From: **Witkowski, Piotr [SUR]** pwitkowski@surgery.bsd.uchicago.edu
Subject: Request for the urgent intervention regarding regulation for islets for transplantation
Date: June 4, 2021 at 5:50 PM
To: Frank Holloman FHolloman@hrsa.gov
Cc: Oyedolamu K Olaitan Oyedolamu_Olaitan@rush.edu, Silke Niederhaus sniederhaus@som.umaryland.edu, Rachel Forbes rachel.forbes@vumc.org, Camillo Ricordi CRicordi@med.miami.edu, Yolanda Becker ybecker@surgery.bsd.uchicago.edu

PW

Chicago, June 4th, 2021

Frank Holloman,

HRSA, Division of Transplantation

Dear Mr. Holloman,

We are writing to you on behalf of concerned members of the UNOS Pancreas and Islet Transplantation Committee as well as the *Islets for US Collaborative* (www.isletsforus.org), a group of more than 50 leaders in the field of transplantation and diabetes (leading members of ASTS, AST, ADA) to request your urgent help and possible intervention to adjust the regulatory framework for islets transplantation in the US.

Human Islets have been regulated by the FDA as drugs and the biological license application (BLA) submitted by drug (islet) manufacturer needs to approve by the FDA. The goal of such regulation is to ensure proper quality and potency of human islet cells before transplantation.

However, on April 15th, 2021, FDA officials after the reviewed the first biological license application for human islets submitted by a private, for-profit company concluded that "**critical quality attributes for islet product, purity and potency did not correlate with the clinical effectiveness** and that **the critical quality attributes may not adequately evaluate lot-to-lot manufacturing consistency".**

It confirmed that the main goal of BLA **cannot be achieved**, that quality and potency of the human islet final product **cannot be confirmed or verified** prior to the transplant.

Therefore, the BLA requirement is obsolete and application of drug manufacturing regulations ineffective to reassure islet product quality and potency.

However, if nevertheless FDA decides to approve the BLA, transplant physicians will have no choice but to purchase human islets of unknown quality and potency for their patients from a commercial BLA holder. The quality and potency cannot be verified, and clinical outcomes remains uncertain.

Altogether, classifying human islets as a drug does not have any scientific basis and is in fact potentially harmful not only to patients but also to further developments in the field as we described in two recent articles (1,2).

As you know and we all know, the quality and potency of any human organs cannot be reassured by any testing prior to the actual transplantation procedure, which is the rationale behind OPTN and UNOS, but not the FDA regulating human organs for transplantation and the reason that regulations developed for drug manufacturing are ineffective when applied to organs (including islets) for transplantation.

The quality and potency of the human organs (including human islets) can only be reassured by the transplant team's continuous assessment of complex clinical parameters and constant supervision during the process of donor selection, pancreas recovery, islet isolation and processing, preservation, transplantation and, finally, post-transplant patient care and monitoring, which is the only way to ensure a safe, effective and appropriate clinical outcome.

Based on this rationale, human islets should be regulated under the HRSA and submitted to the OPTN/UNOS regulatory framework, which is specifically designed and developed to reassure human organ quality and potency as well as safety and effectiveness of the transplantation therapy.

Pancreas as well as other organs are included into the definition of human organs under the OPTN Final Rule which allow them to be regulated by the OPTN and UNOS.

Although, subparts of human organs were included in the statutory definition of human organ under the National Organ Transplantation Act amended (NOTA) in 1988, the human organ definition under OPTN Final Rule has never been amended and islets as subparts of pancreas have not been included.

Therefore, we have requested the Secretary of the Health and Human Services to exercise his authority and include human islets into the definition of human organs under the OPTN Final Rule, which would allow islets to be properly regulated under OPTN and UNOS.

We would be grateful for your assistance in properly resolving this urgent issue and support our request to the Secretary through HRSA to regulate islets as any other organ for transplantation (see attached letter).

Although we published several articles pointing out the problem and proposing solution, the most concise and complete is the

manuscript attached as the interview with Camillo Ricordi, Peter Stock, Ali Naji and myself in press in Transplant International attached for your references to learn more about the problem.

Thank you very much for considering this urgent request.

On behalf of UNOS Pancreas and Islet Transplantation Committee and

Islet for US Collaborative

Piotr Witkowski M.D. Ph.D.
Associate Professor of Surgery
Director, Pancreatic Islet Transplant Program, The University of Chicago Medicine

Oyedolamu Olaitan M.D.

Associate Professor of Surgery
Director, Pancreatic Transplantation Program, Rush University, Chicago

Silke Niederhaus M.D.

Clinical Associate Professor of Surgery

Department of Surgery, University of Maryland School of Medicine, Baltimore, MD

Rachel C. Forbes M.D.

Division of Kidney and Pancreas Transplantation,

Department of Surgery,

Vanderbilt University Medical Center, Nashville, Tennessee, USA

Enclosed:

1. Ricordi C, Naji A, Stock P, Witkowski P, Piemonti L. Islet Transplantation in the US - Quo Vadis? The interview. Transplant International, 2021, *in press.*
2. Witkowski P, Anteby R, Olaitan OK, M.D.4, Forbes RC, Niederhaus S, Ricordi C, Fair J, Harland RC. on behalf of *Islets for US" Collaborative* and *Cellular Transplantation Committee of the American Society of Transplant Surgeons*. Pancreatic Islets Quality and Potency Cannot be Verified as Required for Drugs: Reflection on the FDA Review of a Biological License Application for Human Islets. Journal of Clinical Medicine, 2021. *submitted.*
3. 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. on behalf of *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.
4. Witkowski P, Barth RN, Japour AJ, Bachul PJ, Pyda JS, Nowicki E, Ricordi C. on behalf of *Islets 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.
5. Weir GC, S. Bonner-Weir S. Why pancreatic islets should be regarded and regulated like organs. CellR4 2021; 9: e3083.
6. Abdulreda MH, Berggren PO. The pancreatic islet: a micro-organ in control. CellR4 2021; 9: e3093.
7. Letter to the Secretary of HHS from Islet for US Collaborative on May 23rd, 2021.

1 Article The Intervi...16.pdf

0 Letter to HHS Secret...23.pdf

Letter to UNOS sent Pr...22.pdf