GelTex PHARMACEUTICALS, INC.

August 4, 1998

Martin T. Haber, Ph.D.
Division of Metabolic and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-926
Renagel® Capsules (sevelamer hydrochloride)

Dear Dr. Haber,

In reference to the Renagel Capsule NDA and as requested in our conversation of June 1, 1998, I have enclosed ; 483, EIR and 483 response regarding the Renagel Capsule Pre-Approval Inspection. I have also included the literature reference that describes the preferred use of the

is the manufacturer of the drug product As you may recall, during the pre-approval inspection questions arose regarding the of the drug

. Details of the issue and chronology of events are included in the enclosed package.

If you have any questions, please do not hesitate to call me at 781 290-5888, Ext. 733. We will amend the NDA to include these changes, if acceptable, in our next CMC amendment to the NDA.

Sincerely,

Robert C. Blanks
Senior Director, Quality Affairs

cc: Martha Carter, Vice President of Regulatory Affairs

0001

Nine Fourth Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

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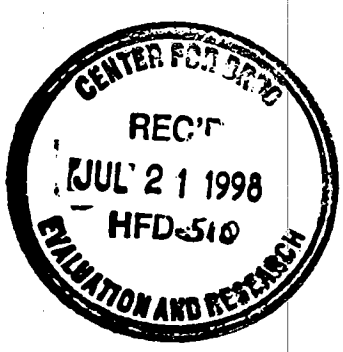

July 16, 1998

Martin Haber, Ph.D.
Division of Metabolic & Endocrine Drug Products, HFD-510
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-926
RenaGel® (Sevelamer hydrochloride) 403 mg Capsules

Dear Dr. Haber:

Thank you for taking the time to speak with me on July 2, 1998 about the trademark, RenaGel®. In our conversation you suggested that we drop the upper case "G" to lower case, and move the word "Capsules" closer to "RenaGel" to address the agency's concerns about the trademark. We are willing to make these changes, and have attached artwork to show you how the name will appear. If you have any comments about this, please contact me as soon as possible so we can address whatever concerns may remain.

We would like to thank you for your constructive suggestions, and for helping us to resolve this matter in an expeditious fashion. If you need to contact me, I may be reached at (781) 290-5888, extension 766.

Thank you, Dr. Haber.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

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March 13, 1998

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
Division Document Room, 14B-03
HFD-510
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-926 RenaGel® Capsules
Amendment Number 005
Four Month Safety Update

Dear Dr. Sobel:

Enclosed please find one archive and one review copy of the Four Month Safety Update Report for RenaGel (NDA No. 20-926). It includes a complete revision of the Integrated Summary of Safety (including all data available through November 1, 1997), and the analysis tables. A comparison of the major findings in the Integrated Summary of Safety submitted within NDA No. 20-926 and the Integrated Summary of Safety prepared for the Four Month Safety Update Report can be found in the Preface (Section 9.1). As discussed in our teleconference on March 6, 1998, a second interim analysis for the extension study GTC-37-901 and case report forms are available upon request.

Should you have any questions or require additional information, please do not hesitate to contact the undersigned at (781) 290-5888, extension 266 or Lisa D'Attanasio, Regulatory Affairs Coordinator at extension 216.

Sincerely,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

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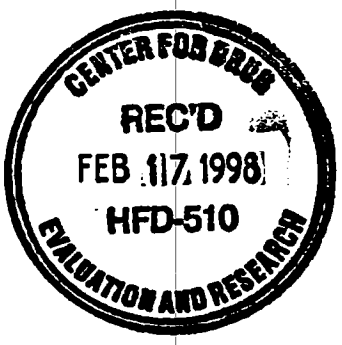
GelTex
PHARMACEUTICALS, INC.

February 13, 1998



Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrine Drug Products
Food and Drug Administration
CDER
Division of Metabolism and Endocrine Drug Products
Division Document Room, 14B-03
HFD-510
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-926 RenaGel® Capsules
Amendment Number 004
General Correspondence: Non-absorbability of RenaGel

Dear Dr. Sobel:

During GelTex's visit to the FDA on January 17, 1998 to train the agency on the use of RenaGel CANDA (NDA 20-926), a question was raised by Dr. Schneider and Dr. Jones as to why the human absorption study was conducted in normal volunteers rather than in patients with end-stage renal failure. GelTex would like to understand the division's concern with this issue as this question did not arise during the clinical development of RenaGel either during the end of Phase II meeting or the pre-NDA meeting.

The following is a summary of the key points related to GelTex's establishment of RenaGel as a non-absorbed drug.

1. GelTex conducted a human ADME study to investigate the potential absorption of RenaGel. GelTex performed the study in normal volunteers since the measurement of urine radioactivity is more sensitive than blood radioactivity for absorbed drugs. Most end-stage renal failure patients have little or no glomerular filtration and conducting an absorption study in these patients would have reduced the chance of detecting absorbed radioactivity. The design was presented to the Division at the end of Phase II meeting and no objections were raised. The results from this study are presented in Section 6 of the RenaGel NDA.

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ensure that the CMC, nonclinical, and clinical development plan for RenaGel would be adequate to support the approval of this NDA.

GelTex Pharmaceuticals, Inc. requests consideration for a priority review of the NDA for RenaGel capsules. The rationale for this request is the following:

(a) Hyperphosphatemia is a life-threatening and severely-debilitating condition in patients with end stage renal failure (ESRF). Effective control of serum phosphorus reduces the morbidity and mortality of ESRF patients.

(b) Existing therapies for hyperphosphatemia include approved and unapproved drugs which are unsatisfactory in a significant percentage of patients due to side effects of treatment, thus creating an unmet medical need for optimal long-term management of hyperphosphatemia in ESRF patients. PhosLo® (calcium acetate), the only FDA approved and labeled phosphate binder, causes frequent hypercalcemia which complicates and compromises patient care. To avoid hypercalcemia, physicians lower the dose of calcium acetate which jeopardizes adequate control of serum phosphorus control, or they discontinue calcitriol (1,25-dihydroxyvitamin D) which is deficient in ESRF patients and is necessary to maintain normal bone formation.

Despite these efforts to balance control of phosphorus and calcium, patients using calcium acetate (or unlabeled calcium carbonate) still develop hypercalcemia and are eventually switched to aluminum salts, which are not labeled as phosphate binders. Aluminum accumulates in the tissues of renal failure patients and is associated with significant toxicity such as encephalopathy, osteomalacia, and myopathy. Despite the well known risk of aluminum toxicity, a significant percentage of dialysis patients in the United States continue to receive aluminum salts as a means to control phosphorus and lower serum calcium.

The widespread use of unlabeled aluminum salts underscores the critical need for an effective non-aluminum, non-calcium-based phosphate binder. RenaGel is an effective phosphate binder that will allow treatment of hyperphosphatemia without promoting hypercalcemia or hyperaluminemia as do currently available treatments.

The following points of information and clarification pertaining to this NDA should be made in order to assist the reviewers:

1. As requested by the Division, GelTex is providing both a paper copy and a Computer-Assisted New Drug Application (CANDA) for this NDA.
2. The CANDA will be installed at the FDA on November 6, 1997, and GelTex is working with Mr. Randy Hedin (CSO) to schedule training sessions for the reviewers.

3. The dates on the electronic versions of the SAS data outputs are different from those on the paper copies. Although there are different dates, the data presented in each version are identical.
4. As agreed with the Division at the Pre-NDA meeting on April 16, 1997, poly(allylamine) manufactured under current Good Manufacturing Practices is now being used to manufacture RenaGel, and all new pertinent CMC information has been included in this submission.
5. SAS transport files will be submitted to Biostatistics in a separate submission.

If you have any questions or comments about this NDA please contact either:

Lisa D'Attanasio
Regulatory Affairs Coordinator
Phone (781) 290-5888 x216
Fax (781) 290-5890

Steven K. Burke, M.D.
Vice-President of Clinical Research
Phone (781) 290-5888 x241
Fax (781) 290-5890

Thank you very much for your time and consideration.

Very sincerely yours,

Steven K Burke

Steven K. Burke, MD
GelTex Pharmaceuticals, Inc.

APPEARS THIS WAY
ON ORIGINAL

GelTex
IMACEUTICALS, INC.

November 3, 1997

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
U.S. Food and Drug Administration
Center for Drugs Evaluation and Research
HFD-510
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 20-926 RenaGel® Capsules
ATTN: Document Room 14B-19

Dear Dr. Sobel:

Per 21 CFR 314, enclosed please find the New Drug Application (NDA) by GelTex Pharmacueticals Inc. for RenaGel® phosphate binder capsules indicated for the control of hyperphosphatemia in end stage renal failure. This NDA was preassigned the number 20-926 by CDER on October 3, 1997. The enclosed submission includes the following:

1. One archival copy (blue)
2. Two review copies of the chemistry, manufacturing and controls (CMC) section (red)
3. Three copies of the methods validation and labeling sections (red)
4. One copy of the nonclinical pharmacology and toxicology section (yellow)
5. Two copies of the human pharmacokinetics and bioavailability section (orange)
6. One copy of the clinical data section (tan)
7. One copy of the statistical section (green)
8. Five additional copies of the draft labeling (blue)
9. Five copies of volume one of the NDA, which contains Sections 1, 2 and 3, which should be distributed to each reviewer for his or her reference

In addition, field copies have been sent to GelTex Pharmaceuticals' home FDA district office (Boston District), the two drug substance manufacturers' home FDA district offices District and District), and the drug product manufacturer's home FDA district office (District) to facilitate the pre-approval inspection process.

The research and development of RenaGel conducted to support this submission was performed under IND 46,601 in collaboration with, and under the supervision of the Division of Metabolic and Endocrine Drug Products. IND was originally filed on October 27, 1994. GelTex Pharmaceuticals, Inc. has worked closely with this Division to

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SECTION 1

GelTex
PHARMACEUTICALS, INC.

October 15, 1997

PATENT INFORMATION

Patent Number:	5,496,545
Date of Expiration:	August 11, 2013
Type of Patent:	Method of Use Patent and Drug Product Patent
Patent Owner:	GelTex Pharmaceuticals, Inc. Waltham, Massachusetts

Original Declaration:

The undersigned declares thet Patent No. 5,496,545 covers the composition and the method of use of RenaGel® phosphate binder. This product is the subject of this application for which is being sought.

GELTEX PHARMACEUTICALS, INC.

By: _____
Mark Skaletsky
President and CEO

Nine Fourth Avenue Waltham, MA 02154 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

GelTex
PHARMACEUTICALS, INC.

October 15, 1997

PATENT INFORMATION

Patent Number:	5,667,775
Date of Expiration:	September 16, 2014
Type of Patent:	Method of Use Patent and Drug Product Patent
Patent Owner:	GelTex Pharmaceuticals, Inc. Waltham, Massachusetts

Original Declaration:

The undersigned declares thet Patent No. 5,667,775 covers the composition and the method of use of RenaGel® phosphate binder. This product is the subject of this application for which is being sought.

GELTEX PHARMACEUTICALS, INC.

By: _____

Mark Skaletsky
President and CEO

Nine Fourth Avenue Waltham, MA 02154 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

EXCLUSIVITY SUMMARY FOR NDA # 20-926 SUPPL #_____

Trade Name Renagel Generic Name Sevelamer-hydrochloride

Applicant Name Genzyme HFD # 510

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /___/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? Didn't specify years.

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active

moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____

_____	_____
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/

Signature
Title: CSO

10/26/98
Date

/S/

Signature of Division Director

10/28/98
Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

October 28, 1998

CERTIFICATION PURSUANT TO 21 U.S.C. SECTION 335a(k)(1)

GelTex Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. Section 335a(a,b)) in connection with this application.

GELTEX PHARMACEUTICALS, INC.

By: _____

Mark Skaletsky

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20926	**Trade Name:**	RENAGEL (SEVELAMER HCL) 403MG CAPS
Supplement Number:		**Generic Name:**	SEVELAMER HCL
Supplement Type:		**Dosage Form:**	
Regulatory Action:	AP	**Proposed Indication:**	Renagel Capsules are indicated for the reduction of serum phosphorus in patients with end stage renal disease. The safety and efficacy of Renagel Capsules in end stage renal disease patients who are not on hemodialysis have not been demonstrated.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
Sevelamer hydrochloride is indicated for end stage renal disease patients on hemodialysis, and there would not be a pediatric patient population to study. Pediatric end stage renal disease patients would generally be eligible for a kidney transplant.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, RANDY HEDIN

/S/
Signature

10/23/98
Date

October 22, 1998
Memorandum
To: the File NDA 20-926 Renagel Capsules(sevalamer hydrochloride)
From: Solomon Sobel, M.D., Director Division of Metabolic and Endocrine Drug Products
/S/
Subject: Approval of NDA

Renagel is a polymeric phosphate binder for oral use.It is indicated for the reduction of serum phosphorus in end stage renal disease.
In a cross over comparison study with calcium acetate (a conventional treatment for hyperphosphatemia) Renagel and calcium acetate were equally effective in lowering serum phosphorus. However, Renagel had the advantage of inducing significantly fewer episodes of hypercalcemia.
Renagel was well tolerated.
There remains one outstanding issue which will be addressed in phase 4 studies. The company will perform in vitro and in vivo studies to study possible drug binding effects of Renagel. The current label has recommended the precaution that other drugs should be taken either 1 hour before or 3 hours after the administration of Renagel.

Conclusion:
The Division recommends approval of this NDA.
Solomon Sobel
/S/

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

CC: Arch NDA 20-926
HFD-510
HFD-510/SSobel/GTroendle/BSchneider/RHedin

GelTex
PHARMACEUTICALS, INC.

ORIGINAL

October 5, 1998

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
Document Room, 14B-03
HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-926 Renagel® Capsules
Amendment Number 015
Safety Update

Safety update unacceptable
/S/
HFD-510

Dear Dr. Sobel:

Reference is made to the NDA cited above for Renagel® Capsules. The purpose of this submission is to provide the enclosed safety update to NDA 20-926. Please note the four-month safety update was submitted as Amendment No. 005 on March 13, 1998.

Should you have any questions or require additional information, please do not hesitate to contact the undersigned at (781) 290-5888, extension 766 or Lisa D'Attanasio, Regulatory Affairs Coordinator at extension 716.

Sincerely,

Martha J. Carter

Martha J. Carter
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

e Fourth Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

GelTex PHARMACEUTICALS, INC.

March 13, 1998

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
Division Document Room, 14B-03
HFD-510
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-926 RenaGel® Capsules
Amendment Number 005
Four Month Safety Update

Dear Dr. Sobel:

Enclosed please find one archive and one review copy of the Four Month Safety Update Report for RenaGel (NDA No. 20-926). It includes a complete revision of the Integrated Summary of Safety (including all data available through November 1, 1997), and the analysis tables. A comparison of the major findings in the Integrated Summary of Safety submitted within NDA No. 20-926 and the Integrated Summary of Safety prepared for the Four Month Safety Update Report can be found in the Preface (Section 9.1). As discussed in our teleconference on March 6, 1998, a second interim analysis for the extension study GTC-37-901 and case report forms are available upon request.

Should you have any questions or require additional information, please do not hesitate to contact the undersigned at (781) 290-5888, extension 266 or Lisa D'Attanasio, Regulatory Affairs Coordinator at extension 216.

Sincerely,

Martha J. Carter

Martha J. Carter
Vice President, Regulatory Affairs

/S/

line Fourth Avenue Waltham, MA 02154 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

GelTex
PHARMACEUTICALS, INC.

October 5, 1998

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
Document Room, 14B-03
HFD-510
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-926 Renagel® Capsules
Amendment Number 016
Labeling

Dear Dr. Sobel:

Reference is made to the NDA cited above and to our videoconference of October 2, 1998. We are pleased to provide a revised package insert for Renagel Capsules which reflects the outcome of our discussions. In particular, we would like to draw your attention to the "Adverse Reactions" section, where we have added the information requested during the conference. We hope this meets with the Division's and the Office's approval. We have used strikeout and 18 point font to highlight changes from the version faxed to us on October 2, 1998.

We would like to offer the following comment about our approach to the "Adverse Reactions" section. While we understand the desire to include the data from the calcium acetate controlled study, this represents only 20% of the entire patient safety database. We feel it is important to include some information from the randomized, double-blind, placebo-controlled study and the long term extension study. Therefore, a paragraph has been included about each study in this section.

Also included in this submission are copies of the bottle and carton labeling, as well as the artwork for the imprint on the capsule which has been changed from "RenaGel" to "G403."

Nine Fourth Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

Re: NDA 20-926 Renagel® Capsules
Amendment Number 016
Labeling

Should you have any questions or require additional information, please do not hesitate to contact the undersigned at (781) 290-5888, extension 766 or Lisa D'Attanasio, Regulatory Affairs Coordinator at extension 716.

Sincerely,

Martha J. Carter

Martha J: Carter
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

2. Numerous pharmacokinetic studies (see Section 5 of RenaGel NDA), utilizing both single- and repeated-dose administration regimens were performed in both rats and dogs to examine the absorption, distribution and excretion profile of RenaGel. All of these studies were performed utilizing RenaGel. RenaGel was using three different methods to assess fully its potential absorption: was used to label the backbone; was used to label the cross-linker; and the final cross linked aminopolymer was using These studies consistently showed that RenaGel was excreted entirely in the feces with no significant absorption in any study.

3. Since the meeting in January, GelTex has contacted its licensee, , which is developing RenaGel phosphate binder for use in recently has completed two nonclinical studies that further address this issue: The ADE of RenaGel in Uremic Rats and The ADE of RenaGel in gastrointestinal ulcerated rats. The preliminary results from these studies are described in more detail in Attachment 1. In summary, RenaGel had a similar ADE profile in uremic rats and rats with gastrointestinal ulcers as compared to control animals. These studies indicate that RenaGel is not absorbed in rats with compromised anatomy of the gastrointestinal tract.

In summary, numerous nonclinical ADE studies and one human ADME study submitted in the RenaGel NDA demonstrate that RenaGel is not absorbed. The design of these studies was discussed with the Division and were accepted to support the RenaGel NDA submission. In addition, two additional studies recently conducted by , demonstrate that RenaGel is not absorbed in uremic or gastrointestinal ulcerated rats.

We feel that the nonclinical and clinical studies submitted in the RenaGel NDA along with the additional data on uremic and gastrointestinal ulcerated rats should answer your concerns. At your earliest convenience, representatives from GelTex's preclinical, clinical, and regulatory groups would like a meeting or teleconference with the appropriate division personnel to confirm that we have resolved this issue.

Thank you for your time and consideration.

Sincerely,

Steven K. Burke, MD
Vice-President, Clinical Affairs

GelTex
PHARMACEUTICALS, INC.

January 21, 1998

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
U.S. Food and Drug Administration
Center for Drugs Evaluation and Research
HFD-510
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-926 RenaGel® Capsules
Amendment Number 003
Chemistry Manufacturing and Controls Information
ATTN: Document Room 14B-19

Dear Dr. Sobel:

We are submitting one archive and one chemistry copy of this information amendment in reference to NDA No. 20-926 for RenaGel® Capsules.

[redacted]) will no longer be listed as drug substance (active pharmaceutical ingredient) manufacture. Notification has also been sent to the Chicago District Office.

If you have any questions or comments about this amendment please contact either:

Lisa D'Attanasio
Regulatory Affairs Coordinator
Phone (781) 290-5888 x216
Fax (781) 672 5822

Steven K. Burke, M.D.
Vice-President of Clinical Research
Phone (781) 290-5888 x241
Fax (781) 672 5822

Thank you very much for your time and consideration.

Sincerely,

Steven K. Burke

Steven K. Burke, M.D.
GelTex Pharmaceuticals, Inc.

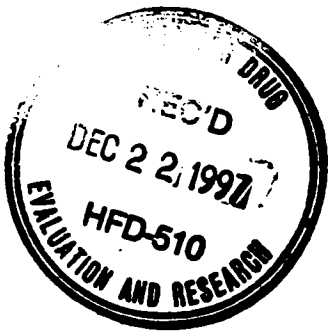
Nine Fourth Avenue Waltham, MA 02154 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

ORIG AMENDMENT ORIGINAL

B2

GelTex PHARMACEUTICALS, INC.

December 19, 1997



Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
U.S. Food and Drug Administration
Center for Drugs Evaluation and Research
HFD-510
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-926 RenaGel® Capsules
Amendment Number 002
Response to Fax Dated December 5, 1997
ATTN: Document Room 14B-19

Dear Dr. Sobel:

On December 5th, 1997 GelTex Pharmaceuticals, Inc. received a fax requesting information relative to the Human Pharmacokinetics section of the RenaGel NDA No. 20-926. GelTex contacted Dr. Jones on December 8th, 1997 for clarification of these issues. Listed below in bold are the agency's faxed items, and GelTex's subsequent response.

Fax Item No. 1
Information regarding the various formulations (clinical trial and to-be-marketed) used should be submitted, or you should direct our biopharmaceutics reviewer (Dr. Carolyn Jones) as to where in the submission this data can be located.

GelTex Response to Fax Item No. 1
The formulation information has been submitted in the RenaGel NDA No. 20-926 in Section 6, Volume 029, Page 0008, Table 6.2 and Section 4, Volume 002, Page 0153, Table 4.65. Photocopies of these pages are included as an attachment to this correspondence (See Appendix I).

Nine Fourth Avenue Waltham, MA 02154 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

Fax Item No. 2
Information regarding the two manufacturers used in the development of this drug was not discussed in section 6. This data should be submitted to the NDA file, or you should direct Dr. Jones as to where in the submission this data can be found.

GelTex Response to Fax Item No. 2
The information regarding the two manufacturers has been submitted in the RenaGel

Photocopies of these pages are included as an attachment to this correspondence (See Appendix II).

Fax Item No. 3
Please submit data to demonstrate an adequate dissolution methodology and specification.

GelTex Response to Fax Item No. 3
RenaGel is an insoluble crosslinked amine polymer. Because RenaGel is insoluble in all common solvents, dissolution is not a suitable methodology. Instead disintegration is employed. Solubility was discussed and submitted in the RenaGel NDA No. 20-926 Section 4, Volume 002, Page 0041 and Page 0178. The Disintegration data can be found in Section 4, Volume 002, Page 0180, Table 4.71. Photocopies of these pages are included as an attachment to this correspondence (See Appendix III).

Fax Item No. 4
All raw data for the absolute bioavailability study should be sent to the Agency as ASCII files, and human pharmacokinetics summary information should be submitted in Word Perfect 6.1.

GelTex Response to Fax Item No. 4
GelTex contacted Dr. Jones informing her that raw clinical data for the pharmacokinetics study (GTC-10-801) would be sent to the NDA file in the form of SAS Transport files. Dr. Jones stated SAS Transport files were an acceptable format. An additional copy of SAS Transport files for study GTC-10-801 is enclosed on diskette, as well as, Section 6 in Word Perfect 6.1 format (See Appendix IV).

We are submitting one archive and one pharmacokinetic review copy of these items in reference to NDA No. 20-926 for RenaGel® Capsules.

If you have any questions or comments about this amendment please contact either:

Lisa D'Attanasio
Regulatory Affairs Coordinator
Phone (781) 290-5888 x216
Fax (781) 672 5822

Steven K. Burke, M.D.
Vice-President of Clinical Research
Phone (781) 290-5888 x241
Fax (781) 672 5822

Thank you very much for your time and consideration.

Very Sincerely Yours,

Lisa A. D'Attanasio
For Steven K. Burke, M.D.

Steven K. Burke, M.D.
GelTex Pharmaceuticals, Inc.

GelTex
PHARMACEUTICALS, INC.

February 13, 1998

Ms. Jena Weber
Regulatory Health Project Manager
Food and Drug Administration
CDER
Division of Metabolism and Endocrine Drug Products
Division Document Room, 14B-03
HFD-510
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-926 RenaGel® Capsules
Amendment Number 004
General Correspondence: Non-absorbability of RenaGel

Dear Ms. Weber:

As requested, enclosed are desk copies of our recent submission to the RenaGel NDA, 20-926, with regards to the non-absorbability of RenaGel. There are three copies: one for yourself, Dr. Schneider and Dr. Jones.

If you have any questions, please call me at 781 290-5888 Ext. 216. I will be calling you later in the week with regards to this matter.

Sincerely,

Lisa D'Attanasio
Regulatory Affairs Coordinator

Nine Fourth Avenue Waltham, MA 02154 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

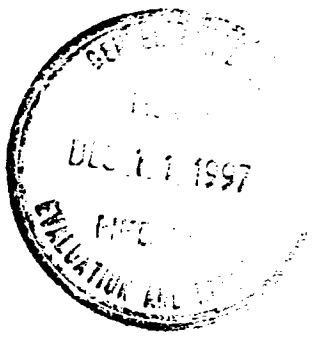
ORIGINAL

DRUG AMENDMENT

GelTex
PHARMACEUTICALS, INC.

December 10, 1997

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
U.S. Food and Drug Administration
Center for Drugs Evaluation and Research
HFD-510
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-926 RenaGel® Capsules
Amendment Number 001
Submission of SAS Transport Files
ATTN: Document Room 14B-19

Dear Dr. Sobel:

We are submitting one archive and one statistics review copy of the following items for one Phase I study, three Phase II studies, two Phase III studies, one extended use study and a pharmacokinetic study:

1. SAS Transport files of the raw data on diskettes,
2. an output of the PROC CONTENTS in paper copy,
3. and annotated case report forms in paper copy.

The information submitted is in reference to NDA No. 20-926 for RenaGel® Capsules.

If you have any questions or comments about this amendment please contact either:

Lisa D'Attanasio
Regulatory Affairs Coordinator
Phone (781) 290-5888 x216
Fax (781) 672 5822

Steven K. Burke, M.D.
Vice-President of Clinical Research
Phone (781) 290-5888 x241
Fax (781) 672 5822

Thank you very much for your time and consideration.

Very Sincerely Yours,

Steven K Burke

Steven K. Burke, M.D.
GelTex Pharmaceuticals, Inc.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

e Fourth Avenue Waltham, MA 02154 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com