Letter to the Editor: 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.

Running title: Reflection on the FDA Review of a Biological License Application for Pancreatic Islets

Piotr Witkowski, MD, PhD,[1] Roi Anteby, MD[2.3], Oyedolamu K Olaitan, MD[4], Racheal C. Forbes, MD[5], Silke Nieder-haus, MD[6], Camilo Ricordi, MD[7] on behalf of the Islets for US Collaborative; Jeffrey H Fair, MD[8], Robert C Harland MD[9] on behalf of the Cell Transplantation Committee of the American Society of Transplant Surgeons (ASTS)

Affiliations:

1) Transplantation Institute, Department of Surgery, University of Chicago, Chicago, IL, USA
2) Harvard T.H. Chan School of Public Health, Boston, MA, USA
3) Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
4) Department of Surgery, Rush University Medical Center, Chicago, IL, USA
5) Division of Kidney and Pancreas Transplantation, Department of Surgery, Vanderbilt University Medical Center, Nashville, TN, USA
6) Department of Surgery, University of Maryland School of Medicine, Baltimore, MD, USA
7) Diabetes Research Institute and Cell Transplant Center, University of Miami, Miami, FL, USA
8) Department of Surgery, University of Texas Medical branch, Galveston, TX, USA
9) Department of Surgery, University of Arizona, Tucson, AZ, USA

Funding: None
Conflict of interest: None
Data availability statement: Data will be available from the corresponding author on request

Authorship: Conceptualization, P.W., C.R., W.J.; writing—original draft preparation, P.W.; writing—review and editing, P.W, R.A., O.K.O, R.C.F, S.N., J.H.F., R.C.H.; supervision, P.W., C.R.; All authors have read and agreed to the published version of the manuscript.

Corresponding author:
Piotr Witkowski, MD, PhD, Transplantation Institute, Department of Surgery, University of Chicago, Chicago, IL, USA; pwitkowski@surgery.bsd.uchicago.edu; Tel: 773-834-3524;

Dear Editors,

Human pancreatic islets are regulated as a drug in the US, requiring a biological license application (BLA) approval for allotransplantation outside of clinical trials[1]. The goal of the BLA is to prove that drug manufacturing consistently provides a well-defined, high quality product, with verified characteristics that assure the desired clinical effect. Such verification is considered essential for clinical safety and efficacy of any drug.

No US academic institutions have been capable of submitting a BLA for pancreatic islets over the last 20 years, which led to a gradual demise of the field[1]. Recently, a private company has filed a BLA for human islets and the Food and Drug Administration (FDA) Advisory Committee members reviewed the application on April 15th, 2021[2]. Herein, we share findings from that meeting as they have major implications for the field of islet transplantation.

FDA advisors confirmed that islets transplantation has a favorable benefit-risk profile for certain patients with type 1 diabetes. This conclusion is not surprising to the transplant community, as favorable clinical outcomes have been well documented over the last 20 years[1].

However, the main question: whether the BLA should be approved, was not asked and remains unanswered. Moreover, during the meeting, the FDA presented its own analysis of the BLA data. FDA concluded that "the quality and potency of the human islets may not be reliably defined, and critical quality attributes of the islets (islet characteristics based on the release criteria) did not correlate with islet function"[2]. Basically, this means that the main goal of the BLA has not been achieved. Thus, BLA approval has no merit. However, the final FDA decision is yet to be made.

Based on the scientific evidence, we call the FDA to reach the most rational decision: reject the BLA and allow human pancreatic islets to be included into the definition of human organs under the OPTN Final Rule. This will result in proper islet regulation, as with any other organ for transplantation. This was proposed in recent publications and directly to the FDA and Health and

Human Services (HHS)[3,4]. Unfortunately, an FDA representative recently renounced our proposition[5].

Alternatively, an FDA decision to reject the BLA but continue holding the same drug related requirements would inevitably prevent any clinical use of human islets indefinitely in the US. On the other hand, the FDA approval of a clearly deficient BLA, would be detrimental. The BLA holding commercial entity would be authorized to sell human islets of unverifiable quality and potency. Transplant centers will have no choice but to purchase and transplant them in patients. Such regulation would compromise patient safety and FDA credibility. Moreover, it would be impossible to verify the islet manufacturer performance, even when islet graft fails, since the ultimate reason for failure cannot be established.

These new FDAs findings provide further strong evidence that islets do not fit into drug regulatory framework and should be instead included into the organ for transplant regulations by the HHS Secretary.

Acknowledgments: None.

References

1. Witkowski P, Philipson L, Kaufman DB, et al. The "Islets for US" Collaborative. The Demise of Islet Allotransplantation in the US: A Call for an Urgent Regulatory Update. *Am J Transplant*, 2020, 21(4), 1365-1375

2. Cellular, Tissue, and Gene Therapies Advisory Committee April 15, 2021 Meeting Announcement. Available online: https://www.fda.gov/advisory-committees/advisory-committee-calendar/cellular-tissue-and-gene-therapies-advisory-committee-april-15-2021-meeting-announcement-04152021 (accessed on 20 May 2021)

3. Witkowski P, Barth RN, Japour AJ, et al. on behalf of the "Islets for US Collaborative". Regulatory updates are needed to prevent the commercialization of islet transplantation in the US. *Am J Transplant*, 2021, Online ahead of print

4. Islets for US Collaboration. Available online: www.isletsforus.org (accessed on 20 May 2021)

5. Tucker ME. Transplanted Pancreatic Islets: Are They Drugs or Organs? (blog), 14 May 2021. Available online: https://www.medscape.com/viewarticle/951142#vp_2 (accessed on 20 May 2021)