Dear Advisory Committee Members,

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On behalf of the Islets for US Collaborative, we ask the Advisory Committee to recommend **against approval** of BLA 125734 for **allogeneic human islets**, as it raises significant legal, policy, and public health considerations that **should be first properly addressed** by the Secretary of Health and Human Services.

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Islets for US Collaborative **consists of** more than 40 experts and leaders in the fields of transplantation, diabetes and cellular therapy, **from leading US academic institutions**, who have **longstanding concerns** about the regulatory status of islet transplantation in the US.

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Human pancreatic islets are isolated from deceased donor pancreas and transplanted into the **recipient liver**. Islets transplant recipients require **the same complex medical therapy** including immunosuppression medications as **any other patients** receiving organ transplantation.

**Islets are human micro-organs** and should be regulated as **pancreas and other human organs**, which are not regulated by FDA and **for which**, a BLA is not required.

**Islets are not drugs** and they are **not cellular therapy**.

**Islets as any other organ** for transplantation:

- **Exist naturally in human body**, they are not **artificially manufactured**
- They **consist of many different** types of cells with **unique**, very well integrated function
- **Islets as any other organ** have their **own internal blood vessel** and **neural network**
- They **maintain their own morphology, structure and biological characteristics** during processing and preparation for and after transplantation
- **Islets connect their own vasculature** to the **recipient blood vessel network** after the transplantation
- **Islets as any other organ** cannot be frozen, and can be preserved only for a **short period** of time
- Most importantly, in contrast to drugs, the **potency of islets as any other organ** for transplantation **cannot be reassured by a single test** prior to transplant, **but can be reassured only by the transplant team continuous assessment** of complex parameters and supervision from the moment of donor selection, through pancreas recovery, processing, preservation, transplantation and, **finally post-transplant patient care**, in
order to provide safety, effectiveness and appropriate clinical outcome of the transplant procedure.

- That is why islets as any other organ--cannot be kept on the “shelf” and there are no human organ banks providing organs or islets for transplantation. Organ and islet potency can ONLY be verified based on successful clinical outcome and that is why transplant programs are hold accountable for that.

- As we see and heard today, human islets as well as human organs are naturally highly variable and most importantly

Islets as well as organs for transplant have not and will not fit into the frame of drug regulations, including drug assessment of purity, potency, consistency,

but despite that, organs and islets do benefit patients when they are transplanted in proper settings and with proper clinical oversight.

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FDA’s position that allogeneic islets are drugs and require a BLA, has prevented islet transplantation from becoming a standard of care procedure in the U.S., in contrast to many other countries

Many academic transplant centers in the US have successfully processed human islets for transplantation in clinical trials benefiting diabetic patients, without a BLA over the last 20 years.

However, transplant centers are not drug manufacturers, and are not in a position to sponsor a BLA or comply with FDA’s other drug manufacturing requirements.

BLA submissions are not aligned with the mission of academic transplant centers, they lack of appropriate organizational structure and resources, making it extremely difficult, and practically impossible, to meet necessary BLA demands.

Nor are such requirements in fact necessary for safe and effective islet transplantation.

Consequently, after 20 years of research and clinical trials, islets transplantation is still not broadly available to Americans with type 1 diabetes.

Over the last 5 years, the number of patients treated with islets transplantation dropped to only few per year, in the entire country as depicted in the figure.

In contrast, many other countries in Europe, Canada, Australia and Japan regulate islets not as drugs, but as organs for transplantation and have already implemented clinical islet transplantation as a standard of care procedure. In fact, their programs have directly benefited from US islet isolation and transplantation technology, developed through millions of dollars of federally- funded research.
Granting a BLA to a private, for-profit company, will not solve the problem of islet transplantation in the US but it will lead to its further demise.

Once the BLA is approved, a for-profit entity

- will have a right to commercialize human islets as a biological drug for use in transplantation
  - This is inconsistent with the federal prohibition on commercialization of human organs
- for-profit entity will have 7 years of marketing exclusivity for human islets under the Orphan Drug Act,
- for-profit entity will have a significant leverage in the terms of the contract with any transplant center to provide islets for transplantation, including the price for the islets
- for-profit entity will have significant influence over which transplant centers are able to offer their patients islet transplantation

As a consequence

- Transplant centers will have no alternative source of islets for clinical use
- Transplant centers will have less control over the quality of islets for their patients
- Access to islet transplantation may be reduced because of cost and limited availability of islets

Granting this BLA will also compromise patient safety

- The Health Resources and Services Administration (HRSA) developed regulations to ensure the safe and ethical allocation and transplantation of human organs in the US
- Under HRSA, Organ Procurement and Transplantation Network OPTN/UNOS oversee transplant programs that provide complex medical therapy through a multidisciplinary team of transplant physicians.
- OPTN/UNOS oversight framework is critical to reassure patients safety and effectiveness of this very complex transplant therapy.
  - As a result of the BLA requirement, islets will NOT be included into the complete OPTN/UNOS oversight
    - The commercial BLA-holder, and patients after islet transplantation, will not be subject to OPTN/UNOS post-transplant monitoring of patient outcomes

As the result, islets will be LESS regulated than all other human organs
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As a Solution we propose that
Human islets should be regulated as organs by HRSA through OPTN and UNOS, not as drugs by FDA

The National Organ Transplantation Act defines a human organ to include both whole organs and subparts of organs. (42 USC § 274e(c)(1) amended in 1988). Islets are subparts of the pancreas, and therefore should be regulated as human organs and should not be subject to a BLA.

However, the problem is that the definition of human organ under the OPTN Final Rule has not been amended to match the statutory definition and to include human islets.

Consequently, for the past 20 years, FDA has taken the position that islets are a biological drug requiring BLA.

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We propose that the Secretary of HHS under his authority should 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, 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 secretary’s decision in 2013 to include vascularized composite allografts (VCAs) under OPTN/UNOS, rather than under the FDA jurisdiction, was stimulated by the same organ like nature and safety rationale and provides a strong precedent for including human islets under the OPTN final rule.

5. A solution that regulates islets as an organ rather than a drug, would not compromise islet processing regulatory oversight, which could remain subject to FDA Good Tissue Practice (GTP) requirements as currently is the case for islets for autologous use, processed in the same manner as islets for allogeneic use.
FDA’s position that a BLA is required for unrelated allogeneic islets is inconsistent with the agency’s approach to autologous islets.

- If islets are for use in the same person (autologous use) - no BLA is needed, and no drug manufacturing conditions are required for processing (just GTP)
- If islets are for use in the first-/second degree relatives in allogeneic settings - again, no BLA is needed, no drug manufacturing conditions are required for processing (GTP)
- But If islets are for use between unrelated people in allogeneic use - then BLA and drug related regulations (GMP) are indeed required

Although the same islet isolation technique is used for allogeneic and autologous islets, only unrelated allogeneic islets require a BLA.

Despite FDA applies different regulatory requirements depending only on clinical use, FDA in fact does NOT provide any regulatory oversight over clinical transplantation.

It is not FDA, but OPTN/UNOS regulations which provide an appropriate regulatory framework for the clinical use of allogeneic organs and islets and assure safety and effectiveness, therefore islets should be rather regulated as organs, not as drugs.

Regulating islets under OPTN/UNOS will allow academic centers to continue process and transplant human islets, which leads to healthy competition stimulating progress in the field and access to the procedure for the patients.

Here is another illustration

On the left - Application of drug manufacturing regulations does not provide appropriate regulatory oversight of patient care and clinical outcomes,

in contrast on the right, OPTN/UNOS constantly monitor transplant programs for appropriate clinical outcomes as a condition for maintaining the accreditation. Outcomes are also under public scrutiny and available on the UNOS public website.
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In conclusion

- BLA 125734 raises significant legal, policy, and public health considerations that should be properly addressed by the Secretary of HHS
- We are concerned that the Advisory Committee may have not been aware of the adverse, potentially irreversible consequences to patient safety and access of a recommendation to approve the BLA
- We therefore ask the Advisory Committee to recommend against approval of BLA 125734 for allogeneic human islets for transplantation.

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This is a list of supplementary materials, which includes our request letter to the Secretary of HHS, as well as our articles with more information related to this presentation.

Thank you very much