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BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE MARCH 20-21, 2000

Briefing Document for Discussion on Human Pancreatic Islets

SCOPE

Issues related to the use of human, allogeneic pancreatic islets for the treatment of type 1 diabetes. This meeting of the BRMAC will focus on product development issues relating to the procurement, processing and characterization of islets. Additional discussion topics include perspectives on preclinical animal models for islets transplantation.

Many issues related to allogeneic islets will be also relevant to other types of islet cell therapies, such as xenogeneic islets, autologous islets or other types of modified islets or islet replacements. However, specific issues raised by the use of non-allogeneic products are beyond the scope of this meeting.

BACKGROUND

The International Islet Transplantation Registry, reports that 329 islet allogeneic transplants were performed between 1989-1999 (see attachments). Analysis of data for 267 transplants revealed that in recipients receiving a single allograft, 10% were insulin independent for ≥ 7 days and 7% were insulin independent ≥ 12 months, with the longest reported case being 70 months. By contrast, data from 114 autologous islet transplants performed during the same time period, show that 69% of autograft recipients remained insulin independent for ≥ 7 days and 50% remained insulin independent for ≥ 12 months, with the longest reported case being 7 years. Approximately 71% of patients who received at least 300,000 of their own islets have remained insulin independent for ≥ 12 months.

Thus, data suggest that technical challenges to producing functional islet preparations, at least in the autologous setting, can be overcome. It is likely that further improvement in success rates for recipients of autologous islet transplants will occur as the impact of processing methods on islet engraftment, survival and function become better understood.

As reviewed by Hering and Ricordi (1999, see attachments), allogeneic islet preparations must overcome other technical challenges, in addition to issues of immunogenicity. Many of these technical challenges relate to methods of pancreas procurement, techniques used in islet processing, and establishment of uniform methods to characterize islet preparations to ensure they consistently retain the functional attributes necessary to give the desired clinical effect.

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REGULATORY FRAMEWORK

FDA is charged with safeguarding the public health while at the same time promoting development of new products. Safety is a primary concern throughout the development of new investigational products.

For biologics, product safety is accomplished by control of the manufacturing process, adequate characterization and demonstration that the final therapeutic product can be manufactured consistently. As experience is gained, the controls and processes used are expected to become more specific based upon accumulated data and documentation.

Since cell and tissue based therapies are generally not considered well defined products, control and characterization of each stage of the production process is critical to ensure product consistency and safety.

Allogeneic islets present an additional level of complexity since they must be isolated directly from a donor pancreas within a short time after organ procurement. It is now recognized that organ procurement and handling (time, temperature, ischemia, etc.), in addition to the inherent characteristics of the donor organ (age, size, etc.), play a significant role in the ability to obtain sufficient numbers of islets that are both viable and functional. Consequently, manufacturing of islets must also encompass control of organ procurement and handling, in addition to processing, to successfully obtain islet preparations of high quality and safety.

Following the submission of an application for an investigational new drug (IND), the FDA has 30 days to perform a preliminary review to ensure that the product meets minimum pre-clinical, product and clinical safety standards for use in humans. In addition to product safety testing, the final investigational product should meet established specifications, such as those for identity, purity and potency for release of the product for patient administration. The types of lot release specifications a product must meet is generally dependent upon the stage of clinical development (e.g., Phase I, Phase II, Phase III). To ensure that product safety testing and lot release specifications are consistent across cellular and tissue based therapies, product reviewers in the Division of Cellular and Gene Therapies use a product review template to assist in ensuring that the IND application contains all of the necessary product information (see attachments).

Since 1991, CBER has received 16 IND applications for islets, encompassing allogeneic, xenogeneic and autologous sources. Based on this review experience and data published by the islet transplant community, CBER has identified a significant number of product development issues related to allogeneic islets and would like to receive outside expert advice on them. Many of these issues concern organ procurement, islet processing and islet characterization. CBER believes that obtaining the advice of the members of the BRMAC at this point in product development is timely given the renewed interest in this field.

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It is expected that the advice obtained will prove useful in establishing the appropriate islet processing controls and types of characterization needed for manufacture of consistent islet preparations which retain desired functional attributes.

It is further hoped that such advice will also facilitate pre-clinical evaluations of different doses of islets and/or immunosuppressive regimens in appropriate animal models, as well as human studies.

MEETING GOALS

- Describe the regulatory framework important for early product development of cell and tissue-based therapies, including both product and pre-clinical issues.
- Obtain advice on appropriate methods of procuring, processing and characterizing human pancreatic islets that will help FDA to effectively regulate this field.
- Obtain advice about the need for investigators to explore pre-clinical animal models to establish proof of concept, and accrue dosing and toxicity data.
- Reach general consensus with investigators in the field of islet transplantation with regard to the safety, processing and characterization necessary to consistently prepare islets of high quality.

ATTACHMENTS:

- Summary Data from International Islet Transplant Registry
- "Islet Transplantation for Patients with Type 1 Diabetes", *Graft*, 2:12-27, 1999
- Somatic Cell Product Review Template