**From:** **Lard, Sherry** Sherry.Lard@fda.hhs.gov
**Subject:** re: Islet transplantation- Urgent Issue
**Date:** December 14, 2019 at 7:13 AM
**To:** Witkowski, Piotr [SUR pwitkowski@surgery.bsd.uchicago.edu
**Cc:** Marks, Peter Peter.Marks@fda.hhs.gov

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Dear Dr. Witkowski,

Thank you for your October 10, 2019 letter regarding the regulatory status of allogeneic human islet cells for transplantation. That letter was referred to me for a response.

As explained in the November 11, 2018 communication from CBER's Office of Tissues and Advanced Therapies, the Agency does not agree that allogeneic pancreatic islets meet the criteria for regulation solely under section 361 of the Public Health Service (PHS) Act and the regulations in 21 CFR Part 1271, nor is transfer of these cells analogous to organ transplantation with regard to safety and efficacy considerations.

Under FDA's risk-based approach for human cell, tissue or cell or tissue-based products (HCT/Ps), in order to be eligible for regulation solely under section 361 of the PHS Act and the regulations in 21 CFR Part 1271, products must meet all of the criteria listed in 21 CFR 1271(a), or be subject to one of the exceptions listed in 21 CFR 1271.15. Products that do not meet all four criteria present safety and/or efficacy questions, including potential concerns related to product consistency, that should be addressed through the premarket review and licensure process. As you note in your October 10, 2019 letter, allogeneic islet cells fail two of the four criteria in 21 CFR 1271.10(a) that must be met for an HCT/P to be regulated solely under section 361 of the PHS Act and the regulations in 21 CFR Part 1271. Accordingly, allogeneic islet cells are regulated as biological products subject to premarket requirements under Section 351 of the Public Health Service Act.

CBER is committed to working with sponsors to address the unique clinical and manufacturing challenges associated with development of cellular therapies. Indeed, our guidance *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions* (https://www.fda.gov/media/120267/download), emphasizes our commitment to facilitating the development of regenerative medicine therapies that are being developed to address unmet medical needs in patients with serious conditions, including rare diseases. We will work with sponsors of these products and encourage consideration of flexible approaches to clinical trial design. For example, as you are aware, CBER is amenable to considering innovative trial designs whereby multiple clinical sites participate in a trial investigating a regenerative medicine therapy with the intent of sharing the combined clinical trial data to support BLAs from each of the individual centers/institutions. This paradigm is described in more detail in our guidance and in the March 2018 article by Drs. Peter Marks and Scott Gottlieb (NEJM 2018; 378: 954-959; https://www.nejm.org/doi/full/10.1056/NEJMsr1715626). We would be happy to meet further with you or your colleagues to discuss how to support a biologics license application (BLA) based on such a development program, as well as other innovative approaches to clinical development that you may be considering.

Sincerely,
Sherry Lard

Sheryl Lard-Whiteford, Ph.D.
Associate Director for Quality Assurance, CBER Product Jurisdiction Officer
Center for Biologics Evaluation and Research
US FDA

CBERProductJurisdiction@fda.hhs.gov
Sherry.lard@fda.hhs.gov

**From:** Witkowski, Piotr [SUR] <pwitkowski@surgery.bsd.uchicago.edu>
**Sent:** Sunday, October 20, 2019 3:12 PM
**To:** Sharpless, Norman (NIH/NCI) [E] <norman.sharpless@nih.gov>
**Subject:** Islet transplantation- Urgent Issue

Dear Dr. Sharpless

We are writing to you not only as to the Commissioner of FDA but as to a physician with extremely urgent and important matter related our patients with life threatening brittle type 1 diabetes mellitus, which can be solved with one administrative decision.

Human Islet isolated for clinical transplantation has been regulated by FDA for the last 30 years as a biological drug (section 351 PHS act) based on the stipulation that islets are/will be "**more than minimally manipulated**" because they can "significantly change their biologic characteristics" during suspension in the media for 72-hour prior to transplantation".

After last 20 years of our research, multicenter clinical trials funded by NIH (>$100M), and over 2,000 islet transplant procedures (CITR), we have proven that human islets are **NOT** "more than minimally manipulated" since **do NOT** "change substantially their biological characteristics" during 72 preservation in the incubator, therefore based on scientific evidence, we are requesting to re-categorize human islet as " **a minimally manipulated human product"** (section 361, PHS Act), as it is classified in all other countries worldwide.

As the consequences of re-categorization, human islet transplantation would be exempt from the Biological License Application and related regulations. BLA requirement has been logistical and financial barrier introduction of islet transplantation as a standard of care procedure in the US for last 20 years. The re-classification would prevent over-regulation, allow patients with life threatening condition to get immediately access to this procedure in the USA as well as maintain its current cost saving huge amount of tax payers money necessary for the reimbursment by the CMS. (see Report- 2)

All leading professional societies and organizations in the US (UNOS/OPTN, ADA, ASTS, ACOT, IPITA) found merit in our request and support it as you can find in attached letter (file 1).

In 1993, FDA commissioner Kessler introducing current regulation stated: **"…** As these novel therapeutic applications are explored and knowledge about the risk and benefit accumulates, the FDA regulatory approach may well be modified…" (NEJM, 1993) .

Our request for assistance was denied by FDA in fall of 2018 (letters attached- 3,4).

Link to article in lay language about described problem (STAT Boston Globe Media, Aug 2019) https://www.statnews.com/2019/08/27/islet-cells-transplant-type1-diabetes/

Patient perspective- https://www.pwitkowski.org/islet-diabetes-patient-stories

Thank you very much for your considerations,

Looking forward to  hearing from you,

Best regards,

**Piotr Witkowski M.D. Ph.D**

Associate Professor of Surgery
Director, Pancreatic Islet Transplant Program
Director, Transplant Fellowship Program

The University of Chicago Medical Center,
Department of Surgery
Transplant Institute
5841 S. Maryland Ave. MC5027, Room J-517
Chicago, IL 60637
tel 773 702 2447  fax 773 702 2126  mobile 773 251 6167
www.pwitkowski.org

**Camillo Ricordi, MD, FNAI**
Stacy Joy Goodman Professor of Surgery and Chief, Division of Cellular Transplantation
Distinguished Professor of Medicine
Professor of Biomedical Engineering, Microbiology and Immunology
Director, Diabetes Research Institute and Cell Transplant Center, University of Miami
Fellow, National Academy of Inventors, USA
Member, Italian Supreme Council of Health

Twitter: @camilloricordi
FB and Instagram: Camillo Ricordi