Food and Drug Administration
Center for Biologics Evaluation and Research
BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE
Meeting #37, March 18-19, 2004
Hilton Hotel, Silver Spring, Maryland

List of Questions:

Manufacturing:

Cellular products for treatment of cardiac disease may be obtained from bone marrow, peripheral blood or skeletal muscle of autologous or allogeneic donors. The products may be administered without manipulation or may be subjected to one or more selection, purification, cryopreservation or culture procedures. Because the specific cells, mechanisms of action and cell-device interactions are still in the early stages of investigation, the appropriate and adequate safety testing and characterization have not yet been defined and may vary based on the cell source and type of manipulation.

1. Please discuss the different intrinsic safety concerns for cellular products for the treatment of cardiac injury, and the testing that should be performed to ensure administration of a safe product, with consideration of the following variables:

    a. Donor source (autologous or allogeneic)
    a. Tissue source (bone marrow, peripheral blood, muscle)
    b. Type and degree of product manipulation (cell isolation, cell selection, culture, expansion)
    a. Final formulation (buffers, excipients, cell concentration)
    b. Storage conditions (time, temperature)
    c. Route and site of administration

2. Please comment on the elements of product identity and characterization necessary to generate data demonstrating safety and efficacy. Please consider the following:

    a. The degree of heterogeneity present in administered cellular products appears to be an important variable. Are there specific biomarkers that can identify cell types involved in cardiac repair? Are there specific biomarkers that can identify contaminating or damaged cells that may lead to adverse events when introduced into myocardial tissue?

    b. Based on the current state of knowledge, are there safety issues the agency should consider in relation to the type and relative percentage of cell types that can be identified by biomarkers including phenotype and/or other *in vitro* indicators in cellular products for cardiac repair? For example, can the relative percentages of fibroblasts in myoblast products or T-cells in stem cell products affect product safety or interfere with product performance?

    c. What other parameters could be assessed to further characterize these products for safety and potency?

Preclinical:

3. Various animal models have been proposed to support the safety of cellular products used in the treatment of cardiac disease. These include studies of both small (e.g., mouse, rat, rabbit) and large (e.g., dog, pig) species and studies utilizing either immune competent or immunocompromised animals. Each model provides distinct advantages and limitations. For instance, human cellular products can be tested in genetically immunocompromised rodents, but these animals provide limited clinical monitoring of cardiac function, and cannot be used to assess the safety of the devices used to administer the cells as proposed in the clinical studies. Large animal models allow for more extensive clinical monitoring of cardiac function and the use of the same delivery device intended for clinical use. However, use of immune competent species eliminates the ability to evaluate the safety of administration of the human cellular product.

   Please discuss the potential benefits, along with the limitations of various large and small animal species for providing pharmacologic, physiologic, and toxicologic support for cellular products used in the treatment of cardiac diseases.

4. A central tenet of preclinical animal safety testing is that the test agent must possess biological activity in the animal model in order to provide meaningful data on both safety and activity endpoints. For cellular products, this tenet often necessitates using an analogous product in animal models in order to preserve biological activity. In particular, preclinical evaluation of cellular products for ischemic heart disease often employ animal models of acute ischemic heart disease (ameroid constrictor, embolism, etc.), which can be used to generate safety data to support clinical trials. Specific issues that potentially can be addressed in animal models of disease include, but are not limited to, overall extent and duration of the effect of different doses of the injected cells on cardiac function and the effect of the route of administration and cell placement location on physiologic and safety outcomes**.**

   Please discuss the merits of animal models of ischemic disease with respect to the ability to generate proof of concept (physiologic) data and to generate toxicologic data of relevance to the clinical disease.

Device:

5. Many novel combinations of delivery systems and cellular products are currently being evaluated. It is anticipated that additional delivery devices to deliver cellular products for cardiac diseases will be proposed by investigators. Types of delivery devices that have been proposed to date include: transepicardial administration via syringe and needle, transendocardial administration via needle injection catheters, and pressurized intravascular infusion into coronary arteries or veins that may be occluded via a balloon catheter.

   Please provide recommendations regarding strategies for the use of animal models to evaluate the performance and safety of these delivery approaches including, but not limited to, comments on the specific points below.

a. Adverse effects on viability and function of the components of heterogeneous cellular product due to the extended exposure to metals (such as nitinol or stainless steel) and polymers.

b. Direct injection of cellular products into the myocardium usually requires delivery of small volumes of highly concentrated product. This may increase the likelihood of catheter obstruction. Please comment on factors, in addition to "simple" viscosity and cell concentration, that may contribute to this phenomenon.

c. Endovascular injection of cellular products into the myocardium may inadvertently lead to injection into the pericardial space, thoracic space, or systemic circulation. Please discuss ways to prevent unintentional injections into these sites.

d. To what extent are you concerned that depth of injection and spread of the injected cell suspension within the myocardium affect physiologic activity? How should these factors be evaluated in preclinical models of ischemic heart disease?

Clinical:

6. Please discuss the major types of adverse events you believe sponsors should focus upon during the follow-up evaluation of subjects receiving cardiac cellular therapy products. Additionally, what frequency and duration of follow-up do you recommend? In addition to any other events, please consider the following potential adverse pathological and clinical events in your discussion items:

    a. Scar formation
    b. Left ventricular dysfunction and congestive heart failure
    c. Ventricular arrhythmias
    d. Heart block
    c. Neoplasia

7. Some adverse events potentially due to administration of these products, such as ventricular arrhythmias and worsening left ventricular contractility, may be identical to events that occur due to the natural history of the underlying disease. Consequently, adverse events related to the cellular product or its administration might not be discernible without concomitant controls. However, invasive procedures are frequently utilized to deliver these cellular products. Please discuss the pros and cons of using control groups in these early clinical studies, including any need for randomization or masking. Within your discussion, please also comment upon the use of placebos in the studies (e.g., transendocardial saline injection into the heart).