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FDA Regulation of Allogeneic Islets as a Biological Product

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Abstract

This article describes the Food and Drug Administration's recent manufacturing review experience with investigational new drug applications submitted for allogeneic pancreatic islets of Langerhans for the treatment of type 1 diabetes mellitus. In addition, considerations of islet preparation issues that will need to be resolved before the submission of a biologics license application are discussed.

Index Entries: Somatic cell therapy; Food and Drug Administration; pancreatic islets; biologics license application; investigational new drug application; cGMP; comparability.

INTRODUCTION

In 1991, the first investigational new drug (IND) application proposing the use of allogeneic islets for the treatment of type 1 diabetes mellitus was reviewed by the US Food and Drug Administration (FDA). In 1993, pancreatic islets of Langerhans and other types of somatic cell therapies were formally determined to be subject to regulation by the FDA as biological products *(1)*. Since that time, the FDA has reviewed more than 35 INDs for use of allogeneic islets to treat this disease. The majority of these INDs have been submitted to the FDA since 2000, a reflection of the renewed interest in this somatic cellular therapy as a result of the success reported by the Edmonton group *(2)*. A significant number of these INDs are intended to treat additional diabetic patient populations; many use different islet manufacturing processes. Although most clinical studies of islets are not at advanced stages, this article is intended to summarize the FDA's review experience with recent islet IND submissions, with particular emphasis on islet preparation issues, and also to look toward the future to identify manufacturing considerations to be addressed before FDA approval of allogeneic pancreatic islets as a licensed biological product for treatment of type 1 diabetes.

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PANCREATIC ISLETS AS AN EXPERIMENTAL SOMATIC CELLULAR THERAPY

Transplantation of allogeneic islets to treat type I diabetes mellitus is considered experimental somatic cellular therapy. Therefore, clinical studies must be conducted in accordance with FDA IND regulations *(3,4)*. The FDA's expectations regarding INDs for allogeneic islets have recently been described in detail *(5)*. FDA review principles are based on the presumption that products under IND will be developed for marketing approval. A biologics license (BLA) will be issued on submission of adequate data to demonstrate safety and clinical efficacy, as well as other assurances that the product "meets standards designed to assure that the biological product continues to be safe, pure, and potent...."*(6)*. The FDA's expectation for licensing of allogeneic islets of Langerhans for treatment of type 1 diabetes falls within this regulatory framework. However, FDA review of recent islet IND submissions suggests that there are numerous issues that remain to be resolved before a BLA is submitted. For example, since 2000, approx 70% of islet INDs have been placed on "clinical hold" after FDA review. Before this, the clinical hold rate for islet INDs was approx 20%. A clinical hold for a phase I study means that a given islet IND submission was considered deficient in safety information in one or more areas such as manufacturing, preclinical data, or clinical protocol design. Reasons for this higher percentage of clinical holds for recently submitted islet INDs is likely the result of a combination of factors including a significant increase in the number of new islet transplant programs becoming involved that are unfamiliar with FDA's IND review process and expectations. Common reasons for placing an islet IND on clinical hold include: (1) failure to submit data demonstrating ability to prepare high-quality islets in the proposed facility; (2) failure to submit supporting preclinical data for novel combinations of immunosuppressives or sites of implantation; and (3) failure to follow good clinical practices. In most cases, islet IND sponsors are able to satisfactorily address these hold issues within a few months.

SOME MANUFACTURING CONSIDERATIONS FOR ISLET PRODUCTS PREPARED UNDER IND

For products prepared under IND, the FDA has adopted a flexible "step-wise" approach for the application of the regulatory requirements for manufacture of somatic cellular therapies. For example, in a phase I study, in which safety is of paramount importance, assurances of aseptic manufacturing must be provided and appropriate microbiological safety testing must be performed. Assuming safety considerations are addressed, it is not compulsory to prepare the product in a facility that is fully compliant with current good manufacturing requirements (cGMP), nor is it expected that the product will be fully characterized or the manufacturing process optimized for phase I. However, as product development and clinical trials advance (phase 2 and phase 3), increased compliance with lot release testing, product characterization, and cGMP requirements must be implemented. By the time a BLA is submitted, all facility requirements are met and associated validations for the manufacturing process are complete. Therefore, for products still under development in the IND process, it is understood that the manufacturing process will continue to be optimized, methods to fully characterize the product undertaken, and product specifications refined based on data collected. However, by the time a BLA is submitted, it is expected that only a single, well-defined manufacturing process will be used that meets established lot release specifications.

SOME MANUFACTURING CONSIDERATIONS FOR ISLETS AS AN FDA-LICENSED THERAPY

In conjunction with evaluating the safety and efficacy data submitted in a BLA for use of

allogeneic islets to treat type 1 diabetes, the FDA will also review the manufacturing data. The FDA will determine if there is a well-established islet preparation process and a track record of product manufacturing consistency; confirm that the islets will be prepared in a manufacturing facility meeting cGMP requirements; and verify compliance with lot release testing requirements (e.g., safety, identity, purity, potency) described in 21 CFR 610 "General Biological Products Standards."

This issue is of particular significance for the islet transplant community because isolation methods to prepare islets for clinical use continue to evolve, with the net result that the FDA frequently receives requests to allow modifications to the islet manufacturing process for ongoing clinical studies under an existing IND. In addition, most groups with islet INDs prepare their islets differently from other groups. Though the FDA has no expectations that different IND sponsors will use the same manufacturing process to prepare safe and functional islets, it can be problematic when a sponsor chooses to change the manufacturing process for an ongoing clinical study.

In general, for early-stage clinical studies, changes to the manufacturing process are acceptable when they are minor and are likely to improve the safety without changing the inherent characteristics of the final product. However, for more significant changes, such as moving from a fresh product to one that has been cultured or cryopreserved, the FDA may ask that a new IND be submitted, particularly in the absence of data showing that final product prepared under the new process is comparable to the old process. The rationale for this approach to biological products such as islets is the recognition that the characteristics of the final product are process-dependent. Changes in manufacturing could result in changes in product safety or clinical outcomes as a result of changes in the composition of the final product (e.g., islet vs nonislet ratio), or in yield, identity, purity, viability, potency, stability, and other key parameters. This is one of the reasons the FDA requests sponsors preparing biological products to collect product characterization data and measure manufacturing consistency between lots. This becomes helpful when changes in product manufacturing are proposed because data will be available to clearly demonstrate how the changes impact the final product prepared under the different processes. In regulatory parlance this is referred to as "product comparability" and is a particularly challenging issue for many biological products, including cellular and tissue-based therapies such as islets. For example, it is unclear how differences in methods to prepare islets by various groups affect the characteristics of the final islet product. On an individual basis, many of these changes appear to be minor, such as including additives (e.g., protease inhibitors, DNase) in the dissociation medium; manual vs semiautomated dissociation; refrigerated or nonrefrigerated COBE cell processor for islet enrichment; or using fresh islets versus short-term culture vs longer term cultured islets. However, cumulatively, these differences are likely to be significant. Without sufficient data to demonstrate that islets prepared using different methods are essentially the same (comparability), it may not be possible for the FDA to accept manufacturing data in a license application that is "pooled" from islet preparations in which the manufacturing process used was different. This becomes increasingly important in the context of who may eventually choose to submit a BLA for marketing approval of allogeneic islets to treat type 1 diabetes. Hypothetically, an individual, an academic center, a consortium of transplant centers, a company, or even a nonprofit entity/special interest group can submit a BLA as long as they have permission to access the primary supporting preclinical, manufacturing, and clinical safety and efficacy data for submittal to the FDA. On a practical level, there are a number of constraints; not the least of which is determining how many islet manufacturing facilities could be encompassed into a single BLA. This would depend to a large extent on each facility using the same islet

manufacturing scheme and specifications in a cGMP environment and demonstrating that the final islet product is comparable with those prepared at all the other manufacturing sites included in the BLA. Facilities using significantly different isolation methods would likely require a separate BLA because of issues of product comparability, as discussed previously. Though a well-defined islet isolation method should be chosen and supported by data, it is not necessary to incorporate all the latest developments and improvements for the manufacturing method to be licensed. Any future manufacturing improvements can be incorporated at a later time after the initial approval as a "supplement" to the license. Consequently, it is likely that the IND review process for allogeneic islets will continue to exist even after issuance of a BLA to "test" manufacturing and clinical improvements, with the resultant data used to supplement the original license.

CONCLUSION

Given the inherent variability of donor pancreata, it may be necessary to grant some flexibility in how allogeneic islets are prepared. However, it is imperative that islet IND sponsors collect sufficient manufacturing data during ongoing clinical studies to demonstrate product comparability, particularly if the process they use has changed over time and especially if one or more groups of islet INDs sponsors is contemplating sharing data to support the submission of a BLA at some point in the future. Sponsors contemplating such approaches are advised to discuss these issues with the FDA well in advance of submittal of a license application.

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