Advancing Transfusion and Cellular Therapies Worldwide

August 08, 2008

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE – Docket FDA-2008-D-0293, 22 May 2008, Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products

Via electronic submission:
http://www.regulations.gov/fdmspublic/component/main?main=SubmitComment&o=09000064805f846d

Dear FDA Dockets Manager:

AABB is an international association dedicated to advancing transfusion and cellular therapies worldwide. Our members include more than 1,800 hospital and community blood centers and transfusion and transplantation services as well as approximately 8,000 individuals involved in activities related to transfusion, cellular therapies and transplantation medicine. For over 50 years, AABB has established voluntary standards for, and accredited institutions involved in, these activities. AABB is focused on improving health through the advancement of science and the practice of transfusion medicine and related biological therapies, and developing and delivering programs and services to optimize patient and donor care and safety.

AABB appreciates the opportunity to comment on this draft guidance document. On behalf of AABB, the following comments to the draft "*Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products"* are submitted.

The comments are arranged in the following format:

Section – language from draft guidance reprinted with page # and other identifying information.

Recommendation – recommendation with rationale.

Background – information supporting the recommendation.

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Section II. Manufacturing Quality and Control Considerations, A. Demonstrating Quality Source Material, page 2:

Health Resources and Services Administration (HRSA) regulates organ procurement and allocation (see 42 CFR Part 121). However, consistency of islet cell product manufacturing is highly dependent on the quality of the organ delivered to the manufacturing facility. Therefore, you may wish to consider having discussions with your local organ procurement organization, regarding collection of data for things such as:

- *organ harvesting procedures,*
- *ischemia time (both warm and cold),*
- *organ preservation methods, and*
- *shipping containers and conditions.*

Recommendation: We recommend that "organ harvesting procedures" and "shipping containers and conditions" be deleted from the list of items for collection of data.

Background: At the present time, each transplant center involved in islet cell manufacture interacts with a large number of Organ Procurement Organizations (OPOs) around the country, each with its own practices for organ procurement, preservation and shipment. Each OPO, in turn coordinates with several surgical teams, which actually harvest the organs, once the consent for donation is obtained. Collection of data on organ harvesting procedures and shipping methods would require extensive and formal OPO education programs as islet transplant programs vary in size and very few transplant programs are able to afford these types of training initiatives.

It is important to note that strides have been taken to standardize donor organ acceptance criteria, in the absence of formally standardized OPO organ procurement practices. It is critical to maintain focus on the necessary data pertinent to delineating the donor, donor history, organ, and organ procurement and preservation characteristics that favorably modulate both the islet isolation and transplantation outcomes.

Section IV. Clinical Study Protocols, B. Eligibility Criteria, page 6:

1. You should consider the following specific inclusion criteria:

- *Subjects should be men or women ≥ 18 years of age who have had documented Type 1 diabetes mellitus for at least five years prior to enrollment in the study. Stimulated C-peptide should be < 0.3 ng/mL.*
- *The distributions of body weight and body mass index (BMI) should be representative of the intended treatment population, subjects with brittle Type 1 diabetes. Similarly, the baseline daily insulin requirements should generally conform to those of the target population. It is best to exclude patients with extremes of body weights or insulin requirements.*
- *Subjects should have a documented history of severe hypoglycemia, metabolic instability, or both. The following are metabolic parameters that may be used for documentation of metabolic instability and hypoglycemia. You need not use every one of these parameters, nor should you be restricted to this list alone. We suggest that you discuss the following specific details with us during an end-of-phase 2 meeting:*
  - *The number of severe hypoglycemic events (e.g., hypoglycemia requiring assistance of another individual) during the year prior to enrollment;*

- *Quantification of hypoglycemia and metabolic lability using for example, the hypoglycemic score (HYPO score) and Lability Index;*
- *Measurement of hypoglycemia unawareness using the Clarke scoring system;*
- *24-hour studies of the mean amplitude of glucose excursion; and*
- *History of frequent hospital admissions for diabetic ketoacidosis.*

2. *Exclusion Criteria Considerations*

You should consider the following specific exclusion criteria:

- *Subjects who are significantly overweight (e.g., BMI > 28 kg/m ^{2}) or underweight.*
- *Subjects with high baseline insulin requirements (>1 unit/kg/day), as the mass of islets that can be successfully transplanted may not be able to supply adequate quantities of insulin to maintain euglycemia in such individuals.*
- *Subjects with a history of the following diabetes-related complications:*
  - *unstable coronary artery disease,*
  - *active or untreated proliferative retinopathy,*
  - *macroproteinuria (> 300 mg albumin/gm creatinine),*
  - *elevated serum creatinine (e.g., > 1.6 mg/dL), or*
  - *clinically significant reduction in glomerular filtration rate (e.g., creatinine clearance < 70 mL/min).*
- *Subjects with Hemoglobin A1c (HbA1c) > 12%.*
- *Subjects with conditions that may place them at increased risk for the use of immunosuppressive agents:*
  - *untreated or inadequately treated hyperlipidemia (e.g., low-density lipoprotein – cholesterol (LDL-C) >130 mg/dL);*
  - *chronic infections such as hepatitis B, hepatitis C, human immunodeficiency virus, and/or tuberculosis;*
  - *lack of previous exposure to Epstein Barr Virus; or*
  - *a history of malignancy with the exception of successfully resected squamous or basal cell carcinoma of the skin or cervical carcinoma in situ.*
- *Subjects with inadequately treated blood pressure elevation (systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg).*
- *Subjects with any medical condition that would place them at increased risk during the islet infusion procedure (e.g., portal hypertension, history of bleeding diathesis, elevated liver function tests, cholecystitis, pancreatitis, or active ulcer disease).*
- *Subjects with panel-reactive antibodies (PRA) to Human Leukocyte Antigens (HLA) > 20%. In subjects with a PRA ≤ 20% and measurable antibody levels, we recommend that antigen specificity be determined.*
- *Subjects who require treatment with systemic glucocorticoids.*
- *Subjects who have recently been treated with any anti-diabetic agent, other than insulin.*

Recommendation: We applaud FDA for proposing standardized criteria for clinical trial subjects, however we believe that this section is too prescriptive and encroaches on the practice of medicine. We recommend that the specific limits for the criteria be deleted from the guidance document and each clinical trial Principal Investigator be permitted to determine those limits based on prior trial history and clinical practice. Specifically, the exclusion criteria for subject BMI appears to be in conflict with the inclusion criteria for subject Body Mass Index (BMI) thus should be deleted from the list of exclusion criteria. Individual investigators should be allowed

to discuss these issues with FDA at an appropriate time, such as during the end-of-phase II meetings.

Background: We do realize that the clinical inclusion/exclusion criteria of the draft guidance closely follow the Clinical Islet Transplant (CIT) Consortia, a multi-center Phase II/III clinical study initiative. However, the CIT Phase II/III clinical trial is a multi-center study, able to reach and screen large numbers of potential study participants. Individual islet transplant centers might not have the ability to access an extended population of patients with long-term *Type 1 diabetes mellitus*, who experience severe metabolic instability and well documented iatrogenic hypoglycemia. It appears that the draft guidance is written in such a way as to leave sufficient room to design specific clinical trials undertaken by individual islet transplant programs. We, therefore, feel that a more beneficial approach is to establish detailed clinical inclusion/exclusion study criteria in individual IND(s) submitted to the FDA for consideration and approval.

Please direct all questions regarding these comments or requests for additional information, to myself at 301-215-6515 or jgiglio@aabb.org.

Sincerely,

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