CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-127

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 22-127	Submission Date(s): 12/20/2006 and 03/02/2007
Brand Name (proposed)	Renvela
Generic Name	Sevelamer Carbonate
Reviewer	Robert O. Kumi, Ph.D.
Team Leader	Patrick Marroum, Ph.D.
DCP	1
OND	Cardiovascular and Renal Drug Products
Applicant	Genzyme
Formulation; Strength(s)	Tablet, 800 mg
Class/Indication	Phosphate Binder

Table of Contents

1.0 EXECUTIVE SUMMARY 3

1.1 Recommendation 3
1.2 Phase 4 Study Commitments: None. 3
1.3 Summary of Clinical Pharmacology/Biopharmaceutics Findings 3

2.0 QUESTION BASED REVIEW 4

2.1. General attributes of sevelamer product 4
2.2. General clinical pharmacology 6
2.3. Intrinsic Factors 8
2.4. Extrinsic Factors 8
2.5. General Biopharmaceutics 8
2.6 Analytical section 11

3 LABELING 12

4 APPENDICES 13

4.1 Package insert (proposed and annotated) 14
4.2 Clinical pharmacology and biopharmaceutics individual study review 29
4.3 Consult reviews 45
4.4 Cover sheet and OCPB filing/review form 45

1.0 EXECUTIVE SUMMARY

Genzyme submitted NDA 22-127, Renvela (proposed tradename), sevelamer carbonate on December 20, 2006. The applicant developed sevelamer carbonate as a pharmaceutical alternative to the currently approved salt, sevelamer hydrochloride (Renagel® NDA 20-926 and 21-179), which is indicated for the control of serum phosphorus in patients with chronic kidney disease (CKD) on hemodialysis. Renvela is a phosphate binder which is proposed for the same indication as that for the approved product, Renagel.

The sevelamer carbonate clinical development program consists of in vitro phosphate binding studies and an in vivo study, GD3-163-201. The in vivo study was conducted to bridge the existing clinical data for the hydrochloride salt of sevelamer to the carbonate salt in the target population. Sevelamer carbonate was studied in approximately 70 adult CKD patients on hemodialysis. This clinical pharmacology review is focused on the in vitro phosphate binding studies.

1.1 Recommendation

The Office of Clinical Pharmacology finds the clinical pharmacology and biopharmaceutics information submitted to NDA 22-127 acceptable. However, the following additional information is needed to provide supportive in vitro evidence of the comparability of sevelamer carbonate to sevelamer hydrochloride:

- Study equilibrium phosphate binding under physiologically relevant conditions, such as over the entire pH range likely to be encountered in gut
- Study kinetics of phosphate binding under physiologically relevant conditions, such as over the entire pH range likely to be encountered in gut
- Definitively determine which critical factors influence phosphate binding, such as varying ionic strength and disintegration time

The outlined studies may be conducted post-marketing assuming the product is approved based on the information provided in the current NDA submission. It should be noted that the proposed commercial formulation's phosphate binding characteristics (k1 and k2 values) differed from that of the formulations used in the pivotal clinical study. Thus assessment of the outlined studies prior to approval or shortly thereafter is strongly recommended.

1.2 Phase 4 Study Commitments: None.

1.3 Summary of Clinical Pharmacology/Biopharmaceutics Findings

- Sevelamer carbonate tablets have comparable (similar magnitude) phosphate binding as sevelamer hydrochloride (HCl) tablets with acid pre-treatment; without acid pretreatment the affinity constant of the HCl is twice as high as that of the carbonate
- Sevelamer carbonate and sevelamer HCl bind phosphate in a similarly rapid manner, although binding to the HCl is more rapid initially and higher overall than the carbonate, especially under low initial phosphate concentrations (2.5 mM)

2.0 QUESTION BASED REVIEW

This clinical pharmacology and biopharmaceutics review employs an abridged version of QBR since critical QBR elements have been previously addressed in NDA 21-179. In essence, NDA 22-127 represents a formulation change, with respect to a salt form (hydrochloride to carbonate). Please refer to NDA 21-179 for information on human pharmacokinetics and bioavailability, clinical pharmacology and biopharmaceutics. QBR sections relevant for NDA 22-127 follow.

2.1. General attributes of sevelamer product

Regulatory Background/Marketing History of Sevelamer Hydrochloride

Sevelamer hydrochloride was approved in the US on October 30, 1998 for capsules (NDA 20-926) and July 12, 2000 for tablets (NDA 21-179). Sevelamer hydrochloride (HCl) is indicated for the control of serum phosphorus in patients with CKD on hemodialysis. One should note that the HCl tablets were approved solely based on phosphate binding information.

What is the main basis for developing a sevelamer carbonate formulation?

Sevelamer carbonate is an oral anion exchange resin with the same polymeric structure as sevelamer HCl in which carbonate replaces chloride as the counterion. Consequently, these two sevelamer salts have the same active moiety, sevelamer, and are expected to perform similarly with respect to phosphate binding ability. The main anticipated benefit of the carbonate salt ($HCO3^-$) over the HCl salts is a reduction in the frequency of monitoring for serum chloride and carbonate. The Renagel label has a precaution related to this acid-base balance in patients. In sum, the sevelamer carbonate development program was designed to demonstrate that the phosphate binding properties of sevelamer carbonate and sevelamer HCl are equivalent.

Reviewer's Comment/Note

The similar anticipated phosphate binding is based on the expectancy that both salt forms will yield a comparable number of binding sites (similar degree of ionization).

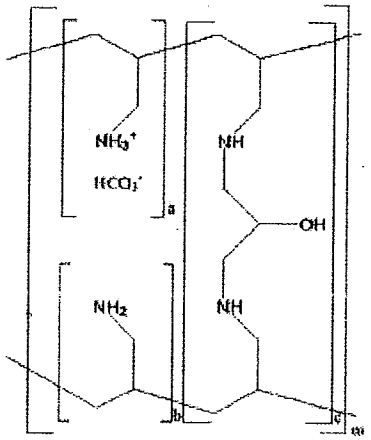
2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation?

The applicant has proposed the marketing of sevelamer carbonate tablets. Sevelamer carbonate is known chemically as poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane), carbonate salt. The physical-chemical properties of sevelamer carbonate are expected to be the same as that for the HCl (see NDA 21-179). These characteristics are briefly described in a generic manner as follows.

Sevelamer with the accompanying salt is a non-absorbed, cross-linked polymer that is formulated in a tablet form. The drug substance is compressed and coated as a tablet for oral dosing. Sevelamer exists as a hydrogel that can absorb about 20- times its weight in water, but is insoluble. Sevelamer contains multiple amine groups separated by one carbon from the polymer backbone (see Figure 1).

Figure 1:

Structure of Sevelamer Carbonate



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

Reviewer Note on 'carbonate' Naming Convention

In this reviewer's view the adopted naming convention, carbonate, is inappropriate. Typically, the HCO_3^{-1} ion is referred to as bicarbonate, rather than carbonate; clarification will be sought from the Chemistry Reviewer. This review will use the term 'carbonate' for clarity and consistency.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s) of sevelamer carbonate?

Proposed Mechanism of Action

Sevelamer carbonate is a phosphate binder; phosphate sequestered by the polymer is not absorbed into the blood, but passes through the intestine and is excreted in the feces. The sequence of events is as follows:

1. Upon ingestion, the tablets undergo rapid disintegration.
2. The counterion of the polymer, carbonate, disassociates in the low pH environment of the gastrointestinal tract leading to protonation of the amines associated with the polymer
3. the positively charged amine groups bind negatively charged ions in the intestine, such as phosphate that are liberated during the digestive process.

According to the applicant the interaction between sevelamer and phosphate occurs primarily in the small intestine.

Proposed Indication

Hyperphosphatemia, defined as a serum phosphorus level > 5.5 mg/dL or 1.8 mmol/L, is common in patients with CKD on dialysis; sevelamer carbonate will be used to control serum phosphorus in these patients.

2.1.3. What is the proposed dosage and route of administration?

A 800 mg tablet containing sevelamer carbonate has been proposed for oral administration. The drug will be initiated at a dosage of one to two 800 mg tablets three times per day with meals. Subsequently, the dosage will be adjusted by one tablet per meal in two-week intervals, as needed, to obtain target serum phosphorus levels.

2.2. General clinical pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

One clinical study was conducted: A double blind, randomised cross over study comparing sevelamer carbonate and sevelamer HCl in adult haemodialysis patients.

Selected Design Features

Some study design features for Study 306743 or GD3-163-201 are tabulated below.

Title	GD3-163-201/Protocol 306743/Report A29431
General Study Design	multicenter, double-blind, randomized, cross-over
Doses and Treatment Groups	Dose titrated to effect
Objectives	1. compare effects of sevelamer salts on serum phosphorus in CKD patients on hemodialysis 2. compare safety of salts in target population 3. compare effects of salts on serum lipid profiles
Treatment duration (period)	8 weeks per salt Two-week washout period
Formulations	Test: Sevelamer Carbonate, 800 mg tablets, Lot numbers 21068 and 21069 Reference: Renagel, 800 mg tablets, Lot number 20769
Number of subjects randomized (completed both treatments)	N = 79 (69)
Endpoint	Serum phosphorus levels at the end of each treatment period
Selected Inclusion Criteria	• men or women 18 years of age or older • serum phosphorus measurements ≥ 3.0 and ≤ 6.5 mg/dL within sixty days of screening • iPTH ≤ 600 pg/mL

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

The primary response endpoint (variable) was change in serum phosphorus level. This marker is well established as a marker of hyperphosphatemia and was accepted by the clinical division, Division of Cardiovascular and Renal Products.

2.2.3 Exposure-response

Exposure-response was not specifically evaluated in this NDA.

2.2.3.1 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose and dosing regimen selected by the sponsor appears reasonable based on the observed clinical information. Administration of sevelamer carbonate led to maintenance or a reduction of serum phosphorus levels.

Evidence of Effectiveness (Comparison of Sevelamer Salts), Per Sponsor

The mean serum phosphorus was 4.6 ± 0.9 mg/dL during sevelamer carbonate treatment and 4.7 ± 0.9 mg/dL during sevelamer HCl treatment. The geometric least square mean ratio (sevelamer carbonate/sevelamer HCl) was 0.99 with a corresponding 90% confidence interval of 0.95- 1.03. The confidence interval is within the interval of 0.80-1.25, suggesting that sevelamer carbonate and sevelamer HCl are equivalent in controlling serum phosphorus (PD variable).

Evidence of Effectiveness (Drug withdrawal period/washout)

A two-week washout period was included following the active treatment period to confirm that the patients enrolled in this trial were hyperphosphatemic. At the end of the randomized treatment periods the serum phosphorus was 5.0 ± 1.3 mg/dL in all patients participating in the washout. Following the two-week washout period, the serum phosphorus level increased significantly (1.5 ± 1.9 mg/dL; $p<0.001$). This increase in serum phosphorus during the washout period was seen regardless of the salt form of sevelamer prescribed immediately preceding the washout. In patients treated with sevelamer carbonate prior to washout, serum phosphorus increased 1.3 ± 2.2 mg/dL ($p=0.022$) and in patients treated with sevelamer HCl immediately preceding the washout, serum phosphorus increased 1.7 ± 1.5 mg/dL ($p<0.001$).

Reviewer Note on Effectiveness (in vivo) vs. In vitro binding

In this reviewer's opinion, the effectiveness information suggests that the sevelamer carbonate formulation demonstrates efficacy in controlling serum phosphorus. However, this reviewer (Office of Clinical Pharmacology) will defer to the Clinical Division's conclusions in the evaluation of the efficacy information. The effectiveness (in vivo) information takes precedence over the in vitro information, thus all carbonate formulations (Lots 20769, 21068 and 21069) used in the clinical trial are considered comparable to HCl formulation.

Dose Selection

The dose proposed is consistent with the dosing applied in the clinical trial. It is noted that sevelamer carbonate will be titrated to effect.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

No specific exposure-response relationship was evaluated. However, the applicant reports that in Study GD3-163-201, the safety profiles of sevelamer carbonate and HCl were similar. The proportion of patients with adverse events was comparable in both treatment groups (~ 80 %). The most common AEs were GI-related.

2.3. Intrinsic Factors

Intrinsic factors were not specifically evaluated as part of NDA 22-127.

2.4. Extrinsic Factors

Extrinsic factors were not specifically evaluated as part of NDA 22-127

2.5. General Biopharmaceutics

2.5.1 What information is known about the formulation?

Please refer to Section 2.1.1.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the formulation used in the pivotal clinical trial?

A relative bioavailability (BA) assessment was not required since the to-be-marketed formulation is identical to the formulation used in the pivotal clinical trials. Furthermore sevelamer is minimally absorbed systemically, thus, if needed, relative BA would have to be assessed by an alternative approach (e.g. PD measures).

2.5.3 What basis does the Applicant have for using in vitro binding studies in conjunction with an in vivo study to request approval of sevelamer carbonate?

The applicant postulates that the clinical efficacy of sevelamer, evidenced by the control of serum phosphorus in patients with CKD on dialysis, is dependent upon the phosphate binding capabilities of sevelamer. As both sevelamer carbonate and sevelamer HCl are non-absorbed polymers, standard pharmacokinetic, dissolution, or bioavailability studies will not be suitable to demonstrate the equivalency of the sevelamer salt forms. Consequently, the applicant decided to evaluate the equivalency/comparability of the two salt forms using in vitro methods: equilibrium and kinetic binding studies. This approach is consistent with FDA's 1993 Interim Guidance entitled, "Cholestyramine Powder In Vitro Bioequivalence". Cholestyramine is a non-absorbed polymer as is sevelamer.

The equilibrium studies were conducted to potentially demonstrate a similar affinity and capacity of both salts, whereas, the kinetic experiments of phosphate binding potentially show that phosphate is bound by sevelamer carbonate and sevelamer HCl in a similarly rapid manner, independent of initial phosphate concentration. The in vitro evaluations were conducted under some physiologically relevant conditions, including acid pretreatment (pH < 1), without acid (pH = 7) and varying concentrations of phosphate that are representative of phosphate concentrations encountered in GI tract.

2.5.4 How do the in vitro phosphate binding conditions and specifications ensure in vivo performance and quality of the product?

The in vitro phosphate binding conditions and specifications are useful in ensuring quality of the product but their value in ensuring in vivo performance is unclear. The limitations with respect to in vivo performance are two-fold:

- absence of an assessment of in vitro- in vivo relationships
- some pertinent physiologically relevant conditions were not evaluated in the study

It should be noted that sevelamer is titrated, thus minor variations in the in vitro binding characteristics may not profoundly affect in vivo performance.

Phosphate binding data were generated from the following sevelamer lots (Table 1):

Table 1: Sevelamer Formulations Used in Phosphate Binding Evaluations2

Sample ID	Status (date)	Report Number1 (Date)
Sevelamer HCl 800 mg Tablets (I) Lot No. 7351	Commercial	TR-1906-04-SC/ n = 2
Sevelamer HCl 800 mg Tablets Lot No. 20769	• Clinical • Commercial	TR-2119-06-SC (26 Jun 2006)/ n = 6
Sevelamer Carbonate 800 mg Tablets Bulk (I) Lot/Pkg Lot No. 19442/21068	Clinical*	TR-1906-04-SC (27 Dec 2004) / n = 2
Sevelamer Carbonate 800 mg Tablets Bulk (I) Lot/Pkg Lot No. 19443/21069)	Clinical (2004)*	TR-1906-04-SC (27 Dec 2004) / n = 2
Sevelamer Carbonate 800 mg Tablets Bulk Lot/Pkg Lot No. 19443/21069	Clinical (2005)*	TR-2119-06-SC (26 Jun 2006)/ n = 6
Sevelamer Carbonate 800 mg Tablets Lot No. 44247	Registration	TR-2383-06-SC (20 Jul 2006)/ n = 6

* same as registration lot, without branding I – ionic composition was equalized (carbonate = chloride)
(date) – year in which data were analyzed

Sevelamer carbonate is the test formulation and sevelamer HCl is the 'reference' formulation. Binding was evaluated under acidic and neutral (no acid) conditions (see Table below).

	Nonlinear Method		Linear Method				
Condition	K1	K2	K1'	K2'	Intercept	Slope	R^2
	Carbonate Salt						
ACID	0.483 – 0.687	6.52 – 7.37	0.470 – 0.737	6.51 – 7.38	0.208 – 0.288	0.136 – 0.154	≥ 0.999
NO ACID	0.277 – 0.394	5.98 – 6.73	0.262 – 0.374	5.97 – 6.75	0.447 – 0.565	0.148 – 0.168	≥ 0.998
	Hydrochloride Salt						
ACID	0.631 – 0.777	6.22 – 6.67	0.628 / 0.820	6.23 – 6.66	0.196 – 0.239	0.150 / 0.161	≥ 0.999
NO ACID	0.821 / 0.875	5.85 / 6.23	0.849 / 0.863	5.89 / 6.15	0.192/ 0.197	0.163 / 0.170	≥ 0.999

Overall, the phosphate binding data suggest that the phosphate binding capacity (k2) and affinity (k1) are comparable for the two salts. Two major observations from the data are:

- Calculation Method: nonlinear method and linear method yield similar k1 and k2 estimations
- Overall the HCl salt appears to have a higher binding affinity, based on k1 values, than the carbonate formulation. Differences in phosphate binding affinity between the two salts, are most pronounced under non-acidic conditions

The latter finding appears to be due to the lack of complete ionization of the carbonate form at pH = 7. Additionally, the applicant demonstrated a dependence of k1 values on carbonate concentrations that may be related to ionic strength. It is noted that k2 did not depend on the bicarbonate concentration. These relationships are depicted in the following figures provided by the applicant (Ref: TR-1984-030SC: Drug Discovery and Development Memo on Impact of Carbonate on phosphate binding isotherms Renagel 800 mg tablets by IC at pH 7 with BES; enumerated as Graphs 2 and 3).

Figure 2: Variation of k1 with $NaHCO_3$ concentration

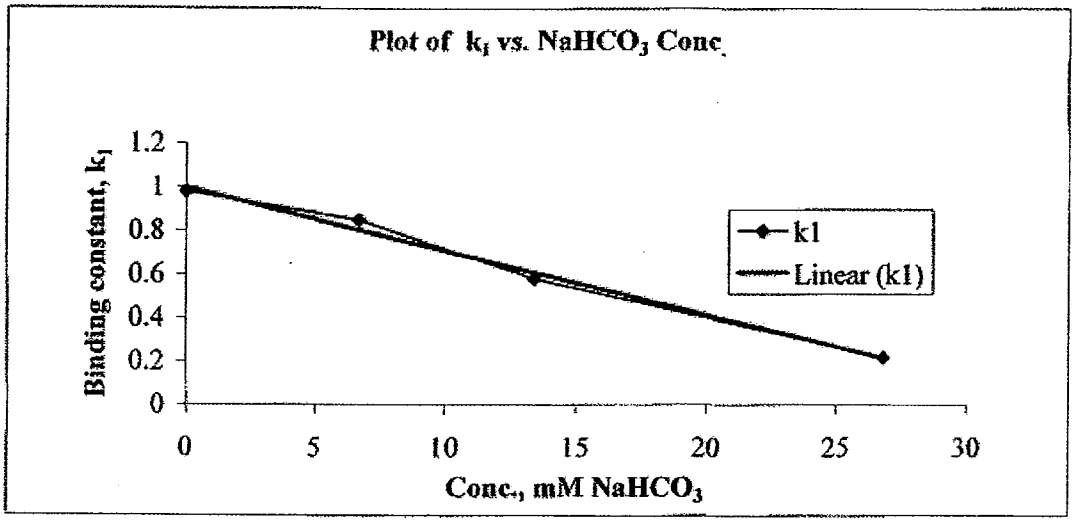
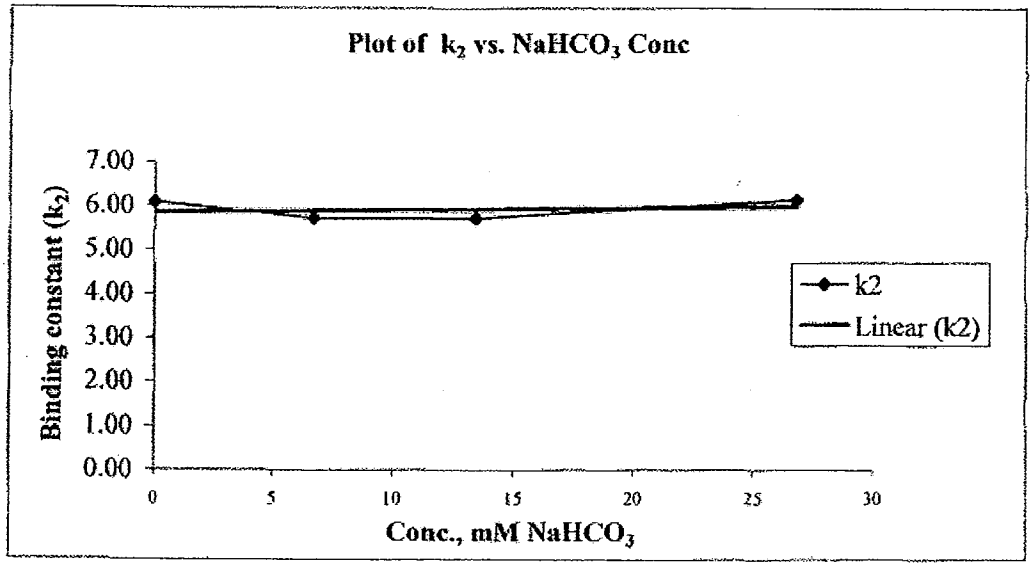


Figure 3: Variation of k2 with $NaHCO_3$ concentration



Potential Limitations of Binding Experiments

The binding experiments did not establish the pH binding profile of sevelamer; it is likely that different results will be obtained at different pHs. However, the studies conducted provide some information on the pH-binding profile: the evaluated pHs approximately bracket pHs typically encountered in the GI during transit and binding in the GI. The experiment with acid yields a pH $\leq$ 1 and the experiment without acid is at pH 7. The

capacity constant, k2, was fairly constant at the two extremes of pH, suggesting that saturation of binding does not occur at the two studied pHs.

2.5.5 Composition of Sevelamer Carbonate Tablets (Renvela)

The composition of 800 mg Renvela tablets is in the table below.

Sevelamer Carbonate 800 mg Tablet Composition

Component	Reference to Quality Standard	Function	Composition per 800 mg Drug Substance as Label Claim (%)	Composition per Unit Dose (mg)	Composition per Total Core Weight (%)
Active Substance					

2.6 Analytical section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

NDA 21-127 did not require analytical information for the measurement of the active moieties. However, NDA 22-127 employed similar analytical methods as those for NDA 21-179 with respect to measurements required for the assessment of phosphate binding. Please refer to NDA 21-179 for details on analytical methods.

3 LABELING

Reviewer's labeling recommendations.

The applicant's proposed labeling appears acceptable. It is noted that if approved, the sevelamer carbonate label will be similar to that of Renagel. The applicant requested that sevelamer carbonate labeling be addressed concurrently with sevelamer HCl labeling.

4 APPENDICES

Appears This Way
On Original

4.1 Package insert (proposed and annotated).

Appears This Way
On Original

14 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

4.2 Clinical pharmacology and biopharmaceutics individual study review

Appears This Way
On Original

4.2.1 Equilibrium Binding Studies

Method

Reviewer Note on Method

Generally, the equilibrium binding studies employed the approaches recommended in the Cholestyramine Guidance; however, some modifications (see Table below) were made to account for the higher dosage strength of the sevelamer polymer vs. cholestyramine resin. In addition, the media used to evaluate equilibrium phosphate binding (without acid pretreatment) of sevelamer hydrochloride salt Lot 7531 and sevelamer carbonate Lots 21068 and 21069 (analyzed in 2004) had equalized concentrations of carbonate and chloride. This media was used for the stated lots to minimize the impact of different ionic strength.

Comparison of Cholestyramine Guidance and Sevelamer Carbonate Binding Conditions

Interim Guidance Cholestyramine powder *In Vitro* bioequivalence conditions 10 mg of polymer and 10 mL of bile acid solution		**Phosphate binding conditions** 800 mg of polymer and 300 mL of phosphate solution	
Experiment #	Initial concentration, mM	Initial concentration, mM	Phosphate to polymer ratio: mmol of phosphate per gram of polymer
1	0.1	1	0.4
2	0.3	2.5	0.9
3	1	5	1.9
4	3	7.5	2.8
5	7	10	3.8
6	10	14.5	5.4
7	20	30	11.3
8	30	38.7	14.5

Acid Pretreatment Absent

Each equilibrium binding study compared sevelamer hydrochloride tablets (800 mg) and sevelamer carbonate tablets (800 mg) under conditions of constant time (4 hours on orbital shaker) and temperature (37^0 C) with eight different concentrations of phosphate. The following phosphate concentrations were used: 1, 2.5, 5, 7.5, 10, 14.5, 30, and 38.7 mM KH_2PO_4. Per applicant, the concentration of phosphate varies for different parts of the gastrointestinal tract with a range of approximately 5-30 mM KH_2PO_4.

Acid Pretreatment

The tablets were acid pre-treated by placing one tablet of each sample into a suitable container followed by 20 mL of 1N HCl. The samples were allowed to reach equilibrium (24-hour period) and the pH was less than 1. Excess HCl was removed. Subsequently, the approach described above for "Acid Pretreatment Absent" was adopted.

Reviewer Note on Acid Pretreatment
The approach followed by the applicant follows the general principles of the referenced guidance, however, the physiological relevance of this approach is unclear as GI transit time is anticipated to be less than four hours. An alternative, more robust approach would have been to incubate with acid for various times up to four hours or more.

Calculations (parameter estimations)

The following parameters were obtained from an eight point binding isotherm (phosphate concentration range for each test article (where applicable):

- binding affinity constant (k1)
- binding capacity constant (k2)
- bound and unbound phosphate concentrations
- percent phosphate bound
- average amount (mmol/g) bound at each initial phosphate concentration

The parameters are calculated using a Langmuir-type equation (per Cholestyramine Guidance)

$$\frac{x}{m} = \frac{k_1 k_2 C_{eq}}{1 + k_1 C_{eq}} \qquad \frac{C_{eq}}{x/m} = \frac{1}{k_1 k_2} + \frac{C_{eq}}{k_2}$$

C_{eq} = concentration of the adsorbate (bile acid salt) remaining in the solution at equilibrium;

x = the amount of adsorbate bound to the adsorbent (cholestyramine resin); and

m = the amount of adsorbent used.

The constant, k_1, is defined as the adsorption coefficient or affinity constant and is related to the magnitude of the forces involved in the binding process.

The Langmuir-capacity constant, k_2, indicates the apparent maximum amount of adsorbate that can be adsorbed per unit weight of adsorbent.

Reviewer Note on Calculations (parameter estimations)
The calculations and parameters estimated are consistent with the cholestyramine guidance and are acceptable. However, estimations obtained by direct non-linear methods tend to be more accurate and minimize the effect of forcing a linear fit when the relationship may not be linear. This reviewer followed two approaches for the evaluation:

- calculated k1 and k2 using a non-linear regression algorithm in SAS
- confirmed the applicant's parameter estimates using linear algorithm

The SAS codes used for this reviewer's analyses and relevant SAS output are included in the appendix to this review.

It should be noted that k2 is considered the primary outcome as opposed to k1(Per previous FDA communication by Randy Hedin, Chemistry Reviewer for Renagel)

Formulations

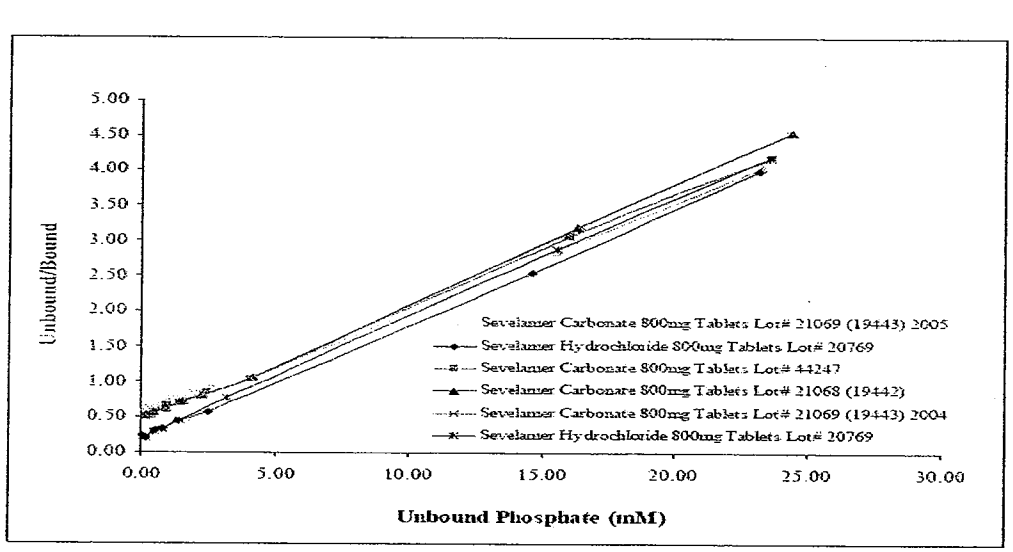
- sevelamer hydrochloride tablets, Lot No. 20769 (clinical, unbranded tablets) - reference
- sevelamer hydrochloride tablets Lot No. 7351 (commercial)- reference from study conducted in 2004
- sevelamer carbonate tablets Lot No. 21069 (Bulk Lot No. 19443, pivotal clinical lot) and Lot No. 44247 (stability, registration lot).
- sevelamer carbonate tablet pivotal clinical Lot No. 21068 (Bulk Lot No. 19442) and Lot No. 21069 (Bulk Lot No. 19943)

Results

1. Equilibrium Study of Binding of Phosphate to Sevelamer Hydrochloride Tablets and Sevelamer Carbonate Tablets Without Acid Pre-treatment

The Langmuir plots are depicted in Figure 1 and the average values for the slope, intercept, and R^2 of each of the Langmuir isotherms and the k1, k2 values are summarized in Table 1.

Figure 1: Langmuir Plots 1 (per Applicant)



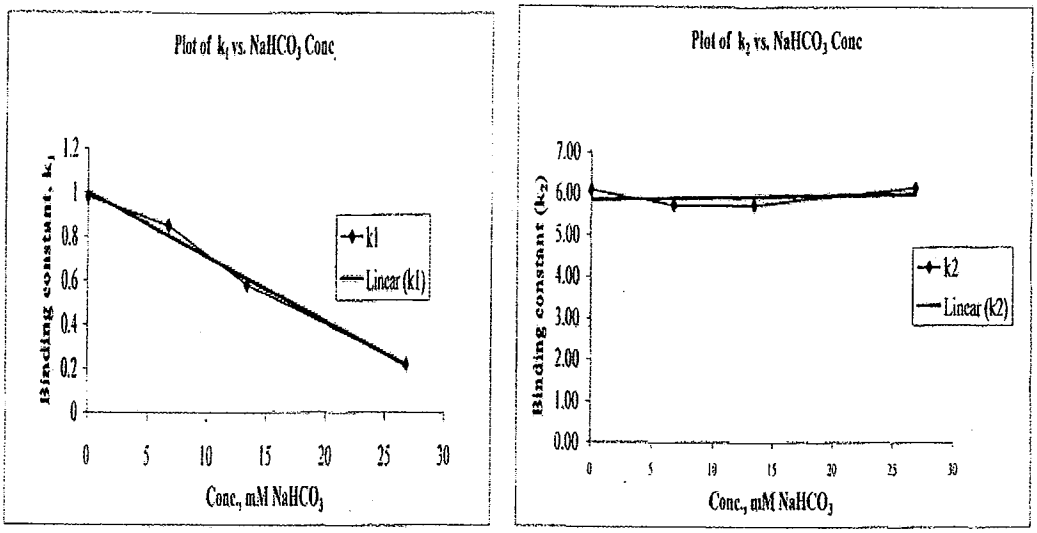
Overall the Langmuir plots for the test articles are comparable, with similar slopes and R^2 values were greater than 0.99. However, visual inspection of the plots indicates that some of the plots are not strictly linear and should not have been described by a simple linear regression equation. In general, the carbonate isotherms appear to have two distinct phases vs. one for the HCl. This finding suggests that the sevelamer carbonate has a different binding profile than the HCl. Additionally, k1 values for HCl were about two times greater than that of the carbonate, suggesting HCL has a greater propensity towards phosphate at neutral pH. The k2 values were comparable for both salt forms.

Table 1: Parameters for Langmuir Plots for Samples without Acid Pretreatment (per Applicant)

Sample ID	Sevelamer Hydrochloride 800 mg Tablets, lot # 7351	Sevelamer Hydrochloride 800 mg Tablets, lot # 20769	Sevelamer Carbonate 800 mg Tablets, lot # 21068 (19442)	Sevelamer Carbonate 800 mg Tablets, lot # 21069 (19443) 2004	Sevelamer Carbonate 800 mg Tablets, lot # 21069 (19443) 2005	Sevelamer Carbonate 800 mg Tablets, lot # 44247
Slope	0.170	0.163	0.167	0.167	0.148	0.159
Intercept	0.197	0.192	0.447	0.449	0.565	0.456
Affinity Constant, k_1	0.863	0.849	0.374	0.373	0.262	0.350
Binding Constant, k_2	5.89	6.15	5.97	5.97	6.75	6.27
RSQ	1.00	1.00	0.999	0.999	0.998	0.997

The applicant notes that the affinity constants (k1) for both sevelamer carbonate and sevelamer HCl tablets show a higher variation than the phosphate binding capacity constants (k2). According to the applicant this higher variation in k1 values is due to the variation in the ionic composition of the media with the sevelamer carbonate and sevelamer HCl without acid pre-treatment. The applicant provided some documentation* (see Figure 2) that indicates that affinity constants will change in a manner dependent on the amount of carbonate added; in contrast the binding capacity (k2) constants are unaffected.

Figure 2: Effect of concentration of $NaHCO_3$ on k1 and k2



* Genzyme Technical Memorandum, to Eugene Zhorov from Yvenet Montauban "Impact of carbonate on phosphate binding isotherms of Renagel 800 mg tablets by IC at pH 7 with BES," 03/02/2005 provided in TR-2417-06-SC Attachment 1) that upon the addition of carbonate to a sevelamer HCl sample,

Reviewer Note on Apparent Phosphate Binding Differences in sevelamer salt forms

Based on the Technical Memorandum cited above, the applicant should have conducted equilibrium studies under different conditions, such as varying ionic composition and pH to determine the impact of these factors on sevelamer's binding properties. Additionally, these studies should use different acid incubation times to determine if binding will be ultimately impacted by GI transit time.

2. Equilibrium Study of Binding of Phosphate to Sevelamer Hydrochloride Tablets and Sevelamer Carbonate Tablets With Acid Pre-treatment

Overall the Langmuir plots for the sevelamer salts are comparable and have R^2 values greater than 0.99. The Langmuir plots for equilibrium binding samples after acid pre-treatment are presented in Figure 3 and equilibrium parameters are summarized in Table 2.

Figure 3: Langmuir Plots 2 (per Applicant)

Langmuir Plots for Equilibrium Binding Samples After Acid Pre-treatment

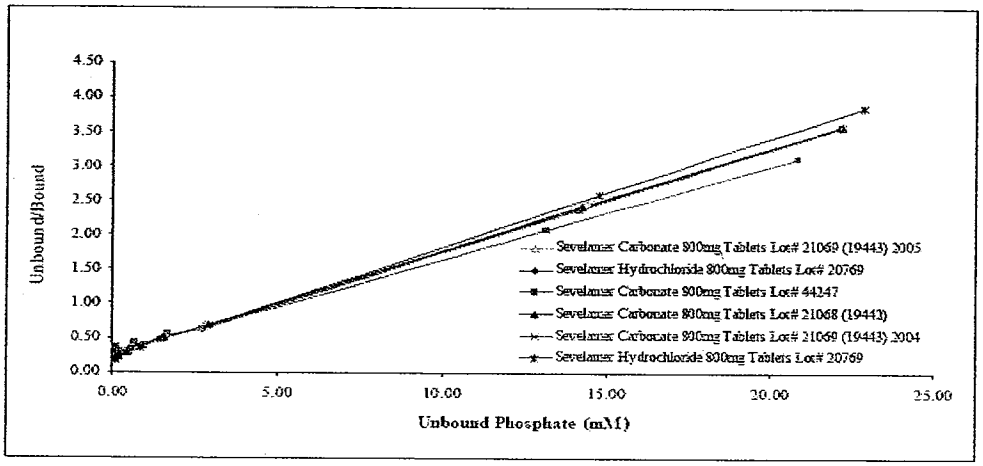


Table 2: Parameters for Langmuir Plots for Samples without Acid Pretreatment (per Applicant)

Parameters of Langmuir plots for Equilibrium Binding Samples after Acid Pre-treatment

Sample ID	Sevelamer Hydrochloride 800 mg Tablets, lot # 7351	Sevelamer Hydrochloride 800 mg Tablets, lot # 20769	Sevelamer Carbonate 800 mg Tablets, lot # 21068 (19442)	Sevelamer Carbonate 800 mg Tablets, lot # 21069 (19443) 2004	Sevelamer Carbonate 800 mg Tablets, lot # 21069 (19443) 2005	Sevelamer Carbonate 800 mg Tablets, lot # 44247
Slope	0.160	0.150	0.152	0.152	0.153	0.136
Intercept	0.196	0.239	0.222	0.219	0.208	0.288
Affinity Constant, k_1	0.820	0.628	0.684	0.691	0.738	0.471
Binding Constant, k_2	6.23	6.66	6.57	6.59	6.52	7.38
RSQ	1.00	0.999	1.00	1.00	0.999	0.999

The binding parameters were comparable for the two salts, with the exception of one carbonate formulation (Lot 44247). This lot had k1 and k2 values that were lower than other sevelamer carbonate and HCl lots. According to the applicant, the apparent atypical result, particularly, k2 = 7.38 mmol/g for sevelamer carbonate registration Lot No. 44247 is due to two higher values on the upper end of the equilibrium curve where the equilibrium curve has reached a plateau and the polymer is near saturation. The applicant claims that the binding capacity for the two highest data points on the equilibrium binding curve are higher than typical values observed for all other lots by 0.4-0.5 mmol/g and do not represent significant variation in the binding properties of the test articles.

Reviewer Note on Sevelamer Carbonate Lot with Apparently Atypical Binding
Lot 44247 is the proposed registration lot that has not been tested in the clinic, whereas the other formulations have been studied or are marketed. The clinical impact of marketing a lot with 'atypical' k1 and k2 values is unclear because IVIVC has not been established. It does not appear that having a higher k2 will have a negative clinical impact, because capacity is increased; however, the lower k1 suggests that ionization may not be complete even under acidic conditions. This reviewer recommends that the applicant should further investigate the reason for the observed anomaly from a CMC quality perspective prior to marketing. It is noted that the degree of phosphate binding per se is not a release specification, and no specific recommendation is made with respect to how close phosphate binding parameter values need to be to conclude similarity.

3. Reviewer Generated Equilibrium Parameters: k1 and k2 values using nonlinear regression method and parameters using linear methods

The Reviewer-generated k1 and k2 values are summarized in Tables 3 and 4. Generally, the k1 and k2 values obtained using nonlinear methods were comparable to those obtained via linear methods. Additionally, this reviewer obtained similar parameter values to that of the applicant (see Appendix) when linear methods were used.

Table 3: Reviewer Generated k1 and k2 Estimates for Sevelamer Phosphate Binding (Without Acid Pretreatment) Using Nonlinear Estimation Model

LOTID	k1 ($mmol^{-1}$)	k2 (mmol/g)
Sevelamer Carbonate Tablets Lot# 21068 (19442)	0.3937	5.9775
Sevelamer Carbonate Tablets Lot# 21069 (19443) 2004	0.3931	5.9684
Sevelamer Carbonate Tablets Lot# 21069 (19443) 2005	0.2772	6.7312
Sevelamer Carbonate Tablets Lot# 44247	0.3576	6.2767
Sevelamer HCl Lot# 7351	0.8751	5.8487
Sevelamer Hydrochloride Tablets Lot# 20769	0.8214	6.2326

Table 4: k1 and k2 Estimates for Sevelamer Phosphate Binding (Acid Pretreatment) Using Nonlinear Estimation Model

LOTID	k1 ($mmol^{-1}$)	k2 (mmol/g)
Sevelamer Carbonate Tablets Lot# 21068 (19442)	0.6406	6.5849
Sevelamer Carbonate Tablets Lot# 21069 (19443) 2004	0.6424	6.6229
Sevelamer Carbonate Tablets Lot# 21069 (19443) 2005	0.6871	6.5247
Sevelamer Carbonate Tablets Lot# 44247	0.4827	7.3693
Sevelamer HCl Lot# 7351	0.7771	6.2228
Sevelamer Hydrochloride Tablets Lot# 20769	0.6312	6.6690

4. Comparison of Equilibrium Studies With and Without Acid Pre-treatment

Generally, the variation in k1 was less with acid pre-treatment of the samples as compared to the non-acid pre-treated samples. The reason for the difference is because under acidic conditions, both sevelamer HCl and sevelamer carbonate are similarly (fully) protonated salts of cross-linked poly(allylamine HCl). Additionally, as previously mentioned, the ionic compositions vary (carbonate concentration) and affect k1: In contrast k2 values did not appear to be affected by acidic vs. non-acidic conditions.

Equilibrium Conclusions/Recommendations

The results demonstrate that sevelamer HCl tablets and sevelamer carbonate tablets:

1. Exhibit comparable phosphate binding under acidic conditions, with respect to k1 and k2 values
2. Exhibit distinct phosphate binding under non-acidic (neutral) conditions vs. acidic with respect to k1 values (k1 for HCl approximately two times higher than carbonate)
3. Exhibit comparable phosphate binding under non-acidic conditions with respect to k2 values

Deficiencies/Recommendations

1. The equilibrium studies were conducted under only two distinct conditions of acidic (24 hour incubation) vs. neutral conditions (4 hour incubation). For a robust comparison the studies should be conducted using various physiological conditions that are likely to be encountered during drug administration (passage through GI). These conditions include varying pH, ionic strength and incubation time.
2. The applicant should definitively determine why the registration lot had different binding characteristics (k2 higher and k1 lower) relative to all other formulations, particularly those used in the clinical trial. This evaluation is useful for approval since in the absence of BA/BE evaluations, it is critical to produce a to-be-marketed formulation with in vitro binding properties (performance/quality) that are comparable or identical to those used in clinical trials.

4.2.2 Kinetic Study of Phosphate Binding

Methodology

[ ]

Reviewer Note on Approaches to Comparing Kinetic Profiles

The Cholestyramine Guidance recommends the following parameters should be reported with regard to kinetic experiments:

- Percent binding of bile acid salt to 10 mg of resin at each time point in tabular and graphical forms

- Micromoles of bile acid salt bound to 10 mg of resin at each time point in tabular and graphical forms.

This reviewer also used a similarity factor approach (adopted from Dissolution Guidance) to complement the visual evaluation.

Results

Figures 4 and 5 depict the percent of phosphate bound vs. time at 2.5 mM phosphate concentration and 38.7 mM phosphate concentrations, respectively for the various sevelamer formulations.

Figure 4: Kinetic Profile at 2.5 mM Phosphate concentration

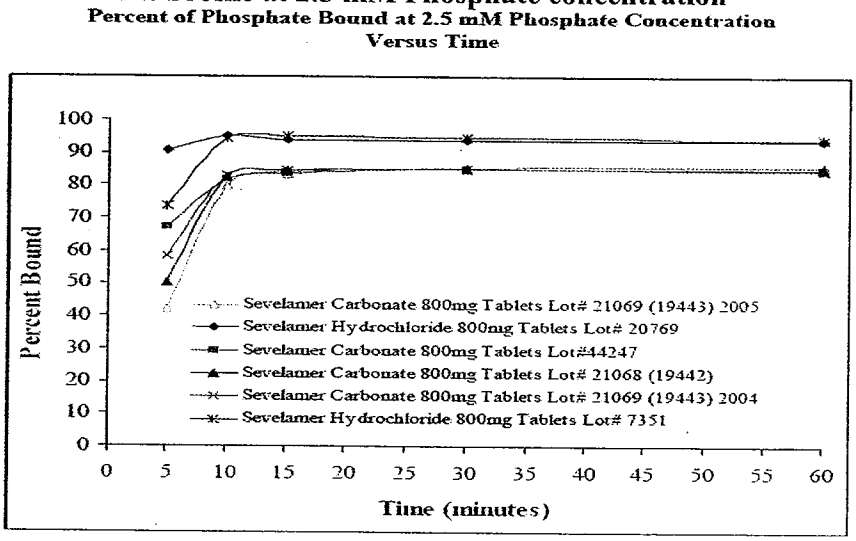
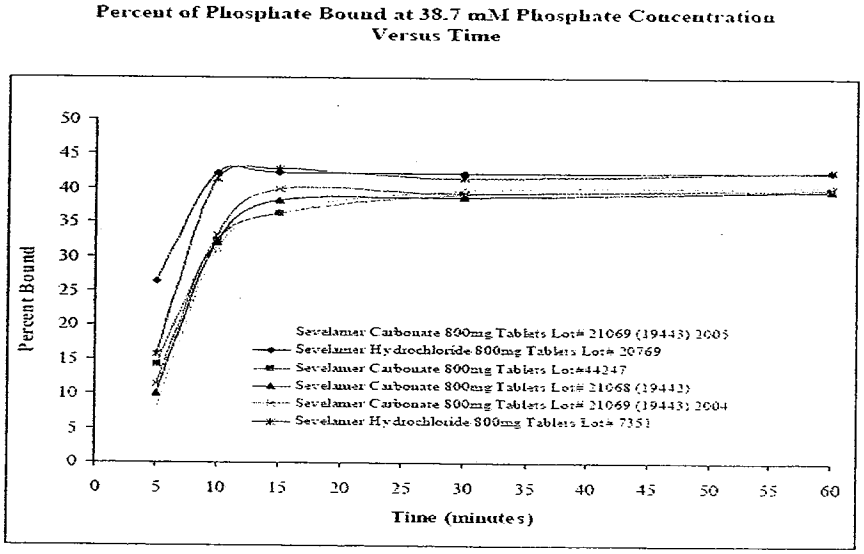


Figure 5: Kinetic Profile at 38.7 mM Phosphate concentration



The binding of phosphate was fast and the equilibrium level (plateau) of binding was reached for both sevelamer carbonate and sevelamer HCl in approximately 15 minutes at both the 2.5 and 38.7 mM initial phosphate concentrations. However, there appeared to be a concentration dependent binding capacity. At the low concentration >= 80 phosphate was bound, whereas at the high concentration only ~ 40 % was bound. Based on the maximal percent bound it appears that saturation of phosphate binding occurs.

Table 5: Kinetic Binding Results at 2.5 mM initial phosphate concentration

Time (min)	Sevelamer HCl 800 mg Tablets, lot # 7351	Sevelamer HCl 800 mg Tablets, lot # 20769	Sevelamer Carbonate 800 mg Tablets, lot # 21068 (19442)	Sevelamer Carbonate 800 mg Tablets, lot # 21069 (19443) 2004	Sevelamer Carbonate 800 mg Tablets, lot # 21069 (19443) 2005	Sevelamer Carbonate 800 mg Tablets, lot # 44247	Average	SD	% RSD
5	0.69	0.85	0.47	0.55	0.39	0.63	0.60	0.164	27.4
10	0.88	0.89	0.77	0.78	0.75	0.77	0.81	0.063	7.8
15	0.89	0.88	0.79	0.79	0.78	0.79	0.82	0.051	6.2
30	0.89	0.88	0.80	0.80	0 .80	0.80	0.83	0.045	5.4
60	0.89	0.88	0.80	0.80	0.80	0.80	0.83	0.044	5.3

Table 6: Kinetic Binding Results at 38.7 mM initial phosphate concentration

Time (min)	Sevelamer HCl 800 mg Tablets, lot # 7351	Sevelamer HCl 800 mg Tablets, lot # 20769	Sevelamer Carbonate 800 mg Tablets, lot # 21068 (19442)	Sevelamer Carbonate 800 mg Tablets, lot # 21069 (19443) 2004	Sevelamer Carbonate 800 mg Tablets, lot # 21069 (19443) 2005	Sevelamer Carbonate 800 mg Tablets, lot # 44247	Average	SD	% RSD
5	15.76	26.30	9.98	11.44	7.80	14.27	14.26	6.561	46.0
10	41.32	42.26	31.98	33.06	30.99	32.12	35.29	5.087	14.4
15	42.79	42.15	38.15	39.75	36.53	36.30	39.28	2.775	7.1
30	41.49	42.17	38.69	39.26	39.67	39.14	40.07	1.415	3.5
60	42.53	42.44	39.70	39.91	40.25	39.71	40.76	1.354	3.3

Visually and numerically (Table 5 and Table 6), there is a clear distinction between the carbonate and HCl lots: HCl has >= 10 % more phosphate bound initially than carbonate, however after approximately 15 minutes the difference in percent bound is < 10 %. The reason for this difference is unclear, but may be related to ionization. Assuming the usual criterion for no difference in bioavailability/bioequivalence (≤ 20 %) is applicable, it appears the formulations have similar kinetic properties. Consequently, the difference in the amount and rate at which phosphate is bound does not appear clinically meaningful. As mentioned earlier this reviewer applied a more quantitative method to evaluate product similarity, the f2 calculation; f2 results are summarized as follows.

- ***Reviewer Generated Similarity Factor Comparisons***

The following f2 values were obtained:

- f2 for low initial phosphate = 38.36
- f2 for high initial phosphate = 54.47

By the f2 definition, the salt forms exhibit different kinetics at low initial phosphate concentrations, but have similar kinetics at high phosphate concentrations. The lack of

difference in kinetics under high initial phosphate may be due in part to saturation of binding that may obscure potential differences in binding. The clinical relevance of the f2 findings is unclear.

The applicant notes that % RSD of the bound phosphate at the 5 and 10 minute time points is relatively high compared to subsequent time points. According to the applicant this is the direct result of slight variations in rupture and disintegration times for each lot of tablets. Furthermore, the time scale over which differences are seen is short relative to the overall residence time of the gastrointestinal tract and no significant differences in phosphate binding in vivo are expected between sevelamer carbonate and sevelamer HCl. This explanation appears reasonable but a more robust evaluation of the effect of disintegration times and other factors (pH and ionic strength) seems prudent, at least from a quality perspective.

Kinetic Conclusions/Recommendations

The results demonstrate that

- sevelamer HCl tablets bind more phosphate than sevelamer carbonate tablets under low initial phosphate conditions (2.5 mM)
- sevelamer HCL tablets bind similar amounts of phosphate as sevelamer carbonate tablets under high initial phosphate conditions (38.7 mM)
- both sevelamer salt forms bind phosphate rapidly and reach equilibrium within 15 minutes under low and high initial phosphate conditions

Deficiencies/Recommendations

The equilibrium studies were conducted under only two distinct conditions, accounting for the extremes of phosphate concentrations that are likely to be encountered during GI transit; however, the evaluations did not account for other factors including varying pH and ionic strength that are likely to be encountered during GI transit and may impact kinetic properties.

APPENDIX

I. EQUILIBRIUM BINDING

Table A: regression estimates for Sevelamer Phosphate Binding (Without Acid Pretreatment) using linear Estimation Model

LOTID	Intercept	slope	R^2	k2	k1
Sevelamer Carbonate Tablets Lot# 21068 (19442)	0.4474	0.1674	0.9992	5.9746	0.3741
Sevelamer Carbonate Tablets Lot# 21069 (19443) 2004	0.4489	0.1675	0.9992	5.9706	0.3731
Sevelamer Carbonate Tablets Lot# 21069 (19443) 2005	0.5646	0.1481	0.9983	6.7524	0.2623
Sevelamer Carbonate Tablets Lot# 44247	0.4571	0.1591	0.9991	6.2871	0.3479
Sevelamer HCl Lot# 7351	0.1967	0.1695	0.9998	5.8994	0.8618
Sevelamer Hydrochloride Tablets Lot# 20769	0.1917	0.1626	0.9996	6.1495	0.8481

Table B: regression estimates for Sevelamer Phosphate Binding (Acid Pretreatment) using linear Estimation Model

LOTID	Intercept	slope	R^2	k2	k1
Sevelamer Carbonate Tablets Lot# 21068 (19442)	0.2223	0.1521	0.9996	6.5745	0.6841
Sevelamer Carbonate Tablets Lot# 21069 (19443) 2004	0.2194	0.1516	0.9996	6.5943	0.6912
Sevelamer Carbonate Tablets Lot# 21069 (19443) 2005	0.2081	0.1535	0.9993	6.5163	0.7374
Sevelamer Carbonate Tablets Lot# 44247	0.2883	0.1355	0.9988	7.3799	0.4701
Sevelamer HCl Lot# 7351	0.1957	0.1605	0.9997	6.2314	0.8201
Sevelamer Hydrochloride Tablets Lot# 20769	0.2392	0.1501	0.9993	6.6602	0.6277

3 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

APPEARS THIS WAY ON ORIGINAL

4.3 Consult reviews

None.

4.4 Cover sheet and OCPB filing/review form

None.

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

/s/

Robert Kumi
8/22/2007 08:34:54 AM
BIOPHARMACEUTICS

Patrick Marroum
8/22/2007 05:07:54 PM
BIOPHARMACEUTICS