Biological Response Modifiers AdvisoryCommittee
Meeting #36
Allogeneic Pancreatic Islets for Type 1 Diabetes
October 9-10, 2003

Manufacturing & Product Quality Questions

1. A key component for ensuring control of a validated islet manufacturing process is the use of pre-defined acceptance criteria to ensure that suitable donor organs with maximal potential for yielding adequate numbers of islets are utilized for manufacturing allogeneic islets, while unsuitable organs are excluded. Acceptance criteria may include donor suitability determination, organ characteristics, harvesting conditions, and transport conditions. Most, if not all, of this information is currently collected by sponsors of islet INDs. Please discuss the use of this manufacturing experience data as a basis for developing pre-defined acceptance criteria for source organs.

2. Based on a given donor organ's characteristics, investigators frequently "customize" an islet isolation procedure by using different reagents, reagent concentrations and processing methods such that no two islet isolation procedures are exactly alike. However, cGMPs and BLA requirements necessitate the use of a well-defined, well-controlled manufacturing process. Is it reasonable to expect that criteria or algorithms can be developed, based on data collected during IND studies, to predetermine under what conditions the use of a specific reagent, reagent concentration, or processing method is appropriate?

3. Please discuss any assay or assays that are currently, or could be, performed on the final islet product before patient administration, which may be predictive of the ability of the islets to perform as expected after patient administration.

4. What should be key criteria for demonstrating allogeneic islet product comparability? Please discuss appropriate analytical assays, bioassays, preclinical studies, and clinical studies that may be required.

Clinical Data Questions

1. Please discuss the clinical importance and limitations of each of the outcomes listed below. Please discuss each outcome with respect to its use in providing substantial evidence of efficacy if adequate and well-controlled clinical studies demonstrate a robust and durable treatment effect on the outcome.

    a. "Insulin independence." This outcome may be defined in many ways but, in addition to any other definitions you regard as important, please specifically comment upon the following definition: "cessation of insulin treatment or decrease in insulin requirement in the setting of sufficient glycemic control." If you regard this as an important endpoint, please comment upon what you regard as evidence of "sufficient glycemic control."

    c. Use of hemoglobin A1C, serum C-peptide concentration and mean amplitude of glycemic excursions (independently or in various composites) as measures of glycemic control and/or islet function.

    d. Acute diabetic complications. Please identify those complications that you regard as important outcomes (e.g., episodes of hypoglycemic unawareness, hospitalizations, death).

    e. Long-term diabetic sequelae. Please identify those complications that you regard as important outcomes (e.g., nephropathy, neuropathy, etc.).

    f. Other outcomes you regard as important.

Clinical Data Questions (continued)

2. Regarding the overall clinical development program for a sponsor's allogeneic islets, please discuss the importance and/or meaningfulness of the following types of clinical data with respect to the ability to form a risk-benefit assessment for the product.

   a. Certain types of safety data: Specifically, the nature and extent of "long-term" clinical data that must be submitted in order to form a reasonable risk-benefit assessment. For example, must clinical follow-up for a certain number of subjects extend over a protracted period of time (e.g., 3, 5 or more years)? If so, please comment upon what you regard as a reasonable period of time and describe the types of data that must be obtained during this period, both pre- and post-licensure.

   b. Historically controlled clinical data: Specifically, the appropriateness of the use of historical controls in the development program for a product, and whether data from studies that use no concurrent controls could be sufficient to provide substantial evidence of effectiveness of the product.

   c. Clinical data from studies that only enrolled subjects with certain specific baseline characteristics: Specifically, the use and potential generalizability of clinical data from studies that enrolled a small subset of subjects with type 1 DM (for example, only subjects with a history of certain manifestations of "hypoglycemic unawareness"). Additionally, please discuss those baseline characteristics that you regard as important for a sponsor to consider in the clinical development of their product (e.g., age, extent and nature of diabetic complications, etc.).