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Regulatory Challenges in Manufacturing of Pancreatic Islets

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Abstract

At the present time, transplantation of pancreatic islet cells is considered an experimental therapy for a selected cohort of patients with type 1 diabetes, and is conducted under an Investigational New Drug (IND) application. Encouraging results of the Edmonton Protocol published in the year 2000 sparked a renewed interest in clinical transplantation of allogeneic islets, triggering a large number of IND applications for phase I clinical trials. Promising results reported by a number of centers since then prompted the Food and Drug Administration (FDA) to consider the possibility of licensing allogeneic islets as a therapeutic treatment for patients with type 1 diabetes. However, prior to licensure, issues such as safety, purity, efficacy, and potency of the islet product must be addressed. This is complicated by the intricate nature of pancreatic islets and limited characterization prior to transplantation. In this context, control of the manufacturing process plays a critical role in the definition of the final product. Despite significant progress made in standardization of the donor organ preservation methods, reagents used, and characterization assays performed to qualify an islet cell product, control of the isolation process remains a challenge. Within the scope of the FDA regulations, islet cells meet the definition of a biologic product, somatic cell therapy, and a drug. In addition, American Association of Blood Banks standards that address cellular therapy products apply to manufacturing facilities accredited by this organization. Control of the source material, isolation process, and final product are critical issues that must be addressed in the context of FDA and other relevant regulations applicable to islet cell products.

ISOLATION OF HUMAN pancreatic islet cells represents a challenge from the standpoint of the applicable regulatory framework. While the starting material for this process is a solid organ, the end result is a cellular product, to which a number of federal and other pertinent regulations apply. The Food and Drug Administration (FDA) is not involved in the regulation of solid organs intended for transplantation. However, it does oversee cellular products and tissues derived from such organs,[1,2] which meet the regulatory criteria for biologic products. As a cellular product derived from a human pancreas, allogeneic islet cells are considered biologic and are subject to regulation by the FDA, under Section 351 of the Public Health Service Act. They also meet the definition of a drug, falling under the regulatory authority of the Federal Food, Drug and Cosmetic Act. In addition, as a biologic product, allogeneic islet cells meet the statutory definition of somatic cell therapy, described as the administration of living autologous, allogeneic, or xenogeneic somatic cells

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manipulated or processed to change their biologic characteristics, or intended as a replacement therapy, as is the case with treatment for diabetes mellitus.[4] The FDA considers somatic cell therapy in the United States to be "experimental," rather than a standard medical practice. Therefore, allogeneic islet cells cannot be used clinically without an Investigational New Drug application or an approved Biologics License Application (BLA) issued to licensed products. In addition, before allogeneic islets can be marketed as a viable therapy for a selected cohort of patients with type 1 diabetes, several issues such as islet safety, potency, and effectiveness need to be addressed. This is complicated by the intricate nature of pancreatic islet cells and a limited number of reliable characterization assays able to accurately assess the quality of the final product and estimate its functional capacity before transplantation.[4] In view of these facts, the manufacturing process (islet isolation) plays a critical role in the standardization and definition of the final product. Before allogeneic islet cells can be licensed, the final product and the process used to manufacture it will need to be defined and validated to demonstrate consistency of the product quality and.[1,2,5]

CONTROL OF THE MANUFACTURING PROCESS

Applicable Regulatory Framework

Several federal regulations put forth by the FDA apply to the manufacturing of pharmaceuticals and biologics, and, therefore, form a regulatory framework for the manufacture of allogeneic islet cells (Table 1). Among these are (1) current good manufacturing practices (cGMPs), described in 21 CFR Part 210 and 211 and are applicable to the manufacture of pharmaceuticals; (2) standards for biologics, described in 21 CFR Part 600, 601, and 610; and (3) current good tissues practices (cGTPs), described in 21 CFR Part 1271, governing donor eligibility rules, establishment of registration, and other tissue practices. In addition, the American Association of Blood Banks (AABB)-accredited facilities involved in the manufacture of cellular products are expected to comply with the current standards for cellular therapy product services (Table 1), developed by the AABB. Despite the clearly defined regulatory framework, control of the islet manufacturing process (ie, source material), process, and the final product, remains elusive.

Manufacturing Controls

Islet cells are isolated from a pancreas procured from a deceased heart-beating donor. There is a paucity of historical evidence regarding the contribution of donor variables toward the islet cell yield and transplant outcome.[6] Donor organs vary in a number of ways, which include donor age, cause of death, body mass index, condition and size of the organ, and the time period between the cross-clamp and the start of processing. In addition, when cGTPs are taken into account, each donor differs in terms of its medical, clinical, and social histories and must be qualified according to these standards before manufacture. To further complicate the process, each transplant center involved in islet cell manufacture deals with a large number of organ procurement organizations (OPOs) around the country, each with its own practices for organ procurement and preservation. This means that education of OPOs regarding donor screening and testing should play an important role in vendor qualification process. Although important strides have been taken to standardize donor organ acceptance

criteria, it is critical to continue to collect 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.

Over the last decade, numerous modifications have been made[6,7] to improve the quantity and quality of islet cell preparations and standardize the islet isolation process. Initial attempts to isolate islet cells from a donor pancreas were not consistent and involved a disruptive mechanical component.[1] However, introduction of the automated method[1] resulted in a continuous release of large numbers of islet cells during the digestion phase. Another critical development that contributed to the consistently improved islet yield was the availability of the new purified enzyme blend, Liberase (Roche), demonstrated to have low endotoxin levels.[8] Liberase, however, is still associated with lot-to-lot variability, specifically, in terms of the relative content of its components, collagenase, type I and II and thermolysin protease. To complicate matters even further, the use of bovine-derived source material during the Liberase manufacturing process resulted in this product being pulled from the market. Several years ago, a new GMP-grade enzyme preparation, NB1 Collagenase (SERVA Electrophoresis GmbH), blended with separately packaged Neutral Protease (NP) NB (SERVA Electrophoresis GmbH), has been tested by several investigators.[9] However, variables such as concentration of both NB1 Collagenase and NP, time and route of their delivery, calcium concentration, and temperature during the digestion and dilution steps seem to have a significant influence on both islet cell yield and purity, and are still being investigated. In addition to variability in the enzyme blends, a number of other factors significantly influence the islet isolation process. Among these are the digestion time and temperature, additives used during the islet isolation process, purification methods, as well as the temperature and duration of the islet culture. Therefore, at the present time, a number of variations in the islet manufacturing process exist. While these allow for significant flexibility and improvement in the islet isolation process, they also serve as a stumbling block for developing a single standardized and reproducible process, which can be compared and validated between various centers. This indicates that critical factors that would allow for the consistent manufacture of allogeneic islet cells of high quality remain to be identified. Albeit, it is the comparability of the islet isolation process that FDA is looking for, before allogeneic islets can be licensed.

Given the inherent variability of donor organs and the islet isolation process, control of the final product becomes essential. Therefore, each final product (lot) has to be characterized (tested) before it can be released. Final product characterization information addresses critical aspects of lot release criteria used to (1) qualify a given lot; (2) demonstrate control of the manufacturing process; and (3) assure the consistency of the final product and its comparability to previously manufactured lots. While some product characterization methods are imposed by applicable regulations, others are developed by manufacturers based on their experience and available scientific data. Regardless of the type of testing performed, each result should provide meaningful scientific data that address product identity, safety, purity, and potency. Product safety includes testing for sterility to assure that the product is free from adventitious agents. Product identity testing confirms that the final product in its labeled container does, in fact, consist of islet cells, which is verified on the product label. Purity testing measures the level of contamination by the nonislet tissue, as

well as the presence of harmful impurities such as endotoxin. Potency measures relevant biological activity of the islet product and should encompass such factors as the composition of the islet preparation, including β cells as well as other islet cell types, viability, stability, islet cell dose, and size distribution. Although the need for analytical methods able to assess islet potency was underlined previously,[4] until recently, a selected test capable of assessing the potency of a final preparation and predictive of a successful islet transplantation outcome was not available. However, a newly developed method for the assessment of cellular composition and β-cell viability[4] has provided an additional opportunity to prospectively assess and correlate β-cell mass and fractional viability of an islet product to its functional performance. This methodology was the first of its kind to not only discern between different islet cell subsets but also identify potentially apoptotic cells. Although not part of the final product lot release criteria yet, data on assessment of cellular composition and β-cell viability are being collected in order to validate this assay.

DISCUSSION

Promising results reported by a number of centers since the publication of the Edmonton Protocol[7,10] prompted the FDA to address the requirements for a possible BLA toward an eventual licensure of allogeneic islets for treatment of patients with the most severe forms of type 1 diabetes. However, before a BLA can be submitted, issues pertaining to safety, purity, efficacy, and potency of the islet product must be addressed. Significant progress has been made toward the standardization of donor organ acceptance criteria, process controls, and final product lot release criteria. However, additional work is necessary and is now underway to reach an adequate level of control and reproducibility in the islet isolation process.

UNCITED REFERENCES

This section comprises of references that occur in the reference list but not in the body of the text. Please position each reference in the text or, alternatively, delete it. Any reference not dealt with will be retained in this section.[3]

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Table 1

Federal and Other Regulations Applicable to the Manufacture of Allogeneic Islet Cells

cGMP 21 CFR Part 210 and 211	cGTP 21 CFR Part 600, 601, and 610	cGTP 21 CFR Part 1271	Standards for Cellular Therapy Product Services
■ Organization and personnel	■ In addition to cGMPs	■ Prevention and introduction,	■ Procurement
■ Buildings and facilities	■ Inspections	transmission, and spread of	■ Processing
■ Equipment	■ Adverse events	communicable diseases	■ Storage
■ Manufacturing procedures	■ Product licensing	■ Receipt and distribution	■ Administration
■ Control of components	■ Final product testing	■ Tracking	■ Quality systems
■ Process and product control	Potency	■ Reporting requirements	
■ Packaging and labeling	Safety	■ Complaints	
■ Holding and distribution	Purity	■ Inspections and imports	
■ Documentation/records	Identity	■ Establishment of registration	