Guidance for Industry

Considerations for Allogeneic Pancreatic Islet Cell Products

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact Keith Wonnacott, Ph.D., at 301-827-5102.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
May 2008

Table of Contents

Contains Nonbinding Recommendations

Draft – Not for Implementation

Guidance for Industry

Considerations for Allogeneic Pancreatic Islet Cell Products

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to provide recommendations to you, manufacturers, sponsors, and clinical investigators involved in the clinical studies of allogeneic pancreatic islet cell products for the treatment of Type 1 diabetes mellitus. We, FDA, are issuing this guidance to assist you by identifying data and information obtained during investigational new drug (IND) studies that may be helpful in establishing the safety, purity, and potency of a biological product. This guidance is not intended to identify all of the product, preclinical, and clinical data that may be needed to successfully support a biologics license application (BLA).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. MANUFACTURING QUALITY AND CONTROL CONSIDERATIONS

For a BLA, the manufacturing process and the manufacturing facility must be in compliance with the current good manufacturing practice regulations (cGMP) under Title 21 Code of Federal Regulations (21 CFR) Parts 210 and 211 and with the standards of safety, identity, purity, and potency (General Biological Products Standards; 21 CFR Part 610) as well as the other applicable regulations for biological products (see e.g., 21 CFR Parts 600 through 680). Also, because allogeneic islets cannot be terminally sterilized, they must be manufactured using aseptic processing (21 CFR 211.113).[1] The following recommendations are intended to help you navigate some of the challenges unique to islet manufacture that you may encounter in collecting chemistry, manufacturing, and controls data to support approval of your BLA.

[1] For additional information, see Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, available at http://www.fda.gov/cber/guidelines.htm.

A. Demonstrating Quality Source Material

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.

These data will be most useful in manufacturing if they are collected in a way that will allow you to correlate each parameter with manufacturing consistency and clinical outcome. These data should help you and your organ procurement organization to standardize procedures and establish predefined acceptance criteria[2] for harvesting, packaging, and shipping the organ.

Regardless of the degree of standardization of organ procurement, acceptance criteria for organ quality should be established to ensure that unsuitable pancreatic tissue is excluded from manufacturing. At a minimum, the donor testing and screening must meet the requirements for donor eligibility described in 21 CFR Part 1271 (see final rule, "Eligibility Determination for Donors of Human Cells, Tissues and Cellular and Tissue-Based Products").[3] In addition, FDA has published a "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)".[4] We recommend that you review this guidance to ensure that the donor qualification criteria described in your IND are consistent with current recommendations. Additionally, you should collect data and consider establishing acceptance criteria for other characteristics that may affect the quality of the final allogeneic islet cell product such as:

- organ size,
- extent of organ fibrosis,
- donor health status (especially any diabetic conditions),
- donor age, and
- donor body mass index.

---

[2] Acceptance criteria means numerical limits, ranges, or other criteria for the tests described (21 CFR 600.3(kk)). See also HRSA regulations at 42 CFR 121.6(c).

[3] Published in the *Federal Register* of May 25, 2004 (69 FR 29786) available at http://www.fda.gov/cber/rules/suitdonor.pdf. Correction published March 24, 2006 (71 FR 14798) available at http://www.fda.gov/cber/rules/suitdonorcor.pdf.

[4] Announced in the *Federal Register* of February 28, 2007 (72 FR 9007) available at http://www.fda.gov/cber/gdlns/tissdonor.pdf.

B. Control of the Manufacturing Process

Manufacturing process variations may allow for increased yield and quality of islet cells. During investigational studies you should define the critical manufacturing steps that impact safety, purity, and potency and establish controls at these critical manufacturing steps. Examples of manufacturing controls that may improve allogeneic islet cell quality include:

- varying quantity (weight or units) of dissociation enzymes,
- varying digestion conditions such as time, temperature, and shaking,
- using certain additives (DNase, Pefabloc, etc.), and
- using short-term culture of varying length and condition.

For the manufacturing controls referenced above, you should develop and establish specifications that are appropriate for your manufacturing process. Data collected during investigational studies may be important to support both your established specifications and the established limits of process variation. This should allow some flexibility in the exact procedures used for a specific pancreas, but should also ensure that the process is standardized for consistency.

As part of establishing a processing algorithm, you should collect data to demonstrate how processing parameters affect the product potency. We also recommend that you determine, to the extent possible, the effect of processing parameter changes on clinical outcome.

C. Potency Testing

For a BLA, you must use an appropriate assay to measure potency of your allogeneic islet product that meets the regulatory requirements under 21 CFR 610.10. In general, assays for product potency are intended to show the ability of the product to effect a given result (see 21 CFR 600.3(s)).

The accuracy, sensitivity, specificity, and reproducibility of the potency assay must demonstrate lot-to-lot consistency and stability of the product (21 CFR 211.165(a) and (e); see section 351(a)(2)(C) of the Public Health Service Act). Restoration of euglycemia in a diabetic nude mouse currently appears to be the most predictive assay of islet potency; however, results from the diabetic nude mouse model would not be available for product release as a result of the time required for the assay. Therefore, we recommend that, during the IND process, you explore the development of rapid analytical assays for potency.

Collection of data using both the diabetic nude mouse model and your potency assay for product lots manufactured during your investigational studies should aid product development. For example, you could correlate the biological activity of the final

product, as measured using the diabetic nude mouse assay, with a rapid analytical assay performed on the final product to ensure that your analytical assay is a reliable measure of potency.

III. PRECLINICAL CONSIDERATIONS

A. Goals of Preclinical Safety Studies

The overarching goals of preclinical safety studies are: (1) to provide supportive data for an initial safe starting dose and subsequent dose escalation scheme; (2) to aid in determining a risk/benefit assessment for the proposed clinical studies; (3) to identify potential endpoints for detection of toxicity and the clinical monitoring for those toxicities; and (4) to guide in designing appropriate clinical trials. Frequently, many, if not all, of the regulatory expectations for preclinical data to support clinical studies of allogeneic islets can be met by submission of data from previously conducted studies (preclinical or clinical). However, there are circumstances for which additional preclinical studies may be appropriate prior to initiation of clinical studies. For example, novel routes of administration and untested immunosuppressive regimens may create the need for additional studies.

B. Animal Models Appropriate for Use in Preclinical Studies

Preclinical investigations of allogeneic islets have been supported by studies in a wide range of animal species (e.g., mouse, rat, dog, pig, monkey, and baboon). Many different approaches to generating animal models for diabetes have been used, for example, genetic mutation (i.e., inbred non-obese diabetic mice), medication/toxin-induced (i.e., streptozocin treatment, corticosteroid treatment) and pancreatectomy. Each of these models has inherent strengths and weaknesses, thus no single model is completely predictive of the safety and clinical efficacy. In order to generate scientifically valid data for use in safety and "proof of concept" assessments, the allogeneic islet cell product being tested should be biologically active in the animal species used. The study should be long enough to provide data to support the proposed durability of the proposed treatment in clinical use. The duration of the study depends upon the specifics of the animal model, the allogeneic islet cell product and the proposed clinical use.

C. Immunosuppressive Regimen

You should submit preclinical toxicology data in appropriate animal model(s) that are intended to support the safety of the short-term and long-term use of each individual immunosuppressive agent used, as well as any combination of agents, prior to initiation of a clinical trial proposing use of the respective regimen. Data derived from models of whole organ transplantation and previous clinical trials may be adequate to support the use of an immunosuppressive regimen in an IND study of allogeneic islet cell products.

In addition, we recommend that you discuss the adequacy of data from existing reproductive/developmental and carcinogenic toxicity testing of the intended immunosuppressive regimen(s) prior to phase 3 clinical trials.

D. Route of Administration

Some clinical investigators of allogeneic islet cell product IND studies have proposed innovative routes of administration as alternatives to the widely used percutaneous transhepatic portal vein delivery. Alternative routes (such as a trans-jugular approach or intra-operative administration) have been suggested to provide improved islet function, as well as a better overall safety profile. Consistent with the discussion in the March 20 and 21, 2000, Biological Response Modifiers Advisory Committee meeting,[5] if you are proposing innovative delivery methods for allogeneic islet cell products, you should demonstrate an adequate safety profile (e.g., safety of the delivery system and interaction of cells with the components of the delivery system) in animals prior to proceeding to clinical trials.

E. Modified Allogeneic Islet Cell Products

Although details regarding the manufacturing, preclinical, and clinical studies for modified allogeneic islet cell products are beyond the scope of this guidance, a manufacturing change that results in a significant modification of the product characteristics should lead to the consideration of the need for additional preclinical studies. Encapsulation of allogeneic islets provides a useful example of a modification for which additional preclinical studies may be needed. For example, you should consider the need to provide data that support the safety of both the encapsulation material, including the safety of any likely synthetic or degradation products, and the final encapsulated islet product. You should also consider "proof of concept" studies to demonstrate that the encapsulated islets are able to function in an animal model of disease for a sufficient duration to suggest that the risk of clinical administration of the product is likely to be outweighed by the potential clinical benefit. Although, data on immunological effects of encapsulated islets should be collected to the degree possible from the safety and "proof of concept" studies, additional focused preclinical studies and/or clinical monitoring of immunological effects of the encapsulation (both on activity of the islets and potential autoimmune pathologies) should be considered for encapsulated islet products.

F. Potential for Reproductive, Developmental and Carcinogenic Risks

At this time, sponsors of clinical trials for the administration of allogeneic islet cell products which are collected, isolated, and/or processed by conventional methods that are frequently reported in the scientific literature, are not expected to submit preclinical studies to address directly reproductive, developmental toxicity, and carcinogenic

[5] Currently available at http://www.fda.gov/cber/advisory/ctgt/ctgtmain.htm.

potential of these allogeneic islet cell products (e.g., literature). However, the potential need for reproductive, developmental, and carcinogenicity studies should be discussed with us in the context of each individual IND submission as some or all of these studies may be appropriate for those innovative products that incorporate novel features such as encapsulation or non-traditional cell source.

IV. CLINICAL STUDY PROTOCOLS

A. Design

Evidence of clinical safety and efficacy for licensure is generally derived from prospective, randomized, controlled clinical trials. However, for the evaluation of allogeneic islet cell products, a single-arm, open-label trial may be able to provide substantial evidence of efficacy and safety in subjects with metabolically unstable Type 1 diabetes. In this design, a historical control arm may be used.

Below, we will address trial design issues for the evaluation of allogeneic islet cell products in individuals who have ***not*** previously received an organ transplant (e.g., kidney transplant). These trials in patients who have not received an organ transplant are commonly referred to as islet alone trials. Subjects who have received an organ transplant will have ongoing requirements for systemic immunosuppression and therefore the risk/benefit estimate for these individuals will differ. Sponsors contemplating clinical trials to evaluate islet cell products in individuals who have previously received an organ transplant should discuss trial design with FDA as early as possible.

B. Eligibility Criteria

1. Inclusion Criteria Considerations

Subjects enrolled in trials of allogeneic islet cell products should have established Type 1 diabetes with a well-documented chronic history of severe metabolic instability. Subjects most likely to benefit from islet cell transplantation are those who cannot achieve acceptable metabolic control without experiencing multiple episodes of severe hypoglycemia, often with unawareness. Other eligible subjects may have lesser degrees of hypoglycemia, but still cannot be adequately managed with intensive insulin therapy alone. In screening subjects for clinical trials, we recommend that you document that such metabolic instability has persisted despite intensive diabetes management delivered by a qualified diabetes team for at least six months prior to enrollment.

You should consider the following specific inclusion criteria:

- Subjects should be men or women $\geq$ 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 $\leq$ 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.

C. Study Conduct

1. Dosing

Decision criteria for proceeding to a second or third islet cell infusion should be pre-specified in the clinical trial protocol. We recommend that subjects receive no more than three islet cell infusions during the trial.

2. Immunosuppressive Regimens

We recognize the increase in the number and variety of immunosuppressive regimens available to investigators. For pivotal trials, we recommend that you utilize a single immunosuppressive regimen and suggest that you discuss the regimen with FDA.

3. Adverse Experience (Risk) Reporting

All adverse experiences (AEs), serious adverse experiences (SAEs), and deaths must be reported as specified in FDA regulations (21 CFR 312.32). In addition to the required reporting, you should conduct additional analyses focusing on procedure-related experiences and experience related to the immunosuppressive medications.

Single-arm trials do not permit a detailed comparison of treatment group-related AEs. Further, small studies may provide an insufficient database to evaluate less common AEs. If you plan to supplement safety information obtained during the course of the study with that available in literature or in safety databases such as

the Collaborative Islet Transplant Registry (CITR). You should consider using standard induction and maintenance protocols so that the data from your studies can readily be compared to those in the database.

4. Stopping Rules

All pivotal islet cell transplantation trials should have pre-specified stopping rules, with periodic monitoring by an independent Data Safety Monitoring Board.

D. Study Endpoints

As noted above (section IV.A.), single-arm, open-label trials with historical controls provide sufficient evidence of efficacy for patients with metabolically unstable Type 1 diabetes. In part, this is because the major observed benefits (insulin independence, spontaneous loss of hypoglycemia with attainment of good metabolic control) do not appear in the natural course of the disease. The rationale and the selection of endpoints should be discussed in advance with us (i.e., in end-of-phase 2 meetings).

1. Primary Endpoint

A composite endpoint consisting of normal range HbA1c level (e.g., HbA1c $\leq$ 6.5%) and elimination of hypoglycemia is acceptable for licensure. In addition to clinical importance, other advantages of this endpoint include ease of measurement, reproducibility, and relative durability. The data analysis should be based on the proportion of subjects achieving both elements of this composite endpoint. The two components should not be treated as separate co-primary endpoints in the primary efficacy analysis.

Some islet cell transplant recipients who become free of hypoglycemia may demonstrate substantial reduction in HbA1c levels, but fail to achieve a target level of 6.5% or less. This outcome may also represent a clinical benefit. Depending on the patient population, we may consider expanding the primary endpoint to include, for example, a clinically meaningful reduction in baseline HbA1c level and absence of hypoglycemia. This endpoint is best reserved for subjects who have significant hypoglycemia at baseline, despite intensive therapy by a diabetes team. Determination of appropriate reductions in HbA1c from baseline should be discussed with FDA prior to initiation of the pivotal trial.

The primary endpoint should also assess the durability of islet cell transplantation. With this in mind, the primary endpoint should be measured at least 12 months after the final islet infusion.

2. Analysis of Other Key Clinical Outcomes

a. Insulin independence and hypoglycemia

Insulin independence is almost always associated with freedom from severe hypoglycemia. Insulin independence may be employed as a primary or secondary endpoint. If insulin independence is chosen as the primary endpoint, it must be strictly defined, in consultation with us.

b. Measures of glucose metabolic control

Improvements in metabolic control constitute important clinical outcomes of islet transplant trials. Standard methods for measurement of the degree of control of blood glucose include the fasting plasma glucose level, two-hour postprandial plasma glucose level, HbA1c level, and the mean amplitude of glucose excursion. Sponsors may also wish to measure such parameters as insulin sensitivity, glucose variability by continuous glucose monitoring, etc.

Of these metabolic parameters, HbA1c levels have been most frequently used as an endpoint in diabetes trials. HbA1c measurements are convenient, provide an integrated measure of glucose control over time, and have been shown to correlate with progression of diabetes complications. HbA1c measurements can be compared to baseline or to a pre-specified target level (e.g., $\leq 6.5\%$), that are justified by current practice guidelines. Other glucose metabolic parameters may be used as secondary outcomes.

c. Loss of serious hypoglycemia/unawareness

Hypoglycemia may be established and quantified by history (e.g., frequency of events requiring the assistance of another person) or by more precise quantitative means, such as HYPO scores or the Clarke hypoglycemia awareness score. Lability of glucose control may also be quantified using the mean amplitude of glycemic excursion score or the more recently developed Lability Index.[6]

[6] Ryan, E.A., et al., Assessment of the severity of hypoglycemia and glycemic lability in Type 1 diabetic subjects undergoing islet transplantation. Diabetes 2004, 53:955-962.

3. Secondary Endpoints

a. C-peptide

Plasma C-peptide levels have proven essential in monitoring islet graft viability and function during clinical trials and C-peptide levels should be measured during pivotal trials. C-peptide levels should not in themselves be used as primary clinical efficacy endpoints, but may be used as secondary endpoints.

b. Insulin requirements

To the extent that the daily insulin regimen is simplified, reduction in total daily insulin may constitute an added benefit. Furthermore, reduction in insulin requirements reflects graft function. Accordingly, reduction in daily insulin requirements should be measured as a secondary outcome.

c. Health-related quality of life

Although successful islet transplantation should have a major impact on quality of life, measuring the perceived positive and negative outcomes of the transplantation regimen, in an open-label trial is quite complex. We recommend that any assessment of subject reported outcome evaluate both the positive and negative aspects of the subject's experience and that the choice of instrument be discussed with us prior to implementation.

E. Data Analysis Plan

A formal data analysis plan should be submitted to FDA for review, prior to initiation of the study. We recommend the use of composite endpoints that measure glucose metabolic control and the frequency of hypoglycemic events (described above in section IV.D.2.b and c). The primary analyses of all outcomes should be performed on an intent-to-treat (ITT) population. The ITT population should include all enrolled subjects who have received any single component of the transplantation regimen, i.e., attempted transplant or one dose of an immunosuppressive medication. You should include in the data analysis plan the statistical assumptions, rules for imputation of missing data, and descriptions of how all subjects will be accounted for in the analysis. The data analysis plan should include methodology for analyzing the numerous secondary outcomes, recognizing that most of these are inter-related.

The primary analysis should be performed at least one year after the last islet cell transplant. The protocol should include measurement of the primary efficacy endpoint(s) and as many of the secondary endpoints as feasible, for at least one further year (i.e., until two years after the final transplant).

Sponsors who intend to compare their outcomes, and/or supplement their safety databases, with results taken from a meta-analysis of published literature or from other sources (such as CITR) should discuss the suitability of the databases with us prior to initiation of the clinical trial. The statistical approaches to these comparisons should be part of the data analysis plan and should be discussed in advance with us.

F. Follow-Up

Long-term follow-up is important to assess the results of islet cell transplantation as completely as possible. However, the limited number of subjects enrolled in a single-arm clinical trial, with a short study duration, and lack of concurrent controls (as described in section IV. A) preclude a formal assessment of the effect of islet cell transplantation on progression of major complications of diabetes (retinopathy, nephropathy, neuropathy and macrovascular events), long-term durability of therapeutic effect, and collection of AEs due to the islet cell product, or the concomitant immunosuppressive regimen such as an increase in malignancies or infections. Nonetheless, such trials should include provisions for long-term monitoring of renal, ophthalmological (e.g., worsening of retinopathy), neurological, and cardiovascular status (coronary artery disease and peripheral artery disease, including foot ulcers and amputations), islet function, and AEs. Accordingly, long-term follow-up should be built into each of these trials and the informed consent document must explain the purpose and duration of long-term follow-up observations, including the timing and location (office visit, telephone contact, etc.) of data collection (21 CFR 50.25). Details of long-term follow-up should be discussed with us prior to initiation of pivotal clinical trials.