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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** receving 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.**

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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

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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.**

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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.

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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