

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-318

ENVIRONMENTAL ASSESSMENT



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office**

Memorandum

Date: January 26, 2009

From: Raanan A. Bloom, Ph.D.
OPS/IO/PARS

To: Donghao Lu, Ph.D.
OPS/ONDQA/DPAI

Through: Jon Clark, M.S.
OPS/IO/PARS

Subject: NDA 22-318; Sevelamer Carbonate (Renvela) Powder for Suspension for Oral Use

Genzyme Corporation, Inc.
500 Kendall Street
Cambridge, MA 02142

Background

Genzyme Corporation, Inc. is requesting approval of an NDA for sevelamer carbonate powder for suspension for oral use. An EA has been submitted pursuant to 21 CFR part 25.

Discussion

The review appended below was conducted by Ruth Ganunis, Ph.D., under contract to the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (Completion date: January 15, 2009). Also attached is an Executive Summary.

Comments and Conclusions

Based on an evaluation of the information provided in this EA and in FDA guidance, and on the scientific validity of the "no effects" conclusions of the EA, no significant adverse environmental impacts are expected from the introduction of Sevelamer Carbonate residues into the environment due to the use of Renvela Powder for suspension for oral use for the control of serum phosphorous in patients with chronic kidney disease (CKD) on dialysis.

**Environmental Assessment Review, NDA 22-318
Sevelamer Carbonate Powder for Suspension for Oral Use
Control of serum phosphorous in patients with chronic kidney disease (CKD) on dialysis**

EXECUTIVE SUMMARY

This environmental assessment dated August 24, 2007, supports new drug application NDA 22-318, sevelamer carbonate powder for suspension for oral use, indicated for the control of serum phosphorous in patients with chronic kidney disease (CKD) on dialysis. The EA was prepared in accordance with 21 CFR Part 25 by Genzyme Corporation.

This EA describes the potential fate and effects of sevelamer carbonate in the environment. Sevelamer hydrochloride is currently approved for use under a related application, NDA 21-179, for sevelamer hydrochloride 400 mg and 800 mg tablets. A FONSI was issued May 14, 1998 for NDA 21-179. Sevelamer carbonate is currently approved for use under NDA 22-127, for sevelamer carbonate 800 mg tablets. A FONSI was issued November 18, 2007 for NDA 22-127. This EA for NDA 22-318 contains no new information, and is identical to the EA reviewed for NDA 22-127.

Sevelamer carbonate and sevelamer hydrochloride are cross-linked polymers that are insoluble. Sevelamer carbonate is expected to enter the aquatic environment from patient use and disposal. Due to its chemical nature, sevelamer carbonate may associate with sewage biosolid and enter the terrestrial environment by application to agricultural land. Since the definitive environmental fate could not be ascertained, in this EA the firm assesses the two worst case scenarios, that all material enters the aquatic environment and that all material enters the terrestrial environment. From a finding of no environmental effect in both of these worst case scenarios, no environmental effects are predicted for the “real” intermediate situation.

The total quantity of sevelamer carbonate (tablets and powder) and sevelamer hydrochloride (tablets) required in any of the next 5 years is expected to be _____ Considering the scenario where all material enters the aquatic environment, the EIC_{aquatic} is _____. The PEC_{aquatic} (or EEC_{aquatic}) is _____. Considering the scenario where all material enters the terrestrial environment, the concentration in biosolids is _____. The PEC_{soil} (or $EEC_{\text{terrestrial}}$) is _____.

b(4)

b(4)

The data submitted to this EA include ecotoxicological studies of daphnia, algae, higher plants, earthworm and soil microbes, which were submitted to the EA for sevelamer carbonate tablets (NDA 22-127) and were previously reviewed and found adequate (FONSI dated November 18, 2007). In addition, this EA references ecotoxicological studies of fish, daphnia and algae which were submitted to the EA for sevelamer hydrochloride (NDA 21-179) and were previously reviewed and found adequate (FONSI dated May 14, 1998).

With regard to the aquatic ecotoxicology data, green algae is the most sensitive species of those tested. The ratio of $LR_{50}/EIC_{\text{aquatic}}$ for green algae is _____, which is greater than the tier 2

b(4)

assessment factor of 100. The firm calculates the Predicted No Effect Concentration (PNEC) to be _____ The Predicted Environmental Concentration (PEC)/ Predicted no Effect Concentration (PNEC) ratio is _____, indicating certainty in the test result. The data indicate that the compound is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

b(4)

With regard to the terrestrial ecotoxicology data, all test systems showed the same degree of sensitivity. The ratio of $L(E)_{50} / EEC_{\text{terrestrial}}$ is _____ which is greater than the tier 2 assessment factor of 100. The firm calculates the Predicted No Effect Concentration (PNEC) to be _____ mg/kg. The Predicted Environmental Concentration (PEC)/ Predicted No Effect Concentration (PNEC) ratio is _____, indicating certainty in the test result. The data indicate that the compound is not expected to be toxic to terrestrial organisms at the expected environmental introduction concentration.

b(4)

The data provided indicate that it is unlikely that sevelamer carbonate or hydrochloride, used at the levels proposed in this application, represent a risk to the aquatic or terrestrial environment.

Environmental Assessment Review, NDA 22-318

**Sevelamer Carbonate Powder For Suspension for Oral Use
Control of serum phosphorous in patients with chronic kidney disease (CKD) on dialysis**

- I. DATE:** August 24, 2007
- II APPLICANT:** Genzyme Corporation, Inc
- III ADDRESS:** 500 Kendall Street
Cambridge, MA 02142

IV DESCRIPTION OF PROPOSED ACTION:

- a. Requested Approval: Genzyme is requesting approval for sevelamer carbonate powder, for suspension for oral use (2.4 g sachet). This EA has been submitted pursuant to 21 CFR part 25.
- b. Need for Action: Sevelamer carbonate is proposed to be indicated for the control of serum phosphorous in patients with chronic kidney disease (CKD) on dialysis. The proposed method of administration of sevelamer carbonate is by oral ingestion with meals. The duration of use will be lifetime.
- c. Locations of Use: Hospital, clinics and patients homes throughout the United States.
- d. Disposal Sites: Empty or partially empty containers from U.S. hospitals, pharmacies or clinics will be disposed of according to hospital, pharmacy or clinic procedures. Empty or partially empty containers from home use typically will be disposed by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of the unused drug may be disposed in the sewer system.

ADEQUATE

V IDENTIFICATION OF CHEMICALS

USAN Name: Sevelamer Carbonate

Brand Name: Renvela

Chemical Name:

Poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) carbonate
(CAS)

2-Propen-1-amine, polymer with (chloromethyl)oxirane, carbonate (CAS)

Oxirane, (chloromethyl)-,polymer with 2-propen-1-amine,carbonate (CAS)

Allylamine polymer with 1-chloro-2,3-epoxypropane, carbonate (IUPAC)

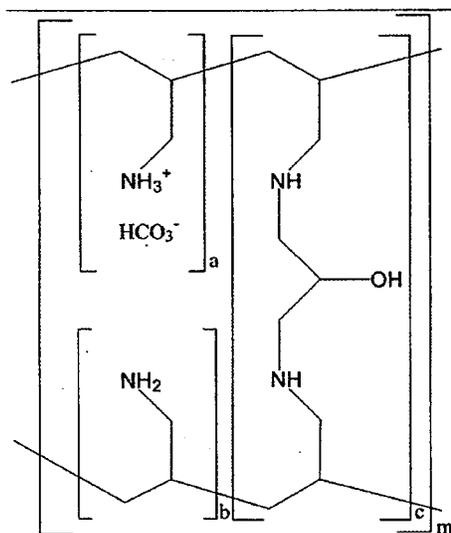
CAS Number: 845273-93-0

Molecular Formula: $(C_3H_7N \cdot nH_2CO_3)_{810z}(C_9H_{18}N_2 \cdot nH_2CO_3)_{95z}$ where z equals a large number

Molecular Weight:

Each particle is one molecule due to cross-links between polymer chains. Therefore the molecular weight of an individual particle is equal to the weight of the particle itself. For a 45 μm particle size, a typical molecular weight would be estimated (*i.e.* theoretical) to be in the range of 10^{16} amu.

Structural Formula:



Where:

a,b = number of primary amine groups ($a + b = 9$)

c = number of cross-linking groups ($c = 1$)

m = large number to indicate extended polymer network

ADEQUATE

VI ENVIRONMENTAL ISSUES / Assessing Toxicity to Environmental Organisms

This EA describes the potential fate and effects of sevelamer carbonate and sevelamer hydrochloride in the environment.

The data supporting this EA were the subject of previous reviews: A FONSI issued was May 14, 1998 for NDA 21-179, sevelamer hydrochloride 400 mg and 800 mg tablets. A FONSI was issued November 18, 2007 for NDA 22-127, sevelamer carbonate 800 mg tablets.

This EA for NDA 22-318 contains no new information, and is identical to the EA reviewed for NDA 22-127.

ADEQUATE

VII MITIGATION MEASURES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

VIII ALTERNATIVES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

IX PREPARERS

Names, job titles and qualifications were provided.

ADEQUATE

X REFERENCES

Listed, p. 14.

XI APPENDICES

Nonconfidential

1. Data Summary Table
2. Abbreviations

Confidential

1. Projected Total Usage of Sevelamer Carbonate and Sevelamer Hydrochloride in the United States
2. Basis for Aquatic Expected Introduction Concentrations (EIC) and Concentrations in Biosolids
3. Expected Environmental Concentration (EEC)/ Predicted Environmental Concentration (PEC)
4. Basis for L(E)L₅₀/(EIC,ECC) and PEC/PNEC Calculations
5. Sevelamer Carbonate: Alga, Growth Inhibition Test, OECD 201
6. Sevelamer Carbonate: Acute Toxicity to *Daphnia Magna*, OECD 202
7. Sevelamer Carbonate: Determination of Activated Sludge Respiration Inhibition, OECD 209
8. Determination of Acute Toxicity (LC₅₀) of Sevelamer Carbonate to Earthworms (OECD (1984) Guideline 207)
9. Terrestrial Plant Growth Test with Sevelamer Carbonate
10. Soil microorganisms: Nitrogen Transformation Test with Sevelamer Carbonate (OECD Guideline for the Testing of Chemicals, Document 216.

ADEQUATE

Review by: Ruth Ganunis, Ph.D., January 15, 2009
Under contract to:
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Raanan Bloom
1/26/2009 04:07:52 PM
ENV ASSESSMENT

Jon E. Clark
1/27/2009 12:04:36 PM
CHEMIST

PREPARED BY:

Ruth Ganunis, Ph.D.
under contract to
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

and

Raanan A. Bloom, Ph.D.
Senior Environmental Officer
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

CONCURRED BY:

Jon Clark, M.S.
Associate Director for Policy
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

CONCURRED BY:

Moheb Nasr, Ph.D.
Director, Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Attachment:

Non-Confidential Environmental Assessment dated August, 2007
Appended Electronic Signature Page

ENVIRONMENTAL ASSESSMENT

NONCONFIDENTIAL [FREEDOM OF INFORMATION ACT (FOIA)]

(Referenced Confidential Information Has Been Provided Under Separate Cover)

SEVELAMER CARBONATE

AUGUST 2007

**Genzyme Corporation, Inc
500 Kendall Street
Cambridge
MA 02142**

FINDING OF NO SIGNIFICANT IMPACT

NDA 22-318

Sevelamer Carbonate Powder for Suspension for Oral Use

Control of serum phosphorous in patients with chronic kidney disease (CKD) on dialysis

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.

NDA 22-318 requests approval of Sevelamer Carbonate Powder for Suspension for Oral Use for control of serum phosphorous in patients with chronic kidney disease (CKD) on dialysis. In support of its new drug application, Genzyme Corporation Inc. prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts from the use and disposal of this product.

Sevelamer carbonate is a cross-linked polymer. Sevelamer carbonate and its metabolites and conjugates may enter the aquatic environment from patient use and disposal. Sevelamer carbonate may enter the terrestrial environment through the application of biosolids to land. The toxicity of sevelamer carbonate to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to aquatic or terrestrial 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 or clinic procedures. Empty or partially empty containers from home use typically will be disposed by a community's solid waste management system which may include landfills, incineration and recycling. Minimal quantities of the unused drug are expected to be disposed of in the sewer system.

No adverse effects are anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places. The Center for Drug Evaluation and Research has concluded that no adverse environmental effects are expected from the use and disposal of this product. The information provided supports the conclusion that a Finding of No Significant Impact (FONSI) is appropriate.

ENVIRONMENTAL ASSESSMENT**SEVELAMER CARBONATE****SUMMARY**

Genzyme Corporation Inc. is providing an environmental assessment (EA) in support of sevelamer carbonate. Genzyme Corporation Inc., anticipates no adverse effects to environmental organisms as a result of excreted sevelamer carbonate entering publicly owned treatment works (POTW) and subsequent release environments.

Sevelamer carbonate is not categorically excluded from assessment of environmental impact as dictated in the Federal Register. The use of sevelamer carbonate will result in one major pathway to the environment, sewage treatment facilities receiving waste from the general public. Wastes generated from production facilities are regulated by Federal, State and local environmental protection agencies and are not considered in this environmental assessment.

1 DATE

August 24, 2007

2 NAME OF APPLICANT/PETITIONER

Genzyme Corporation, Inc

3 ADDRESS

500 Kendall Street
Cambridge
MA 02142

4 DESCRIPTION OF PROPOSED ACTION**a Requested Approval**

Genzyme Corporation is filing an NDA pursuant to section 505 (b) of the Federal Food, Drug and Cosmetic Act for sevelamer carbonate tablets (800 mg); subsequently, a formulated powder NDA will also be filed. This Environmental Assessment (EA) is being submitted pursuant to 21 CFR § 25, following the Centre for Drug Evaluation and Research (CDER), "Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications," dated July 1998¹.

b Need for Action

Sevelamer carbonate is proposed to be indicated for the control of serum phosphorous in patients with chronic kidney disease (CKD) on dialysis. The proposed method of administration of sevelamer carbonate is by oral ingestion with meals. The duration of use will be lifetime.

c Locations of Use

Sevelamer carbonate will be used in hospitals, clinics and patients' homes throughout the United States.

d Disposal Sites

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

5 IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION**a Nomenclature****i Established Name (U.S. Adopted Name-USAN)**

Sevelamer Carbonate

ii Brand/Proprietary Name

Renvela

iii Chemical Names

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

b Chemical Abstracts Service (CAS) Registration Number

845273-93-0

c Molecular Formula

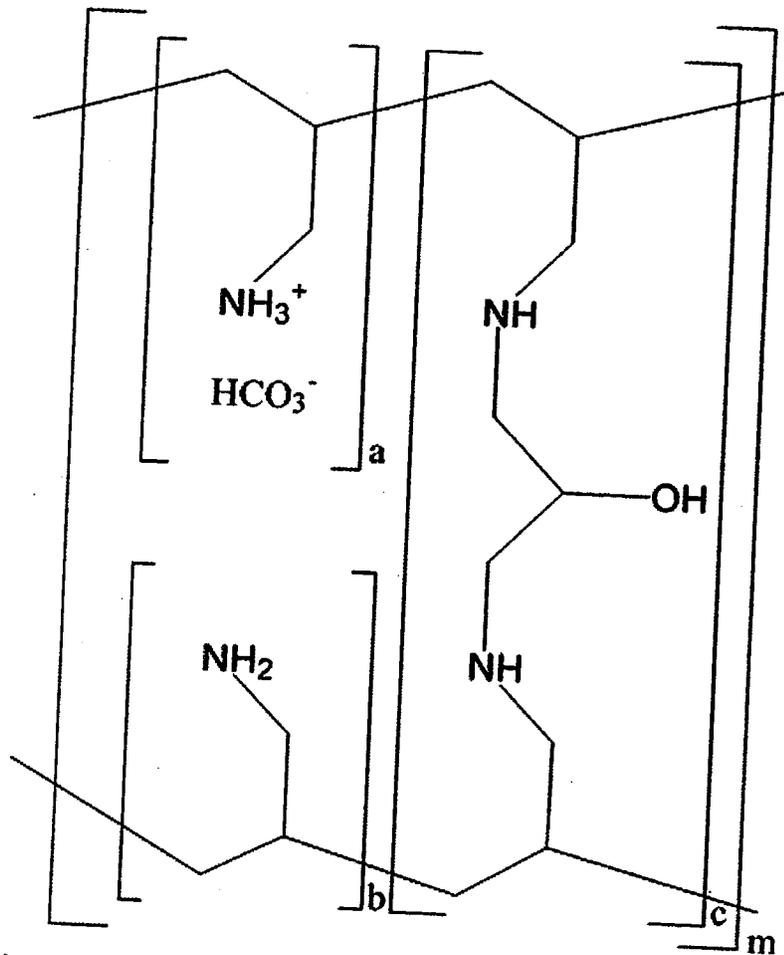
$(C_3H_7N \cdot nH_2CO_3)_{810z}(C_9H_{18}N_2 \cdot nH_2CO_3)_{95z}$ where z equals a large number

d Molecular Weight

As 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 cross-links between polymer chains. Therefore the molecular weight of an individual particle is equal to the weight of the particle itself.

For a 45 μ m particle size, a typical molecular weight would be estimated (ie theoretical) to be in the range of 10^{16} amu.

e Structural (graphic) Formula



Where:

- a,b = number of primary amine groups ($a + b = 9$)
- c = number of cross-linking groups ($c = 1$)
- m = large number to indicate extended polymer network

6 ENVIRONMENTAL ISSUES

Section One – Assessing Toxicity to Environmental Organisms

The primary focus of this EA is the potential fate and effects of sevelamer carbonate in the environment. However section III.A.2. of the CDER EA guidance document¹, requires that the assessment should take account related applications. Related applications include those for other dosage forms using the same active moiety and for products using different forms of the active moiety (e.g. level of hydration, salt, free acid/base). In this instance, two related applications exist for sevelamer hydrochloride. NDA 20-926 includes all drug substance information (including the EA report) and drug product information for 403 mg capsules, which was later removed from the market, and NDA 21-179 which includes all

drug product information pertaining to 400 mg and 800 mg tablets. A Finding Of No Significant Impact (FONSI) for sevelamer hydrochloride was issued May 14, 1998.

Calculations for exposure concentrations will therefore include the highest quantity of both materials produced over the next five years for direct patient use.

The highest usage for both sevelamer carbonate and sevelamer hydrochloride (both separately and when assessed in combination), results in a projected estimated concentration in the aquatic environment exceeding 1 ppb at the point of entry.

a **Environmental Fate of Released Substances**

i **Identification of Substances of Interest**

Sevelamer carbonate and sevelamer hydrochloride are non-absorbed polymers and as such are completely excreted in the faeces (100% of the oral dose).

ii **Physical and Chemical Characterization**

Refer to Data Summary Table (Appendix 1) for an overview of the physical/chemical data for sevelamer carbonate and sevelamer hydrochloride. It should be noted that due to the nature of this material, *ie* extremely large molecular weight and insolubility, deriving all values experimentally was not possible and therefore many of the following values are based on theoretical values, estimated for Category 3 polymers (molecular weight >1,000 Daltons) as described in "Interpretive Guidance Document (IGD) for Assessment of Polymers" produced by the U.S. Environmental Protection Agency (USEPA), June 2006².

- **Water solubility**

Sevelamer carbonate and sevelamer hydrochloride are highly cross-linked polymers that are insoluble in water.

- **Dissociation Constant(s)**

Sevelamer carbonate and sevelamer hydrochloride are polyelectrolytes, as such there is no discrete dissociation constant.

- **Particle Size Distribution**

Sevelamer carbonate 25 – 65 μm (from MSDS)

- **Swellability**

Sevelamer carbonate has a swelling index ≤ 11 (from Certificate of Analysis batch no. 2580012).

- **Octanol/Water Partition Coefficient**

Sevelamer carbonate and sevelamer hydrochloride are not soluble in water or organic solvents, therefore the Log K_{ow} cannot be calculated.

- **Vapour Pressure**

$< 10^{-8}$ mm Hg (estimated from IGD²)

iii **Environmental Depletion Mechanisms**

- **Biodegradation**

The vast majority of polymers are essentially non-biodegradable (IGD²). The results for the ready biodegradation test (OECD 301) conducted with sevelamer

hydrochloride (Appendix 1), showed no net biodegradation over a 28 day period. As the polymer backbones are the same between the two salt forms, the same level of biodegradation is expected for sevelamer carbonate.

- Hydrolysis

Hydrolysis of susceptible groups on polymers is solubility dependent. Polymers with poor water solubility may have reduced susceptibility to hydrolysis (IGD²). It is thought that hydrolysis will not be a rapid depletion mechanism for either sevelamer carbonate or sevelamer hydrochloride.

- Photolysis

No experimental or modelled data are available for photolysis, therefore, using the precautionary principle (*ie* assume the worst case scenario in the absence of empirical data), it is assumed that photolysis will not be a rapid depletion mechanism for either sevelamer carbonate or sevelamer hydrochloride.

- Sewage Sludge Adsorption and POTW removal

The lack of solubility makes calculation of adsorption/desorption coefficients (K_{oc} / K_d) not possible. The IGD document² suggests that cationic, amphoteric and non-ionic polymers will generally adsorb strongly to organic carbon. Sevelamer carbonate and sevelamer hydrochloride are insoluble in water and polymeric, it is theoretical that substances such as this may flocculate with organic material in sewage sludge and therefore become incorporated into the sewage biosolids.

iv Environmental Concentrations

The limited empirical data available on physical and chemical characteristics makes the definitive environmental fate of sevelamer carbonate and sevelamer hydrochloride difficult to confidently predict. This being the case, a pragmatic approach to assessing the fate of the two molecules, is to conduct an environmental assessment based on the precautionary principle, by assessing two "worst case" scenarios. The first scenario assuming the total load of both materials being discharged in to the aquatic environment (*ie* no removal in POTWs) and the second assuming the total load is associated with sewage biosolids and therefore enters the terrestrial environment via application to agricultural land. As the actual environmental exposure will lie between these two extreme scenarios, a finding of no environmental effect in both scenarios will allow a conclusion that no effects are predicted in the "real" intermediate situation.

Aquatic Scenario

(1) Expected Introduction Concentration ($EIC_{aquatic}$):

The $EIC_{aquatic}$ value represents an estimate of the concentration of sevelamer carbonate and sevelamer hydrochloride in wastewater prior to discharge into receiving waters (*ie* rivers). The $EIC_{aquatic}$ is calculated as follows:

$$EIC_{aquatic} \text{ (ppb)} = A \times B \times C \times D$$

Where:

A = kg/year production (Confidential Appendix 1)

B = $1/1.214 \times 10^{11}$ litres/day entering POTW's

C = years/365 days

D = 10^9 $\mu\text{g}/\text{kg}$ (conversion factor)

The EIC_{aquatic} in effluents from POTWs was calculated to be >1 ppb (Confidential Appendix 2). The calculations are based on total projected use of both sevelamer carbonate and sevelamer hydrochloride. Using a conservative approach, no adjustments have been made to account for metabolism, or for degradation in wastewater effluents.

(2) Aquatic Expected Environmental Concentration (EEC_{aquatic}):

The EEC_{aquatic} value represents an estimate of the concentration of sevelamer carbonate and sevelamer hydrochloride in receiving waters (*ie* rivers). The EEC_{aquatic} is also referred to as the Predicted Environmental Concentration for surface water ($PEC_{\text{surface water}}$), a worst case prediction of the concentration likely to be encountered by aquatic wildlife. The $PEC_{\text{surface water}}$ is calculated as follows:

$$PEC_{\text{surface water}} \text{ (ppb)} = EIC_{\text{aquatic}} \times \frac{100 - R}{100 \times DF}$$

Where: % Removal (R) = 0
 Dilution Factor (DF) = 10

The $PEC_{\text{surface water}}$ was calculated to be < 1 ppb (Confidential Appendix 3). The $PEC_{\text{surface water}}$ calculation includes factors accounting for removal processes in POTWs (*ie* biodegradation or removal through adsorption to sludge), and dilution in receiving waters. The $PEC_{\text{surface water}}$ was calculated using 0% removal (as no biodegradation is thought to be likely, and as no experimentally determined sludge sorption coefficient (K_d) is available). A conservative dilution factor of 10 for dilution of wastewater effluents into receiving waters was applied (Confidential Appendix 3).

Terrestrial Scenario

An estimated 55.5% of biosolids were land applied or composed across the United States in 1999³; of the 44.5% of sewage sludge that was not land applied, 22% was incinerated, 14% was land-filled, 7.5% was put to other beneficial uses such as daily landfill covers, and 1% was disposed of by other means.

A conservative estimation of the concentration of combined sevelamer carbonate and sevelamer hydrochloride in biosolids can be calculated from the annual total production volume (kg/year) and an estimate of the national annual production volume of biosolids (kg/year dry weight).

(1) Concentration in Biosolids (adapted from May 2006 FDA/CFSAN guideline ⁴):

$$\text{Concentration in biosolids (ppm)} = A \times B \times C$$

Where: A = kg/year production
 B = $1/6.4 \times 10^9$ kg sewage dry sludge/year³
 C = 10^6 mg/kg (conversion factor)

This value is analogous to an EIC concentration and represents an estimate of the concentration of sevelamer carbonate and sevelamer hydrochloride in biosolids prior to disposal (*ie* to agricultural land).

The above estimation assumes that usage of sevelamer carbonate and sevelamer hydrochloride is evenly distributed across the United States, there is no metabolism in patients, and that there are no environmental removal processes or depletion

mechanisms. An estimate for concentration of sevelamer carbonate and sevelamer hydrochloride in biosolids is presented in Confidential Appendix 2.

(2) Terrestrial Expected Environmental Concentration ($EEC_{\text{terrestrial}}$):

The $EEC_{\text{terrestrial}}$ value represents an estimate of the concentration of sevelamer carbonate and sevelamer hydrochloride in agricultural land after application of biosolids. The $EEC_{\text{terrestrial}}$ is also referred to as the PEC_{soil} , a worst case prediction of the concentration likely to be encountered by soil wildlife.

The application of biosolids to agricultural land is the main disposal route of for biosolids. Application is regulated through "The Standards for the Use or Disposal of Sewage Sludge" (Title 40 of the Code of Federal Regulations [CFR], Part 503). Biosolids must be applied at a rate that is equal to or less than the agronomic rate for nitrogen for the crop to be grown. The total nitrogen content of biosolids varies, as do agronomic rates for a particular crop between States. The USEPA has published (1994) the following typical biosolids agricultural application scenarios ⁵:

Crop	Application Frequency	Application Rate Dry tons/acre
Corn	Annually	5-10
Small grains	Up to 3 times per year	2-5
Soybeans	Annually	5-20
Hay	Up to 3 times per year	2-5

The above table indicates that typically, the highest biosolid application rate applied to agricultural land annually, is 20 tons/acre, which is equivalent to 4.5 kg/m². Biosolids are routinely incorporated ⁶ to a depth of 15 cm in agricultural soils, by ploughing or sub-surface injection, and are therefore diluted by receiving soil.

The PEC_{soil} is calculated using the above parameters as follows (Confidential Appendix 3).

$$PEC_{\text{soil}} \text{ (ppm)} = \frac{\text{Biosolid}_{\text{conc}} \times \text{Application}_{\text{max}}}{\text{RHO}_{\text{soil}} \times \text{Depth}_{\text{field}}}$$

Where:

- $\text{Biosolid}_{\text{conc}}$ = Concentration in biosolids (mg/kg)
- $\text{Application}_{\text{max}}$ = Maximum application rate (4.5 kg/m²)
- RHO_{soil} = Bulk density of dry soil⁶ (1200 kg/m³)
- $\text{Depth}_{\text{field}}$ = Depth of field incorporation (0.15 m)

*One ton is equivalent to 907.18 kg, therefore 20 tons is equivalent to 18,144 kg; one acre is equivalent to 4,047 m². Twenty tons/acre is equivalent to (18,144 kg / 4,047 m²) 4.5 kg/m².

v Summary: Environmental Fate

Following the assumptions above, sevelamer carbonate and sevelamer hydrochloride may enter the aquatic environment through effluents discharged by POTWs and the terrestrial environment by application of biosolids to land. Sevelamer carbonate and sevelamer hydrochloride are not volatile and therefore will not enter the air compartment.

Sevelamer carbonate and sevelamer hydrochloride are not anticipated to be rapidly removed from either the aquatic or terrestrial compartments.

b Environmental Effects of Released Substances

Refer to Data Summary Table (Appendix 1) for an overview of the ecotoxicological data for sevelamer carbonate and sevelamer hydrochloride.

It should be noted that some of the following sections refer to “loading rates” of material in the aqueous environment, this is because neither compound forms a true solution and therefore loading rate best describes the testing situation, and additionally, is most relevant to the environmental situation.

i Microbial Inhibition Testing

Activated Sludge Respiration Inhibition Test (ASRIT) results are available for both sevelamer carbonate and sevelamer hydrochloride. The median effective loading rate, resulting in a 50% inhibition of respiration (EL_{r50}) was >1000 mg/L for sevelamer carbonate and >2000 mg/L for sevelamer hydrochloride, these loading rates being the highest tested in each respective test. These values are >100,000 times higher than the EIC_{aquatic} predicted for sevelamer carbonate and sevelamer hydrochloride in POTWs. Based on these data, sevelamer carbonate and sevelamer hydrochloride, assessed individually or combined have no significant potential to inhibit microorganisms and therefore would not disrupt wastewater treatment processes. Refer to Appendix 1 & Confidential Appendix 7.

ii Aquatic Ecotoxicity Testing

Testing followed the approach described in the EA Guidance for Industry Document ¹.

Using the conservative approach, the acute toxicity of sevelamer carbonate and sevelamer hydrochloride was determined using 3 species from different taxonomic classes and with different functions within the aquatic ecosystem.

In total, data from five acute ecotoxicity studies are available, three for all species for sevelamer hydrochloride and two additional bridging studies for sevelamer carbonate with non-vertebrate species (to avoid potentially unnecessary vertebrate testing). Refer to Appendix 1 & Confidential Appendices 5 and 6.

Aquatic Ecotoxicity Results:

Decision criteria: Median lethal (effective) loading rate [L(E)L_{r50}] / EIC_{aquatic} < 100

Species	L(E)L _{r50}	
	Sevelamer carbonate	Sevelamer hydrochloride
<i>Daphnia magna</i>	>1000 mg/L	>1000 mg/L
Rainbow trout	(read across)	82 mg/L
Green alga	63 mg/L	25 mg/L

The lowest L(E)L_{r50} / EIC_{aquatic} ratio is for green alga, and is >100 (Confidential Appendix 4) indicating no further testing is required.

It should be noted that the studies conducted for sevelamer hydrochloride used test solutions that were prepared by direct addition to the test water, after which the test organisms were added. The tests with sevelamer carbonate were conducted as sevelamer hydrochloride, with the exception that solutions were filtered prior to

exposure of the test organisms, so that only the water soluble portion of the test item (water accommodated fraction) was assessed. The method used with sevelamer hydrochloride was an acceptable method at the time of testing, however subsequent OECD guidance (Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, 2000⁷), suggests that non-dissolved material should be removed from test vessels prior to addition of the test organism, so that physical effects such as smothering and irritation are not misinterpreted as direct toxicity mechanisms attributed to the test material.

iii Aquatic Predicted No Effect Concentration (PNEC)

The PNEC was calculated by applying an assessment factor (AF) to the ecotoxicology data:

$$\text{PNEC} = (\text{NOEC} / \text{NOELr} \text{ or } \text{L(E)}\text{L}_{r50} / \text{EC}_{50}) / \text{AF}$$

The assessment factor represents the degree of uncertainty in extrapolating test data on a limited number of species, to the natural environment. In general, the greater number of species tested, the longer the study duration (chronic) and the inclusion of sub-lethal end-points, the smaller the degree of uncertainty and the size of the assessment factor.

The PNEC for algae (the most sensitive species, based on a NOELr of 6 mg/L; see Appendix 1) for sevelamer carbonate and sevelamer hydrochloride was calculated using the standard tier 2 assessment factor of 100. The PNEC for sevelamer carbonate / sevelamer hydrochloride is therefore 60 µg/L.

It should be noted that standard aquatic test media has a low total organic content (TOC), which may result in artificially high toxicity of polycationic and amphoteric polymers in those media. Surface waters tend to have higher total organic content and dissolved organic content (DOC). It has been shown that DOC, particularly humic and other acidic compounds, reduces the toxicity of cationic and amphoteric polymers to the aquatic environment².

Additionally, since both sevelamer carbonate and sevelamer hydrochloride are phosphate binding polymers (this bringing about the therapeutic effect in patients), it is possible that toxicity to algae is associated with the chelation of phosphate ions by the polymers, thereby reducing the concentration of this essential mineral in the test medium and reducing growth (*ie* indirect toxicity). In reality, these chelation sites will be filled either by the passage through the patient or in the phosphate rich environment of the POTWs, and will essentially be in an inactive form when discharged into the environment.

iv Aquatic Risk Quotient (RQ)

The risk quotient is a simple method to communicate potential risks to the environment from substances. The risk quotient is derived by dividing the PEC (EEC) by the PNEC to obtain the PEC:PNEC ratio. The PEC is used instead of an EIC, as the PEC is a more realistic estimate of exposure. If this ratio is less than one, the risk is considered acceptable, conversely, if this ratio is greater than one, potential risks cannot be ruled out from the use of the substance. The RQ_{aquatic} for sevelamer carbonate / sevelamer hydrochloride has been calculated in Confidential Appendix 4 and is less than one, indicating negligible/acceptable risk.

v Toxicity to Soil Organisms

The acute toxicity of sevelamer carbonate was determined using 3 test systems, representing different functional groups within the soil ecosystem. Tests were conducted with three plant species, earthworms and soil microbes. The tests were conducted at a maximum soil concentration of 1000 mg/kg sevelamer carbonate. In all of the tests, no adverse or detrimental effects were noted. For the results of the studies, please refer to Appendix 1 & Confidential Appendices 8-10. Test concentrations in soil are expressed as concentration of sevelamer carbonate in terms of mg/kg (soil dry weight).

Terrestrial Ecotoxicity Results:

Group / Species	L(E)C ₅₀	
	Sevelamer carbonate	Sevelamer hydrochloride
Terrestrial Plants (wheat, mung bean, radish)	>1000 mg/L	(read across)
Earthworm (<i>Eisenia foetida foetida</i>)	>1000 mg/L	(read across)
Soil Micro-organisms (nitrogen transformation)	>1000 mg/L	(read across)

Note: As no effects were noted, the L(E)C₅₀ cannot be estimated further than stating that it is higher than the maximum value tested.

vi Terrestrial Predicted No Effect Concentration (PNEC)

The PNEC was calculated by applying an assessment factor (AF) to the terrestrial ecotoxicology data obtained.

$$\text{PNEC} = (\text{NOEC or L(E)C}_{50}) / \text{AF}$$

The PNEC for terrestrial soil organisms for sevelamer carbonate was calculated using the standard tier 2 assessment factor of 100. The PNEC for sevelamer carbonate / sevelamer hydrochloride is therefore 10 mg/kg.

vii Terrestrial Risk Quotient (RQ)

The RQ_{terrestrial} for sevelamer carbonate / sevelamer hydrochloride has been calculated in Confidential Appendix 4 and is less than one, indicating negligible/acceptable risk.

viii Summary: Environmental Effects

Upon approval of the subject NDA, introduction of sevelamer carbonate, (in addition to previously approved sevelamer hydrochloride), into the environment through use and disposal by consumers is projected to result in an insignificant amount of sevelamer in the environment.

Based on RQ_{aquatic} and RQ_{terrestrial} values both being less than one, it is unlikely that sevelamer in either form, represents a risk to the aquatic or terrestrial environment.

Though degradation of sevelamer in the environment has not been demonstrated, it is likely that sevelamer will biodegrade at least slowly over time. This being the case, there exists the possibility that sevelamer could accumulate, particularly in agricultural land. However, assuming no degradation in soil and an annual application rate of 20 tons/acre, it would take in excess of 600 years (with current

estimates) to reach a level of 1000 mg/kg, a level which has been shown to be non-toxic in all the studies conducted for this assessment. It is quite possible that as a result of soil microbial adaptation to sevelamer, accumulation will be reduced to levels well below the above safe value.

Section Two – Use of Fauna or Flora

The subject application does not include the use of fauna or flora.

7 MITIGATION MEASURES

No adverse effects have been identified for this proposed action. No mitigation measures to the proposed action are required.

8 ALTERNATIVES TO THE PROPOSED ACTION

No potential effects have been identified for this proposed action. No alternatives to the proposed action are required.

9 **LIST OF PREPARERS**

Peter McDonnell, PhD, Senior Technical Director, Technical Department, Genzyme
Twenty-one years experience in chemical development within the pharmaceutical industry.

Thomas L. Hargreaves, Environmental Scientist, Charles River Laboratories.
BSc Environmental Toxicology. Member of SETAC (Society of Environmental Toxicology
and Chemistry), 10 years experience in environmental health and safety
testing/assessment.

10 REFERENCES

- 1 "Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications," U.S. Food and Drug Administration (FDA); Centre for Drug Evaluation and Research (CDER), July 1998; CMC 6; Revision 1
- 2 "Interpretive Guidance Document for Assessment of Polymers" U.S. Environmental Protection Agency (USEPA), June 2006
(<http://www.epa.gov/oppt/newchemicals/pubs/sustainable/polymer-igd-0606.pdf>)
- 3 "Biosolids Generation, Use and Disposal in the United States" EPA 530-R99-009, U.S. Environmental Protection Agency (USEPA), September 1999
- 4 "Guidance for Industry Preparing a Claim of categorical Exclusion or an Environmental Assessment Submission to the Centre for Food Safety and Applied Nutrition; Final Guidance", U.S. Food and Drug Administration (FDA); Centre for Food Safety and Applied Nutrition (CFSAN) May 2006
- 5 "Biosolids Recycling: Beneficial Technologies for a Better Environment" EPA 832-R-94-009. U.S. Environmental Protection Agency (USEPA), Washington, D. C. 1994
- 6 Harrass, M. C., Eirkson C. E., Nowel L. (1990) "Role of Plant Bioassays in FDA Review: Scenarios for Terrestrial Exposure" Second Symposium on Use of Plants for Toxicity Assessments; Sponsored by the American Society for Testing and Materials, Committee E47 on Biological Effects and Environmental Fate and Subcommittee E47.11 on Plant Toxicity; April 23-24, 1990, San Francisco California
- 7 "OECD Series on Testing and Assessment Number 23; Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures" ENV/JM/MONO(2000)6, Organisation For Economic Co-Operation And Development (OECD), September 2000, Paris

11 APPENDICIES

Non-confidential

1. Data Summary Table
2. Abbreviations

Confidential

1. Projected Total Usage of Sevelamer Carbonate and Sevelamer Hydrochloride in the United States

EIC/PEC/PNEC

2. Basis for Aquatic Expected Introduction Concentration (EIC) and Concentrations in Biosolids
3. Expected Environmental Concentration (EEC) / Predicted Environmental Concentration (PEC)
4. Basis for L(E)L₅₀/(EIC,ECC) and PEC/PNEC Calculations

Environmental Effect Studies

5. Sevelamer Carbonate: Alga, Growth Inhibition Test, OECD 201
6. Sevelamer Carbonate: Acute Toxicity to *Daphnia Magna*, OECD 202
7. Sevelamer Carbonate: Determination of Activated Sludge Respiration Inhibition, OECD 209
8. Determination of Acute Toxicity (LC₅₀) of Sevelamer Carbonate to Earthworms (OECD (1984) Guideline 207)
9. Terrestrial Plant Growth Test with Sevelamer Carbonate
10. Soil Microorganisms: Nitrogen Transformation Test with Sevelamer Carbonate (OECD Guideline for the Testing of Chemicals, Document 216)

CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of Genzyme Corporation, Inc's knowledge.

Name:

Dr Peter McDonnell

Title:

Senior Technical Director

Department:

Technical Department
Genzyme

Signature: *Peter McDonnell* Date: 24th Aug 2007

NON-CONFIDENTIAL APPENDICIES

Appendix 1: Data Summary Table

Physical/Chemical Characterization		
	Sevelamer carbonate	Sevelamer hydrochloride*
Water solubility	insoluble	Insoluble
Dissociation Constant (pKa)	N/A	N/A
Octanol /Water Partition Coefficient	N/D	N/D
Vapour Pressure (estimate)	<10 ⁻⁸ mm Hg	<10 ⁻⁸ mm Hg
Depletion Mechanisms		
	Sevelamer carbonate	Sevelamer hydrochloride*
Sorption Coefficient (K _d)	N/D	N/D
Hydrolysis	N/D	N/D
Aerobic biodegradation	Read Across	Not Readily Biodegradable
Soil Biodegradation	N/D	N/D
Photolysis	N/D	N/D
Metabolism	N/D	N/D
Environmental Effects: Aquatic		
	Sevelamer carbonate	Sevelamer hydrochloride*
Activated sludge respiration inhibition test	LR ₅₀ > 1000 mg/L	LR ₅₀ > 2000 mg/L
<i>Daphnia magna</i> 48 hour	LR ₅₀ > 1000 mg/L	LR ₅₀ > 1000 mg/L
	NOELr = 450 mg/L	NOELr = 62.5 mg/L
Rainbow trout 96 hour	Read Across	LR ₅₀ = 82 mg/L
		NOELr = 15.6 mg/L
Green alga 72-h	LR ₅₀ = 63 mg/L	LR ₅₀ = 25 mg/L
	NOELr = 18.0 mg/L	NOELr = 6.0 mg/L

N/A: Not Applicable

N/D: Not Determinable

*: Sevelamer hydrochloride data publicly available, source NDA No. 20-926, RenaGel®, FONSI issued May 14, 1998

Appendix 1 (continued): Data Summary Table

Environmental Effects: Terrestrial		
	Sevelamer carbonate	Sevelamer hydrochloride*
Higher Plants (wheat, mung bean, radish)	L(E)C ₅₀ > 1000 mg/L	Read across
Earthworm <i>Eisenia foetida foetida</i>	LC ₅₀ > 1000 mg/L	Read across
Soil microbes: nitrogen transformation	EC ₅₀ > 1000 mg/L	Read across

223 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jon E. Clark
1/27/2009 12:03:56 PM

Moheb Nasr
2/3/2009 10:00:59 AM