Center for Biologics Evaluation and Research
Biological Response Modifiers Advisory Committee

SUMMARY MINUTES
Meeting #37, March 18-19, 2004
Hilton Hotel, Silver Spring, Maryland

COMMITTEE MEMBERS
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*Not Participating

GUESTS/GUEST SPEAKERS
Richard O. Cannon, M.D.
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Silviu Itescu, M.D.
Robert J. Lederman, M.D.
Philippe Menasché, M.D.
John F. Neylan, M.D.
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FDA PARTICIPANTS
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COMMITTEE MANAGEMENT SPECIALIST
Rosanna Harvey

EXECUTIVE SECRETARY
Gail Dapolito

The summary minutes for the March 18-19, 2004 meeting of the Biological Response Modifiers Advisory Committee were approved on 07/02/04.

I certify that I attended the March 18-19, 2004 meeting of the Biological Response Modifiers Advisory Committee and that this report accurately reflects what transpired.

Gail Dapolito, Executive Secretary

Mahendra S. Rao, M.D., Ph.D., Chair

FDA BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE
SUMMARY MINUTES
MEETING # 37, March 18-19, 2004

The Biological Response Modifiers Advisory Committee (BRMAC) met on March 18-19, 2004 at the Hilton Hotel, Silver Spring, MD. In open session, the committee discussed issues related to the design of early phase clinical trials of cellular therapies for the treatment of cardiac diseases.

On March 18, Mahendra Rao, M.D., Ph.D., Chair, called the meeting to order and introduced the members, consultants and guests. The Executive Secretary read the conflict of interest statement into the public record. This statement identified members and consultants of the committee with an appearance of a financial conflict of interest, for whom FDA issued waivers to participate. Copies of the waivers are available from the FDA Freedom of Information Office.

The FDA provided an introduction and regulatory perspective related to preclinical and clinical development and manufacturing issues for cellular products for the treatment of cardiac disease. Guest experts provided presentations related to 1) clinical and preclinical studies of cellular products for cardiac diseases and 2) cardiac catheter delivery systems.

During the Open Public Hearing the Committee heard comments from individuals of the public, including presentations from researchers at the School of Veterinary Medicine, University of California-Davis and representatives of Genzyme, Gen Vec and Viacel.

The FDA asked the Committee to discuss and make recommendations related to manufacturing, preclinical testing and pilot clinical design questions.

The Committee discussed manufacturing questions related to:

- Intrinsic safety concerns for cellular products for the treatment of cardiovascular diseases and the testing that should be performed to ensure administration of a safe product

- Elements of product identity and characterization necessary to generate meaningful data about safety and efficacy

The Committee agreed on the following outline for the discussion of manufacturing issues:

- Would focus on issues specific to a particular cell type as it is applied to administration of the cellular product into the heart

- Would not focus on issues generic to manufacturing of all cellular products and other Biologics, i.e. testing for adventitious agents, GMP requirements

- Would not include discussion of allogeneic cells due to the fact that autologous cells have been administered in the majority of ongoing or previously conducted clinical trials

- Would distinguish between cells manufactured using *in vitro* culture (such as skeletal myoblasts and mesenchymal stem cells) and cells manufactured without *in vitro* culture (such as bone marrow and peripheral blood progenitor cells)

In a discussion of cellular products manufactured using *in vitro* culture prior to administration, the Committee generally agreed on the following:

- Cultured cells should be tested for the appropriate characteristics and properties periodically during culture and when prepared for administration, and
    - The appropriate characteristics and properties need to be defined for each product and criteria established
    - Appropriate methodologies need to be developed and optimized to determine these characteristics and properties
- More information should be obtained regarding the composition of cellular products administered to patients

  Critical information includes cell subtypes present in the product, differentiation, karyotype stability, serum requirements/exposure, residual culture materials in the final product, cell passage number/doubling time, cell density, and formulation for administration

- Testing for cell damage due to high-pressure delivery in a small gauge needle is critical
    - Large cell types such as myoblasts and mesenchymal stem cells are more likely to be damaged by small gauge needles
- More data are needed on the characteristics of the cells prior to and following administration to monitor cell survival, differentiation, etc.
    - Studies to date suggest that most injected cells die shortly after administration. Therefore, trials need appropriate endpoints that will provide biologic information about the cells that are administered and the cells that survive in order to establish the appropriate characteristics of the desirable cell populations.

- Drug-biologic interactions should be characterized prior to the start of clinical trials
    - Drugs the patient receives concomitantly or prior to the collection or administration of cellular product may affect cell survival, differentiation, and/or other properties.
- Dose-response and cell death rate should be evaluated
    - Once the desirable cell populations are defined and characterized, manufacturing techniques should be developed to maximize their survival. When manufacturing is optimized it will be possible to obtain data on the minimum cell dose necessary for clinical benefit

- The Committee also discussed cells that are manufactured without *in vitro* culture and generally agreed on the following: Cell populations should be characterized by phenotype
    - Need to characterize contaminating subpopulations and determine whether they may cause adverse events.
- Cells should be tested for viability and sterility prior to administration

The Committee also discussed issues that were relevant to cellular products manufactured with or without *in vitro* culture, and generally agreed on the following:

- Surrogates for potency assays are needed that are representative of *in vivo* the function(s) of the cells
    - There are small animal immunosuppressive models available to serve as surrogate potency assays
        - In-vivo potency assays may not be helpful in acute situations
        - Committee split on whether or not in-vivo bioassays must be reproducible between laboratories
- Cannot extrapolate from one cell type to another
- Cannot extrapolate within a cell type if the manufacturing methods differ

The Committee summarized that at this time it is difficult to provide conclusions related to manufacturing issues without a better understanding of the product and offered a broad recommendation for overall consistency and facility quality in the manufacture of cardiac cellular products.

The Committee discussed preclinical questions related to the identification and use of appropriate animal models to:

- Assess the safety of cellular therapies for cardiac diseases:
    - Appropriate species and disease model to provide proof of concept data
    - Appropriate species and disease model to generate pharmacologic, physiologic and toxicologic data
- Assess safe starting dose prior to initiating clinical trials
- Assess acute and chronic toxicity of cellular therapies for cardiac diseases

The Committee generally agreed:

- It is critical to perform preclinical safety studies prior to initiating clinical studies
    - Academic sponsor-investigators need to adhere to the same requirements for preclinical studies as larger corporate sponsors
    - Types of preclinical safety studies may include cell migration ("biodistribution") studies (karoytyping or mouse assay).

- Selection of a preclinical model depends on the clinical population under investigation (i.e., chronic CHF, acute MI, etc.)
    - Safety studies in animals should mimic the clinical trial design as closely as possible
        - There is no perfect animal model of heart failure for human cardiac diseases
        - Large animal models (ex. pigs, dogs, non-human primates) can provide information on the safety and effectiveness of delivery systems, arrhythmogenesis and potentially safe starting doses for the Phase 1 clinical trial
        - Small animal models (ex. immunocompromised rodents) can provide information regarding the ability of the human cellular product to target the myocardium, as well as potential safety issues of the human product

There was discussion among the Committee and participants regarding time of follow-up in animal models in that it was thought that the length of follow-up should be sufficient to identify both potential acute (administration-related) and chronic toxicities (related primarily to the action of the cellular products), although a consensus on a specific timeframe for length of study was not reached.

The Committee discussed device delivery questions related to:

- Potential interactions between cellular products and cardiac catheters
    - Potential adverse affects of catheters on viability and functionality of a specific cell product
    - Factors contributing to potential adverse events (e.g. clogging, cell embolization) by injection via needle catheter into systemic circulation or pericardial space
- Effects of spread of cells in the myocardium and systemic exposure

The Committee recommended in-vitro and in-vivo testing of new catheters and of catheters approved for other indications.. Committee members recognized there are catheter systems currently in use that are very precise and accurate and can be manipulated safely when used in the manner described in the "Instructions for use", however the committee stated animal and bench safety data are needed when these systems are proposed for use in novel sites, for delivery of novel product, or for other off label use. The Committee agreed data should not be extrapolated from one type of catheter/delivery system to another.

The Committee recognized that cell damage could occur

- Due to contact of cellular product with catheter polymers
- Due to mechanical perturbation of heart by manipulation of catheter/needle

- When cells are delivered through a small gauge needle at high pressure.
  - Safety issues related to needle based delivery include
    - significant loss of cells either in the left ventricular chamber or into the myocardial vasculature
    - arrhythmias

In light of these risks, the Committee recommended a conservative approach to clinical studies of cellular products for cardiac diseases that include *in-vitro* and preclinical studies prior to initiating clinical studies, therefore preclinical studies should be designed as follows:

- Must be able to monitor events to assess the risk of micro-emboli, particularly if delivering to arteries or veins
- Follow-up of a month should be sufficient to detect device related injury in an animal model

The Committee discussed clinical questions related to design elements of early-phase clinical trials of cellular products for cardiac diseases including:

- Potential population groups
- Appropriate frequency and duration of patient follow-up
- Appropriate use of control groups in early clinical studies
  - Randomization and masking
  - Use of placebos

The Committee highlighted two potential populations groups:

- Patients with acute myocardial infarction (MI)
- Patients with chronic heart failure

The Committee stated these groups need different monitoring. Acute MI patients can be monitored by non-invasive means such as echocardiograms. Patients might be monitored several times during the first 2 weeks following treatment, then potentially every 3 months and every 6 months. Patients with chronic heart failure will need more intensive monitoring.

Some Committee members suggested patients with currently implanted intracoronary devices might be an appropriate population for initial studies. Other members stated intracoronary devices might interfere with the ability to evaluate surrogate markers such as MRI assessment.

Examples of long-term follow-up of cardiac patients receiving cellular products include:

- Frequent clinic/office visits
- Non-invasive measures such as periodic echocardiograms, radionuclide angiography, exercise capacity

- Autopsy of patients who die
- Monitoring left ventricular function
  - The Committee recommended long-term monitoring of left ventricular function but stated long-term studies should not be required prior to licensure provided there is sufficient preclinical safety data. Long-term follow-up should monitor heart damage as a well as re/trans-differentiation of cells.
- Systemic inflammation markers

There was consensus among the Committee members that in order to determine the definitive safety of cellular products for cardiac diseases, clinical studies should be double blind, randomized trials. The Committee strongly agreed that a control group is necessary to determine if adverse events are due to the therapy or the natural history of heart disease.

The Committee also stated that monitoring plans should be pre-specified in the clinical protocol. The Committee recommended appropriate monitoring so that short-term benefit does not mask long-term failure.

This concluded the Committee discussion and the Chair adjourned the meeting.

For more detailed information concerning the open session presentation and Committee discussion summarized above, please refer to the meeting transcripts available on the FDA website at http://www.fda.gov/ohrms/dockets.

Please submit all external requests to the Freedom of Information Office.