CELL GENESYS

November 21, 2005

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2005D-0310, CBER 200523.
Draft Guidance for Industry on Gene Therapy Clinical Trials—Observing Participants for Delayed Adverse Events

Dear Sir/Madam:

Cell Genesys, Inc. appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) "Draft Guidance for Industry on Gene Therapy Clinical Trials—Observing Participants for Delayed Adverse Events." Reference is made to CBER's Draft Guidance for Industry on *Gene Therapy Clinical Trials—Observing Participants for Delayed Adverse Events*, published August 23, 2005 (Docket No. 2005D-0310, CBER 200523).

On October 24, 2001, a meeting of the Biological Response Modifiers Committee (BRMAC) was held in which BRMAC proposed that FDA require sponsors to follow all gene transfer patients for at least 15 years, regardless of vector type. In June 2004, prior to the ASGT annual meeting, a workshop on long term follow up (LTFU) was held in which very useful and germane discussions pertinent to the current understanding of gene therapy products and the need for LTFU for all patients occurred. In the time from the first BRMAC meeting to the present, recommendations for LTFU of gene transfer investigational products have evolved based on increased information on these types of products.

Cell Genesys, Inc. wishes to thank FDA/CBER for its continued support in the development of gene transfer products and for its active role in gathering comments from industry, investigators, and affected parties for the creation of the draft LTFU guidance. The guidance clarifies the FDA position on LTFU and consolidates recommendations for following patients who have been treated with gene transfer products.

However, Cell Genesys, Inc. would like to make the following comments on the draft guidance for the Agency's consideration.

- The draft guidance makes recommendations regarding LTFU for patients treated with vectors that integrate into host cell DNA and which could potentially cause

Cell Genesys, Inc.
500 Forbes Boulevard
South San Francisco, CA 94080
(650) 266-3000
Fax (650) 266-3010
www.cellgenesys.com

transforming events leading to malignancy or other delayed adverse events. However, the guidance does not clearly differentiate amongst the various types of cells that could potentially be targeted with a vector, whether the cell targeted is the patient's cell or a cellular therapy to be administered to the patient, and the potential for long-term persistence of the gene modified cell. For example, *ex vivo* retrovirus modified tumor cells or cell lines that have been lethally irradiated prior to patient administration pose no threat of long term persistence and, therefore, present a low to negligible risk of delayed adverse events due to integration events. We therefore suggest that the risk assessment be modified to consider the long term persistence or fate of the modified cell, especially for *ex vivo* gene modified cell strategies which incorporate lethal irradiation or other inactivating approaches that limit the life expectancy of the administered product. We recommend that the LTFU evaluation of patients treated in such a manner for integration and persistence not be required, and that the guidance be modified to address this class of patients.

- The guidance calls for regular and uniform monitoring of patient material treated with an integrating virus for virus persistence and integration site analysis. Although we agree that the risk of malignant transformation has been demonstrated in at least one clinical trial (SCID X-1 gamma RTV trial), we do not believe the uniform application of integration site monitoring is warranted in all patients treated with this class of vectors. Sampling of *in vivo* tissue can be problematic depending on the targeted tissue, and may not reflect the population of cells as a whole. In fact, assessment of pre-event (leukemia) patient material (gene modified CD34+ cell prep) for clonal integration sites failed to detect the malignant clone integrant discovered in the first case of gamma/delta T-cell Leukemia/Lymphoma in Alain Fischer's trial of common gamma chain encoding retrovirus for SCID X-1. This example shows that not all integrant sites and clones can be evaluated from random sampling.

  Regular and uniform monitoring of patient material treated with an integrating virus for virus persistence and integration site analysis may indeed identify integration sites in regions of known oncogenes or tumor suppressor genes. However, it is anticipated that treatment or intervention would be based on the clinical setting and sequelae, not on the specific molecular abnormality. Based on this rationale, monitoring patients previously treated with higher risk, integrating viruses should be adverse event based with molecular assessment and investigation to follow the discovery of such an event. This practical application of the molecular assessment only in the setting of a clinically significant event eliminates the potential for clinically irrelevant findings in this population. We therefore recommend that the guidance be modified such that a clinically relevant adverse event would trigger the molecular assessment of integrating virus treated patient material for persistence and integration site analysis.

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We thank the FDA for the opportunity to present our comments on this draft guidance and look forward to working with the Agency in the future.

Sincerely,

Alice M. Varga for

Carol C. Grundfest
Vice President, Regulatory Affairs and Project Management