Clinical and Regulatory Hurdles Facing Islet Transplantation in the US

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FDA quality assurance for drugs and biologics

For the BLA approval a sponsor needs to prove that:
1. The drug is clinically safe and effective for the proposed use and that the benefits outweigh the risks
2. The labeling is appropriate and contains all necessary information about the drug
3. Manufacturing methods provide consistently drug/biologic with specific characteristics, which are correlated with the appropriate clinical outcome.

- Defining appropriate drug/biologic identity, strength, quality, and purity, which is proven to be responsible for appropriate clinical outcome, is a cornerstone for the drug/biologic quality assurance system.
- Confirmation of those quality (attributes) characteristics in the final product assures safety and effectiveness of the clinical application.
FDA drug/biologics quality assurance does not work for human organs for transplantation

Preclinical studies (in-vitro, animals)  Clinical Trials Phase ½ Phase 3 multicenter  New Drug Application Biologic License Application  Human organ quality cannot be reassured prior to Tx by commercial suppliers  Tight oversight of the organ commercial suppliers Does NOT guarantee of the safety and effectiveness of Tx

The current clinical preparation of the human organ for Tx would NOT get BLA approval from the FDA

Criteria for the BLA approval:

1. Organ transplantation is safe and effective for the proposed use and that the benefits clearly outweigh the risks
2. The labeling is appropriate and contains all necessary information about the organ
3. Human organs are naturally highly variable, and their appropriate characteristics for required clinical outcome cannot be defined and verified prior to transplantation

Therefore,

- Human organs require different quality assurance system than FDA applies for drug/biologics
- Special quality assurance system for human organ for transplantation was developed under HRSA rather than FDA oversight, and has been implemented successfully by the OPTN/UNOS in the US
Human organ quality assurance

Appropriate quality of the human organ for transplantation is reassured directly by the transplant programs by continuous oversight of every element of the organ transplantation procedure.

Transplant programs closely oversee or execute on its own and take ultimate responsibility for:

- patient selection and preparation
- organ donor selection and preparation
- organ procurement
- organ assessment and acceptance
- organ shipping
- organ preparation for transplant
- transplantation procedure
- recipient complex medical care after the transplantation
- the ultimate clinical outcome

Full control over all elements of organ transplantation and ultimate responsibility for the outcomes is a cornerstone of the human organ quality assurance as a part of the organ transplantation quality, safety and effectiveness assurance system implemented by OPTN/UNOS.
Organ transplantation in the US

Congress - National Organ Transplantation Act 1983 (NOTA)
(defines human organ, its distribution, regulation and protection from commercialization)

Health and Human Services (Secretary)

Health Resource Services Administration (HRSA)

Organ Procurement and Transplantation Network (OPTN Final Rule)

United Network for Organ Sharing (UNOS)

OPTN/UNOS accredited Tx Programs

OPTN/UNOS accreditation is based on the implementation of appropriate structure, systems, procedures, protocols and personnel, which assures patient safety and effectiveness of the Tx procedures. This includes appropriate infrastructure, qualified personnel, clinical protocols, SOPs, QC/QA system.
Organ transplantation in the US

- National Organ Transplantation Act 1984 (NOTA)
- Health and Human Services (Secretary)
- Health Resource Services Administration (HRSA)
- Organ Procurement and Transplantation Network (OPTN Final Rule)
- United Network for Organ Sharing (UNOS)
- OPTN/UNOS accredited Tx Programs

Importantly, Transplant Programs are scrutinized by:

- **OPTN/ UNOS**
  The maintenance of the UNOS accreditation is contingent on extensive reporting and providing expected clinical outcomes as an ultimate measure of the quality of the transplantation and medical care provided

- **Scrutiny of outcomes by insurance company**, which relates to contracting for Tx procedures

- **Public scrutiny** of clinical outcomes reported on the UNOS website for each Tx program
Regulation of islet Tx in the US

NOTA 1983
1989 amendment included subparts of human organs into the definition of human organ

HRSA

Human organs

OPTN/UNOS
(human organ definition under Final Rule was not updated to include islets)

kidney, pancreas, heart etc for Tx

Health and Human Services (Secretary)

FDA (1993)

Not human organs
Human cells, tissues products (HCT/Ps)

PHS 351 Act

HCT/Ps as biologics (drugs)

Clinical trials, BLA,

- more the minimally manipulated (biological characteristics is substantially altered)
  - stem cells, Tregs, CART cells,

- allogeneic islets isolated from unrelated deceased donor pancreas

- autologous islets isolated from patient own pancreas

PHS 361 Act

HCT/Ps exempt from BLA

- for homologous use
- minimally manipulated
- autologous use
- allogeneic use in first and second family members
Timeline of islet allotransplantation in the USA

- Edmonton Protocol, *NEJM*
- Insulin independence after ITx
- FDA confirms allogeneic islets for Tx needs to be regulated and developed as any new drug

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**U.S. FOOD & DRUG ADMINISTRATION**

Vaccines, Blood & Biologics

**Dear Colleague Letter to Transplant Centers: Allogeneic Pancreatic Islets for Transplantation**

Department of Health and Human Services
Public Health Service
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

September 8, 2000
Timeline of islet allotransplantation in the USA

**USA**

- 2000: FDA confirms allogeneic islets for Tx needs to be regulated and developed as any new drug
- 2002: Edmonton Protocol, *NEJM*
  - Patients insulin free after ITx
- 2007: IND/IRB
  - Phase 1/2 clinical studies
- 2014: IND/IRB
  - Phase 3, multicenter CIT Consortium
- 2020: REQUIREMENTS
  - Biological License Application (BLA) approval by the FDA to the individual centers
  - Cost $4-5M

**Other countries**

- 2007: $100M NIH, JDRF, centers own funding
- 2014: FDA confirms allogeneic islets for Tx needs to be regulated and developed as any new drug
- 2015: Demise of the field of Islet Tx as no transplant centers have been able to submit BLA
- 2020: ITx cannot be SOC and reimbursed without BLA approval
FDA’s position that allogeneic islets require a BLA has prevented the procedure from becoming standard of care in the U.S., in contrast to many other countries.

Academic transplant centers
• processed human islets for transplantation successfully without BLA in clinical trials over last 20 years
• are not drug manufactures, are in position to sponsor the BLA or comply with other FDA’s drug manufacturing requirements
• have a different mission
  • lack of appropriate organizational structure and resources
  • unable to meet financial and legal BLA demands

Consequently, after 20 years of research, islets transplantation still cannot be broadly available to Americans with Type 1 Diabetes.
Islets alloTx is a **recognized and approved medical procedure**. It is reimbursed by the national health systems in Canada, UK, Italy, Switzerland, Nederland, Sweden, Norway, Czech R, Poland, France, Japan.

Outside the US, Islet Tx has not been regulated as a drug, but as organ/tissue for transplantation (no BLA required).

**Requirements**
- Biological License Application (BLA) approval by the FDA to the individual centers.
- Cost $4-5M.

**Timeline of islet allotransplantation in the USA**

- 2000: FDA confirms allogeneic islets for Tx needs to be regulated and developed as any new drug.
- 2002: Edmonton Protocol, *NEJM*
- 2003: Patients insulin free after ITx
- 2007: IND/IRB Phase 1/2 clinical studies
- 2007: IND/IRB Phase 3, multicenter CIT Consortium
- 2014: Requirement
  - Biological License Application (BLA) approval by the FDA to the individual centers.
  - Cost $4-5M.
- 2020: Demise of the field of Islet Tx.
- 2020: Outside the US, Islet Tx has not been regulated as a drug, but as organ/tissue for transplantation (no BLA required).
- 2020: $100M NIH, JDRF, own funding.
Timeline of islet allotransplantation in the USA

USA

FDA confirms allogeneic islets for Tx needs to be regulated and developed as any new drug

$100M NIH, JDRF, own funding

IND/IRB Phase 1/2 clinical studies

IND/IRB Phase 3, multicenter CIT Consortium

REQUIREMENTS
- Biological License Application (BLA) approval by the FDA to the individual centers
- Cost $4-5M

Demise of the field of Islet Tx

CellTrans submitted BLA, pending review...

BLA approval for CellTrans
- Tx of islets provided by CellTrans could be recognized as a SOC and reimbursed

Other countries

Edmonton Protocol, *NEJM*
- Patients insulin free after ITx


2007

2002

2000

2000

2000

2000

2000

2000
Will the FDA approve the BLA for CellTrans?

For the BLA approval the sponsor needs to prove:

1. The drug is clinically safe and effective for the proposed use and that the benefits outweigh the risks
2. The labeling is appropriate and contains all necessary information about the drug
3. Manufacturing methods provide islets consistently with a specific biological characteristics correlated with appropriate clinical outcome.

After the BLA review during the FDA’s Advisory Committee Meeting on April 15th, 2021

• Advisors voted 12 to 4 (with one abstention) YES to the FDA’s question about safety and efficacy of islet transplantation (confirmation that islet Tx has overall favorable benefit – risk ratio for some patient with T1DM)

• However, Dr. Jayachandra presenting results of CBER/FDA review of the CMC (chemistry, manufacturing, controls) part of the CellTrans BLA, concluded that:

“…the critical quality attributes (purity and potency) of the islets

1. did not correlate with clinical effectiveness, and
2. may not adequately evaluate lot-to-lot manufacturing consistency

Now, FDA needs to make determination whether BLA for Celltrans will be approved or rejected. FDA’s decision is expected within next 2 months.
FDA determination that “...the critical quality attributes (purity and potency) of the islets did not correlate with clinical effectiveness, and may not adequately evaluate lot-to-lot manufacturing consistency” practically means that

• appropriate quality of the isolated islets cannot be determined prior to transplantation based on islet characteristics
• there was no consistency in islet characteristics in other words
• It cannot be determined, if islets after isolation have appropriate quality to provide expected beneficial outcome to the patient after transplantation in other words:
• clinically sufficient quality of the islets cannot be confirmed prior to transplantation

In such situation granting the BLA approval to the manufacturer would provide false reassurance to the customers about the quality of the offered islets
• CellTrans- for-profit, private company would obtain permission to market and sell human islets, which quality cannot be verified.  
• Transplant centers will have no choice but purchase human islets of unknown and unverifiable quality from CellTrans and transplant them to patients.

In my and many experts in the field opinion, such situation should not take place and the BLA should not be approved.
After 20 years of clinical testing as required by FDA, it has been shown that the application of the drug manufacturing (GMP) protocols and BLA requirement failed to assure appropriate human islet quality, which would translate to assurance of patient safety and clinical effectiveness.
Should the BLA be required and should the islets continue be regulated as drugs?

Taking into considerations two main facts that:

1. It has been proven that the quality of the human islets cannot be controlled and determined by the application of the drug manufacturing regulations and BLA requirements, and that
2. requirement of the BLA and drug regulation have been main obstacle to clinical implementation of islet transplantation by the academic centers as a standard of care for patients with T1DM in the US

We conclude that allogenic islets should be exempt from BLA requirement

There is also plenty of arguments that islets should not be regulated as biologics, but rather as any other organ for transplantation, which would properly secure patient safety and clinical outcome.

As leaders in the field of islet transplantation, we have been aware of the need for regulatory update and BLA exemption based on finding from multiple clinical trials and has been requesting that from FDA for last several years.
Regulatory Inquires

- 2018 August - CIT Consortium Investigators inquire about possible BLA exemption - regulation under PHS Act 361 instead of 351,
- 2019 Letter to the FDA Commissioner signed by 15 leaders of CIT Consortium, and leaders of the ASTS, AST, ADA
- 2020 February, November,
- 2021 January - meeting with CBER/FDA leadership and discussion
- FDA conclusion - allogeneic islets still needs to be regulated as drug and BLA is required

Islet for US Collaborative

- Experts and leaders of ASTS, AST, ADA undertaken joint efforts to analyze the situation, point out to detrimental effect of current regulations and proposed solutions
American Society of Transplant Surgeons (ASTS)

Marwan S. Abouljoud, MD; President
Kenneth Andreoni, MD; Council-At-Large
Robert Harland, MD; Cellular Transplantation Committee
Lloyd Ratner, MD; Immediate Past President
Dixon B. Kaufman, MD PhD; Past President
Peter Stock, MD PhD; Past President
Mark A. Hardy MD; Past President
Jason Wellen, MD
Peter L. Abrams, MD
Marlon Levy, MD
Chirag S. Desai, MD
Michael Millis, MD
Robert J. Stratta, MD
Jonathan A. Fridell, MD
Tomasz Kozlowski, MD
Rolf N. Barth, MD
Piotr J. Bachul, MD
Jordan S. Pyda, MD, MPH
Kumar Jayant, MD
Martin Wijkstrom MD
Joseph Leventhal MD PhD
Shakir Hussain, MD
Abbas Rana, MD

American Diabetes Association (ADA), Experts in Diabetology and Islet Transplantation

Louis Philipson, MD, PhD; Immediate Past President, John Buse, MD, PhD; Past President
R. Paul Robertson MD; Past President
Rodolfo Alejandro, MD
David Baidal, MD
Melena Bellin, MD
Fouda Kandeel, MD, PhD
Jason Gaglia, MD
Raghavendra G. Mirmira, MD, PhD

International Pancreas and Islet Transplantation Association

James F. Markmann, MD, PhD; President
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University of Wisconsin, Madison, WI
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Washington University, St. Louis, MO
Wake Forest, Winston-Salem, NC
Indiana University, Indianapolis, IN
Oklahoma University, Oklahoma City, OK
University of Chicago, IL
University of Chicago, Chicago, IL
Harvard Medical School, Boston, MA
University of Chicago, Chicago, IL
University of Pittsburgh, Pittsburgh, PA
Northwestern University, Evanston, IL
Detroit Medical Center, Detroit, MI
Baylor Medical College, Houston, TX

United Network for Organ Transplantation (UNOS)

David Mulligan, MD; President
Silke Niederhaus, MD; Immediate Past President
Rachel C. Forbes, MD; Chair of Pancreas ad Islet Tx Committee
Oyedamola K. Olatunji, MD; Vice Chair of Pancreas ad Islet Tx Committee

American Society of Transplantation

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John Fung, MD, PhD; Council

American College of Surgeons

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Experts in Cellular Therapy

Yossi Schwartz, MD; Secretary, World Apheresis Association
Amrittha Wickrema, MD
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Islet Processing Experts

Karolina Golab, PhD
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Drugs, Biologics, and Medical Device Development Advisor

Anthony J. Japour, MD

Legal Expert (FDA Regulations)

Gail Javitt, JD, MPH
M Eryk Nowicki JD
Arguments against BLA approval and for islets to be regulated as other organs for transplantation

- we presented during the FDA's Advisory Committee Meeting on April 15th, 2021 during the Open Public Hearing Session
- Accepted for publications in the Journal of Clinical Medicine and Transplantation.
1. **Islets are human micro-organs** and should be regulated consistent with pancreas and other human organs, which are not regulated by FDA, and for which BLA is not required

- Islets are not drugs, and are not a type of cell therapy,

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

- are built from many different type of cells with very well-integrated function
- have own internal blood vessel and neural network
- maintain own morphology and structure during processing and after transplantation
- connect own vasculature to the recipient blood vessel network after the transplantation
- cannot be frozen
- can be only preserved for short period of time

- **require constant supervision by the transplant team** starting from the moment of donor selection through pancreas recovery, processing and preservation, transplantation and finally post-transplant patient care in order to assure safety, effectiveness and appropriate clinical outcome of the transplant procedure
2. **Requiring BLA does not provide reassurance of organ quality**

**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 of the field ITx**

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
- 7 years of **marketing exclusivity** under the Orphan Drug Act,
- a significant leverage in the terms of **the contract** with every transplant center, including **the price for the islets**
- a significant influence over which transplant centers are able to offer their patients islet transplants
- the **quality of the islets cannot be verified prior to Tx**, which may lead to failures and patient harm

**As a consequence**

- Transplant centers will have no alternative source of islets for clinical use
- Transplant centers will have no control over the quality of islets for their patients
- Access to islet transplantation might be reduced because of cost established by a private company and limited availability of islets
3. Granting a BLA will compromise patient safety

- The Health Resources and Services Administration (HRSA) developed regulations to ensure the safe and ethical allocation and transplantation of human organs.

- Under HRSA, Organ Procurement and Transplantation Network (OPTN) and United Network for Organ Sharing (UNOS) oversees transplant programs that provide complex medical therapy through a multidisciplinary team of transplant physicians.

- UNOS/OPTN oversight framework is critical to reassure patients safety and effectiveness of this very complex transplant therapy which extends beyond the transplant procedure.

  - 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.
    - Islets will be LESS regulated than all other human organs.

- Regulating islets as drugs subject to a BLA results in removal of the critical safeguards applied by OPTN/UNOS, which will jeopardize the safety of our patients.
4. **Solution**

Human islets should be regulated as organs under HRSA through OPTN and UNOS, not as drugs by FDA

- Congress included human organ subparts into the NOTA’s definition of human organ in the amendment in 1988, which applies to islets as subparts of the pancreas (42 USC § 274e(c)(1) amended in 1988), **but**

- the definition of human organ under the OPTN Final Rule has not been amended to include human islets.

- consequently, for the past 20 years, FDA has taken the position that islets are a biological drug requiring premarket approval of a biologics license application.
4. **Solution**

The Secretary of HHS 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 1988).

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’ decision in 2013 to include vascularized composite allografts (VCAs) under OPTN/UNOS jurisdiction provides a strong precedent for including human islets under the OPTN final rule.

5. It 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.
Additional arguments that regulation of islets without BLA requirements and under OPTN/UNOS oversight as for organs would work well

- Over last 20 years there has been over 2,000 islet transplant procedures performed without BLA in the multiple US centers and worldwide with appropriate patient safety and effectiveness (data from the NIH sponsored Collaborative Islet Transplantation Registry and multiple publications).

- Islet transplantation has been successfully regulated as organ/tissue for transplantation in Canada, several EU countries, Australia allowing for implementation as a standard of care.

- Chair of the FDA Advisory Committee, as well as several other committee members highlighted that they voted YES confirming safety and efficacy islet transplantation not based on BLA data but mainly based on data of nearly 700 ITx procedures performed in Edmonton, Canada, where islets have been regulated as organ/tissue for transplantation over last 20 years, processed and transplanted in the same transplant center without commercial islet supplier.
Arguments that regulation of islets without BLA requirements and under OPTN/UNOS oversight as for organs would work well

• Inclusion of the human islets into the definition of the human organ under OPTN Final Rule would lead to following expected positive effects:
  • Implementation ITx as a SOC since the last obstacle- BLA requirement is removed
  • SOC approval would lead to procedure reimbursement in the accredited transplant centers
  • Processing of islet Tx can take place in multiple independent Tx centers, which could stimulate positive competition, promote cost-effectiveness, and improve access to the procedure for diabetic patients
  • Unnecessary cost of the implementation of drug related FDA regulation would be avoided, making the procedure more affordable
  • Reimbursement of the procedure would offset of the cost of the research related to ITx, which would stimulate progress in the field
  • Progress in ITx would stimulate progress in other beta cell replacement therapies and in regenerative medicine.
We hope that our voice and arguments will be heard and taken into consideration by the FDA, HRSA and HHS, while making the decision about the BLA and updates in the regulations regarding allogeneic islet for transplantation.

It is critical for the sake of our patients and future of the field in the US.

Thank you very much