DEPARTMENT OF HEALTH & HUMAN SERVICES

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

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

MAR 0 8 2002

Dear Colleague:

We want to advise you that FDA has jurisdiction over human cells or tissues intended for transplant into a human recipient that have ex-vivo contact with live nonhuman animal cells, tissues, or organs. The Department of Health and Human Services defines xenotransplantation as "any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source, or (b) human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues or organs." (PHS Guideline on Infectious Disease Issues in Xenotransplantation, January 29, 2001). Human embryos co-cultured with living nonhuman animal cellular material, such as bovine tubal cells or Vero cells, are within the scope of this definition. FDA considers feeder layer cells irradiated to render them nonproliferative for use in co-cultures to be living and within the definition of xenotransplantation.

The transfer into a human recipient of human embryos that have undergone ex-vivo contact with cells of nonhuman origin constitutes a clinical investigation involving xenotransplantation. An investigational new drug application (IND) should be submitted to FDA if you are planning to co-culture human embryos with living nonhuman animal cells for transfer into a human recipient. While FDA plans to enforce IND requirements for investigations involving further production of embryos co-cultured with live nonhuman animal cells, currently it is not our intent to take enforcement action based on the transfer of already existing embryos created by co-culture with live nonhuman animal cells. However, if you have ever co-cultured human embryos with live nonhuman animal cells and have proceeded or intend to proceed with the transfer to a human recipient, the FDA would like to discuss with you our concerns about this technique and our recommendations regarding follow-up of patients who have received this material. A document outlining some of this information has been enclosed and also posted on the web at http://www.fda.gov/cber/infosheets/humembclin.htm.

The FDA regulatory process governing clinical investigations includes requirements applicable to manufacturing processes, the study of the safety and efficacy of such cells, and the protection of human participants in such studies. If you plan to co-culture human embryos with living nonhuman animal cells for transfer into a human recipient, we can provide you with information and guidance regarding filing such an application. FDA's Xenotransplantation Action Plan website (http://www.fda.gov/cber/xap/xap.htm) contains relevant guidance documents for the clinical use of human cells that have been exposed to animal cells. They include the following:

- PHS Guideline on Infectious Disease Issues in Xenotransplantation, January 19, 2001.
- Draft Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans, February 7, 2001.

- Draft Guidance for Industry: Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Intimate Contacts, February 1, 2002.

- Guidance for Industry: Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans, April 6, 1999.

FDA's regulations on investigational new drugs, including those for the submission and review of an IND, are described in Title 21 of the Code of Federal Regulations (CFR), Parts 50, 56, and 312. The agency has discussed the applicability of these requirements to cellular and tissue-based products in many public forums and in various published documents available at http://www.fda.gov/cber/. They include the following:

- A Federal Register (FR) notice describing FDA's authority over cell and gene therapy products ("Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products," October 14, 1993, 58 FR 53248).

- A comprehensive regulatory program for the regulation of human cellular and tissue-based products, based on a tiered, risk-based assessment ("A Proposed Approach to the Regulation of Cellular and Tissue-Based Products," February 28, 1997).

- "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing," Final Rule, January 19, 2001 (66 FR 5447). This rule establishes the criteria for regulation of human cells, tissues, and cellular and tissue based products (HCT/Ps), including reproductive cells and tissues, solely under the authority of section 361 of the Public Health Service Act. HCT/Ps that do not meet the criteria are regulated under section 351 of the Public Health Service Act and/or the Food Drug and Cosmetic Act (FDCA), as biological products, drug products, and/or medical devices.

- "Suitability Determination for Donors of Human Cellular and Tissue-Based Products; Proposed Rule," September 30, 1999 (64 FR 52696).

- "Current Good Tissue Practice for Manufacture of Human Cellular and Tissue-Based Products; Inspection and Enforcement; Proposed Rule," January 8, 2001 (66 FR 1508).

If you are unable to access the internet to obtain information on submitting an IND to the FDA, please call or write and we'll supply you with the needed information:

Center for Biologics Evaluation and Research
Office of Communication, Training & Manufacturers Assistance
Manufacturers Assistance and Technical Training Branch
1401 Rockville Pike, HFM-44
Rockville, MD 20852-1448
800-835-4709 or 301-827-1800
matt@cber.fda.gov

The specific information required in an IND will depend upon the cells under investigation and on the phase of study. For assistance in determining whether you need to file an IND submission and in preparation of a submission, please contact the Regulatory Project Manager, Deborah Lavoie at 301-827-5101.

Sincerely,

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

Enclosure:
Information and Recommendations for Physicians involved in the Co-culture of Human Embryos with Nonhuman Animal Material