Center for Biologics Evaluation and Research
Biological Response Modifiers Advisory Committee

SUMMARY MINUTES
Meeting #36, October 9-10, 2003
Holiday Inn, Gaithersburg, MD

COMMITTEE MEMBERS
Mahendra S. Rao, M.D., Ph.D., Acting Chair
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Alice J. Wolfson, J.D. [*]
[+] Recused [*] Not Attending

CONSULTANTS
John J. O'Neil, Jr.
Camillo Ricordi, M.D.

GUESTS/GUEST SPEAKERS
Francisca Agbanyo, Ph.D.
James Burdick, M.D.
Thomas L. Eggerman, M.D., Ph.D.
Bernhard J. Hering, M.D.
James Shapiro, M.D., Ph.D., FRCSC
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TEMPORARY VOTING MEMBERS
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FDA PARTICIPANTS
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EXECUTIVE SECRETARY
Gail Dapolito

COMMITTEE MANAGEMENT SPECIALIST
Rosanna Harvey

The summary minutes for the October 9-10, 2003 meeting of the Biological Response Modifiers Advisory Committee were approved on _____.

I certify that I attended the October 9-10, 2003 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.

FDA BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE
SUMMARY MINUTES
MEETING # 36, October 9-10, 2003

The Biological Response Modifiers Advisory Committee (BRMAC) met on October 9-10, 2003 at the Holiday Inn, Gaithersburg, MD. In open session, the committee discussed issues related to manufacturing data and clinical evidence to be provided in a biologics license application for marketing licensure approval of allogeneic islet products to treat type 1 diabetes mellitus. The committee also received updates of individual research programs in the Office of Cellular, Tissue and Gene Therapies.

On October 9, 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 member 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 to the topic. The FDA and the Health Resource Services Administration provided information related to federal oversight of allogeneic islet transplantation. The FDA provided an overview of facilities, processing and quality control issues in the development of islet products. Guest experts provided presentations on current standards in islet processing and the current status of islet characterization and quality.

The Open Public Hearing followed the FDA and guest speaker presentations. The committee heard comments from the audience representing the University of Chicago and the Juvenile Diabetes Research Foundation.

Following the Open Public Hearing the committee discussed the following issues related to manufacturing and product quality of islet products:

- ?? Acceptance criteria for source organs
- ?? Criteria for islet isolation/processing
- ?? Potency of final product
- ?? Product comparability

The FDA asked the Committee to discuss the above issues in terms of recommendations for future biologics license applications (BLA) for islet products.

<u>Acceptance criteria for source organs</u>
The Committee generally agreed that inclusion/exclusion criteria are required for source organs. These criteria could include recommendations related to donor age, BMI, diabetic and infectious disease status, and the organ procurement process. However, the committee stated that sufficient data are not available to make definitive recommendations or to define donor criteria predictive of a successful transplant. The Committee strongly recommended that centers continue to collect as much data as possible to assist in development of criteria that ultimately will aid in predicting transplant success.

Criteria for islet isolation/processing

The Committee agreed there is a need for assays, to characterize an islet product, that can be linked to clinical outcome but, at this time, there are not sufficient available data to make recommendations for specific islet processing criteria/asssays. Given the available data, the Committee stated an in vivo nude mouse assay is the best approach to retrospectively assess islet quality and potency but an in vivo nude mouse assay should not be mandated of IND sponsors or BLA applicants.

There was a general sense among the Committee that islet isolation facilities can/should develop, validate and document standard operating procedures (SOPs) that are followed for each isolation and these SOPs must be submitted in a BLA. Some Committee members stated there are parameters in the standard operating procedures from the current three major islet transplant centers (University of Alberta, University of Minnesota, University of Miami) that can be linked to outcomes. However there are instances when SOPs allow for variations (due to different lots of digestion enzymes; differences in donor organs, etc.) and there is not enough information available to determine how "tweaking" standard procedures could/would affect clinical outcomes.

Potency of final product

The Committee stated they did not have sufficient information to recommend specific potency assays that would be required in a BLA. There was a general consensus from the Committee that it would be difficult to establish criteria that should be mandated in every BLA. The Committee agreed that surrogate potency assays must be validated in a biological assay that measures product functionality.

Again the Committee stressed the need for islet transplant centers to start/keep collecting as much additional information as possible to develop/validate additional criteria.

Product comparability

The Committee agreed applicants need to demonstrate comparability as a measure of a well-defined manufacturing process. The Committee suggested that comparability assays are not performed as routinely as release assays therefore, an in vivo mouse model might be an appropriate comparability assay. Applicants need to demonstrate comparability of a product when there are changes/modifications to the manufacturing process of that product.

The Committee also discussed issues related to comparing products/processes between different clinical sites. Some Committee members stated it is difficult to determine comparability because even standardized potency release assays may not result in the same clinical outcome, as it is yet undetermined if it is an approved product or an approved process that provides a certain clinical outcome. Other Committee members believed products may be reasonably comparable if they meet the same standardized potency release assays.

There was an assessment by the Committee that islet isolation procedures at the three major islet transplantation centers were relatively well standardized and those results appeared comparable. However, it is unclear if data from other centers could be compared or pooled.

This concluded Session I of the meeting on October 9. In Session II, the Committee received updates of research programs in the Laboratory of Immunology and Virology, the Laboratory of Stem Cell Biology, Division of Cellular and Gene Therapies and the Laboratory of Biochemistry, Division of Therapeutic Proteins.

Following Session II, the meeting was adjourned and reconvened on the morning of October 10.

On October 10 the Committee Chair opened the meeting, the Committee was introduced and the FDA provided an introduction to the issues related to clinical development of islet products. Guest experts provided presentations to the Committee on the current status of clinical islet transplantation, allocation of pancreata for whole organ and islet transplantation and, ethical considerations in allogeneic islet transplantation. The FDA presented its perspective on clinical development of islet products.

The Open Public Hearing followed the guest speaker and FDA presentations. There were no requests from the public to address the Committee at this time.

Following the Open Public Hearing, the Committee discussed the following issues related to clinical development of islet products:

- ?? Acceptable clinical outcomes for studies of islet products
- ?? Risk-benefit assessment of islet products

Acceptable clinical outcomes for islet products

The Committee stated quality of life measures - that are determined by randomized, masked, controlled trials – are reasonable measures of clinical outcomes. The Committee noted that quality of life measures are very susceptible to uncontrolled bias and their interpretability is largely restricted to masked studies. The Committee discussed episodes of severe hypoglycemic unawareness resulting in medical intervention by paramedics or a trip to the emergency room as a potential outcome measure for acute diabetic complications.

The Committee noted that important clinical studies should preferably use primary endpoints of clear, clinical meaningfulness. The clinical meaningfulness of asymptomatic hypoglycemia is unclear but the Committee provided a general perception that it is probably important in the clinical management of patients.

Avoidance or minimal use of exogenous insulin, when combined with euglycemia was noted as a reasonable primary endpoint for important clinical studies. Currently, the centers are using euglycemia as an endpoint and the Committee stated that if minimal insulin were administered to maintain euglycemia this should not be considered a failure.

The Committee also generally agreed that efficacy of islet products, at this time, may be measured, in part, by surrogate outcomes, specifically, restoration of eugylcemia or normal gylcemia in transplant patients in response to a glucose challenge. The Committee stated other surrogate measures should also be followed in transplant patients including, glycosylated hemoglobin, hemoglobin A1C and serum C-peptide levels.

Risk-benefit assessment of islet products

The Committee noted that historically controlled clinical data present special challenges. Several members stated that the use of concurrent controls was highly preferable for important clinical studies. However, the Committee stated that the use of historical controls was a reasonable option for definitive clinical studies of islet products, contingent upon the sufficiency of other aspects of the study designs.

There was agreement among the Committee members that the predominant risks of islet product administration were the risks associated with long-term immunosuppressive regimens, the level of expertise of the transplant team/center and the administration procedure itself (bleeding, thrombosis).

The Committee suggested reasonable follow-up would be 1 year for acute complications; 2-3 years for immunosuppressive side effects and 5-10 years for long-term sequelae (retinopathy, vascular function).

There was an overall sense of the Committee that data on the benefit of islets from more than one pancreas were clear and that the number of islets for transplantation could be recommended based on the data provided even though efficacy could not be predicted. The Committee cautioned against generalizing the results of the current studies to a larger population. The Committee suggested researchers gather as much information as possible about the biology of the product in the defined population and as more data become available expand into appropriate populations.

This completed 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.