DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA

GelTex Pharmaceuticals, Inc.
Attention

WRITTEN REQUEST

Dear:

Reference is made to your
NDA, Renagel (sevelamer hydrochloride) Capsules, and, Renagel
(sevelamer hydrochloride) Tablets.

To obtain needed pediatric information on sevelamer hydrochloride, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following study:

- *Type of study*: A randomized, open-label, cross-over, multicenter study comparing sevelamer with calcium acetate. Randomization should be stratified by type of dialysis treatment (hemodialysis, peritoneal dialysis, or no dialysis).

- *Indication to be studied (i.e., objective of study)*: To characterize and compare the efficacy and long-term safety of sevelamer to calcium acetate in pediatric patients with hyperphosphatemia and chronic renal insufficiency and pediatric patients with chronic renal failure [glomerular filtration rate (GFR) < 60 mL/min/1.73m^2] at least 50% of whom are on hemodialysis or peritoneal dialysis.

- *Study Design*: Prior to randomization, all patients will undergo a two-week washout from current phosphate-lowering therapy. Patients will then be randomized to either sevelamer hydrochloride or calcium acetate for the first 8-week treatment period followed by a crossover to the other treatment for a second 8-week treatment period. Following completion of the second treatment period, patients will remain on the phosphate-lowering drug to which they were randomized during the second period of the cross-over for approximately 32

additional weeks. An independent Data Safety Monitoring Board should be employed to periodically review safety data from the trial.

- *Age group in which study will be performed*: Six years to 18 years of age, inclusive. Approximately 50% of the study population should be under age 12 years.

- *Study endpoints*: The primary efficacy endpoint will be the change from baseline (washout) in serum phosphorus level after 8 weeks of treatment. Primary safety endpoints will include serum calcium, phosphorus, and Ca X P product.

- *Drug information*:

Dosage forms:	Marketed formulation of sevelamer Calcium acetate tablets (comparator)
Route of administration:	Oral
Regimen:	Titrated per algorithm

- *Drug-specific safety concerns*: The principal safety concerns are for patients with $GFR_s < 20$ mL/min/1.73m^2 and who are not on dialysis. These patients may be at risk of developing hyperchloremia while taking sevelamer. Therefore, the protocol should exclude patients whose renal function is impaired to this degree and are not receiving dialysis. Renagel may increase the risk of gastrointestinal adverse events in patients on peritoneal dialysis. Therefore, physical examinations and monitoring of abdominal signs and symptoms should be performed on a regular basis in these patients. In the event of persistent hyperphosphatemia and/or hypercalcemia, investigators should use their discretion regarding the need to change treatment modalities (i.e., lower dose of vitamin D, switch from calcium acetate to Renagel or vice versa).

- *Statistical information, including power of study and statistical assessments*: Efficacy will be evaluated by comparing serum phosphorus change from baseline (washout) to 8 weeks between sevelamer and calcium acetate treatment regimens. Non-inferiority of Renagel will be assessed using a 97.5% one-sided confidence interval for the mean treatment difference. Assuming a common standard deviation of 0.35, forty patients (20 patients per sequence) are sufficient with 80% power to show that Renagel is non-inferior to the control using a non-inferiority margin of -0.20. To account for a 25% dropout rate, approximately 54 patients should be enrolled.

- *Labeling that may result from the study*: Appropriate sections of the label may be changed to incorporate the findings of the studies.

- *Format of reports to be submitted*: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

- *Timeframe for submitting reports of the study*: Reports of the above study must be submitted to the Agency on or before June 30, 2003. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Randy Hedin, Senior Regulatory Management Officer, at 301-827-6392.

Sincerely yours,

{See appended electronic signature page}

John K. Jenkins, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research