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May 7, 2001

Documents Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Federal Register Docket No. 00D-1662
Written Comments for Draft "Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans"

Dear Sir or Madam:

Genzyme Corporation and Diacrin, Inc. are writing to submit comments to the draft guidance "Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans," published in the Federal Register on February 7, 2001, Docket No. 00D-1662. We have chosen to comment on this guideline since we are sponsors in the field of xenotransplantation research and product development.

Diacrin/Genzyme LLC, a joint venture between Diacrin, Inc. and Genzyme Corporation, has completed several clinical trials using porcine fetal cells: Phase 1 and Phase 2 trial using NeuroCell™-PD, porcine fetal cells for the treatment of Parkinson's disease, and a Phase 1 trial using NeuroCell™-HD, porcine fetal cells for the treatment of Huntington's disease. Diacrin is also the sponsor of additional xenotransplantation clinical trials in stroke, epilepsy, pain, spinal cord injury repair, and hepatic failure.

Genzyme and Diacrin are pleased with the recommendations regarding the source animal characterization. We agree that appropriate source animal qualifications, herd management procedures, and screening for infectious agents are all crucial to assuring adequate safety of xenotransplantation products. We feel that our approach to qualifying and managing production and source animals minimizes the risks to human and herd health. Further, in the development of the clinical studies, our programs were designed to be consistent with the recommendations set forth in the 1996 draft "PHS Guideline on Infectious Disease Issues in Xenotransplantation." We have continued to work closely with FDA and have incorporated their recommendations as our clinical programs have

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progressed and are pleased to see many of the recommendations similarly outlined in this draft guideline, as well as in the "PHS Guideline on Infectious Disease Issues in Xenotransplantation," published in the Federal Register in January 2001. Additionally, it is commendable that this guideline recognizes different classes of xenotransplantation products and provides recommendations based on a tiered-approach.

Genzyme and Diacrin would like to comment specifically on the following major points presented in the draft guideline:

1. Collection of information and records retention for 50 years;
2. Surveillance of health care workers, laboratory personnel, and source animal facility workers, etc.

We recognize the importance of records retention and archiving of tissue samples, especially if the need should arise to trace back information to the source and date of the xenotransplant. However, requiring the sponsor to maintain records and biological samples for 50 years while at the same time requiring the sponsor to submit identical information to a national database places an undue burden on a single company. It is a redundant exercise and counters the goals of establishing and maintaining a national xenotransplantation database, as mentioned in Section I.

Secondly, the surveillance of source animal facility workers, health care workers, and close contacts, as mentioned in Sections III.D.2.e and VIII.F.4, is a requirement that cannot reasonably be met. The guideline advises sponsors to perform "baseline and periodic sampling and storage of serum or plasma for individuals having frequent and close contact with source animals." This additional procedure is unnecessary since the required safety systems currently in place, such as pre-employment health screening for animal facility workers and mandatory supervisor notification in the event of an employee illness, product manufacturing records, and patient monitoring algorithms, adequately assure traceability to these individuals, product batches, and source animals and are designed to contain any spread of infectious disease. Additionally, xenotransplantation animal facility workers appear to be at no greater risk, and probably less risk, of cross-species infection than livestock handlers and workers who are not required to provide blood samples and consent to further invasive monitoring. It would be more reasonable to obtain samples in the event of an investigation, e.g. xenogeneic infection of a recipient.

Furthermore, the guidance document states to obtain and archive baseline samples of plasma and leukocytes from health care providers and other close contacts of the xenotransplant recipient. It would not be possible to identify all workers that have participated in any and all aspects of the xenotransplantation process, from obtaining the source animals to those involved in animal husbandry to identifying all hospital personnel involved in the transplantation of the xenograft or in handling biologic specimens. To subject personnel who have had contact with the xenotransplant recipient to lifelong surveillance would be an unreasonable request, especially since no cross-species infection from a xenotransplantation product has occurred to date. We believe that our

clinical experience and published information on the long-term status of xenotransplant patients (Paradis et al, 1998[1]; Heneine et al, 1998[2]; Patience et al, 1999[3]) establish as far as practical the effective use of state-of-the-art methods in safety of xenotransplantation of porcine cell products. Since the initiation of clinical trials by Diacrin/Genzyme LLC and Diacrin, Inc., there have been no serious adverse events at the biomedical animal facilities used to house source animals, in the clinic, or in our follow-up of treatment patients that would suggest a relationship to xenotransplantation. Personnel in the xenotransplantation field should not be subjected such close scrutiny when sufficient safety measures against transmission of infection have been implemented in health care facilities as universal precautions. Increased surveillance creates unnecessary stress and would unduly invade their privacy. Required precautions and procedures currently in place at health care and biomedical animal facilities that address high risk situations (e.g. HIV transmission in the event of a needle stick) provide adequate protection for employees exposed to similar risks potentially posed by xenotransplantation products.

Genzyme and Diacrin recognize and support these critical efforts to create guidelines for the development of therapies involving xenotransplantation, the ultimate goal of which is to further public health without compromising the safety of patients or health care and animal facility professionals.

Sincerely,

Susan Stewart
Sr. Director, Regulatory Affairs
Genzyme Corporation

And

for

E. Michael Egan
Chief Operating Officer
Diacrin, Inc.

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[1] Patience, C, et al. No evidence of pig DNA or retroviral infection in patients with short term extracorporeal connection to pig kidneys. Lancet (1998). 352: 699-701.

[2] Heneine, W, et al. No evidence of infection with porcine endogenous retroviruses on recipients of porcine islet-cell xenografts. Lancet (1998). 352: 694-699.

[3] Paradis, K, et al. Search for cross-species transmission of porcine endogenous retrovirus in patients treated with living pig tissue. Science (1999). 285: 1236-1241.

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