CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-141 and 21-176

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 21-141

Welchol™ (colesevelam hydrochloride) Capsules

and

NDA 21-176

Welchol™ (colesevelam hydrochloride) Tablets

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and
Endocrine Drug Products (HFD-510)

FINDING OF NO SIGNIFICANT IMPACT

NDA 21-141/21-176

Welchol™ (colesevelam hydrochloride) Capsules and Tablets

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 its new drug applications for Welchol™ (colesevelam hydrochloride) capsules and tablets, 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 from use of the product. Colesevelam hydrochloride is a cross-linked polymer that will be used to treat primary hypercholesterolemia as an adjunct to exercise and diet.

Colesevelam may enter both the aquatic and terrestrial environment from patient use and disposal and is not expected to rapidly degrade. The toxicity of colesevelam 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.

4/27/00
DATE

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

4/27/00
DATE

/S/
CONCURRED
Yuan-yuan Chiu, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

APPEARS THIS WAY
ON ORIGINAL

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4.4 ENVIRONMENTAL ASSESSMENT

4.4.1 Background and Introduction

4.4.1.1 Date

July 29, 1999 (original) (revised February 4, March 23, and April 25, 2000)

4.4.1.2 Name of Applicant

GelTex Pharmaceuticals, Inc.

4.4.1.3 Address

153 Second Avenue
Waltham, MA 02451

4.4.1.4 Description of Proposed Action

4.4.1.4.1 Requested Approval

GelTex Pharmaceuticals, Inc. has filed an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Welchol™ Capsules (colesevelam hydrochloride), 375 mg (anhydrous), packaged in HDPE bottles or Welchol™ Tablets (colesevelam hydrochloride), 625 mg (anhydrous), packaged in HDPE bottles. An Environmental Assessment has been submitted pursuant to 21 CFR § 25.

4.4.1.4.2 Need for Action (Proposed Use)

Welchol™ is indicated for the treatment of primary hypercholesterolemia as an adjunct to exercise and diet. The proposed method of use of Welchol™ is oral capsules or tablets taken with meals. The maximum dose used will be 4.5 grams total per day and the duration of use could be lifetime. It is expected that the drug will be used by patients in their homes.

4.4.1.4.3 Production Locations

4.4.1.4.3.1 Manufacturing of the Drug Substance (Colesevelam Hydrochloride)

Colesevelam hydrochloride is manufactured at DSM Fine Chemicals Austria, located in Linz, Austria, in compliance with applicable state and federal environmental regulations.

Facility Address:

DSM Fine Chemicals Austria
St. - Peter - Straße 25
P.O. Box 933
A - 4021 Linz / Austria

Drug Establishment Registration No. 1810030

Grundsatzbescheid	GZ501/0-1000/84	Magistrat Linz
Gewerbeberechtigung	GZ100-1/6-0515529/100	Magistrat Linz

Description of Surrounding Environment:

DSM Fine Chemicals is situated in the industrial quarter of Linz, the capital of upper Austria (about 300,000 inhabitants). The company's production facilities are located at the large site, "Chemiepark Linz," which is shared with a number of other companies (*e.g.*, pharmaceuticals, agrochemicals). The "Chemiepark Linz" is located on the banks of the Danube River.

Disposal Sites:

Wastes from the manufacture of colesevelam hydrochloride will be treated according to the waste management system employed by DSM Fine Chemicals Austria under the authority of:

Abfallrechtlicher Geschäftsführer Dipl.-Ing. Dr. Christian Ramaseder

DSM Fine Chemicals Austria utilizes the following internal guidelines for disposal:

Abfallerzeugernummer:	01040014
Abfallsammlernummer:	01040024
Abfallentsorgernummer:	01040034

(GZ: UR-250170/63-1999Ko .... Amt der Oberösterreichischen Landesregierung [March 1st, 99])

Solvents, halogenated and non - halogenated, are incinerated at the DSM incineration facility:

- Building 707
  (GZ 501/GB-40/94z.013 Magistrate Linz)
- Building 52
  (GZ 501/G950174k Magistrate Linz)

or are transferred to a state-authorized waste company:

- ASA Abfall Service AG, Niederlassung Asten / Fisching
  A - 4481 Asten / Austria

  (Abfallsammlernummer: 00701726)

Solid waste is transferred to a state authorised waste company:

- LOBBE Abfallentsorgung Werndorf GmbH,
  Vianovastraße 21,
  A - 8402 Werndorf / Austria

  (Abfallsammlernummer: 00703726)

4.4.1.4.3.2 Finish Grinding of the Drug Substance

Facility Address:

Powdersize, Inc.
20 Pacific Drive
Quakertown, PA 18951
U.S.A.

Drug Establishment Registration No. 2530165
Drug Master File No.
Labeler Code 61523

Description of Surrounding Environment:

The Powdersize, Inc. production facility is housed in a 20,000 square foot building located on a 2-acre site in Quakertown, PA. The site is in a light industrial zone in close proximity to commercial and residential zones. The climate is temperate.

Disposal Sites:

Solid pharmaceutical waste generated at Powdersize, Inc. is disposed by:

BFI Waste Systems
731 E. Reliance Rd
Telford, PA 18969
(215) 723-0400

BFI transfers the solid waste to:

Conestoga Landfill
Mineview Drive
Morgantown, PA 19543
610-286-6844

Waste Code: 237951

Liquid Waste:

Trace amounts of colesevelam hydrochloride will enter the facilities main waste water stream during equipment cleaning. This waste will be transferred, via sanitary sewer system, to:

Quakertown Sewage Treatment Plant
55 Erie Avenue
Quakertown, PA 18951
(215) 536-5004

Spent Process Air:

Spent process air that is exhausted from the processing equipment is routed to product collectors that separate processed materials from the spent process air. Spent process air from the product collectors is exhausted to waste collectors where waste material is collected. Waste collectors are vented to the atmosphere. All process air vented to the atmosphere is done so under Commonwealth of Pennsylvania Department of Environmental Protection, Permit No. 09-310-054.

4.4.1.4.3.3 Manufacturing of the Drug Product (Welchol™ Capsules and Tablets)

Facility Address:

Global Pharm Inc.
865 York Mills Road
Toronto, Ontario M3B 1Y

Drug Establishment Registration No. FCCA276
Drug Master File No.
NDC Labeler Code 055983

Description of Surrounding Environment:

The Global Pharm, Inc. production facility is housed in a 161,500 square foot building located on an 8.5-acre site in an urban area of metropolitan Toronto, Ontario, Canada. The site is in a light industrial zone in close proximity to office and residential zones. The climate is temperate.

Disposal Sites:

Solid pharmaceutical waste generated at Global Pharm, Inc. is disposed by:

Owl Environmental
2061 Mount Forest Drive
Burlington, ON
Canada L7P 1H4
(905) 637-2104
Certificates of Approval: A840090, A341906

Owl incinerates the pharmaceutical waste with:

Brobare
Swan Hills Treatment Center
Mail Bag #180
Swan Hills, Alberta
Canada T0G 2C0
(403) 333-4197
Approval: 95-IND-237

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

At hospitals, pharmacies, and clinics in the United States, empty or partially empty packages will be disposed of according to the respective hospital, pharmacy, or clinic procedures. In the home, empty or partially empty containers will typically be disposed of by the respective communities' solid waste management system, which may include landfills, incineration, and/or recycling. Minimal quantities of unused drug may be disposed of in the sewage system.

4.4.1.5 Identification of Chemical Substances That Are the Subject of the Proposed Action

4.4.1.5.1 Nomenclature

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

Colesevelam hydrochloride

4.4.1.5.1.2 Brand/Proprietary Name

Welchol™

4.4.1.5.1.3 Chemical Names

1-Hexanaminium, N,N,N-trimethyl-6-(2-propenylamine)-, chloride, polymer with (chloromethyl)oxirane, 2-propen-1-amine and N-2-propenyl-1-decanamine, hydrochloride. (CAS)

Allylamine polymer with 1-chloro-2,3-epoxypropane, [6-(allylamino)-hexyl]trimethylammonium chloride and N-allyldecylamine, hydrochloride.(IUPAC)

Colesevelam (INN)

4.4.1.5.2 Chemical Abstracts Service (CAS) Registration Number

182815-44-7

182815-43-6 (INN)

4.4.1.5.3 Molecular Formula

$(C_3H_8NCl)_2(C_9H_{20}N_2OCl_2)_1(C_{13}H_{28}NCl)_7(C_{12}H_{28}N_2Cl_2)_6$

4.4.1.5.4 Molecular Weight

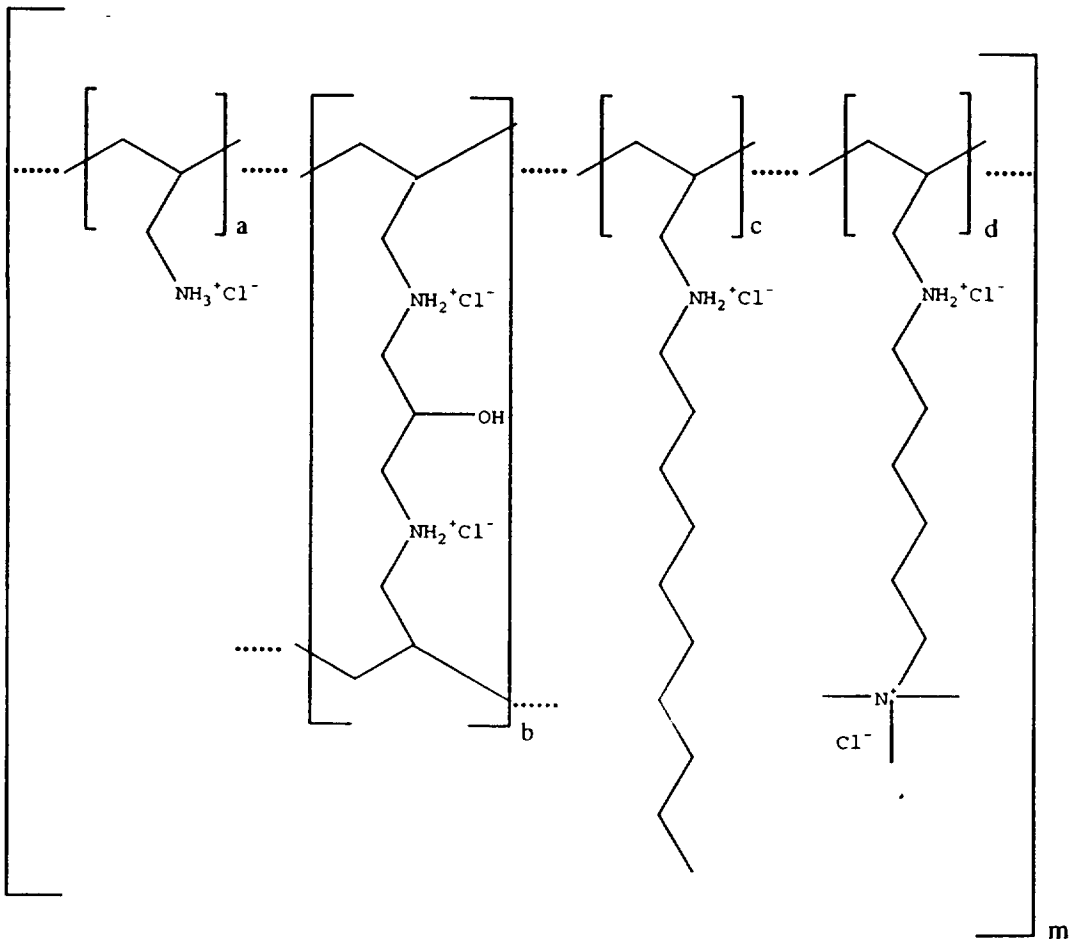
Because colesevelam hydrochloride is a cross-linked polymer, molecular weight does not have the same meaning as that used to define a molecule of a defined discrete structure. Each particle is one molecule due to multiple covalent cross-links between polymer chains. Therefore, the molecular weight of an individual particle is equal to the weight of the particle itself. Because the density of the particle is independent of the particle size, the weight of the particle is proportional to the particle size. Analogous to the molecular weight distribution of soluble polymers, the molecular weight distribution of a cross-linked polymer is a function of the distribution of particle sizes.

The molecular weight of a particle can be calculated from the diameter of the particle, the pycnometric density of colesevelam hydrochloride, and the conversion factor from grams to atomic mass units (amu). Because the pycnometric density of colesevelam hydrochloride is 1.10 g/cm^3, the molecular weight of a 25 µm diameter particle of colesevelam hydrochloride is equal to 5.4×10^{15} amu.

4.4.1.5.5 Structural Formula

The colesevelam hydrochloride chemical structure is illustrated in Figure 4.4-1.

Figure 4.4-1: Colesevelam Hydrochloride Chemical Structure



Where:

a	= number of primary amine groups	a = 0.14
b	= number of cross-linked amine groups	b = 0.12
c	= monoquat alkylated amine groups	c = 0.34
d	= decylbromide alkylated amine groups	d = 0.40
m	> 100 to indicate extended polymer network	

The structure of colesevelam hydrochloride is shown in and can be represented as a tetrapolymer of allylamine, N-decylallylamine, N-(6-trimethylammoniumhexyl) allylamine and N,N'-diallyl-1,3-diamino-2-hydroxypropane. The 2-hydroxypropyl-1,3-diyl group is formed during the cross linking and the N-decyl and N-(6-trimethylammonium) hexyl groups are derived from the alkylation step. No regular order

of the groups is implied by the structure, crosslinking and alkylation are expected to occur randomly along the polymer chains. The mole fraction of protonated amines is ≥ 97%. The polymer is depicted in the hydrochloride form; less than 5% of the halides are bromide.

4.4.1.5.6 Physical Description

White to off-white powder.

4.4.1.5.7 Additives

The drug product will be available in a capsule formulation containing 375 mg of colesevelam hydrochloride and also in a tablet containing 625 mg of colesevelam hydrochloride. The compositions are described in Section 4.2.1.3 and 4.2.2.3.

4.4.1.5.8 Impurities

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

4.4.1.6 Introduction of Substances into the Environment

Colesevelam hydrochloride, the parent compound, is expected to be the only substance entering the environment. Colesevelam hydrochloride has been shown to be stable for a minimum of 12 months at controlled room temperature. Colesevelam hydrochloride is not photosensitive and is not sensitive to freeze-thaw cycling. Only a slight increase in the primary degradation products is noted over time. Stability testing indicates that colesevelam hydrochloride is stable under all tested storage conditions.

Although colesevelam hydrochloride is a highly cross-linked polymer that is insoluble in all tested aqueous and organic solvents, testing was conducted to determine if potential leachables (*i.e.*, impurities trapped in the polymeric matrix) could be extracted from colesevelam hydrochloride by solvents. Various solvents were used in order to solubilize and extract any and all potential leachables in colesevelam hydrochloride. The tested solvents include water, 0.1 N HCl, 0.1 N HCl/50 °C, 1 N ammonium hydroxide, methylene chloride, acetonitrile, and methanol. A minimal amount of material is extracted from colesevelam hydrochloride in all tested solvents except for 1N ammonium hydroxide where an ammonium chloride salt is formed. Water and 0.1 N HCl gave the greatest amount of extractable residue. Very little material was extracted with the three organic solvents.

In addition, the stability of colesevelam hydrochloride was investigated in acid, base, and hydrogen peroxide solution. The only condition where substantial degradation was obtained was exposure of colesevelam hydrochloride to 30% hydrogen peroxide at room temperature, where the pH had been adjusted to 11 with ammonium hydroxide. After 24 hours under these extreme conditions, the total degradants level was 4.3% by ion chromatography and 7.1% by gas chromatography. However, these very aggressive conditions would not typically be encountered in nature.

4.4.1.6.1 Drug Substance: Colesevelam Hydrochloride

The following sections describe the chemical synthesis for colesevelam hydrochloride and provide 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 emissions requirements.

4.4.1.6.2 Air Emissions

4.4.1.6.2.1 List of Components of Emitted Streams

Air component emissions from waste stream nos. 1, 2, 3, 5, 6, and 7 on the colesevelam hydrochloride block flow diagram are presented in Table 4.4-1, and the block flow diagram is located in Appendix 4.4-4.

Table 4.4-1: Component Emissions from Waste Stream Nos. 1, 2, 3, 5, 6, and 7 on the Colesevelam Hydrochloride Block Flow Diagram (Appendix 4.4-4)

COMPONENT	CAS #	MAXIMUM YEARLY RATE (KG/YR)*
Allylamine	107-11-9	42
Epichlorohydrin	106-89-8	2
Methanol	67-56-1	35,000

* Quantities listed are after treatment and are based on 100,000 kg/yr production of colesevelam hydrochloride

4.4.1.6.2.2 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. Austrian emissions laws and respective statute numbers are presented in Table 4.4-2.

Table 4.4-2: Citation of Compliance with Applicable Emissions Laws Required at Federal, State, and Local Levels

AUSTRIAN TITLE	ENGLISH TRANSLATION	AUSTRIAN STATUTE NUMBER
CKW-Anlagenverordnung	Rules for Plants Dealing with Chlorinated Carbohydrates	1994 BGBl 1994/865
Feuerungsanlagenverordnung	Rules for Incinerators	BGBl II 1997/331
Luftreinhaltegesetz für Kesselanlagen	Rules for Emissions Controls of Incinerators	BGBl 1988/380idF
Luftreinhalte-Verordnung für Kesselanlagen	Rules for Emissions Control of Incinerators	BGBl 189/19idF
Vereinbarung über die Festlegung von Emissions-grenzwerten für Luftschafstoffe	Limits on Levels of Emissions of Dangerous Substances into the Air	BGBl 1987/443
Smogalarmgesetz	Rules for Smog Alerts	BGBl 1989/38
Verordnung über die Vorwarnstufe	Rules for Smog Producing Substance Emissions (Early Warning Level)	BGBl 1989/515
Smogalarmplan Großraum Linz	Smog Alarm Plan for Linz	LGBl 1989/69
Ozongesetze	Rules for Limiting Ground Level Ozone	BGBl 1992/210
Emissionsschutzgesetz	Rules for the Protection of Surroundings Against the Emissions of Dangerous Substances into the Air	BGBl I 1997/115

4.4.1.6.2.3 Effect of Approval on Compliance with Current Emissions Requirements at Production Site

Production of colesevelam hydrochloride at DSM Fine Chemicals at the yearly production rates estimated in Appendix 4.4-6 would have no impact on compliance.

4.4.1.6.3 Aquatic Emissions

4.4.1.6.3.1 List of Components of Emitted Streams

Aquatic component emissions from Waste Stream Nos. 1,2, and 4 on the colesevelam hydrochloride block flow diagram are presented in Table 4.4-3, and the block flow diagram is located in Appendix 4.4-4.

Table 4.4-3: Component Emissions from Waste Stream Nos. 1, 2, and 4 on the Colesevelam Hydrochloride Block Flow Diagram (Appendix 4.4-4)

COMPONENT	CAS #	MAXIMUM YEARLY RATE (KG/YR)*
Sodium bromide	7647-15-6	30,000
Allylamine	107-11-9	1,500
Colesevelam hydrochloride	182683-00-7	13,200
Sodium chloride	7647-14-5	72,700

*Quantities listed are before treatment at DSM Fine Chemicals Chemical Waste Water or the POTW operated by the City of Linz and are based on 100,000 kg/yr production of colesevelam hydrochloride

4.4.1.6.3.2 Statement of Controls Exercised

The aqueous streams are discharged to the DSM Fine Chemicals Austria Waste Water Pretreatment Plant (WWPP), where all waste water streams of the whole "Chemiepark Linz" site are treated. The waste water is treated on site in two stages:

1) Physical and chemical treatment for pH control and solids removal, followed by

2) Aerobic biologic treatment.

After pretreatment, all waste water is discharged to the local waste water treatment plant SBL, where it is again treated in an aerobic activated sludge waste water treatment system.

4.4.1.6.3.3 Citation of Compliance with Applicable Emissions Required at Federal, State, and Local Levels

Aqueous discharge from DSM Fine Chemicals Austria is in compliance with the following Austrian laws:

—Wasserschutzgesetz	BGBl 1959/215
—Allgemeine Abwasseremmissionsverordnung	BGBl 1996/186
—Indirektleiterverordnung	BGBl II 1998/222

4.4.1.6.3.4 Effect of Approval on Compliance with Current Emissions Requirements at Production Site

Production of colesevelam hydrochloride at the DSM Fine Chemicals Austria site and at the yearly production rates estimated in Appendix 4.4-6 would have no impact on compliance.

4.4.1.6.4 Terrestrial Emissions

4.4.1.6.4.1 List of Components of Emitted Streams

Terrestrial component emissions from Waste Streams Nos. 2 and 3 are presented in Table 4.4-4 and more detailed information is located in Appendix 4.4-5.

Table 4.4-4: Component Emissions from Waste Stream Nos. 2 and 3 on the Colesevelam Hydrochloride Block Flow Diagram (Appendix 4.4-5)

COMPONENT	WASTE STREAM #	CAS #	MAXIMUM YEARLY RATE (KG/YR)
Methanol	2, 3	67-56-1	3,307,000
Allylamine	2	107-11-9	2,000
Soluble oligomers of PAA.HCl	2	7155-12-4	11,000
Sodium chloride	2, 3	7647-14-5	37,400
Sodium bromide	3	7647-15-6	30,120
Chlorodecane Bromodecane Methoxydecane	3	1002-69-3 112-29-8 7289-52-3	2,000 1,000 1,000
Monoquat (6-bromohexyl) trimethylammoniumbromide	3	32765-81-4	5,000

4.4.1.6.4.2 Statement of Controls Exercised

Liquid wastes are disposed by burning in incinerators located on site.

The Magistrate of Linz has approved the incinerators of DSM Fine Chemicals Austria to be in compliance to applicable Austrian law.

Scrubbers in the exhaust gas stacks of the incinerators wash out salts and residues of incineration. Scrubber waste water is treated in the Waste Water Pretreatment Plant (see Section 4.4.1.6.2.2).

In Table 4.4-5 are listed the relevant statutes for applicable emissions that DSM-FC complies with as required at federal, state, and local levels.

Table 4.4-5: List of the Emissions Compliance Rules Followed by DSM-FC Austria.

AUSTRIAN TITLE	ENGLISH TRANSLATION	AUSTRIAN STATUTE NUMBER
Abfallwirtschaftsgesetz	Law for the Correct Dealing with Hazardous and Non-Hazardous Waste	BGBL 1990/325
Altölverordnung	Rules for Correct Disposal of Waste Oil	BGBl 1987/
Verordnung über die Fortsetzung von gefährlichen Abfällen	Rules for Declaring Hazardous Waste	BGBl II 1997/227
Verpackungsverordnung	Rules for Recycling Non-Hazardous Waste	BGBl 1996/648
Basler Übereinkommen über die Kontrolle der grenzüberschreitende Verbindung gefährlicher Abfälle und ihrer Entsorgung	Prohibition of Sending Hazardous Waste to Certain Countries	BGBl 1993/229
Abfallnachweisverordnung	Rules Governing Waste Inventory	BGBl 1991/65

4.4.1.6.4.3 Effect of Approval on Compliance with Current Emissions Requirements at Production Site

Production of colesevelam hydrochloride at DSM Fine Chemicals Austria, at the yearly production rates estimated in Appendix 4.4-6, would have no impact on compliance with current emissions requirements.

4.4.1.6.5 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. For the open handling of chemicals, adequate personnel protective equipment is described in the operating manual. The protective equipment must be used by employees. They are specially trained in using the equipment. For certain situations, approved respiratory protection is provided to employees, and they are trained in 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.

4.4.1.6.6 Incinerator Emissions Limits, DSM Fine Chemicals Austria

Liquid wastes and offgas from the production of colesevelam hydrochloride are incinerated in the incinerators of DSM Fine Chemicals Austria at Buildings 700 and 52.

The Building 700 incinerator consists of a burning chamber, a steamboiler, and an associated air pollution control equipment (scrubbers, SCR units for DENOX and dedioxination).

The Building 52 incinerator consists of a burning chamber, a steamboiler, and an associated air pollution control equipment (scrubbers, SCR units for DENOX and dedioxination).

Both incinerators are licensed by the Magistrat of Linz. The license stipulates the maximum emissions limits as presented in Table 4.4-6.

Table 4.4-6: Emissions Limits for DSM Fine Chemicals Austria Incinerators

POLLUTANT	EMISSIONS LIMIT FOR BUILDING 700 INCINERATOR (MG/M^3)	EMISSIONS LIMIT FOR BUILDING 52 INCINERATOR (MG/M^3)
Particulate	10	10
Hydrochloride	10	5
CP	50	50
NO_x	100	200
SO_2	50	50
NH_3	10	30
HF	---	1
HBr	5	5
VOC	10	10
Dioxin	0.1×10^{-3}	0.1×10^{-3}

4.4.1.6.7 Waste Water Pretreatment Plant Emissions Limits, DSM Fine Chemicals Austria

The aqueous streams are discharged to the DSM Fine Chemicals Austria Waste Water Pretreatment Plant (WWPP), where all waste water streams of the whole "Chemiepark Linz" site are treated. The permitted daily discharge from the WWPP is listed in Table 4.4-7.

Water used in the incinerator air pollution control equipment is discharged to the Waste Water Pretreatment Plant (WWPP) of DSM Fine Chemicals Austria.

The WWPP operates under Permit No. Wa-200693/45/Spe/Him (December 16, 1994), issued by the Amt der Oberösterreichischen Landesregierung, Wasserrechtsabteilung, Kärntnerstraße 12, A - 4020 Linz/Austria.

Table 4.4-7: Permitted Daily Discharge from the DSM Fine Chemicals WWPP

PARAMETER	UNITS*	LIMITS
Amount of flow	[m^3/h]	450
Temperature	[°C]	< 40
pH	[°C]	6, 5 to 9, 5
Li	[kg/d]	90
Al	[kg/d]	225
Fe	[kg/d]	370
Cu	[kg/d]	2, 5
Ni	[kg/d]	2, 5
Zu	[kg/d]	5
Cl	[t/d]	25
Br	[t/d]	1, 3
NH_4-N	[t/d]	2, 3
NO_3-N	[kg/d]	300
NO_2-N	[kg/d]	70
TKN	[t/d]	5
P	[kg/d]	200
SO_4	[t/d]	20
COD	[t/d]	12
BoD_5	[t/d]	6
TOC	[t/d]	6
AOX	[kg/d]	200
BTX	[mg/L]	0, 1

*t = tonne (1000 kg)

4.4.1.6.8 Finish Grinding of Colesevelam Hydrochloride Drug Substance

Colesevelam hydrochloride is finish ground for DSM Fine Chemicals Austria by:

Powdersize, Inc.
20 Pacific Drive
Quakertown, PA 18951

4.4.1.6.8.1 Substances Expected To Be Emitted

The Powdersize, Inc. facility holds air permits that regulate emissions of spent process air 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 emissions controls, neither colesevelam hydrochloride nor any other drug products are expected to be released to air or water in sufficient quantities to have any significant environmental impact.

4.4.1.6.8.2 Controls Exercised

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.

Waste Water Handling and Treatment:

For waste water handling and treatment, Powdersize, Inc. is permitted to discharge, but a specific discharge permit is not required from the borough of Quakertown. There have been no citations with the borough of Quakertown related to the plant discharge.

All waste water flows to the Quakertown Sewage Treatment Plant.

Disposal of Production Waste and Non-Usable Product:

All significant production waste and non-usable product is collected and disposed of in the normal solid waste stream. This waste includes waste drug product from equipment cleaning and disposable production items such as filters and transfer sleeves.

For nonhazardous industrial waste, disposal is by:

BFI Waste Systems
731 E. Reliance Road
Telford, PA 18969
(215) 723-0400

Waste Code: 237951

For hazardous liquids and solids, disposal is by:

BFI Waste Systems
731 E. Reliance Road
Telford, PA 18969
(215) 723-0400

Waste Code: 237951

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). HEPA filtered dusk masks, gloves, and coveralls (or equivalent) are required during the grinding of Colesevelam hydrochloride. Material Safety Data Sheets (MSDS) are obtained and retained in the company files for each material handled at the facility. MSDS are readily available and accessible to employees for their reference.

4.4.1.6.8.3 Citation of and Statement of Compliance with Applicable Emissions Requirements

The Powdersize, Inc. facility holds a permit for emissions for the State of Pennsylvania Department of Environmental Protection. For waste water handling and treatment, Powdersize, Inc. is permitted to discharge, but a specific discharge permit in not required. The Powdersize, Inc. facility operates in compliance with all emissions requirements, including occupational, set forth in applicable federal, provincial, and local environmental laws and regulations.

4.4.1.6.8.4 Effect of Approval on Compliance with Applicable Emissions Requirements

The Powdersize, Inc. facility currently performs particle size reduction and classification services for many pharmaceutical companies. Approval of the proposed action and subsequent manufacture of production quantities of Colesevelam HCl will not significantly increase facility production and therefore is not expected to affect facility compliance with current discharge or emissions requirements.

4.4.1.6.9 Manufacture and Packaging of Drug Product-Welchol™ Capsules and Tablets

Welchol™ Tablets and Capsules are manufactured for GelTex Pharmaceuticals by:

Global Pharm Inc.
865 York Mills Road
Toronto, Ontario M3B 1Y

4.4.1.6.9.1 Substances Expected To Be Emitted

The Global Pharm facility holds air permits that 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 emissions controls, neither colesevelam hydrochloride 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.

4.4.1.6.9.2 Controls Exercised

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.

Waste Water Handling and Treatment:

For waste water handling and treatment, Global Pharm is permitted to discharge, but a specific discharge permit is not required from the Municipality of Toronto. The Municipality of Toronto samples and monitors the effluent that leaves the site on a regular basis. There have been no citations with the Municipality of Toronto related to the plant discharge.

All waste water flows to the Municipality of Toronto POTW (Publicly Owned Treatment Plant) and is regulated by Canadian By-law No. 153-89

Disposal of Production Waste and Non-Usable Product:

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

For non-hazardous industrial waste, disposal is by:

Owl Environmental
2061 Mount Forest Drive
Burlington, ON
Canada L7P 1H4
(905) 637-2104

Certificates of Approval: A840090, A341906

For hazardous liquids and solids, disposal is by:

Owl Environmental
2061 Mount Forest Drive
Burlington, ON
Canada L7P 1H4
(905) 637-2104

Certificates of Approval: A840090, A341906

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, and uniforms). Dusk masks, gloves, and Pro/Shield®2 suits (or equivalent) are required during the manufacture of Welchol™ Capsules and Tablets. Some operators choose to use respirators, which are NIOSH approved, with HEPA filters. NIOSH organic vapor and acid gas respirators are available if the circumstances require. Material Safety Data Sheets (MSDS) are obtained and retained in the company files for each material handled at the facility. MSDS are readily available and accessible to employees for their reference.

4.4.1.6.9.3 Citation of and Statement of Compliance with Applicable Emissions Requirements

The Global Pharm, Inc. facility is considered a clean manufacturer and is not required to hold a special permit for emissions. When a development product is approved for commercial purposes, an air emissions application is submitted to the Ministry of Environment. The Ministry of Environment certificate of approval covers the emissions of volatile organic compounds (VOCs) and particulate matter.

For waste water handling and treatment, Global Pharm is permitted to discharge, but a specific discharge permit is not required from the Municipality of Toronto. The Municipality of Toronto monitors the effluent that leaves the site on a regular basis. There have been no citations with the Municipality of Toronto related to the plant discharge.

The Global Pharm, Inc. facility operates in compliance with all emissions requirements, including occupational, set forth in applicable federal, provincial, and local environmental laws and regulations.

4.4.1.6.9.4 Effect of Approval on Compliance with Applicable Emissions Requirements

The Global Pharm, Inc. facility currently manufactures formulated drug products for many pharmaceutical companies. Approval of the proposed action and subsequent manufacture of production quantities of Welchol™ Capsules and Tablets will not significantly increase facility production and therefore is not expected to affect facility compliance with current discharge or emissions requirements.

4.4.1.6.10 Expected Introduction Concentrations

The estimated annual production for the first three (3) years following approval is described in Appendix 4.4-6. The highest quantity of product which is expected to be produced in any of the next 5 years is 2×10^5 kg/year.

4.4.1.6.10.1 Expected Introduction Concentration from Use

EIC-Aquatic (ppb) = A × B × C × D

where A = kg/year produced for direct use (as active moiety)
B = $1/1.214 \times 10^{11}$ liters/day entering publicly owned treatment works (POTWs)
C = year/365 days
D = 10^9 µg/kg (conversion factor)

EIC = 2×10^5 kg/year × $1/1.214 \times 10^{11}$ liters/day × 1 year/365 days × 10^9 µg/kg
= 4.5 ppb

4.4.1.7 Fate of Emitted Substances in the Environment

4.4.1.7.1 Identification of Substance of Interest

Colesevelam hydrochloride

4.4.1.7.2 Physical/Chemical Characterization

4.4.1.7.2.1 Water Solubility

Colesevelam hydrochloride is a highly cross-linked polymer that is insoluble in all tested aqueous and organic solvents. Various solvents were used in order to solubilize and extract any and all potential leachables in colesevelam hydrochloride. The tested solvents include water, 0.1 N HCl, 0.1 N HCl/50 °C, 1 N ammonium hydroxide, methylene chloride, acetonitrile, and methanol. A 2.5 g sample of colesevelam hydrochloride was suspended in 40 ml of the solvent to be tested. The suspension was

agitated at room temperature, except where the temperature is specified, for 16 hours. The suspended solids were separated, the extraction solution was evaporated, and the dried dissolved solids were weighed. The table below summarizes the amount of leachables extracted from representative lots of colesevelam hydrochloride. A minimal amount of material can be solubilized and extracted from colesevelam hydrochloride in all tested solvents except for 1N ammonium hydroxide where an ammonium chloride salt is formed. Water and 0.1 N HCl gave the greatest amount of extractable residue. Very little material was extracted with the three organic solvents.

SOLVENTS	LEACHABLES EXTRACTED (WT%)			
	TKFC404-1500	TLMC006-1842	TMAC015-1868	TNCC404-2221-20
Water	NT	0.94	NT	1.34
0.1 N HCl	NT	1.20	NT	0.62
0.1 N HCl/50°C	0.52	NT	0.69	0.70
1 N Ammonium hydroxide	NT	16.22	NT	15.84
Methanol	NT	-0.12	NT	-0.22
Acetonitrile	NT	0.01	NT	-0.10
Methylene chloride	NT	0.03	NT	0.03

4.4.1.7.2.2 Dissociation Constant(s)

Colesevelam hydrochloride is a polyelectrolyte and there is no discrete dissociation constant. Acid-base titration is used to quantitate both the primary and secondary titratable amines in colesevelam hydrochloride. The total titratable amines of colesevelam hydrochloride are from the poly(allylamine hydrochloride) starting material. The total titratable amines range from 4.4 to 4.8 mmoles of amine per gram of colesevelam hydrochloride, on an anhydrous basis. The total titratable amines for a representative lot of colesevelam hydrochloride, Lot TLMC005-1840, is 4.6 mmoles of amine per gram. The experimental value differs from the theoretical amine content of 5.0 mmoles of amine per gram of colesevelam hydrochloride. This difference is likely due to the broad titration curve associated with the titration of polyelectrolytes that results in a small percentage of the amines not being titrated.

4.4.1.7.2.3 Octanol/Water Partition Coefficient

Colesevelam hydrochloride is not soluble in water or hydrocarbon solvents, therefore the octanol/water partition coefficient has not been calculated.

4.4.1.7.2.4 Vapor Pressure

Because colesevelam hydrochloride is a cross-linked polymer, each particle is one molecule due to multiple covalent cross-links between polymer chains. [This is supported by the insolubility of the compound.] Therefore, the molecular weight of an individual particle is equal to the weight of the particle itself. The molecular weight of a particle can be calculated from the diameter of the particle, the pycnometric density of colesevelam hydrochloride and the conversion factor from grams to atomic mass units (amu). Since the pycnometric density of colesevelam hydrochloride is 1.11 g/cm^3, the molecular weight of a 25 µm diameter particle of colesevelam hydrochloride is equal to 5.4×10^{15} amu. A substance with such high molecular weight has no vapor pressure, therefore, a vapor pressure test of colesevelam hydrochloride was not performed.

TGA-FT-IR data confirm that the only volatile compound detected in colesevelam hydrochloride during heating from ambient to 160°C is water. At higher temperatures the compound begins to decompose.

4.4.1.7.3 Environmental Depletion Mechanisms

Colesevelam hydrochloride was evaluated for ready biodegradability following the OECD Method 301B: Manometric Respirometry test guidelines. The final study report is located in Appendix 4.4-7. Oxygen consumption and CO_2 evolution as indicators for biodegradation were measured over a 28-day test period using a Columbus Instruments MicroOxymax respirometer system.

Colesevelam 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 colesevelam hydrochloride showed no evidence for inhibition of biodegradation. The observed O_2 consumption and CO_2 production in the biodegradation 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 colesevelam hydrochloride is not readily biodegradable.

The hydrolytic stability of colesevelam hydrochloride was investigated in acid and in base solution. Approximately 1 g of colesevelam hydrochloride was suspended in 10 mL of 1 N NaOH and 10 mL of 1 N HCl. The mixtures were stored at 60°C for 12 hours. After centrifugation, the supernatant was diluted 1:5 and analyzed by gas

chromatography and ion chromatography. Both the acid- and base-treated samples showed no detectable peaks by gas chromatography. By ion chromatography the total level of stability-indicating impurities was less than 0.1%. These results indicate that colesevelam hydrochloride is very stable in acid and base solution. Please see Section 4.1.10.10 of NDA 21-141 for a description of the degradation testing performed.

Photostability studies were conducted on colesevelam hydrochloride following ICH Guidelines using UV-b, daylight, and fluorescent bulbs (1.2 million-lux hours and 200 watt hours/m^2) with the sample placed in an open petri dish. Colesevelam hydrochloride was found to be stable under these conditions. In addition, photolysis as a potential depletion mechanism was discussed with Dr. Hofer, a toxicologist at Seiberdorf. In his opinion, photolysis is relevant mainly for gaseous materials in the atmosphere. Photolysis of a polymer suspended in water or deposited in sludge is predicted to have no significance for depletion.

In conclusion, neither hydrolysis nor photolysis is expected to be a potential depletion mechanism for colesevelam hydrochloride. Colesevelam hydrochloride is expected to remain intact.

4.4.1.7.4 Expected Environmental Concentration (EEC)

Because colesevelam hydrochloride is not readily biodegradable, the EEC will be similar to the EIC of 5 ppb.

4.4.1.7.5 Summary

Colesevelam hydrochloride is a cross-linked polymer of (poly)allylamine alkylated with 1-bromodecane and, 6-bromohexyltrimethylammonium bromide that is highly stable and does not appear to rapidly degrade biologically. Because it is possible that this compound could enter both the aquatic and terrestrial environments, the following section describes studies performed to assess the potential effects of colesevelam hydrochloride on the environment. Upon introduction into waste water treatment plants and the aquatic environment, colesevelam hydrochloride will remain as suspended particles due to the insolubility of the compound as described in Section 4.4.1.7.2. The true density of colesevelam hydrochloride is 1.1 g/cm^3, therefore any suspended particles will settle out in aquatic systems.

4.4.1.8 Environmental Effects of Released Substances

4.4.1.8.1 - Evaluation of the Acute Toxicity of Colesevelam Hydrochloride to *Daphnia magna* Straus

4.4.1.8.1.1 Objective

The objective of this study was to determine the acute toxicity of colesevelam hydrochloride to the daphnid, *Daphnia magna* Straus. These data will be used to

calculate 24- and 48-hour LC50 and EC50 values and a no-observed-effect concentration, if possible. The final study report is included in Appendix 4.4-8.

4.4.1.8.1.2 Design

Because the test substance is insoluble, a limit test with a loading rate of 100 mg test substance/L was performed. The test substance was ground in a mortar and added to dilution water (reconstituted water according to ISO 6341) at a concentration of 100 mg/L. This preparation was stirred for 24 hours in the dark using a magnetic stirrer. The filtrate (filtration by a pleated filter followed by a 0.2 µm sterile filter) was then used for the test. The extracted colesevelam hydrochloride and extraction solution were chemically analyzed.

Neonates of *Daphnia magna*, hatched from ephippia and not more than 24-hours old, were exposed to the filtrate.

One negative control group was exposed to dilution water only.

Twenty (20) daphnids each, divided into 4 replicates (5 daphnids each), were used for the test substance group and for the control group.

4.4.1.8.1.3 Results

Chemical Analysis:

The recovered colesevelam hydrochloride following extraction was analyzed (IR, elemental analysis, volatile impurities, and titratable amines) and showed little or no change occurred during the extraction process (see table below).

Parameter	**Test substance before incubation Lot TNBC 401**	**Test substance after incubation in *Daphnia*-water and drying**
Dry Substance (IR, 15 min, 120 °C)	98.12 %	97.40 %
Elemental Analysis	C = 54.40 % H = 11.17 % N = 8.60 % Cl = 20.56 % Br = 0.64 %	C = 54.67 % H = 11.20 % N = 8.86 % Cl = 20.44 % Br = 0.67 %
Volatile Impurities	< 0.1% (as specified)	< 0.1%
Titratable Amines	4.56 mmol/g	4.63 mmol/g

The filtrates were analyzed for chloride and bromide (see table below). Since the filtrates contained no organic material, they were not tested for stability. As expected, there was very little extractable material present in colesevelam hydrochloride.

	Acute Toxicity Study in *Daphnia magna* Test Filtrate
Bromide	< 10 ppm
Chloride	230 ppm

Daphnia magna Straus Exposure:

The quality criteria for the OECD guideline were fulfilled:

- Immobilization of control group daphnids was 0% at the end of the test (guideline: maximum of 10%).
- There were no control daphnids trapped at the water surface.
- Dissolved oxygen concentrations in the test vessels were not lower than 8.3 mg/L at each time determined (guideline: higher than 3 mg/L).
- pH of the test substance was stable during the test.

There was no immobilization in the test substance group at 24 or 48 hours.

4.4.1.8.1.4 Conclusion

The EC50/24h and 48h of the aqueous extract of colesevelam hydrochloride was therefore higher than 100 mg/L test medium (loading rate).

The EC0 and 100/48h was higher than 100 mg/L test medium (loading rate).

The trial is representative of what is expected to occur in nature if colesevelam hydrochloride entered the aquatic environment, since colesevelam hydrochloride is not soluble in water.

4.4.1.8.2 Evaluation of the Acute Toxicity of Colesevelam Hydrochloride to the Zebrafish, *Brachydanio rerio*

4.4.1.8.2.1 Objective

The acute toxicity of the soluble components of colesevelam hydrochloride to the Zebrafish, *Brachydanio rerio* was determined in a 96 hours static test. The final study report is located in Appendix 4.4-9.

4.4.1.8.2.2 Experimental Conditions

Because the test substance is insoluble, a limit test with a loading rate of 100 mg test substance/L was performed. The test substance was ground in a mortar and added to dilution water at a concentration of 100 mg/L. This preparation was stirred for 24 hours in the dark using a magnetic stirrer. A filtrate (Miracloth® filter, Calbiochem) was then used for the test. The extracted colesevelam hydrochloride and extraction solution were chemically analyzed.

Local tap water was mixed with deionized water to achieve the appropriate water hardness as required by the guidelines (< 250 mg $CaCO_3$/L). This water was used for holding of the fish and for the control and test medium.

Seven (7) fish (length of approximately 3 cm) were used for the test substance group and for one control group (dilution water only).

4.4.1.8.2.3 Investigations

- Total hardness of the dilution water
- pH in the control and test medium
- Temperature in the control and test medium
- Dissolved oxygen concentration in the control and test medium
- Mortality, observations in life

4.4.1.8.2.4 Results

Chemical Analysis:

The recovered colesevelam hydrochloride following extraction was analyzed (IR, elemental analysis, volatile impurities, and titratable amines) and showed little or no change occurred during the extraction process (see table below).

Parameter	Test substance before incubation Lot TNBC 401	Test substance after incubation in fish-water and drying
Dry Substance (IR, 15 min, 120 °C)	98.12 %	99.22 %
Elemental Analysis	C = 54.40 % H = 11.17 % N = 8.60 % Cl = 20.56 % Br = 0.64 %	C = 54.88 % H = 11.10 % N = 8.92 % Cl = 20.26 % Br = 0.67 %
Volatile Impurities	< 0.1% (as specified)	< 0.1%
Titratable Amines	4.56 mmol/g	4.55 mmol/g

The filtrates were analyzed for chloride and bromide (see table below). Since the filtrates contained no organic material, they were not tested for stability. As expected there was very little extractable material present in colesevelam hydrochloride.

	Acute Toxicity Study in Fish Test Filtrate
Bromide	< 10 ppm
Chloride	215 ppm

Brachydanio rerio Exposure:

The other quality criteria for the OECD guideline were fulfilled:

- Constant conditions were maintained (temperature, pH).
- No mortality occurred in the negative control group.
- The dissolved oxygen concentration was higher than 60% of the air saturation value throughout the test.

No mortality was noted in the test substance group.

The swimming activity of the fish of the test substance group was slightly lower for about 48 hours when compared to the control animals. At the beginning of the test, the test medium was slightly cloudy and after a while small particles were seen at the bottom of the test vessel. These small particles in the filtrate were presumably the cause of the slightly different behavior of the fish in the test substance group.

4.4.1.8.2.5 Conclusion

The LC50/24h, 48h, 72h, and 96h of the soluble components of colesevelam hydrochloride was therefore higher than 100 mg/L test medium (loading rate).

The LC0 and 100/96h was higher than 100 mg/L test medium (loading rate).

The trial is representative of what is expected to occur in nature if colesevelam hydrochloride entered the aquatic environment, since colesevelam hydrochloride is not soluble in water.

4.4.1.8.3 Evaluation of the Acute Toxicity of Colesevelam Hydrochloride to *Selenastrum capricornutum* Printz

4.4.1.8.3.1 Objective of the Study

A *Selenastrum capricornutum* growth inhibition test according to the OECD Guideline 201 and to the EC guideline 92/69/EEC Part C.3 was performed to determine the possible effects of colesevelam on the growth of a unicellular green algae species. The final study report is included in Appendix 4.4-10.

4.4.1.8.3.2 Test Design

Colesevelam hydrochloride is insoluble in water. An aqueous extract of the test substance in double distilled water/concentrated nutrient medium (8:1) was prepared by extracting colesevelam hydrochloride for 24 hours and subsequent filtering. The loading rate for preparing the aqueous extract was 168 mg test substance in 750 mL. This aqueous extract was the stock solution from which the 5 concentrations in the study were obtained by dilution. The extracted colesevelam hydrochloride and extraction solution were chemically analyzed. The concentrations in terms of dilutions of the loading rate were: 12.5, 25.3, 50.4, 100.8, and 201.6 mg/L. The 5 test concentrations were tested against one negative control (double distilled water instead of the aqueous extract). There were 3 replicates for each test and control culture. The cell count of the algae was about 10^4 cells/mL at the start of the exposure in each vessel.

In each vessel the cell density of the algae was determined 24, 48, and 72 hours after the onset of incubation and the pH was measured at the beginning and at the end of the incubation period.

Possible test substance effects were determined by comparison of the areas under the growth curves and by comparison of the growth rates.

4.4.1.8.3.3 Results

The concentrations presented in the results were calculated from the loading rate for preparing the aqueous extract and its dilutions and are therefore given in terms of "loading of COLESEVELAM HYDROCHLORIDE" per liter.

Chemical Analysis:

The recovered colesevelam hydrochloride following extraction was analyzed (IR, elemental analysis, volatile impurities, and titratable amines) and showed little or no change occurred during the extraction process (see table below).

Parameter	Test substance before incubation Lot TNBC 401	Test substance after incubation in algae-water and drying
Dry Substance (IR, 15 min, 120 °C)	98.12 %	97.98 %
Elemental Analysis	C = 54.40 % H = 11.17 % N = 8.60 % Cl = 20.56 % Br = 0.64 %	C = 55.50 % H = 11.18 % N = 8.73 % Cl = 20.11 % Br = 0.52 %
Volatile Impurities	< 0.1% (as specified)	< 0.1%
Titratable Amines	4.56 mmol/g	4.56 mmol/g

The filtrates were analyzed for chloride and bromide (see table below). Since the filtrates contained no organic material, they were not tested for stability. As expected there was very little extractable material present in colesevelam hydrochloride.

	Algae (*Selenastrum capritornutum*) Growth Inhibition Test Filtrate
Bromide	< 10 ppm
Chloride	90 ppm

pH:

The test substance slightly lowered the pH of the test media only at the high loading of test substance of 201.6 mg/L. No marked change in pH occurred in any test substance culture during the incubation period of 72 hours.

Increase in Cell Densities:

During the 72 hours incubation period the cell densities in the control cultures were increased by a factor of about 83 (about 6.4 generations).

Growth Inhibition:

After 72 hours of incubation the algae growth was slightly enhanced at loadings of test substance of 12.5 and 25.3 mg/L. At 50.4, 100.8, and 201.6 mg/L the algae growth was inhibited by about 41 to 92 % based upon the areas under the growth curve, and was inhibited by about 9 to 44 % based upon the growth rates.

NOEC and EC50-Values:

Two "no observed effect concentrations" (NOECs) and two EC50 values were derived based on the area under the growth curves and on the average growth rates:

	$NOEC_{0-72H}$ (IN MG "LOADING OF COLESEVELAM HYDROCHLORIDE" PER LITER)
Based on the area under the growth curves	25.3
Based on the average growth rates	50.4

	$EC50_{0-72H}$ (IN MG "LOADING OF COLESEVELAM HYDROCHLORIDE" PER LITER)
Based on the area under the growth curve: E_bC_{50} (0-72 h)	67.2
Based on the average growth rates: E_rC_{50} (0-72 h)	> 201.6

4.4.1.8.3.4 Conclusion

Based on algae growth effects, the no-observed-effect concentration (NOEC) for colesevelam hydrochloride was 25.3 mg/L based upon the area under the curve, and 50.4 mg/L based upon the average growth rates.

The trial is representative of what is expected to occur in nature if colesevelam hydrochloride entered the aquatic environment, since colesevelam hydrochloride is not soluble in water.

4.4.1.8.4 Evaluation of the Effects of Colesevelam Hydrochloride on Activated Sludge in a Wastewater Treatment Plant

4.4.1.8.4.1 Objective

The study was performed to estimate possible effects of colesevelam hydrochloride on aerobic microbial sewage treatment plants. The test was performed according to the OECD Guideline for Testing of Chemicals 209 "Activated Sludge, Respiration Inhibition

Test" and the EU-Guideline 87/302, using activated sludge from a sewage treatment plant treating predominantly domestic sewage. The final study report is included in Appendix 4.4-11.

4.4.1.8.4.2 Test Design

Five concentrations of the test substance (19, 40, 75, 151, and 300 mg/L) were tested versus 2 negative controls (tap water). As positive control substance 3,5-dichlorophenol was used and tested in 3 concentrations (5, 15, and 45 mg/L).

The microbial inoculum was a preparation of activated sludge collected on the day of the test. The concentration of the microbial inoculum was adjusted to 4 g of dry weight/L, which gives a final amount of 1.6 g dry weight/L in the test medium. The inoculum was kept aerated before beginning the test.

After mixing the inoculum with synthetic sewage solution and appropriate amounts of control or test substance solutions, the samples were aerated for a contact time of 3 hours at 20 °C. Negative controls were run as first and as last sample. After incubation the respiration rates were determined in closed bottles using an oxygen-sensitive electrode. The inhibition of respiration was calculated from the respiration rates using the mean value of the negative controls as 100 %.

4.4.1.8.4.3 Results

The test results fulfilled the criteria for validity:

- the respiration rates of the 2 control samples were within 15 % of each other. Actual values: ± 1.8 %.
- the EC_{50} of 3,5-dichlorophenol was in the accepted range of 5 to 30 mg/L. Actual EC_{50}: 12.1 mg/L.

The test substance did not inhibit the respiration rates of the bacteria up to 300 mg/L.

4.4.1.8.4.4 Conclusion

The EC_{20}, EC_{50}, and EC_{80} values for colesevelam hydrochloride are therefore greater than 300 mg/L. No 95 % confidence limits can be calculated.

EC_{20} > 300 mg/L

EC_{50} > 300 mg/L

EC_{80} > 300 mg/L

4.4.1.8.5 Summary

Colesevelam hydrochloride, the parent compound, is expected to be the only substance entering the environment. If the entire amount of colesevelam hydrochloride produced were to enter the aquatic environment, the level calculated from the "EIC-Aquatic" equation is 4.5 ppb. This amount is 1000 - 10,000 times lower (in the effluent) than the toxicity level. [The EC_{50} in *Daphnia magna* at 24h and 48h is higher than 100mg/L (loading rate). The LC50 in fish (Zebrafish) at 24h, 48h, 72h, and 96h was higher than 100mg/L (loading rate). For algae (*Selenastrum capricornutum*) the $NOEC_{0\text{-}72H}$ was 25.3 mg "loading" per liter and the $EC50_{0\text{-}72H}$ = 67.2 mg "loading" per liter.]

In addition, preclinical studies show that ^{14}C-colesevelam hydrochloride is essentially not absorbed in rats or dogs and clinical studies have confirmed the lack of absorption in humans. Because colesevelam hydrochloride is unabsorbed in mammals, it should be unabsorbed in aquatic species and, therefore, should not bio-accumulate. Colesevelam hydrochloride is not metabolized. The insolubility, molecular weight, and lack of absorption in mammals indicate that colesevelam hydrochloride is not bioavailable. In addition, all toxicity studies indicate a very low level of toxicity.

4.4.2 Use of Resources and Energy

4.4.2.1 Natural Resources and Energy

There will not be a significant impact on total usage of energy or utilities by the DSM Fine Chemicals Austria site in Linz, Austria. 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.

4.4.2.2 Effect on Endangered or Threatened Species

No effect.

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

No effect.

4.4.3 Mitigation Measures

An emergency preparedness plan is in place for the colesevelam hydrochloride production unit and the DSM Fine Chemicals Austria site, which includes on-site fire and emergency response personnel. All storage vessels are equipped with secondary containment to prevent groundwater contamination. All plants have liquid-tight floors to prevent groundwater contamination. Both Buildings 700 and 52 have a retainment device for water and foam for fire-fighting.

4.4.4 Alternatives to the Proposed Action

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

4.4.5 List of Preparers

COMPANY	NAME	JOB TITLE	QUALIFICATION
GelTex	Eugene Zhorov	Associate Director, Analytical Development	Ph.D. (Organic Chemistry)
GelTex	Joseph Tyler	Vice President, Manufacturing	M. S. (Chemical Engineering)
GelTex	Toni Chancellor	Senior Director, Manufacturing	Ph.D. (Organic Chemistry)
DSM	Christian Ramaseder	Environmental Manager	Dr. Dipl.-Ing.*
DSM	Franz Thomas Schwarz	Safety Manager	Dr. Dipl.-Ing.
DSM	Erich Steinwender	Analytical Chemist	Dr. Mag.**
Seibersdorf***	Norbert Bornatowicz	Head of Toxicology Dept.	Dr.
Seibersdorf	Christine Fenzl	Study Director	Mag.
Seibersdorf	Heinz Hofer	Toxicologist	Dr.
Powdersize	Tom Moran	President	BS (Civil Engineering) and MBA
Global Pharm	Thomas Tassou	Project Manager Manufacturing	B.Sc., (Pharm. Tech., R&D)

* Doctorate degree in engineering. ** Doctorate and master's degree.
*** Austrian Research Center (contract testing laboratory)

DSM Fine Chemicals Austria GmbH
St. - Peter - Straße 25
P.O.Box 933
A - 4021 Linz /Austria

Powdersize Inc.
20 Pacific Drive
Quakertown, PA 18951
U.S.A.

Global Pharm, Inc.
Global Pharm Incorporated
865 York Mills Road,
Toronto, Ontario M3B1Y5
Canada

GelTex Pharmaceuticals, Inc.
153 Second Avenue
Waltham, MA 02451

4.4.6 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 1–37) contains non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR § 1506.6.

Joseph E. Tyler

Joseph Tyler
Vice President, Manufacturing
GelTex Pharmaceuticals, Inc.

4/25/00
Date

APPEARS THIS WAY
ON ORIGINAL

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 21-141

Welchol™ (colesevelam hydrochloride) Capsules

and

NDA 21-176

Welchol™ (colesevelam hydrochloride) Tablets

Division of Metabolic and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

Date Completed: April 27, 2000

SUMMARY

A FONSI is recommended.

The product is a new molecular entity that will be used to treat primary hypercholesterolemia as an adjunct to exercise and diet. An EIC of —— ppb is estimated based on a 5 year estimate of 200,000 kg.

The fate information indicates that the compound will not rapidly degrade and most likely will enter the aquatic and terrestrial environments. The toxicity data provided demonstrated no effects at the EIC and that the EIC is at least 1000 fold lower than the EC50/LC50 concentrations for various aquatic organisms. Based on the data, significant environmental effects are not expected.

The test results are as follows:

Test	Result
Water solubility	Not soluble in water
Log Octanol/Water Partition Coefficient	N/A Not soluble in hydrocarbon solvents
Vapor pressure	No vapor pressure because of its high molecular weight
PK_a	Polyelectrolyte with no discrete dissociation constant
Photolysis	Not susceptible to photolysis
Hydrolysis	Not susceptible to hydrolysis
OECD CO_2 evolution test for ready biodegradability	~ ⅛ in 28 days: not readily biodegradable

Organism/Test	LC_{50}/EC_{50}	NOEC
Selenastrum capricornutum (96 hrs)	——	——
Daphnia magna (48 hrs)	>100 ppm (EC_{50})	——
Brachydanio rerio (96 hrs)	>100 ppm (EC_{50})	——
Activated Sludge Respiration Inhibition Test	>300 ppm (EC_{50})	

APPEARS THIS WAY
ON ORIGINAL

ENVIRONMENTAL ASSESSMENT

1. **Date:**

EA dated: 7/29/1999
Review #1: 12/28/2000
EA amend: 2/4/2000
Review #2: 3/7/2000
EA Amend: 3/23/2000
Review #3 4/26/2000

PM: William Koch

2. **Name of applicant/petitioner:**

GelTex Pharmaceuticals, Inc.

ADEQUATE

3. **Address:**

153 Second Avenue
Waltham, MA 02451

ADEQUATE

The following are in response to the deficiencies identified in review #2.

1. 4.4.1.6: Information on the substances expected to enter the environment (i.e., parent compound, metabolites) from use of the drug and the rationale for studying the parent compound should be provided (IV.B.1.a.i).

   The information you provided in the February 4, 2000 response is adequate, however, you need to incorporate it into the EA document

   Response: The revised EA incorporates the information.

   ADEQUATE

2. 4.4.1.7.2 (deficiency a): A brief description of the test method used to determine the

physical/chemical characteristics of colesevelam hydrochloride should be provided (IV.D). If the statements about the characteristics were based on fundamental chemical principles (e.g., chemical structure of the compound) rather than actual testing then this should be included:

a. Solubility-Water: The response cross references a section of the NDA for this information. This needs to be summarized and included in the EA. Only a brief description of the test method (e.g., quantity, temperature, method (e.g., under/over saturation method)) used to determine the solubility in water needs to be provided in section 4.4.1.7.2.1 of the EA.

Response: The procedure used to determine the solubility of the compound in water has been described and supports that the material is not water soluble

ADEQUATE

b. Dissociation constant: The information is adequate but needs to be included in section 4.4.1.7.2.2 of the EA.

Response: The revised EA incorporates the information.

ADEQUATE

3. 4.4.1.7.2 (deficiency b): The statement that colesevelam hydrochloride has "no" vapor pressure needs to be clarified. Substances with very low vapor pressure are typically reported, for example, as having a vapor pressure of $<10^{-3}$ Pa.

The information provided in the February 4, 2000 response is adequate but needs to be incorporated into section 4.4.1.7.2.4

Response: The revised EA incorporates the information.

ADEQUATE

4. 4.4.1.7.3: Hydrolysis and photolysis as potential depletion mechanisms should be discussed (IV.B.1.a.iii).

The information provided in the February 4, 2000 response is adequate but needs to be included in section 4.4.1.7.3 of the EA

Response: The revised EA incorporates the information.

ADEQUATE

5. 4.4.1.7.5: A more detailed discussion of the expected fate of colesevelam hydrochloride, based on its physical/chemical properties, should be provided. For example, because of the insolubility of the compound, what would be expected to happen in the waste water treatment process or if it entered the aquatic environment (IV.B.1.a v):

   a. The first 2 paragraphs deal with a summary of the effects of the drug. The discussion is acceptable but is not included in the EA text. It should be included at the end of section 4.4.1.8.

   Response: The revised EA incorporates the information.

   ADEQUATE

   b. You have stated that that the drug is predicted to _____ _____ This statement should not be included because no formal adsorption/desorption test was performed. Based on the insolubility of the compound the potential to "settle out" in the waste water treatment process and the aquatic environment should be discussed and included in 4.4.1.7.5

   Response: The EA has been revised to provide information about the potential for settling out of the compound in the waste treatment process and the aquatic environment.

   ADEQUATE

6. 4.4.1.8: In the text of the EA for the daphnia and fish studies it is stated that "There is no method of analysis of the soluble components of the test substance available." For the algae test further explanation is included that "Because the soluble components of the test substance are not known, there is no appropriate method of analysis available. Therefore no determination of the actual concentration was performed." In the test reports it is stated that the solutions of the test substance were analyzed for stability of the test substance by the sponsor. These conflicting statements should be explained. The EA text should fully explain and justify why analysis was not performed for each occurrence:

   The information provided is adequate. However, this information needs to be included in the EA and the EA needs to be revised to deleted the incorrect statements that indicate no testing was performed.

   Response: The EA has been revised as requested.

ADEQUATE

7. 4.4.3: Information on any mitigation measures necessary based on the use of the drug should be provided (IV.A.7):

You added a statement to section 4.4.4 that _____ This does not address the issue. An EA focuses on the potential environmental affects of the use of drug. The mitigation measures included in the EA only pertain to the manufacturing site. Mitigation measures necessary because of any environmental affects from the use of the drug need to be discussed. The information that was added to section 4.4.4 should be deleted.

Response: The revised EA deletes the information.

ADEQUATE

8. 4.4.5: The name, job title, and qualifications of the people preparing the assessment should be provided (IV.A.9):

The information provided in the February 4, 2000 response is adequate but needs to be included in section 4.4.5 of the EA.

Response: The revised EA incorporates the information.

ADEQUATE

On April 25, the applicant was asked to submit a clean copy of their EA (submitted EA was redlined and struck out). The applicant sent this in on April 25, 2000 with the one addition of adding their proprietary name to the document.

APPEARS THIS WAY
ON ORIGINAL

Endorsements:

HFD-357/NBSage /S/ 4/27/00

HFD-800/YYChiu /S/ 4/27/00

CC: Original to NDA 21-176/through WKoch/HFD-510
Copy to NDA 21-141/through WKoch/HFD-510
EA File 21-141

APPEARS THIS WAY
ON ORIGINAL

Simcek

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office): HFD-357 WOC II Rm 3073 Nancy Sager Ph: (301) 594-5638			FROM: HFD-510 Div. of Metabolic and Endocrine Drug Products
	IND NO.	NDA NO. 21-141	TYPE OF DOCUMENT Environmental Assessment / DATE OF DOCUMENT February 4, 2000
NAME OF DRUG Welchol (Colesevelam HCl)	PRIORITY CONSIDERATION High*	CLASSIFICATION OF DRUG 1S	DESIRED COMPLETION DATE March 15, 2000

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY —
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER (SPECIFY BELOW): Environmental Assessment (Response)

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR - 9 2000
HFD-510

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILTY STUDIES
- PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please Review EA For this pending NDA, Included with Package is Enclosure (1) February 4, 2000 Submission
Contact Chemist M Haber (301)-827-6388
Project Manager is W Koch (301) 827-6412
Geltex Pharm Contact is Martha Canter (781)434-3442
(or) Dean Algen (781)434-3421

Draft closed 3/8/00 different /S/

*NOTE: User Fee May 30 2000

SIGNATURE OF REQUESTER /S/ P. 7-6418 2/4/00

METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND

SIGNATURE OF RECEIVER /S/ 2/10/00

SIGNATURE OF DELIVERER

cc:
Original NDA 21-141
Div File

Team Leader /S/

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 21-141

Cholestagel® Capsules and Cholestagel® Tablets

(colesevelam hydrochloride)

Division of Metabolic and
Endocrine Drug Products (HFD-510)

Center for Drug Evaluation and Research

Date Completed: March 7, 2000

SUMMARY

A FONSI is not recommended at this time. A deficiency list is included at the end of the review.

The test results are as follows:

Test	Result
Water solubility	Not soluble in water
Log Octanol/Water Partition Coefficient	N/A Not soluble in hydrocarbon solvents
Vapor pressure	No vapor pressure because of its high molecular weight
PK_a	Polyelectrolyte with no discrete dissociation constant
Photolysis	Not susceptible to photolysis
Hydrolysis	Not susceptible to hydrolysis
OECD CO_2 evolution test for ready biodegradability	– % in 28 days: not readily biodegradable

Organism/Test	LC_{50}/EC_{50}	NOEC
Selenastrum capricornutum (96 hrs)	—	—
Daphnia magna (48 hrs)	>100 ppm (EC_{50})	—
Brachydanio rerio (96 hrs)	>100 ppm (EC_{50})	—
Activated Sludge Respiration Inhibition Test	>300 ppm (EC_{50})	

APPEARS THIS WAY
ON ORIGINAL

ENVIRONMENTAL ASSESSMENT

1. **Date:**

   EA dated: 7/29/1999
   Review #1: 12/28/2000
   EA amend: 2/4/2000

   PM: Margaret Simoneau

2. **Name of applicant/petitioner:**

   GelTex Pharmaceuticals, Inc.

   ADEQUATE

3. **Address:**

   153 Second Avenue
   Waltham, MA 02451

   ADEQUATE

The following are in response to the deficiencies identified in review #1:

1. 4.4.1.4.1: The citation to the regulations in not correct (IV.A.4.a).

   The regulatory citation has been corrected.

   ADEQUATE

2. 4.4.1.4.3: The expected locations of use should be specified (IV.A.4.c).

   The drug is expected to be used by patients in their homes.

   ADEQUATE

3. 4.4.1.6: Information on the substances expected to enter the environment (i.e., parent compound, metabolites) from use of the drug and the rationale for studying the parent compound should be provided (IV.B.1.a.i).

The applicant describes the stability of the product. The product is very stable. Information on metabolism was included in response to deficiency #7 (does not metabolize). The information is adequate. However, they did not incorporate this information into the EA document.

DEFICIENT

4. 4.4.1.6.10: The highest quantity expected to be produced in any of the next 5 years should be used in the calculations (III.A.2).

The calculation from the current guidance is included and the estimate, based on the highest quantity in any of the next 5 years, was calculated. The estimate, based on 200,000 kg, is 4.5 ppb.

ADEQUATE

5. 4.4.1.7.2:

a. A brief description of the test method used to determine the physical/chemical characteristics of colesevelam hydrochloride should be provided (IV.D). If the statements about the characteristics were based on fundamental chemical principles (e.g., chemical structure of the compound) rather than actual testing then this should be included.

Water solubility: The response cross references a section of the NDA for this information.

Octanol Water Partition Coefficient: The information repeats what is already in the EA which was already sufficient.

PKa: Acid base titration is used. The information is adequate but needs to be included in section 4.4.1.7.2.2 of the EA.

DEFICIENT

b. The statement that colesevelam hydrochloride has "no" vapor pressure needs to be clarified. Substances with very low vapor pressure are typically reported, for example, as having a vapor pressure of $<10^{-5}$ Pa.

The applicant describes the physical chemical characteristics of the compound. Because of its high molecular weight the substance has no vapor pressure and no vapor pressure test was performed. The information is adequate but needs to be incorporated into section 4.4.1.7.2.4.

DEFICIENT

6. 4.4.1.7.3: Hydrolysis and photolysis as potential depletion mechanisms should be discussed (IV.B.1.a.iii).

The hydrolytic stability of the drug in acid and base and photostability were investigated. The tests were described. Neither hydrolysis or photodegradation are expected to be potential depletion mechanism. The information is adequate but needs to be included in section 4.4.1.7.3 of the EA.

DEFICIENT

7. 4.4.1.7.5: A more detailed discussion of the expected fate of colesevelam hydrochloride, based on its physical/chemical properties, should be provided. For example, because of the insolubility of the compound, what would be expected to happen in the waste water treatment process or if it entered the aquatic environment (IV.B.1.a.v).

The applicant has provided additional information. The first 2 paragraphs deal with a summary of the effects of the drug. It includes a comparison of the EIC to the ecotoxicity results and a discussion of the potential for bioaccumulate (will not bioaccumulate). The discussion is acceptable but is not included in the EA text. It should be included at the end of section 4.4.1.8.

The applicant addresses the deficiency by stating that the drug is predicted to [redacted] This statement should not be included because no formal adsorption/desorption test was performed. Based on the insolubility of the compound the potential to "settle out" in the waste water treatment process and the aquatic environment should be discussed and included in 4.4.1.7.5

DEFICIENT

8. 4.4.1.8: In the text of the EA for the daphnia and fish studies it is stated that "There is no method of analysis of the soluble components of the test substance available." For the algae test further explanation is included that "Because the soluble components of the test substance are not known, there is no appropriate method of analysis available. Therefore no determination of the actual concentration was performed." In the test reports it is stated that the solutions of the test substance were analyzed for stability of the test substance by the sponsor. These conflicting statements should be explained. The EA text should fully explain and justify why analysis was not performed for each occurrence.

The applicant explains that the test materials were analyzed at the beginning and end of the studies. The test solutions were prepared by grinding the test substance and adding it to water at the desired concentration, stirring for the required time and filtering. The recovered colesevelam hydrochloride was analyzed (IR, elemental analysis, volatile impurities, and titratable amines). The data demonstrated little or no change. This explanation addressed the deficiency. However, the applicant did not include this explanation in the EA or delete the incorrect statements that indicate no testing was performed.

DEFICIENT

9. 4.4.3: Information on any mitigation measures necessary based on the use of the drug should be provided (IV.A.7).

The applicant adds a statement to section 4.4.4 that [redacted] This does not address the issue. An EA focuses on the potential environmental affects of the use of drug. The mitigation measures included in the EA only pertain to the manufacturing site. Mitigation measures necessary because of environmental affects from the use of the drug need to be discussed. The information that was added to section 4.4.4 to address this deficiency should be deleted.

DEFICIENT

10. 4.4.5: The name, job title, and qualifications of the people preparing the assessment should be provided (IV.A.9)

The requested information was provided and is adequate but was not incorporated into the EA.

DEFICIENT

EA Deficiency List – NDA 21-141

General comment: Environmental Assessments (EAs) are considered public documents and are available once an application is approved. You may want to obtain copies of recently approved EAs to guide you in the preparation of your EAs in the future.

The following deficiencies in the environmental assessment that was submitted on February 4, 2000 should be corrected and a revised EA submitted. The deficiency from the first review is listed followed by the recommended revision.

1. 4.4.1.6: Information on the substances expected to enter the environment (i.e., parent compound, metabolites) from use of the drug and the rationale for studying the parent compound should be provided (IV.B.1.a.i):

   The information you provided in the February 4, 2000 response is adequate, however, you need to incorporate it into the EA document.

2. 4.4.1.7.2 (deficiency a): A brief description of the test method used to determine the physical/chemical characteristics of colesevelam hydrochloride should be provided (IV.D). If the statements about the characteristics were based on fundamental chemical principles (e.g., chemical structure of the compound) rather than actual testing then this should be included:

   a. Solubility-Water: The response cross references a section of the NDA for this information. This needs to be summarized and included in the EA. Only a brief description of the test method (e.g., quantity, temperature, method (e.g., under/over saturation method)) used to determine the solubility in water needs to be provided in section 4.4.1.7.2.1 of the EA.

   b. Dissociation constant: The information is adequate but needs to be included in section 4.4.1.7.2.2 of the EA.

3. 4.4.1.7.2 (deficiency b): The statement that colesevelam hydrochloride has "no" vapor pressure needs to be clarified. Substances with very low vapor pressure are typically reported, for example, as having a vapor pressure of $<10^{-5}$ Pa:

   The information provided in the February 4, 2000 response is adequate but needs to be incorporated into section 4.4.1.7.2.4.

4. 4.4.1.7.3: Hydrolysis and photolysis as potential depletion mechanisms should be discussed (IV.B.1.a.iii):

The information provided in the February 4, 2000 response is adequate but needs to be included in section 4.4.1.7.3 of the EA.

5. 4.4.1.7.5: A more detailed discussion of the expected fate of colesevelam hydrochloride, based on its physical/chemical properties, should be provided. For example, because of the insolubility of the compound, what would be expected to happen in the waste water treatment process or if it entered the aquatic environment (IV.B.1.a.v):

   a. The first 2 paragraphs deal with a summary of the effects of the drug. The discussion is acceptable but is not included in the EA text. It should be included at the end of section 4.4.1.8.

   b. You have stated that that the drug is predicted to [redacted] This statement should not be included because no formal adsorption/desorption test was performed. Based on the insolubility of the compound the potential to "settle out" in the waste water treatment process and the aquatic environment should be discussed and included in 4.4.1.7.5

6. 4.4.1.8: In the text of the EA for the daphnia and fish studies it is stated that "There is no method of analysis of the soluble components of the test substance available." For the algae test further explanation is included that "Because the soluble components of the test substance are not known, there is no appropriate method of analysis available. Therefore no determination of the actual concentration was performed." In the test reports it is stated that the solutions of the test substance were analyzed for stability of the test substance by the sponsor. These conflicting statements should be explained. The EA text should fully explain and justify why analysis was not performed for each occurrence:

   The information provided is adequate. However, this information needs to be included in the EA and the EA needs to be revised to deleted the incorrect statements that indicate no testing was performed.

7. 4.4.3: Information on any mitigation measures necessary based on the use of the drug should be provided (IV.A.7):

   You added a statement to section 4.4.4 that [redacted] This does not address the issue. An EA focuses on the potential environmental affects of the use of drug. The mitigation measures included in the EA only pertain to the manufacturing site. Mitigation measures necessary because of any environmental affects from the use of the drug need to be discussed. The information that was added to section 4.4.4 should be deleted.

8. 4.4.5: The name, job title, and qualifications of the people preparing the assessment should be provided (IV.A.9):

The information provided in the February 4, 2000 response is adequate but needs to be included in section 4.4.5 of the EA.

Endorsements:

3/7/00

HFD-357/NBSager /S/

HFD-800/YYChiu /S/ 3/8/00

CC: Original to NDA 21-141/through MSimoneau/HFD-510
EA File 21-141

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

1S 9/28/99

TO (Division/Office): HFD-357 WOC 2 Rm 3069 73 Nancy Sager Phone 594-5629 33		FROM: HFD-510 Division of Metabolic and Endocrine Drug Products	
September 28, 1999	IND NO.	NDA NO. 21-141	TYPE OF DOCUMENT: Environmental Assessment DATE OF DOCUMENT: July 30, 1999
NAME OF DRUG: Cholestagel (Colesevelam HCl)	PRIORITY CONSIDERATION: High	CLASSIFICATION OF DRUG: 1S	DESIRED COMPLETION DATE: February 1, 2000

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER (SPECIFY BELOW): Environmental Assessment

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review EA for this pending NDA. Included with package is a Copy of Volume 1.13

Contact Chemist is Martin Haber 301-827-6388

Project Manager is Margaret Simoneau 301-827-6418

Geltex Pharm Contact is Martha Carter - 781-434-3443 or Dean Alger - 781-434-3421 (Sponser)

Consult completed 1/4/00
EA deficient
/S/ 1/10/00

NOTE: User Fee May 30, 2000

SIGNATURE OF REQUESTER /S/ 9/28/99

METHOD OF DELIVERY (Check one): ☒ MAIL ☐ HAND

SIGNATURE OF RECEIVER /S/ 9/30/99

SIGNATURE OF DELIVERER

cc: Original NDA 21-141
DivFile
HFD 510 / MHABER

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 21-141

Cholestagel® Capsules and Cholestagel® Tablets

(colesevelam hydrochloride)

Division of Metabolic and
Endocrine Drug Products (HFD-510)

Center for Drug Evaluation and Research

Date Completed: December 28, 1999

SUMMARY

A FONSI is not recommended at this time. A deficiency list is included at the end of the review.

APPEARS THIS WAY
ON ORIGINAL

ENVIRONMENTAL ASSESSMENT

1. **Date:**

   EA dated: 7/29/1999

   PM: Margaret Simoneau

2. **Name of applicant/petitioner:**

   GelTex Pharmaceuticals, Inc.

   ADEQUATE

3. **Address:**

   Nine Fourth Ave.
   Waltham, MA 02451

   ADEQUATE

4. **Description of the proposed action:**

   a. **Requested Approval:**

   The applicant is requesting approval to market Cholestagel® Capsules (375 mg anhydrous) and Cholestagel® Tablets (625 mg anhydrous) packaged in HDPE bottles. The active ingredient is colesevelam hydrochloride.

   The regulations are incorrectly cited in this part of the EA.

   DEFICIENT

   b. **Need for Action:**

   The product is indicated for the treatment of primary hypercholesterolemia as an adjunct to exercise and diet.

   ADEQUATE

c. **Expected Locations of Use (Drug Product):**

The applicant does not specifically discuss where the drug product is used. Based on the indication is will most likely be used in hospitals, clinics and private residences throughout the United States. The applicant will be asked to specify this information.

DEFICIENT

d. **Disposal Locations:**

Disposal at hospitals/pharmacy/clinics will be in accordance with their procedures. A community's solid waste management system will typically be used for material disposed of from home use. Solid waste management systems may include landfills, incineration and recycling. Minimal quantities of the unused drug could be disposed of in the sewer system.

ADEQUATE

5. **Identification of chemical substances that are the subject of the proposed action:**

Drug Substance: colesevelam hydrochloride (Cholestagel®)

Chemical Name: 1-Hexanaminium, N,N,N-trimethyl-6-(2-propenylamine)-chloride, polymer with (chloromethyl)oxirane, 2-propen-1-amine and N-2-propenyl-1-decanamine, hydrochloride. (CAS)

Allyamine polymer with 1-chloro-2,3,epoxypropane, [6-allylamino)-hexyl]trimethylammonium chloride and N-allyldecylamine, hydrochloride. (IUPAC)

CAS #: 182815-44-7
182815-43-6 (INN)

Molecular Weight: N/A because it is a cross linked polymer. Density of the particle is independent of the particle size so the weight of the particle is proportional to the particle size (e.g., 25µm diameter particle weighs 5.4×10^{15} amu).

Molecular Form.: $(C_3H_8NCl)_2(C_9H_{20}N_2OCl_2)_1(C_{13}H_{28}NCl)_7(C_{12}H_{28}N_2Cl_2)_6$

Structural Form.: Provided on page 9 of the EA.

Physical Descrip: White to off-white powder

Additives: The additives are described in a confidential appendix.

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

ADEQUATE

Note: The applicant provided detailed information on manufacturing sites including emission streams and emission permits and information on use of natural resources and energy. This information is not routinely needed since the regulations at 21 CFR 25 were revised in July 1997. This information would only be needed if there was an extraordinary circumstance. There is no evidence of an extraordinary circumstance. Therefore, the information was only scanned and no detailed review has been documented.

6. Environmental Issue:

a. Identification of Substances of Interest:

The applicant has not provided information on what is expected to enter the environment (i.e., parent compound, metabolites) from use of the drug nor a rationale for studying the parent compound if other structurally related substances are entering the environment from use.

DEFICIENT

b. Environmental Fate of Released Substances:

Test	Result
Water solubility	Not soluble in water
Log Octanol/Water Partition Coefficient	N/A Not soluble in hydrocarbon solvents
Vapor pressure	"No vapor pressure" is stated
PK_a	Polyelectrolyte with no discrete dissociation constant
Photolysis	Not discussed
Hydrolysis	Not discussed
OECD CO_2 evolution test for ready biodegradability	— % in 28 days not readily biodegradable

The biodegradability data were generated in accordance with GLPs using an OECD procedure. The test report is provided and the testing was scientifically sound and adequate.

The applicant does not describe the testing, if any, that was used to determine the water solubility, dissociation constants, octanol/water partition coefficient, or vapor pressure of colesevelam hydrochloride. The statement that colesevelam hydrochloride has no vapor pressure needs to be better explained. Substances with very low vapor pressure are typically reported as, for example $<10^{-5}$ PA. Hydrolysis and photolysis as potential depletion mechanisms are not discussed.

The applicant concludes that the compound could enter both the aquatic and terrestrial environments. While this is most likely the case, additional explanation should be provided based on the fate data as to what will happen to the compound once it enters the POTW or aquatic environment (i.e., settle in sediment). No rapid environmental depletion mechanism has been identified.

DEFICIENT

c. **Environmental Concentrations:**

The expected environmental introduction concentration is —ppb based on a 3 year forecast of 200,000 kg. The highest quantity expected to be produced in any of the next 5 years should be used in the calculations.

DEFICIENT

d. **Environmental Effects:**

Organism/Test	LC_{50}/EC_{50}	NOEC
Selenastrum capricornutum (96 hrs)	—	—
Daphnia magna (48 hrs)	>100 ppm (EC_{50})	—
Brachydanio rerio (96 hrs)	>100 ppm (EC_{50})	—
Activated Sludge Respiration Inhibition Test	>300 ppm (EC_{50})	

Test reports are provided for the effects tests. OECD test methods were used and the testing was performed under GLPs. In each case the testing was limited

because of the compounds insolubility. For the Daphnia, fish, and algae tests the substance was ground in a mortar and added to the diluent at a concentration of 100mg/L. The preparation was then stirred for 24 hours in the dark, filtered and used in the test. In the text of the EA it is stated that "There is no method of analysis of the soluble components of the test substance available." For the algae test further explanation is included that "Because the soluble components of the test substance are not known, there is no appropriate method of analysis available. Therefore no determination of the actual concentration was performed." In the test reports it is stated that the solutions of the test substance were analyzed for stability of the test substance by the sponsor. These are conflicting statements that need to be explained. The EA text should fully explain why analysis was not performed in each instance. For the ——— the test substance was weighed and added directly to the system.

DEFICIENT

7. **Mitigation measures:**

Information is provided about mitigation measures for manufacturing sites but none is provided for the use of the drug.

DEFICIENT

8. **Alternatives to the proposed action:**

No adverse environmental effects have been identified and therefore no alternatives are considered.

ADEQUATE

9. **List of preparers, & their qualifications (expertise, experience, professional disciplines) and consultants:**

The name, job title, and qualifications of the people preparing the assessment are not provided only the names of the companies involved.

DEFICIENT

10. **References:**

No references are provided.

ADEQUATE

Appendices:

Confidential appendices containing manufacturing information, production estimates and test reports are provided.

ADEQUATE

The EA is appropriately identified with confidential and nonconfidential sections.

EA Deficiency List

General comment: In July 1997 FDA's regulations regarding environmental assessments (21 CFR Part 25) were revised. A revised guidance entitled *Environmental Assessment of Human Drug and Biologics Applications* (July 1998) was issued. The environmental assessment (EA) submitted in support of NDA 21-141 is based on the previous regulations and guidance and provides information that is now not routinely needed such as information on manufacturing sites. You may retain this information while revising this EA if you choose. However you may wish to consider not providing this information in future EAs unless specifically needed because of an extraordinary circumstance.

The following deficiencies in the environmental assessment submitted for NDA 21-141 should be corrected and a revised EA submitted. The citations included at the end of the deficiency refer to the section number of the EA guidance (cited above) which should be consulted when addressing the deficiency.

1. 4.4.1.4.1: The citation to the regulations in not correct (IV.A.4.a).

2. 4.4.1.4.3: The expected locations of use should be specified (IV.A.4.c).

3. 4.4.1.6: Information on the substances expected to enter the environment (i.e., parent compound, metabolites) from use of the drug and the rationale for studying the parent compound should be provided (IV.B.1.a.i).

4. 4.4.1.6.10: The highest quantity expected to be produced in any of the next 5 years should be used in the calculations (III.A.2).

5. 4.4.1.7.2:

   a. A brief description of the test method used to determine the physical/chemical characteristics of colesevelam hydrochloride should be provided (IV.D). If the statements about the characteristics were based on fundamental chemical principles (e.g., chemical structure of the compound) rather than actual testing then this should be included.

   b. The statement that colesevelam hydrochloride has "no" vapor pressure needs to be clarified. Substances with very low vapor pressure are typically reported, for example, as having a vapor pressure of $<10^{-5}$ Pa.

6. 4.4.1.7.3: Hydrolysis and photolysis as potential depletion mechanisms should be discussed (IV.B.1.a.iii).

7. 4.4.1.7.5: A more detailed discussion of the expected fate of colesevelam hydrochloride, based on its physical/chemical properties, should be provided. For example, because of the insolubility of the compound, what would be expected to happen in the waste water treatment process or if it entered the aquatic environment (IV.B.1.a.v).

8. 4.4.1.8: In the text of the EA for the daphnia and fish studies it is stated that "There is no method of analysis of the soluble components of the test substance available." For the algae test further explanation is included that "Because the soluble components of the test substance are not known, there is no appropriate method of analysis available. Therefore no determination of the actual concentration was performed." In the test reports it is stated that the solutions of the test substance were analyzed for stability of the test substance by the sponsor. These conflicting statements should be explained. The EA text should fully explain and justify why analysis was not performed for each occurrence.

9. 4.4.3: Information on any mitigation measures necessary based on the use of the drug should be provided (IV.A.7).

10. 4.4.5: The name, job title, and qualifications of the people preparing the assessment should be provided (IV.A.9)

Endorsements:

HFD-357/NBSager /S/ 12/28/99

HFD-800/YYChiu /S/ for 4/C 1/4/00

CC: Original to NDA 21-141/through MSimoneau/HFD-510
EA File 21-141

APPEARS THIS WAY
ON ORIGINAL

/S/ 9/28/99

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office): HFD-357 WOC 2 Rm 3069 Nancy Sager Phone 594-5629			FROM: HFD-510 Division of Metabolic and Endocrine Drug Products	
DATE: September 28, 1999	IND NO.	NDA NO. 21-141	TYPE OF DOCUMENT: Environmental Assessment	DATE OF DOCUMENT: July 30, 1999
NAME OF DRUG: Cholestagel (Colesevelam HCl)	PRIORITY CONSIDERATION: High		CLASSIFICATION OF DRUG: 1S	DESIRED COMPLETION DATE: February 1, 2000
NAME OF FIRM: [redacted]				

REASON FOR REQUEST

I. GENERAL

- ☐ OL
- ☐ PORT
- ☐ PONDENCE
- ☐ TISING
- ☐ ACTION REPORT
- ☐ RING CHANGE/ADDITION
- ☐ ANNED BY —

- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT

- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER (SPECIFY BELOW): Environmental Assessment

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ IER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES

- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review EA for this pending NDA. Included with package is a Copy of Volume 1.13

Contact Chemist is Martin Haber 301-827-6388

Project Manager is Margaret Simoneau 301-827-6418

Geltex Pharm contact is Martha Carter – 781-434-3443 or Dean Alger – 781-434-3421 (Sponsor)

NOTE: User Fee May 30, 2000

SIGNATURE OF REQUESTER: /S/ 9/28/99

METHOD OF DELIVERY (Check one): ☒ MAIL ☐ HAND

SIGNATURE OF RECEIVER: [illegible]

SIGNATURE OF DELIVERER

cc: Original NDA 21-141
DivFile