From: **Witkowski, Piotr [SUR]** pwitkowski@surgery.bsd.uchicago.edu
Subject: FDA rejected URGENT need for regulatory update-islet transplantation for patients with type 1 diabetes,
Date: September 24, 2020 at 3:00 AM
To: Alex Azar HHS Secretary Secretary@HHS.gov
Cc: Eric.hargan@hhs.gov

PW

Dear Secretary Azar,

Thank you for referring our letter regarding urgent need for regulatory update to CBER/FDA.
However, we have just received a negative response from Mr. Richards, Chief of Consumers Affairs Branch.

FDA position is based on the statement that allogeneic islets fail to meet two of four criteria in 21 CFR 1271.10(a) to be regulated under solely under 361 of the PHS act.

1) As we highlighted In our attached report, one of the quoted criterion- specifically 21 CFR 1271 (a) 4(ii) (*b*) "*For allogeneic use in a first-degree or second-degree blood relative" was* established in 1993, and today is outdated and does NOT reflect the current state of scientific knowledge and standards of the clinical practice. Moreover, following that criterion is DANGEROUS for the health and well being of our patients. We are demanding updating it to protect safety of our patients and American people and replacing it with more accurate criterion " For allogeneic use in immunologically compatible recipients"

2) Statement that allogeneic islet more more than minimally manipulated is again outdated, as based on knowledge from the year of 1993. Today, based on over 20 years of basic and clinical research, we have scientifically proven evidence that allogenic islets are NOT more than minimally manipulated during the processing. Ignoring results and conclusions from scientific research again is harmful for our patients and the field.

All together, as leading scientist and clinical leaders in the field of transplantation, we feel obligated to inform you as the the highest health authority in the US and well as American people, that the FDA does NOT follow the current state of scientific knowledge and standards of clinical practice, which can severely compromise public health and well beings of Americans.

In such situation, we feel that only President Trump and his executive order could restore proper regulations regarding islet transplantation and cellular therapy for the benefit of American people.

Thank you very much for your considerations,

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

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Begin forwarded message:

From: Piotr Witkowski <pwitkowski@surgery.bsd.uchicago.edu>
Subject: **URGENT need for regulatory update-islet transplantation for patients with type 1 diabetes**
Date: September 21, 2020 at 12:36:54 PM CDT
To: Alex Azar HHS Secretary <Secretary@HHS.gov>

Dear Secretary Azar,

I represent the leaders of the clinical transplantation in the United States, we are writing to you deeply concerned about our patients with type 1 diabetes. Islet transplantation is routinely used today in Europe, Canada, Japan and Australia. Due to outmoded FDA regulations, which treat islet transplantation as a biologic, we will be unable to help our desperate patients. We have used islet transplantation successfully in clinical trials. The most reasonable approach would be to categorize human allogenic islets for regulation solely under Section 361 of the Public Health Service Act.

Current islet regulation is inappropriate, does not promote expected clinical outcomes and is inefficient for integration into the US healthcare system. It inadvertently commercializes and monopolizes this treatment option for a vulnerable patient population. FDA regulations lag behind the rest of the world.

We support a rationale to consider islets as organs for transplantation and to be handled by the appropriate US agency. Proposed changes to definitions would protect our patients and permit new clinical trials to further advance this promising treatment option. Regulatory updates that incorporate current clinical standards and research findings are indispensable for the re-introduction of ethical, safe, effective and affordable treatment in the United States.

Our last hope is President Trump, as we believe that only his executive order could resolve the problem for the benefit of American people with diabetes as it did last year for patients requiring kidney transplantation. We believe that President Trump's decisive executive action would not only benefit American people but will also highlight all President's and current administration's efforts to reassure public health and safety related to imminent threats of COVID and diabetes.

Below we provide a summary of our proposal for your review.

Thank you very much for your consideration. I would be pleased to discuss this matter with appropriate members of your staff.

Sincerely,

Piotr Witkowski M.D. Ph.D
Associate Professor of Surgery
Director, Pancreatic Islet Transplant Program
Director, Transplant Fellowship Program
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Please find attached:

1. Our request letter to the FDA- Oct 2019

2. Response from the FDA- Dec 2019.

3. Full report regarding the need for urgent regulatory update with list of coauthors- experts in the field .

4. Link to our patient short testimony to illustrate the value of islet transplantation
https://youtu.be/w8xwpuRBaDc

5. Link to more patient testimonies and details regarding procedure. https://www.pwitkowski.org/islet-diabetes-patient-stories

SUMMARY OF THE PROPOSAL OF THE REGULATORY UPDATE

Current regulation related to the islet transplantation in the US.

Based on considerations from 1993, human islets are "more than minimally manipulated" during the preparation for transplantation therefore, need to be regulated under Section 351 PHS Act, as any other biological drug. Consequently, federally funded clinical trials ($100) have been accomplished over 5 years ago, and yet none of the academic centers have been in position to obtain the Biological License Application approval from FDA due to heavy regulatory, financial ($6.7M), logistical and

position to obtain the Biological License Application approval from FDA due to heavy regulatory, financial ($0-7M), logistical and legal hurdles. (100,000 pages of documents, reports of 5 million data points collected 3 times for validation). Lack of BLA approval has been the only major obstacle preventing from islet transplantation to become a standard of care reimbursed procedure in the US. Consequently, today Americans with type 1 diabetes and severe hypoglycemic episodes do not have access to this life-saving procedure.

Current regulations related to islet transplantation in other developed countries

Based on results from US clinical trials, regulatory agencies worldwide confirmed that "Islets are NOT more than minimally manipulated", therefore are not regulated as a drug but as a tissue/organ for transplantation. Such position allows Islet to be isolated from deceased donor pancreas in CGMP facilities, which meet FDA standards for drug production but without need for BLA and drug related regulation. In addition, as organ transplantation, islet transplantation can be performed only within nationally accredited transplant programs, which provides proper clinical oversight and reassure clinical outcomes. Such regulation also prevent from human pancreas and islet from commercialization.

Recommendations.

1. **To update the FDA regulations** to reflect current state of scientific knowledge and clinical practice, which would allow allogenic islet to be exempt from BLA and regulated solely under solely by Section 361 of the PHS Act :

   Specifically, we recommend that the FDA:

   A) Confirm that islet allograft meets minimal manipulation criteria based upon current evidence in the US trials and ongoing practices throughout the world. Specifically, it should be noted that short-term incubation prior to islet allograft infusion does not substantially change the biological characteristics of human islets.

   B) Update criterion 4 (ii) (b), which currently states: "*use for in first and second degree relatives"* to be in accord with current scientific understanding and practice. We propose revising the phrase to "*use in immunologically compatible donors and recipients*" instead, as this is more valid and accurately reflects the current clinical standards of matching in organ and cell/tissue transplantation, and better ensures safety and efficacy of the HCT/P.

2. **Need for additional clinical oversight from OPTN/UNOS**

   In accordance with the current FDA regulations, islets manufactured after BLA approval will fall under the purview of drug regulation without the need for any clinical outcome oversight . However, allo-ITx is similar to solid organ transplantation and involves risks of immunosuppression, transmission of infection and allo-sensitization. Thus, the care of these patients, demands multidisciplinary, highly specialized and properly structured medical support to achieve optimal clinical benefit. There are no legal obstacles to implement such clinical oversight based on the legal opinion from OPTN/UNOS counsel.

   What will happen if we do NOT update the islet allograft regulation?

   As inadvertent negative consequences of current regulation is imminent commercialization and monopolization of human organ-pancreas and islets. For-profit CellTrans submitted BLA in May of this year, and if approved, will obtain exclusive rights for marketing of human islets for 7 years in the US based on holding orphan drug designation. More negative consequences include:

- ethical and legal dilemma of a private company profiting from altruistic human organ donation;
- loss of public trust in the nation's organ donation system may lead to a decline in overall donation rates and risks the lives of people waiting for life-saving organ transplantation;
- cost of the procedure will sky rock from $200,000 exceeding $500,000 per transplant due to enormous cost of BLA and subsequent operation accruing to related regulations;
- price charged for the procedure will be unnecessarily overinflated, essentially cost prohibitive and not reimbursed by payors based on an unfavorable cost/benefit ratio. If private payors cover it, in contrast to Center for Medical Services (CMS), this would disadvantage mostly patients with low social-economic status.
- continuous lack of reimbursement will unequivocally hinder clinical progress and promote indifference in patients with T1DM.
- lack of effective clinical oversight (only voluntary drug adverse event reporting) will lead to poor clinical outcomes
- lack incentives fror manufacturing/quality improvements

What will happen once requested updated regulations for allo-ITx are put in place?

- The human pancreas and iislets will be protected from commercialization and remain a public resource as in any other country.
- BLA related regulatory barriers will be removed, allowing allo-ITx to become a standard-of-care procedure based on the recommendation by experts and professional societies.
- Payors can be approached for reimbursement.
- Not-for-profit academic centers will be able to process the islets, providing safe and cost-effective treatments.

- Clinical oversight from OPTN/UNOS will reassure the optimal outcomes.
- The number of islet isolation centers will increase and competition will drive improvement in quality, cost-effectiveness and patient access to the procedure.
- As the cost of the procedure declines, it will be more affordable and comparable to pancreas transplantation even if two or three allo-ITx's are required.
- Significant allo-ITx clinical activity will reinvigorate interest in research.

Each of these listed factors would further facilitate scientific understanding and clinical progress. Advances in islet (a micro-organ) transplantation would stimulate progress in regenerative medicine, cellular therapies and organ bioengineering. Ultimately, this would benefit our patients and support our national health care delivery system.

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