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SELECTED FOOD AND DRUG ADMINISTRATION REVIEW ISSUES FOR REGULATION OF ALLOGENEIC ISLETS OF LANGERHANS AS SOMATIC CELL THERAPY

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The Food and Drug Administration has seen a significant increase in investigational new drug (IND) applications for the use of allogeneic islets of Langerhans to treat type 1 diabetes mellitus. The current regulatory framework for clinical use of allogeneic islets of Langerhans is described. In addition, expectations and considerations for information to be included in the manufacturing, preclinical, and clinical sections of an IND for allogeneic islets of Langerhans to treat type 1 diabetes mellitus are discussed.

Over the past 12 years, the Food and Drug Administration (FDA) has reviewed more than 35 investigational new drug (IND) applications for the use of allogeneic islets to treat type 1 diabetes mellitus. Because of the success reported by the Edmonton group (*1*), there has been a renewed interest in the use of allogeneic islets. The FDA convened an advisory committee on March 20 to 21, 2000 (*2*), and invited outside experts, including many of the contributors to this Forum, to discuss manufacturing, preclinical, and clinical issues related to the use of allogeneic islets for treating type 1 diabetes mellitus. The scope of this article is to provide a description of the IND review process for each of the review disciplines (manufacturing, preclinical, and clinical) as it applies to allogeneic islet products within the context of a somatic cell therapy. Information discussed in this article should not be construed as replacing or superseding any existing FDA policy or guidance relevant to somatic cell therapies or other biologic products, but rather is intended to introduce regulatory concepts to a potential sponsor of an islet product IND.

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REGULATORY STATUS

The FDA does not regulate the use of whole vascularized organs, such as pancreata. However, clinical uses of cells and tissues derived from whole organs typically meet one or more of the criteria (*3*) for regulation as a biologic product. As such, allogeneic transplants of islets of Langerhans fall within the definition of somatic cell therapy (*4*, *5*) under the statutory authority of the Food and Drug Administration and require premarket approval as a biologic product under the Public

Health Service Act (*6*). Islets also meet the definition of a drug under the Federal Food, Drug and Cosmetic Act and are subject to applicable provisions of that law (*7*). Currently, allogeneic islets to treat type 1 diabetes mellitus are considered experimental therapy. Therefore, clinical studies are needed to gather safety and effectiveness data in accordance with FDA IND regulations (*8*, *9*). As a somatic cell therapy requiring premarket approval, a biologics license would be issued on demonstration that allogeneic islets of Langerhans "meets standards designed to assure that the biological product continues to be safe, pure, and potent. . ." (*6*). To date, all active allogeneic islet INDs are in early phase clinical studies.

IND REVIEW PROCESS

The FDA's primary objective for investigational clinical studies is to ensure the safety and rights of subjects in all phases of the investigation. The intent of the IND review process is to ensure that the quality of the scientific evaluation of the investigational product is adequate to permit an evaluation of its safety and effectiveness (*10*). Consequently, the emphasis of the review is on data to support product safety, characterization, manufacturing control, the use of sound scientific principles to support preclinical studies, and a well-developed clinical protocol. This comprehensive review of the IND is accomplished using a team approach consisting of experts in the following disciplines: a product reviewer who examines product safety and manufacturing issues, a pharmacology and toxicology reviewer who examines the supporting preclinical studies, a clinical reviewer who examines the proposed clinical study design and analysis, and a regulatory project manager who is responsible for the administrative management of the IND. Reviewers with additional expertise may be assigned to review the IND as needed. Within 30 days of receiving an IND submission, the FDA is required to notify the IND sponsor of all "clinical hold" issues that must be addressed before treating patients.

MANUFACTURING

The manufacturing review framework for islets is essentially the same as that for any other somatic cell therapy and emphasizes product safety, product characterization, and the importance of stringent manufacturing controls for these complex mixtures to obtain a final product with the desired properties and to prevent the introduction of adventitious agents (*11*).

Product Safety

Ensuring that the final product has been prepared to be as safe as possible for humans is of paramount importance and should be addressed at all stages of manufacturing, with emphasis on aseptic processing (*12*). This would include information on donor screening and testing, and data demonstrating that any materials from an animal or human source used in the manufacturing process are free of adventitious agents. In addition, the final product must undergo tests for sterility, mycoplasma (if cultured), and pyrogenicity or endotoxin. Sterility testing poses a particular challenge for many somatic cell therapy products, such as islets, that cannot be stored until results of sterility culture results are available. Consequently, the FDA has adopted a flexible approach whereby sponsors ensure all reagents used are sterile and obtain negative results from a Gram stain before release of the islet product for clinical use. At the same time, the sponsor also initiates sterility cultures on the final product as required. Because results for sterility are only available retrospectively, the sponsor also must develop a plan of action for patient notification and treatment in case the sterility culture results are positive for contamination. For other types of final product safety testing where results can be obtained within a few hours, such as endotoxin testing, the FDA requires that acceptable test results be available at the time of release of the final product. In some cases, this has meant the islet IND sponsor has had to develop internal testing programs to comply with the regulatory requirements.

Product Characterization

Characterization is particularly important for allogeneic islets, given the variability of the donor organ as a result of variable size, donor age, ischemia time, transport conditions, and the potential need to "customize" the enzyme dissociation and purification process to account for these differing qualities of each pancreas. Product characterization information is used to address important aspects of lot release testing requirements such as those for identity, purity, and potency and will provide critical information to demonstrate manufacturing control (discussed below) and product consistency across multiple islet preparations (lots) to support applications for marketing approval. As a baseline, this should encompass monitoring the composition of the islet preparation, including both β cells and other islet cell types; measuring levels of contaminating, nonislet tissue in the preparation; measuring islet size distribution; and, on the basis of the data collected, establishing specifications for islet identity, purity, viability, measures of function, and other properties as needed.

Control of Manufacturing

Control of the product manufacturing process is achieved largely by identifying critical manufacturing process controls, documenting the processing procedures to be used in preparing the product, establishing a qualification program for key components, developing in-process and lot release specifications to ensure lot-to-lot reproducibility, developing a system to ensure tracking and segregation of products within the facility to prevent mixups and cross-contamination, and implementing a quality control and quality assurance plan. These are important elements of current good manufacturing practices (*13*), which are standards that apply to both the manufacturing process and facilities and are gradually implemented as product development proceeds. In this regard, islets present an additional level of complexity because they must be isolated directly from a donor pancreas within a short time after organ procurement. Working closely with organ procurement organizations and developing acceptance criteria for the pancreata will help assert some control over the source material, because it is understood that organ procurement methodology and the characteristics of the donor organ play a role in the ability to isolate high-quality islets (*14*). FDA review experience of islet INDs has found that controlling the manufacturing process for islets can be difficult to achieve. Consequently, data should be provided demonstrating that under the proposed process, islets can be consistently prepared that would meet basic lot release re-

quirements. Similarly, if the final product is to be transported from the site of manufacturing to a distant clinical site, data are needed to show that under the proposed shipping conditions, the islets remain sterile, viable, and potent. Specifications for an expiration dating period should be established and based on available data. In addition, as product development proceeds, attention must be given to collecting additional data on product stability, development of improved methods for lot release testing (*15*), such as potency, and fully implementing current good manufacturing practices. Finally, it should be noted that the FDA has no expectation that all INDs will follow the same islet manufacturing procedures, particularly when it is evident that technical improvements continue to be made in organ preservation and islet isolation, culture, and preservation (*16–19*).

PRECLINICAL

The criteria used to determine the need for preclinical studies in islet cell applications are not fundamentally different from those used with any biologic product. In essence, preclinical studies (in vivo and/or in vitro) should be performed when they can be reasonably expected to identify, characterize, or quantify a safety concern with the product. The FDA does not require preclinical studies that do not substantially add to the safety database on the product used in the particular regimen proposed. If an application raises safety concerns that can be reasonably addressed by preclinical studies, the FDA will generally request that the sponsor conduct such studies.

The animal models of type 1 diabetes mellitus in the open literature use many species including mouse, rat, dog, monkey, and baboon and various diabetogenic mechanisms such as mutation, streptozocin treatment, corticosteroid treatment, and pancreatectomy. None of the commonly available systems are ideal for modeling human allogeneic islet cell transplant procedures; however, each may be used to address specific questions related to clinical safety. Animal models can be used both to provide scientific rationale and to evaluate possible toxicities before human use for potential therapies including islet cell transplant. Previous investigations have been essential in "proving the concept" of islet cell transplants as a treatment for type 1 diabetes mellitus and have provided essential information on islet cell function, islet cell biodistribution, and islet cell delivery. For example, Shapiro and colleagues (*1*) cited dog studies demonstrating the deleterious effects of prednisone on islet autografts (*20*); dog, mouse, and rat studies to support the activity; combined use and potential synergism of tacrolimus and sirolimus (*21–24*); and comparative studies of human and large-animal isolated islets for development of islet quantification standards (*25*) in the landmark "Edmonton protocol" study. Notably, the in vivo studies of tacrolimus and sirolimus in combination (*23*, *24*) cited by Shapiro et al. were in contradistinction to previous in vitro pharmacology studies (*26*). Future well-designed, focused animal studies have the potential to provide further insights for improvements in islet function, immunosuppressive regimens, and islet product. For example, recent work in animal models has addressed acute islet dysfunction and survival (*27–29*), the immunomodulatory effects of CTLA4-Ig (reviewed in Benhamou (*30*)), cyclosporine A, mycophenolate mofetil, and leflunomide as an immunosuppressive combination in a pig-rat xenograft model (*31*), and effects of different culture conditions on islet function in rodent models (*16*, *32*). In addition to the present armamentarium of systems, at least one novel mutant diabetic mouse has been recently characterized (*33*), and various animal models used to evaluate immunosuppressive regimens for whole-organ transplantation could conceivably be adapted to evaluate similar regimens for the islet transplant setting or for a combined solid-organ, islet cell setting. In order for these models to be of maximal utility, however, they should be thoroughly grounded in the previous work in both fields. The grafting of toxicity endpoints to a well-designed "good laboratory practices (GLP)" or "GLP-like" animal model of disease study can provide valuable data on potential toxicities before human clinical trials. The use of a well-characterized animal model of disease as a framework on which to build a toxicity model includes by design the essential principle that the agents being tested should have biologic activity in the toxicity model for the model to be effective in assessing human risk. Animal studies can be used to support or refute in vitro pharmacologic findings before clinical trials (*26*). In addition, animal studies, in general, have the advantages of increased subject number and increased control over the state of animal health and treatment as compared with human trials, and the benefits of universal necropsy at predetermined times after treatment (or at signs of morbidity) may allow early identification of occult toxicities or areas for increased clinical monitoring.

CLINICAL

The general principles of the clinical review of an islet IND submission are the same as for other biologic or drug therapies. The clinical review is important in all stages of clinical development, which are often categorized by numeric phases (*34*). Generally, considerations of safety assessment are singularly important during phase I testing. These trials are characterized by enrollment of a small number of subjects, usually at one or a few institutions with close subject monitoring to facilitate rapid detection of toxicities. Phase II studies are exploratory in nature, and are designed to obtain early evidence of biologic activity of the product and to optimize the dose and dosing regimen. Phase III trials are designed to establish the product's effectiveness and in the aggregate provide a sufficiently large database that has the potential to show evidence of less common adverse events (AE). Several phase III trials may be needed to provide sufficient efficacy and safety experience for licensure (*35*). These phases of development are not always distinct but serve to provide a conceptual framework for planning study objectives and discussions with the FDA. Most islet cell transplantation protocols previously published can be characterized as a combination of phase I and phase II. Gathering safety information is the paramount objective, but assessment of attainment of insulin independence or decreased exogenous insulin needs are also stated goals. Clinical trials involving islet cell transplantation are expected to be conducted according to good clinical practices (GCP) (*36*). GCP are a set of principles and procedures implemented for protection of the rights and confidentiality of human research subjects and to ensure, to the extent feasible, that relevant scientific data are generated from the trial. The GCP and the FDA regulations outline the responsibilities of the sponsor of clinical research and the investigators directly involved in the clinical studies (*37*).

In summary, the sponsor is responsible for selecting investigators, reporting safety information to the FDA, and informing and monitoring investigators in an accurate and timely fashion. Investigators have responsibility for selection of study participants with adequate information and consent from those selected, welfare of the subjects, compliance with the institutional review board (IRB)-approved protocol and its specified evaluations, timely reporting of safety information to the sponsor and IRB, maintenance of accurate records, and provision of annual updates to the IRB.

In IND submissions received by the FDA for islet cell transplantation, the investigator often is also the sponsor, and one individual performs both of these sets of responsibilities. In these situations, the ordinary checks and balances designed to minimize bias and maximize the safety of subjects are lessened, and therefore the FDA recommends that additional formalized mechanisms be used in these circumstances. One such additional oversight mechanism is a qualified Data Monitoring Committee (DMC), often also called a Data Safety Monitoring Board. Members of the DMC should be independent of the sponsor-investigator, and must be able to analyze critical safety information in real time during the trial. To be an effective instrument, the DMC charter needs to provide authority to recommend safety actions to the sponsor, including a halt to the trial or modifications to the study design. Another important safety mechanism often used in clinical studies is an explicit set of stopping rules. These are detailed rules stating specific numbers of AE, at specific toxicity grade levels (e.g., grade 3 or grade 4 using the National Cancer Institute Common Toxicity Criteria (*38*) or the Modified World Health Organization Grading of Acute and Subacute Toxicities), that will result in suspension of recruitment of new patients pending a full safety review. It is the role of the sponsor-investigator to collect and document AE information, generally through the use of specific Case Report Forms, to update the IRB, and to report safety information to the FDA. Any adverse event experience associated with the use of the drug that is both serious and unexpected (in this case, associated with either the islet cells or any concomitant treatment) must be reported in writing within 15 calendar days. If the AE is life threatening or fatal, the report needs to be communicated by phone or fax within 7 calendar days of the receipt of the information. The annual report will provide a summary of the most frequent and serious AE (*39*).

In essence, an adequate clinical trial safety monitoring program can take many forms and include various combinations of safety monitoring mechanisms. Effective programs, however, always are designed to reflect the realities of the specific protocol and institution with which they are intended to operate. Although individual protocols vary in content, an islet cell transplantation protocol submitted for review under IND typically will contain at least the following elements:

- Background information on the product and the investigator and the institution's prior experience (clinical or in animals) in the field.
- Goals of the proposed study and a scientific rationale for the selected approach to test the experimental therapy (e.g., using particular immunosuppressive combinations or other adjunct therapies, immunoisolation barriers).
- The overall design of the trial, describing whether it is a single-center or multicenter study, open label, single- or double-blind, and single-arm or a controlled study, and whether subjects are randomized or not to assigned treatments for comparison.
- Well-defined eligibility criteria, appropriate for the phase of development, with meticulous consideration related to the balance of risks and benefits, existence of alternative therapies, and other considerations. In the case of islet cell transplantation, eligible subjects are usually patients with type 1 diabetes mellitus who, despite adequate therapy, are unable to maintain adequate blood glucose control, and who have risk factors that justify a more aggressive experimental intervention (e.g., hypoglycemia unawareness). Specific risk factors need to be taken into consideration when limiting eligibility, such as ongoing or future pregnancy or lactation, allergy or contraindication to components of the product or the treatment, presence of active or latent infections or neoplasia (when immunosuppressants are contemplated), local hepatic factor(s) when the islets are to be infused in the portal vein, or other systemic conditions that either significantly limit the potential benefit or endanger the subject.
- Specific and clear criteria defining the groups of subjects to be enrolled in the study. If two or more groups of subjects are intended to be enrolled (e.g., brittle diabetics or diabetic recipients of an allogeneic kidney), clear criteria for each and the specific treatment regimen for each should be stated.
- Adequate safety monitoring of the islet transplantation procedure and the consequences of immunosuppression, at prespecified time points during the procedure and follow-up; in addition, adequate monitoring of the parameters of islet bioactivity, such as appropriate insulin secretory reserve, end-organ sensitivity, and adequate blood glucose control.

As product development proceeds to phase II and III trials, additional complexity in trial design and implementation will be needed to ensure that the data produced are of sufficient reliability to serve as the "substantial evidence" (*7*) required for market approval. In more advanced phases of development, trials intended to be adequate and well-controlled investigations must include prespecified endpoints and a statistical plan for endpoint analyses in their protocols. In addition, in multicenter trials (irrespective of the stage of clinical development), the sponsor must ensure consistency of clinical monitoring, data entry, and AE reporting among numerous sites.

The FDA has reviewed and continues to review new IND submissions that explore innovative approaches to islet cell transplantation. Many of these are variations of the Edmonton protocol that differ in design in areas such as number and source of islets, transplantation procedures, immunosuppressive regimen and concomitant treatments, patient eligibility, endpoints, and stopping rules. The FDA understands that different sponsors will have different approaches to developing a therapy for this disorder and is supportive of individual sponsors choosing the approach they believe will be most beneficial. Each sponsor will formulate a clinical development program to carefully evaluate his or her chosen approach. The FDA, sponsors, investigators, and patients all hope that exploration of novel methods will provide insights ultimately resulting in conquering the challenges of treating type 1 diabetes mellitus.

CONCLUSION

At the present time, all clinical studies using allogeneic islets of Langerhans to treat type 1 diabetes mellitus are required to be performed under IND regulations. The IND regulations and FDA oversight of somatic cell therapies define the parameters that must be met regarding product safety and manufacturing, supporting preclinical studies and human subject protection and trial design. However, within these parameters there is substantial opportunity for innovation that should lead to needed improvements in the ability to prepare high-quality islets from substandard pancreata, the ability to store and transport islets to distant clinical sites, and opportunities to test specific immunosuppressive combinations or adjunct therapies and to carry out evaluations of the appropriateness of various type 1 diabetic subpopulations. Assuming safety and efficacy are demonstrated, the regulatory framework described here is intended to provide an efficient pathway to FDA marketing approval of allogeneic islets of Langerhans for treatment of type 1 diabetes mellitus.

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