DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

JAN 28 2005

Certified Mail
Return Receipt Requested

Reference No. 05-HFD-45-0101

Mark D. Gessler
Chairman & CEO
Gene Logic, Inc.
708 Quince Orchard Road
Gaithersburg, MD 20878

Dear Mr. Gessler:

Between October 6 and 17, 2003, Charles M. Kerns, Michael F. Skelly, Ph.D., and CT Viswanathan, Ph.D., representing the Food and Drug Administration (FDA), inspected the following nonclinical laboratory studies conducted by your firm:

1. Protocol [ ] entitled "28-Day Repeated Dose Toxicity and Efficacy of [ ] in [ ] Rabbits," performed for [ ]
2. Protocol [ ] entitled "28-Day Oral Toxicity Study of Hydrocodone Bitartrate in [ ] Dogs," performed for [ ]

This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research, to ensure that the rights, safety, and welfare of the human subjects have been protected, and to verify compliance with Title 21 of the Code of Federal Regulations (CFR), Part 58. The regulation at 21 CFR Part 58 applies to nonclinical laboratory studies of products regulated by FDA.

At the conclusion of the inspection, Mr. Kerns and Dr. Skelly presented and discussed the items listed on Form FDA 483, Inspectional Observations. Following our review of the establishment inspection report and related documents, including your letter dated October 27, 2003, we conclude that you violated FDA regulations governing the conduct of nonclinical laboratory studies. This letter provides you with written notice of the violations. The applicable provisions of the CFR are cited for each violation.

1. **Your testing facility management failed to assure that mixtures of test and control articles were appropriately tested for stability, strength, and uniformity. [21 CFR Part 58.31(d), 21 CFR 58.105(b), and 21 CFR 58.113]**

Testing facility management failed to assure that the mixture of the test article [ ] and the control (the vehicle) were appropriately tested for strength, stability, and uniformity. Specifically, stability was not determined for test articles in studies [ ] and [ ] and for control articles in study [ ] In addition, no tests were conducted for

strength and uniformity of the mixture of test article with vehicle for study [ ]. The [ ] suspensions and control article were not assayed for vehicle components and you provided no quantitative information on vehicle composition.

In your response to FDA Form 483, you provided assay results for samples of [ ] suspensions (the mixture of test article and vehicle) that were performed 3 months after the date on the Certificates of Analysis (CoAs) for these samples. These results indicate that the samples had deteriorated to 38%, 48%, and 59% of the nominal [ ] concentrations. Your response indicates that you believe the suspension samples deteriorated after they were shipped from [ ] to the facility that performed the assays. However, deterioration may have occurred prior to that (e.g., before dosing or during the 28 days of the study) or the suspensions may have been non-uniform, or both. For these reasons, the actual dose of test article administered is unknown and the study could not provide a meaningful assessment of the toxicity of the test article. For example, a conclusion of no toxicity for a given theoretical dose would be erroneous if the actual dose administered was sub-potent due to test article instability prior to dosing.

2. **You prepared final study reports that failed to include strength, purity, and stability data for the test and control articles in final study reports. [21 CFR Part 58.185(a)(4),(5)]**

For study [ ] the strength, purity, stability, and uniformity data for test and control articles, and for mixtures of the test article and the vehicle (the control), were not included in the final report.

For study [ ] the strength, purity, and stability data for the test article (hydrocodone bitartrate, HCBT) were not included in the final report.

3. **You prepared final study reports that failed to include a description of all circumstances that may have affected the quality or integrity of data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis. [21 CFR Parts 58.185(a)(9) and 58.185(a)(11)]**

For study [ ] the final report failed to discuss that the lack of information on stability of the test or control article under the conditions of administration and on uniformity of the mixtures of test article and vehicle are circumstances that may have affected the quality or integrity of the study data. The study director also failed to discuss that the bioanalytical method for concomitant toxicokinetic measurements was not sufficiently sensitive and specific to detect or measure [ ] concentrations in the bloodstream. The sporadic findings of [ ] in plasma samples could only have resulted from assay non-specificity, sample contamination, or accidental release from blood platelets. The study director did not discuss these implausible toxicokinetic results, except to say that they had no toxicologic significance.

For study[ ]there was no record that the study director or the veterinary cardiologist analyzed and evaluated electrocardiograms (ECGs) for quantitative changes such as prolongation of the Q-T interval, or to assess the significance of elapsed time between dosing and ECG acquisition. The contributing scientist described the ECG records only as "WNL" (within normal limits). However, because the intervals between dosing and ECGs (from 18 minutes to 6 hours and 18 minutes) were not controlled, randomized, or consistent across dose and sex, it is unlikely that either maximal or cumulative effects of hydrocodone and its metabolites were captured. Contrary to your claim, you could not measure cumulative effects of the drug on ECGs in the presence of variable degrees of its acute effects.

4. **The study director failed to assure that the protocol contain documentation indicating that the protocol had been approved by the sponsor. [21 CFR 58.120(a)(11)]**

For study[ ]there was no documentation that the sponsor[ ]approved the protocol and amendments prior to initiation of the study. The protocol and amendments were signed as approved by[ ]Manager of Pharmacology/Toxicology[ ]His name and signature on the protocol and the four subsequent amendments to the protocol are designated as "Sponsor's Representative."

5. **The study director failed to assure that all raw data, documentation, protocols, specimens, and final reports were transferred to the archives during or at the close of the study. [21 CFR 58.33(f)]**

For study[ ] the project manager initialed the[ ] Study Data Organization form on the line where the study director was to assure that the study records and specimens were transferred to the archives, following 21 CFR 58.33(f). No other documentation was available to assure that the study director transferred study records and specimens to the archives, or assured that the records and specimens were transferred to the archives. Your revised SOP[ ](Archiving Procedures) does not comply with 21 CFR 58.33(f), in that Section V.A. assigns responsibility for archiving study files to either the study director and/or project manager. This is solely a responsibility of the study director.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. Your violations of the FDA regulations outlined above resulted in the submission of unreliable data to the sponsors, and the submission of unacceptable data to FDA. You must address these deficiencies and establish procedures to ensure that any on-going or future studies be conducted in compliance with FDA regulations.

Within 15 working days of receipt of this letter, you must notify this office in writing of the specific corrective actions you will take to address all of the deficiencies noted above and to achieve compliance with the FDA regulations. If corrective actions cannot be completed within 15 working days, you may request an extension of time in which to respond by stating the reason for the delay and the time within which the corrections will be completed. We will review your

response and determine whether it is adequate. Failure to provide adequate assurances of compliance with FDA regulations may result in regulatory action without further notice.

Your reply should be sent to:

C.T. Viswanathan, Ph.D.
Associate Director, Bioequivalence
Chief, GLP & Bioequivalence Investigations Branch
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 116, HFD-48
Rockville, MD 20855
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Sincerely

Joanne L. Rhoads M.D

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Director
Division of Scientific Investigations
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