DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

March 6, 2000

Dear sponsor of an IND or master file using or producing a gene therapy product:

Because of the recent events raising concerns regarding the manufacture and testing of gene therapy products, we ask that you submit an amendment containing the following requested information in triplicate to each IND and/or master file within three months.

1. Please provide a list of all lots of all gene therapy products, cell banks (CB), and viral banks (VB), ever produced or generated in your facility for potential use in non-clinical or clinical studies of human gene therapy. Please include the date of manufacture for each, their use (e.g. non-clinical or clinical), and indicate their interrelationships, i.e., which CBs and/or VBs were used to prepare each CB, VB, or product lot.

2. Please provide a list of all IND files that cross-reference your IND(s) or master file(s). In addition, please confirm all IND(s) or master files that you have obtained authorization to cross reference for support of your IND.

3. Please submit all lot release data and characterization testing for each lot of product used in clinical trials, and testing information for all master CB, working CB, master VB and/or working VB used during manufacture of your lots. When possible, please submit this information in tabular form including the lot number or identifier, date of manufacture, test, test method, the sensitivity and specificity of test methods when appropriate, specification, and test result. If you have already submitted this information to your file in the past, you are now requested to send it again as part of a manufacturing summary document to your file.

4. If any lots of product were produced for, but not used in, clinical studies please describe the reason they were not used.

5. Please provide a summary of your product manufacturing quality assurance (QA) and quality control (QC) programs. This should consist of a brief (approximately three pages) description of your system for preventing, detecting, and correcting deficiencies that may compromise product integrity or function, or may lead to the possible transmission of adventitious infectious agents. Also, identify each individual who has authority over the QA and QC programs and list their duties. Please provide the date of your last QA and QC audits of your manufacturing operations and those of contract manufacturers, vendors or other partners.

6. For each clinical trial contained in your IND, please submit a 2-3 page summary of the procedures you have in place to ensure:

   a. there is adequate monitoring of the clinical investigations to demonstrate the trial(s) are conducted in accordance with regulatory requirements and Good Clinical Practices (GCPs), and the protocol; that the rights and well-being of human subjects are protected; and that data reporting, including safety reporting to you (the sponsor), the IRB, and NIH is accurate and complete; and

   b. you, as the sponsor, have adequate oversight over the clinical investigation, as outlined in 21 CFR 312, Subpart D. Please include with your summary an organizational chart identifying each individual responsible for oversight of clinical studies and his or her duties. If you have transferred some or all of these obligations to a Contract Research Organization (CRO), please so indicate, verify that these obligations are being appropriately met, and provide a summary of the CRO's oversight procedures.

   For further guidance regarding sponsors' responsibilities in a clinical trial, including monitoring, please refer to the ICH document on GCPs, which can be found on the Internet at http://www.ifpma.org/pdfifpma/e6.pdf.

7. Please confirm that all animal safety information has been submitted as described in 21 CFR 312.32-33. For any such information not previously submitted, please provide the required information. Please note that results from animal studies that suggest significant clinical risk must be reported, in writing, to this Office and to all investigators within fifteen calendar days after initial receipt of this information and that IND annual reports are to include a summary of major preclinical findings.

We additionally request that, after submitting the above information, you submit yearly brief manufacturing summary reports addressing the information requested in items 1 through 4 above that was obtained during the previous year's product manufacturing, testing and development. At that time, also please affirm that manufacturing QA and QC, and clinical trial oversight and monitoring, have been conducted per the plans submitted in response to items 5 and 6, and submit modifications or updates as appropriate. For administrative convenience, we request that you provide the information described in this paragraph in your annual reports.

Your prompt attention to these matters is appreciated. Please reference the BB-IND or BB-MF number and identify your response as "Response to Gene Therapy Letter." Please address your complete response to each IND and/or master file in triplicate, within the three-month period requested, as follows:

Center for Biologics Evaluation and Research
Attn: Office of Therapeutics Research and Review
HFM-99, Room 200N
1401 Rockville Pike
Rockville, MD 20852-1448

If you have any questions, please contact the assigned Regulatory Project Manager at (301) 827-5101.

Sincerely yours,

Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research