Islets for US Collaborative

THE CURE ALLIANCE

Chicago, March 25th, 2021

The Honorable Xavier Becerra
Secretary,
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201
Secretary@HHS.gov

Dear Secretary Becerra:

Congratulation on your historic nomination to Secretary of the Department of Health and Human Services!

On behalf of the Islets for US Collaborative ("Islets for US Collaborative", www.isletsforus.org), we are writing you to express our deep and urgent concern that patients with type 1 diabetes are being denied access to potentially life-saving therapy because of the FDA's incorrect regulatory approach. In keeping with the National Organ Transplant Act (NOTA), we respectfully call on you to add human islets to the list of human organs regulated under the OPTN Final Rule. We believe that oversight of human islets for transplantation should properly reside with the Health Resources and Services Administration (HRSA) as for all other organs and should not be regulated as a biological drug by FDA. This simple clarification will ensure that Americans with Type 1 diabetes are not deprived of islet transplantation, which is already standard of care therapy in numerous countries including Canada, Australia, Japan, and the EU.

Islets for US Collaborative comprises a group of more than 50 experts who are leaders in the field of transplantation and diabetes. There is a subset of type 1 diabetes patients for whom islet transplantation has been proven to be a life-saving therapy. Despite modern insulin therapy, these patients suffer from debilitating, life-threatening severe hypoglycemic episodes (extremely low blood sugar). These patients and their families live in constant fear of sudden death, develop anxiety, and in many cases, depression.

Islet transplantation is the only minimal invasive procedure that can save these patients and allow them to resume normal life and normal blood glucose control. Islets, which are a subpart of the pancreas, have a distinct structure of micro-organs, have their own internal vasculature, and highly specialized functions regulating the secretion of insulin, glucagon, and other hormones. Islet structure and function are very well preserved during the isolation from a donor pancreas and the transplantation into a recipient. Transplanted human islets secrete insulin in the recipient as they did in the donor and thereby help restore recipients' optimal blood glucose control. The safety and effectiveness of islet transplantation have been demonstrated in over a thousand patients, also through NIH-supported research ($100M).

Pursuant to the 1984 National Organ Transplant Act (NOTA), the Secretary designated HRSA, working with OPTN/UNOS, to develop regulations to ensure the safe and ethical allocation and transplantation of human organs. The OPTN/UNOS framework includes oversight of the transplant programs that provide complex medical therapy through a multidisciplinary team of transplant physicians.

Despite the clear intent of Congress to include human islets, a subpart of the pancreas, within NOTA's definition of human organ, (42 USC § 274e(c)(1) amended in 1988), the definition of human organ under the OPTN Final Rule has not been amended to include human islets. Consequently, **for the past 20 years, FDA has taken the position that islets are a biological drug requiring premarket approval of a biologics license application**. FDA's position has prevented human islets from becoming standard of care therapy in the United States, while it is in Canada, Australia, Japan, and the EU, all of which regulate it as a type of organ transplantation.

To date, islet transplantation has been permitted only in the very limited capacity of sponsored clinical studies, pursuant to FDA's investigational new drug (IND) regulations. In order for transplant surgeons to offer islet transplantation therapeutically (which would expand the availability and permit insurance coverage), the transplant center would first need to submit a biologics license application (BLA) as for any other manufactured drug product. **Essentially, FDA is treating transplant surgeons as manufacturers and human organs as commodities**

The problem may soon get much worse; a BLA for islets was submitted to FDA by a for-profit company and could be approved as soon as April 2021 (an FDA Advisory Committee Meeting to discuss the BLA submission is scheduled for April 15th, 2021). By approving this BLA, FDA would be giving a commercial entity **an exclusive right to commercialize human islets as a biological product for use in transplantation in brittle type 1 diabetes patients**.

We believe that requiring a BLA to distribute human islets for transplantation clearly conflicts with NOTA's prohibition of the sale of human organs and their subparts (42 U.S.C. § 274e) ("It shall be unlawful for any person to knowingly acquire, receive, or otherwise transfer any human organ for valuable consideration for use in human transplantation if the transfer affects interstate commerce."). A BLA is inherently a license to transfer an approved drug product for valuable consideration. By granting a biologics license application (BLA) to a commercial entity, FDA would be authorizing a commercial entity isolate human islets (a subpart of the pancreas) and sell them as a drug to a transplant center. Thus, regulating human islets as drugs and requiring them to be distributed pursuant to a BLA would appear to be in direct conflict with NOTA's prohibition of human organ commercialization.

Of even more concern is patient safety.

Although OPTN/UNOS would allocate a human pancreas to the transplant center, OPTN/UNOS would have no visibility into or control over the actions of the commercial entity as OPTN/UNOS does not oversee the clinical application of drug products. Similarly, the transplant centers, although required to purchase the human islets from the commercial BLA-holder, would have no ability to oversee islet handling, even though this step is integral to the transplant center's role in ensuring the safety and effectiveness of the procedure.

The commercial BLA-holder, and **patients after islet transplantation, would not be subject to OPTN/UNOS post-transplant monitoring of patient outcomes**, as is required of all organ transplantation and which is critical to reassure patients safety and effectiveness of this very complex transplant therapy. Essentially, the lack of regulation of human islets as human organs for transplantation and the absence of related safeguards applied by OPTN/UNOS will be detrimental for our care of patients receiving islet transplantation and puts them in jeopardy.

Of note, once the BLA is approved, the commercial entity will also be entitled to seven years of marketing exclusivity under the Orphan Drug Act, (which applies to drugs but not to human organs) and transplant centers will have no other source of islets for clinical use. Additionally, only those transplant centers that have a valid contract with the BLA-holder for islet supply will be eligible to have donor pancreas allocated by UNOS to them for their patients (2018 OPTN, Notice to Changes to Islet Bylaws, Appendix K, section K3.2.A). Because the transplant center must enter into a commercial agreement with the BLA-holder, the BLA-holder will have significant leverage in the terms of the contract, including the price for the islets, and will thereby have significant influence over which transplant centers are able to offer their patients islet transplants. The price set by the BLA-holder may prevent transplant centers from offering islet transplantation, especially if the cost is not fully covered by insurance. This could negatively affect patient access to transplantation, particularly for patients with low-socio-economic status.

There is clear precedent for the intervention by the HHS Secretary based on very similar patient safety concerns. In 2013 vascularized composite tissues (VCAs), which closely resemble islets, were added to the definition of the human organ under the OPTN Final rule, thereby reallocating oversight from FDA to HRSA in order to provide proper clinical oversight by OPTN/UNOS.

Based on the above, we request the Secretary of HHS to urgently designate allogeneic islets for transplantation as human organs under the OPTN Final Rule.

1. Legally, it would conform with the statutory definition of the human organ under the National Organ Transplantation Act (NOTA).
2. Providing OPTN/UNOS with legal authority for holistic, systematic clinical oversight over islet transplantation (as has been already established for other transplanted organs under NOTA) would protect patients by ensuring the safety and effectiveness of islet transplantation therapy.
3. It would prevent imminent commercialization of human islets, which is prohibited under NOTA, by preventing the FDA from granting a biologics license application (BLA) for human islets to a commercial entity.
4. HHS' decision in 2013 to include vascularized composite allografts (VCAs) under OPTN/UNOS jurisdiction provides a strong precedent for including human islets under the OPTN final rule, as their physical and functional characteristics are very similar.
5. It would not compromise islet processing regulatory oversight, which could remain subject to FDA Good Tissue Practice (GTP) requirements as currently is the case for autologous islets processed in the same manner as allogeneic islets.

Our comprehensive report was published in the American Journal of Transplantation last year (Attachment 1). It describes the unintended negative consequences of the FDA's current regulatory approach and strongly recommends regulatory updates that reflect the current state of scientific knowledge and clinical practice. Unfortunately, our discussions with FDA leadership over the last 18 months have not resulted in any progress toward a solution.

We believe the inclusion of human islets into the definition of human organ under OPTN Final Rule is the optimal solution to address the significant risks to patients described above. It will effectuate the intent of NOTA, has strong precedent (VCAs), and will not require any change to FDA regulations; indeed, FDA's regulations for cellular and tissue-based therapies (HCT/Ps) already exclude human organs regulated by HRSA from FDA oversight. (Attachment 2). We believe the requested action by the i**s critical to ensure that Americans have access to safe, effective, ethical, and affordable islet transplantation as a standard of care therapy**. It is consistent with the current law, beneficial for our patients, and will allow for the progress of the field of islet transplantation, which is only one step from a demise in the US.

We would be grateful for your assistance in resolving this urgent public health issue.

Camillo Ricordi M.D.
Professor of Surgery, Medicine, Biomedical Bioengineering, Immunology at University of Miami
Director of the Diabetes Research Institute (DRI) and the Cell Transplant Center
Expert, Inventor of the islet the transplantation

Piotr Witkowski M.D. Ph.D.
Associate Professor of Surgery
Director, Pancreatic Islet Transplant Program, Director, Transplant Fellowship Program
UNOS, Pancreas and Islet Transplantation Committee

The University of Chicago Medicine
The Transplantation Institute
5841 S. Maryland Ave. MC5027, Room J-517
Chicago, IL 60637
mobile 773-251-6167
pwitkowski@surgery.bsd.uchicago.edu
www.pwitkowski.org

Attachments

1. Witkowski P, Philipson L, Kaufman DB, Ratner L, Abouljoud, Bellin M, Buse J, Kandeel F, Stock P, Mulligan D, Markmann F, Kozlowski T, Andreoni K, Alejandro R, Baidal D, Hardy MA, Wickrema A, Mirmira RG, John Fung J, Becker YT, Josephson MA, Bachul PJ, Pyda JS, Charlton M, Millis JM, Gaglia J, Stratta RJ, Fridell JA, Niederhaus S, Forbes RC, Jayant K, Robertson RP, Odorico J, Levy M, Harland R, Abrams PL, Olaitan OK, Kandaswamy R, Wellen J, Japour AJ, Desai CS, Naziruddin B, Balamurugan AN, Barth RN, Ricordi C. The "Islets for US" Collaborative. The Demise of Islet Allotransplantation in the US: A Call for an Urgent Regulatory Update. Am J Transplant, 2020, Nov 29, doi:10.1111/ajt.16397.
2. Witkowski P, Barth RN, Japour AJ, Bachul PJ, Pyda JS, Nowicki E, Ricordi C. on behalf of the "Islet for US Collaborative". Regulatory updates are needed to prevent the commercialization of islet transplantation in the US. Am J Transplant, 2021, March 8, https://doi.org/10.1111/ajt.16555.
3. Abdulreda MH, Berggren PO· The pancreatic islet: a micro-organ in control. CellR4 2021; 9: e3093.
4. Weir GC, S. Bonner-Weir S. Why pancreatic islets should be regarded and regulated like organs. CellR4 2021; 9: e3083.