott Laboratories NC site will have no effect on property listed in or eligible for listing in the National Register of Historic Places.

1.10 MITIGATION MEASURES

An emergency preparedness plan is in place for the sevelamer hydrochloride production unit and The Dow Chemical Company Michigan Division Site, which includes on-site fire and emergency response personnel. All storage vessels are equipped with secondary containment to prevent groundwater contamination. All operating personnel are trained on both proper industrial hygiene protocols and emergency response procedures.

1.11 ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental impacts have been identified for the proposed action.

1.12 LIST OF PREPARERS

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1.13 CERTIFICATION

The undersigned certifies that the information presented is true, accurate and completed to the best of the knowledge of GelTex Pharmaceuticals, Inc.

The undersigned certifies that the EA document (pages 1-~~23~~ 32) contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR § 1506.6.

10/31/97

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GelTex Pharmaceuticals, Inc.

10/31/97
Date