DEPARTMENT OF HEALTH & HUMAN SERVICES

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

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

JAN 3 0 2002

Dear Colleague:

It has come to the attention of the United States Food and Drug Administration (FDA) that you may be administering allogeneic human cells as a therapy for recurrent miscarriage. This treatment is often referred to as lymphocyte immune therapy (LIT). We want to advise you that the FDA has jurisdiction over such cellular products, and to inform you regarding the FDA regulatory process governing such products. These products are regulated as biological products subject to licensing under Section 351 of the Public Health Service Act (PHS Act). These products also meet the definition of "drug" and are subject to the requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Therefore, until such time as there is an approved Biologics License Application for the product, administration of such cells or cellular products in humans can only be performed as part of clinical investigations, and then only if there is an Investigational New Drug application (IND) in effect.

Prior to authorizing investigations under an IND, FDA reviews manufacturing processes, preclinical and clinical data regarding the safety and efficacy of such cells, and measures to ensure the protection of human participants. Specific concerns regarding LIT therapy include the following:

- A report in the literature (THE LANCET Vol. 354, July 31, 1999, 365) indicates that women who have received LIT may have a higher incidence of subsequent miscarriage than women who did not receive such cellular products.

- Whether LIT uses cells/cellular products from the woman's partner or from other donors, the manufacturing/preparation and administration of such cells/cellular products presents risks to the recipient (e.g., administration of non-sterile cellular products, transmission of communicable diseases).

The regulations describing the submission and review of an IND, informed consent, and institutional review board requirements are found in Title 21 of the Code of Federal Regulations (CFR), Parts 50, 56, and 312. FDA has previously announced that these requirements apply to cellular and tissue-based products in many public forums and in various documents available at http://www.fda.gov/cber/, including the following:

- A Federal Register (FR) notice describing FDA's regulatory approaches to 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 ("A Proposed Approach to the Regulation of Cellular and Tissue-Based Products," February 28, 1997).

- A final rule describing requirements for the regulation of human cells, tissues, and cellular and tissue-based products, including reproductive cells and tissues (Final Rule: Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products, January 19, 2001, 66 FR 5447).

The FDA recognizes that some physicians and others involved in the administration of allogeneic cells or cellular products for prevention of miscarriages remain unaware that such activities require an IND. We remind all institutions, reproductive centers, and physicians with active programs of allogeneic cells or cellular products for treatments of miscarriages that you should refrain from performing any administration of such cells until an IND has been submitted and reviewed by the FDA's Center for Biologics Evaluation and Research (CBER). Such clinical research many proceed only when an IND is in effect.

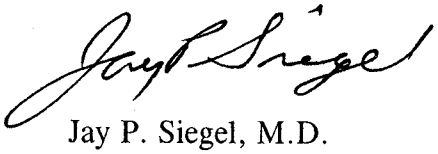
An IND is to be submitted in triplicate to the following address:

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

The specific information required in an IND will depend upon the experimental system and the phase of study. Forms, regulations, guidances, and CBER Standard Operating Procedures and Policies (SOPPs) for INDs are available on our internet page at http://www.fda.gov/cber/ind/ind.htm. For assistance in preparing an IND submission, please contact Dr. Joyce Frey-Vasconcells at 301-817-5102.

Please advise Dr. Frey-Vasconcells (address as above) within 30 days whether or not you plan to submit an IND, and whether or not you plan to continue LIT in the absence of an IND.

Sincerely,



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