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The Demise of Islet Allotransplantation in the US: A Call for an Urgent Regulatory Update
The “ISLETS FOR US” Collaborative

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Abbreviations:

Allo-ITx – pancreatic islet allotransplantation
BLA- Biologics License Application
CITC- Clinical Islet Transplantation Consortium
CFR- Code of Federal Regulations
CMS- Centers for Medicare and Medicaid Services
FDA- Food and Drug Administration
GMP - Good Manufacturing Practice
cGMP- current Good Manufacturing Practice
JDRF- Juvenile Diabetes Research Foundation
HLA – Human Leukocyte Antigen
HRSA- Human Resources Services and Administration
HCT/Ps - human cell and tissue products
NIH- National Institutes of Health
ODD – Orphan Drug Designation
OPTN- Organ Procurement and Transplantation Network
PHS- Public Health Service
SHE- Severe Hypoglycemic Episodes
SRTR- Scientific Registry of Transplant Recipients
T1DM- Type 1 Diabetes Mellitus
UNOS- United Network for Organ Sharing

Abstract

Islet allotransplantation in the United States (US) is facing an imminent demise. Despite nearly three decades of progress in the field, an archaic regulatory framework has stymied US clinical practice. Current regulations do not reflect the state-of-the-art in clinical or technical practices.

In the US, islets are considered biologic drugs and “more than minimally manipulated” human cell and tissue products (HCT/Ps). Across the world, human islets are appropriately defined

as “minimally manipulated tissue” which has led to islet transplantation becoming a standard-of-care procedure for patients with type 1 diabetes mellitus and problematic hypoglycemia. As a result of the outdated US regulations, only eleven patients underwent allo-ITx in the US between 2011-2016 and all in the setting of a clinical trial.

Herein, we describe the current regulations pertaining to islet transplantation in the United States. We explore the progress which has been made in the field and demonstrate why the regulatory framework must be updated to both, better reflect our current clinical practice and to deal with upcoming challenges. We propose specific updates to current regulations which are required for the renaissance of ethical, safe, effective, and affordable allo-ITx in the United States.

Introduction

Human islets are considered a minimally manipulated tissue for transplantation and regulated as solid organ transplantation in many countries.¹ This approach to regulations allowed allogeneic islet transplantation (allo-ITx) to become a standard of care procedure (Table S1B). In contrast, in the United States (US), human islets have been considered a biologic drug and despite the completion of federally funded clinical trials, have remained under development for the last 20 years.^{1,2} A heavy regulatory burden along with financial, logistical, and legal hurdles have limited the development of this therapy.² As a result, a private company is currently the only entity in the process of obtaining exclusive rights for the marketization of human islets. This trend toward commercialization of human organs and the rising cost will negatively affect the field of transplantation.

Herein, we report on the current status of allo-ITx and provide an overview of current regulations vis-à-vis the advances in scientific knowledge and clinical practice in the past 27 years.

We call for an urgent update of the outdated regulatory framework, which would permit islet allografts to be regulated as a minimally manipulated tissue and remain a public resource for transplantation with clinical oversight under the same regulatory framework as organ transplantation.

Regulations related to allo-ITx in the US

The principles of regulation of Somatic Cellular Therapy by the Food and Drug Administration (FDA) remain unchanged since their inception in 1993 (Table 1).^{3,4} Human cell and tissue products (HCT/Ps) are recognized as “more than minimally manipulated”, if their biological characteristics are significantly altered before or following clinical application.⁴ These HCT/Ps follow the same development steps as any new drug under **Section 351** of the Public Health Service (PHS) Act. This requires pre-clinical and clinical testing, pre-marketing approval based on the biologics license application (BLA), and implementation of all necessary standards during production, distribution, and marketing.⁴ The regulatory burden is progressive, with costs increasing dramatically as phases of development are completed.³

However, some HCT/Ps do not require such extensive regulatory oversight and are exempt from BLA approval; they are regulated solely under **Section 361** of the PHS Act.⁴ For example, autologous islets are exempt from BLA since their biological characteristics are not substantially altered during processing. Islet isolation includes mechanical separation and enzymatic digestion of the pancreas to isolate islets from acinar tissue and is routinely performed in FDA certified laboratories known as a Good Manufacturing Practice (GMP) facilities (Table 1;6).

In contrast, the FDA regulates the islet allograft as a new biologic drug and has mandated a BLA for the past 27 years, despite the fact that the entire processing protocol, technology, materials, equipment, and facilities are exactly the same for the isolation of both allogeneic and autologous islets.⁵

Why are allogeneic and autologous islets regulated differently despite being processed identically?

- 1) Autologous islets are infused into the patient immediately following isolation.⁶ In contrast, allogeneic islets are preserved in culture media prior to infusion and could potentially bring upon biological alterations. This assumption has led the FDA to determine that allogeneic islets do not meet the “minimal manipulation” standard met by autologous islets and thus to require BLA approval for allo-islets.⁵

Admittedly, islet allografts were originally cultured for several days to limit acinar tissue in the islet preparation before transplantation. However, this practice was replaced by routine mechanical islet purification 20 years ago.⁷ For example, “fresh” (i.e. uncultured) islet infusions were utilized in a multicenter phase 1/2 clinical trial in the US (2001-2005).⁸ In the subsequent clinical trials, islets were maintained for up to 72 hours prior to infusion for logistical reasons (to prepare the patient for the procedure).⁹⁻¹² Since islets, similarly to whole organs, but in contrast to stem cells, cannot be stored frozen, they were placed in an incubator with the goal of preservation only (i.e. to maintain their biological structure and function).^{9,10} The medium used for islet preservation has no growth factors and contains only supplements that are allowed during “minimal manipulation” according to FDA guidelines (Table 1;3).⁹ Extensive validation studies performed during the Clinical Islet Transplantation Consortium (CITC) trial confirmed that incubation did not alter the relevant biological characteristics of human islets. The integrity and function of the islets were preserved and maintained at optimum quality until infusion.^{9,10} Therefore, short-term incubation of islet allografts meets the criteria for HCT/P preservation and islets should NOT be considered as “more than minimally manipulated”.

- 2) Islet allograft has a systemic effect, and as such, in order to be exempt from BLA, should meet one of the following **21 Code of Federal Regulations (CFR) 1271(a) 4 (ii)** criteria:
- (a) for autologous use,
 - (b) for allogeneic use in a first-degree or second-degree blood relative, or
 - (c) for reproductive use.

Autologous islets meet criterion 4(ii) (a) for BLA exemption. Islet allografts indeed have NOT met any of the 4(ii) criteria, and therefore, have not been exempt from BLA. However, **criterion 4(ii) (b)** for HCT/P with systemic effect, allowing allogeneic use in first or second degree relatives to be exempt from BLA, is an antiquated immunological perspective which no longer reflects the current state of scientific knowledge and clinical practice; degree of relatedness is actually insufficient to ensure the safety and efficacy of HCT/Ps.

In 1993, clinical outcomes were indeed better among first and second-degree relatives than among unrelated individuals. Currently, we no longer rely on biological relationships but instead use appropriate immunological matching. In fact, the risk of immunologic sensitization among first-degree relatives might be higher in the case of exposure of the mother to human leukocyte antigens (HLA)s from the child or father during pregnancy and delivery. Thus, allogeneic transplants' safety and efficacy are ensured by immunological matching/compatibility, based on detection of pre-existing donor-specific HLA alloantibodies in the recipient's blood in addition to the donor and recipient HLA tissue types. In the current era, the safety and efficacy of related and unrelated but appropriately matched donor/recipient pairs are comparable.^{13,14} Additionally, rules of immunological matching might differ among various HCT/P therapies and treated diseases. For example, in type 1 diabetes mellitus (T1DM) we avoid HLA matching due to an increased risk of recurrent autoimmunity.¹⁵ Regardless, criterion 4(ii)b is intended to improve and ensure immunological safety and should be updated in accordance to the advanced immunological matching algorithms that are currently in clinical practice.

Allo-ITx experience in the US

Transformative progress in allo-ITx was achieved in 2000, when a series of seven patients with T1DM remained insulin-free for one year post-procedure.⁷ At that time, the FDA confirmed that islet allografts needed to be regulated and tested as a new drug. Federally funded clinical trials were conducted over a span of the next 15 years and involved several US academic centers with a total

expenditure of over \$100M (Table S1;A). The results achieved by this collaborative endeavor have played a crucial role in the establishment of allo-ITx worldwide, but oddly, not in the US.

Despite proven safety and efficacy, the adoption of allo-ITx has been deterred by US regulatory constraints.² The manufacturer of the islet product has an obligation to perform additional validations and submit documentation for a BLA to the FDA for approval owing to the extensive regulations imposed on new biologics.^{3,4} The cost of preparing a BLA submission is \$5-6 million, alongside other significant costs and responsibilities related to liability, operations, and additional regulations associated with the post-licensing processes.² Unfortunately, even with FDA permission to utilize common clinical results for an individual center submission, none of the academic centers participating in the trials have been able to submit their own BLA due to these logistical, financial and legal challenges.^{2,4}

Consequences of the current regulations on the status of allo-ITx in the US

1) Near extinction of islet transplantation in the US

To date, no BLA has been approved; therefore, no islets have been transplanted outside of clinical trials nor reimbursed by medical insurance in the US. Additionally, limited research funding and the high procedural costs (>\$138,000) are inherent constraints.¹⁶ In the US, only 11 new patients received an allo-ITx in the past four years in contrast to 179 islet transplants performed between 1999-2005 (Figure 1).

2) No access for Americans with severe hypoglycemia to a lifesaving procedure

Among the 1.2 million Americans with T1DM, approximately 375,000 suffer from impaired hypoglycemic awareness and 66% suffer from recurrent severe hypoglycemic episodes (SHE).¹⁷ Most importantly, nearly 70,000 T1DM patients fail to improve despite structured education and advanced technologies for hypoglycemia avoidance.^{18,19} Quality of life for these patients and their families is severely compromised by sudden and unexpected episodes of loss of consciousness, frequently leading to disability and fatal accidents. Additionally, anxiety and depression are related to an increased risk of death secondary to unrecognized hypoglycemia.¹⁹ Despite significant improvements in insulin pumps and

continuous glucose monitoring sensors, hypoglycemic episodes have remained a significant hurdle for patients with T1DM in the US leading to an estimated 40,000 annual visits to emergency departments.^{20,21} Overall mortality rates remain at 4% for medically optimized patients in contrast to no deaths in those who underwent islet transplantation.^{22,23} Pancreas transplantation remains an approved therapeutic option effectively treating diabetes in this subset of patients. However, it requires major surgery with a 10-20% risk of operative complications.²⁴ Allo-ITx is a minimally-invasive alternative especially for nonsurgical candidates with lower morbidity and mortality, improved glycemic control and prevention of SHE, even when subsequent procedures are required to maintain long-term insulin independence (Table S1).^{24,25} Allo-ITx should be avoided in patients with chronic kidney disease to limit immunologic sensitization prior to kidney transplantation, unless applied as simultaneous islet-kidney or islet following kidney transplantation. Islet and pancreas transplantation require continuous administration of immunosuppression. Other modern cellular therapies (encapsulated pluripotent stem cell derived islet transplantation and xenotransplantation) have been tested clinically but are still under development.

3) Islet allografts are exempt from BLA and transplanted in many developed countries, except in the US

Islet processing technology initially developed in the US has been freely adopted worldwide. Results from US clinical trials prompted regulatory agencies in other countries to recognize, in contrast to the FDA, that the biological characteristics of islet allografts do NOT change during processing and preservation/incubation prior to transplantation (Table 1;8)¹. Therefore, islets have been classified as minimally manipulated HCT/Ps and exempt from BLA in these countries (Figure 2). Islets are processed according to cGMP (current GMP) regulations adopted from the FDA (Table 1;6). Clinical safety and efficacy outcomes have remained excellent, while allo-ITx is performed in accredited transplant centers worldwide (Table S1;C).^{22,26,27} Additionally, under the same conditions (i.e. cGMP without BLA), islets

were transplanted during clinical trials in the US. In the most experienced programs, five-year insulin independence rates are ~ 50% and more importantly, allo-ITx confers complete protection from severe hypoglycemic episodes in $\geq 90\%$ of patients (Table S1;D).^{26,28} Notably, countries outside of the US ensure access to human islets by limiting commercialization and providing reimbursement by national health systems (Figure 2, Table S1;B).¹

In 2019 the American Society of Transplantation's Board of Directors and the Council of the American Society of Transplant Surgeons called upon the FDA to address these needed changes in islet allograft regulation. A comprehensive proposal including the data and rationale presented in this article was submitted and presented to the FDA during the meeting in February 2020. However, the FDA has not pursued any updates (Table 1;3).

Recommendations for an updated regulatory framework for islet allografts

Our proposal calls for a regulatory update in line with current scientific knowledge and standards of clinical practice. We propose the implementation of combined oversight of islet transplantation with the FDA regulating islet processing and Organ Procurement and Transplantation Network (OPTN)/ United Network for Organ Sharing (UNOS) overseeing clinical islet transplantation. The US Department of Health and Human Services should promote this structure via agency oversight which aligns with its mission to protect the public's health and improve the health system.

1. Update current FDA regulations

We urge the FDA to update current regulations and allow islet **allografts** to be included in the products listed in 21 CFR 1271.10(a)(4)(ii) that are regulated solely by Section 361 of the PHS Act, allowing exemption from BLA, as is the case for islet **autografts** (Table 1;3).

Specifically, we recommend that the FDA:

A) Confirm that islet allograft meets minimal manipulation criteria based upon current evidence from the US and ongoing worldwide clinical practices. 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 reflect current scientific understanding and practice. We propose revising the phrase to state, “*use in immunologically compatible donors and recipients*” instead, as this more accurately represents the current clinical standards of matching in organ and cell/tissue transplantation, and improves safety and efficacy of HCT/P.

Moreover, the original authors of regulation 21 CFR Part 1271 foresaw the evolving nature of the science of allo-ITx. In 1993, they wrote, “... as these novel therapeutic applications are explored and knowledge about the risk and benefit accumulates, the FDA regulatory approach may well be modified.”³ Consequently, we should re-assess and update allo-ITx regulations in accordance with currently available science and clinical practice.

2. Introduce additional clinical oversight by OPTN/UNOS

In accordance with current FDA regulations, islets manufactured after BLA approval will fall under the purview of drug regulation and can be administered without the need for any clinical outcome oversight nor program accreditation from OPTN/UNOS. However, allo-ITx is similar to solid organ transplantation and involves risks of immunosuppression, transmission of infections, and allo-sensitization. Thus, the care of these patients demands highly specialized, multidisciplinary approach with properly structured medical and social support to achieve optimal clinical benefit. Lack of clinical oversight, as would be provided by OPTN/UNOS, may lead to inadequacy of monitoring and data tracking, and inferior outcomes. Furthermore, islet allograft anatomy, physiology, and preservation techniques more closely resemble those of other human organs rather than any drug or single cell biologics (Figure S1). Similar to other solid organ transplantation, post-procedural outcomes following allo-ITx undoubtedly are better suited to assess the quality of donor tissue after processing than any pre-transplant *in vitro* testing. Therefore, adherence to BLA standards for allo-ITx is conceptually flawed and should be replaced by close post-transplant outcome monitoring by the OPTN/UNOS (Figure 2)(Table 1;9-12).^{28,29}

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

Since not-for-profit organizations have not been able to offset the burden, liability, and costs related to BLA, only a corporate entity with appropriate resources can adhere to the current islet regulatory framework. However, this scenario is unlikely to expand access to safe, affordable, and equitable allo-ITx.

Islets are recognized by FDA as a biological drug for a rare disease (<200,000 patients with T1DM and complicated hypoglycemia in the US) and qualify for Orphan Drug Designation (ODD)(Table 1;7) which portends seven years of marketing exclusivity. Currently, only one entity, a for-profit company, CellTrans, has received an ODD and submitted a BLA to the FDA in May 2020 with decision regarding approval due by April 2021 (personal communication; Dr. José Oberholzer, Aug. 20, 2020). This creates an imminent ethical and legal dilemma in which a private company may have exclusive rights to benefit from altruistic human organ donation. This possibility would undermine the public goods concept of organ donation and may undermine the public's trust in the national organ donation system. Prevention of islet commercialization was one of the reasons cited by the European Union in its decision to exclude islets from regulation as a biologic.^{1,28}

Assurances of a waiver of exclusivity are insufficient, when considered with the market forces generated by the enormous costs of a BLA, pharmaceutical grade production, and quality control, which may triple current allo-ITx costs (up to \$500,000 per transplant). Undoubtedly, a for-profit market approach, especially without competition, can lead to rising prices. Consequently, the price charged for the procedure will become unnecessarily overinflated, less affordable, essentially cost prohibitive, and perhaps not reimbursed by payors based on an unfavorable cost-to-benefit ratio. If private payors provide coverage, rather than the Center for Medical Services (CMS), this may disproportionately disadvantage patients of low social-economic status. Even if CellTrans waives the exclusivity rights, the extreme cost and burden related to BLA submission (100,000 pages of documents, reports of 1.5 million data points) [personal communication; Dr. José Oberholzer, Aug. 20, 2020]] and the cost and burden of operations afterwards in a relatively small market will effectively discourage any potential competitors.

Furthermore, uncontrolled distribution of islet products without any clinical surveillance system in place may lead to poor clinical outcomes and hinder advances in clinical management. Typical post-marketing FDA oversight based only on voluntarily reporting of adverse events to the manufacturer is insufficient to control allo-ITx clinical safety and effectiveness.

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

We anticipate several positive impacts of the proposed regulatory update (Table S2): 1) The human pancreas and isolated islets will be protected from commercialization and remain a public resource as in other countries. The center transplanting a patient will be ultimately responsible for clinical outcomes and may choose to process the islets in its own cGMP facility or to outsource that service. Competition among institutions would lead to direct quality improvements and price regulations. 2) 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. 3) Payors can be approached for reimbursement. 4) Not-for-profit academic centers will be able to process the islets, providing safe and cost-effective treatments. 5) Clinical oversight from OPTN/UNOS will ensure optimal clinical outcomes. 6) The number of islet isolation centers will increase, and competition will drive improvement in quality, cost-effectiveness, and patient access to the procedure. 7) As the cost of the procedure declines, it will be more affordable and comparable to pancreas transplantation even if two or three allo-ITxs are required. 8) 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 strengthen diabetic care in our health system.

Additional safety and quality considerations

If regulations are updated, 1) high standards of allo-ITx will be reinforced by OPTN/UNOS program accreditation and transparent surveillance of outcomes (Table 1;9-12). Similar to pancreas transplant programs, outcome measures including waitlist mortality rates, transplantation rates, and

1-year and 3-year patient and graft survival rates, will be monitored by the OPTN and publicly reported by the Scientific Registry of Transplant Recipients (SRTR) on a bi-annual basis. The OPTN Pancreas and Islet Transplantation Committee remain vigilant and regularly update policies and bylaws to ensure safety and efficacy. Islet graft

failure criteria can be adopted from the experts' consensus.³⁰ 2) Islets would fall under 21 CFR Part 1271 Section 361 PHS, and still require mandatory processing in cGMP facilities emphasized by the FDA and as a prerequisite for program OPTN accreditation.

The FDA established high standards of cGMP for drug manufacturing, specifically to ensure drug sterility, potency, and traceability (Table 1;6). Adherence to cGMP also assures the identity, strength, quality, and purity of drug products by requiring that manufacturers control operations adequately.

Each islet processing GMP facility is subject to FDA registration, certification, and unannounced visits/inspection. Therefore, following FDA cGMP regulations during the islet processing, as we propose, will satisfy islet product safety and efficacy requirements. The BLA requirement is designed

for any new drug entering an open market without any outcome control measures; however, under the proposed regulatory framework, the BLA requirement will become obsolete as human islets will be under oversight by the dual surveillance systems of OPTN/UNOS and FDA cGMP manufacturing control.

Additionally, ample scientific evidence from over 2,000 procedures worldwide, including clinical trials in the US collected by CITR, sufficiently justifies the addition of allo-ITx to the list of other HCT/Ps exempt from BLA without any compromise in safety or outcomes.^{10,28,29} The OPTN

could set expected outcomes initially at the level of a phase 3 CITC trial with the same product release criteria and clinical indications. Standards can be modified based upon observed advances in clinical outcomes. Programs will need to comply with requirements to obtain and maintain

accreditation for allo-ITx and will need to prove their capability and show appropriate track records. Improved results in a number of centers can be expected as more experience is gained.

Underperforming centers will need to improve under supervision of the OPTN Membership and Professional Standards Committee, and if unsuccessful may lose OPTN accreditation and contracts for reimbursement.

Summary

Urgent regulatory updates that incorporate current clinical standards and research findings are indispensable for the re-introduction of ethical, safe, effective and affordable allo-ITx in the United States. The US Department of Health and Human Services should promote updated regulations and a new oversight framework to improve and protect the public's health and strengthen the US health system.

Disclosure-

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

Figures Legend

Figure 1. Catastrophic decline of allo-ITx procedures in the US

NIH- National Institute of Health; JDRF- Juvenile Diabetes Research Foundation;

BLA- Biological License Application

Figure 2. Status of islet transplantation in the US and worldwide proposed regulatory update

- Islet allograft regulated as a drug by FDA since 1993.
- 15 years of clinical research supported by over \$100M of US taxpayer funding did not benefit US patients, although benefits were enjoyed by other patients worldwide; islet allograft processing were recognized by regulatory agencies worldwide as minimal manipulation based on US trial results and islets were exempt from BLA and regulated as a tissue/organ transplantation instead of a drug or biologics.
- Islet transplantation is still not a standard-of-care procedure in the US, despite already being an established procedure in other countries.
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EMA- European Medicine Agency (like FDA in US), ATMP – Advanced Therapy Medicinal Product,

BLA- biological license application, CITR- Collaborative Islet Transplantation Registry, OPTN- Organ

Procurement and Transplantation Network, UNOS- United Network for Organ Sharing, cGMP-

current good manufacture practice, FDA- Food and Drug Administration

Supporting Information

Additional Supporting Information may be found in the online version of this article.

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Table and Figures

Table 1. Selected regulations related to allo-ITx

Regulations related to allo-ITx			
	Regulatory Agency	Title of the regulation	Link to the source
1	Food and Drug Administration (FDA), CBER (Center for Biologics Evaluation and Research)	Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products; Notice	Federal Register. 1993; Vol 58, No. 197, 53248. https://www.fda.gov/media/76647/download
2		FDA. eCFR — Code of Federal Regulations. eCFR - Code Fed Regul. 2019:21CFR1271.10.	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=1271.10
3		Regulatory Considerations for	https://www.fda.gov/media/109176/

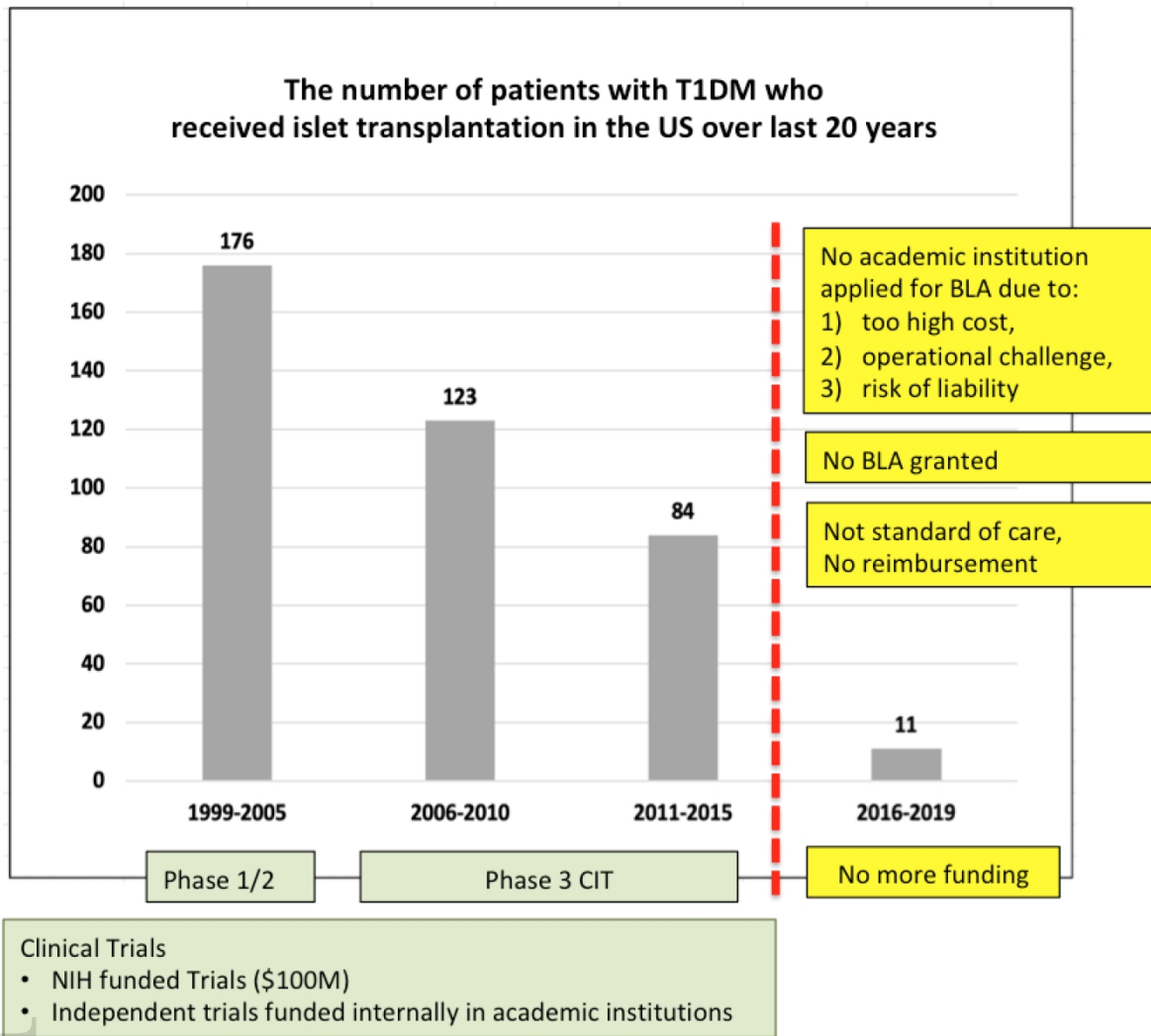
		Human Cell, Tissues, and Cellular and Tissue- Based Products: Minimal Manipulation and Homologous Use Guidance for Industry and Food and Drug Administration Staff. FDA 2020.	download
4		Blood vessels recovered with organs and intended for use in organ transplantation. Final rule. Fed Regist. 2007;72(47):10922-10925.	https://www.govinfo.gov/content/pkg/FR-2007-03-12/pdf/07-1131.pdf
5		FDA's listing of BLA approvals by year	https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biological-approvals-year
6		Facts About the Current Good Manufacturing Practices (cGMPs)	https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps
7		Developing Products for Rare Diseases & Conditions	https://www.fda.gov/industry/developing-products-rare-diseases-conditions#About%20OPD
8	EMA – European Medicines Agency	Reflexion paper on classification of advanced	https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-

	(EU) Committee for Advanced Therapies (CAT)	therapy products. 2015 May. EMA/CAT/600280/2010 rev.1	paper-classification-advanced-therapy-medicinal-products_en-0.pdf
9	HRSA/ OPTN (Health Resources & Services Administration/Organ Procurement and Transplantation Network)	Federal law for organ transplantation, Charter	https://uscode.house.gov/view.xhtml?hl=false&edition=prelim&req=granuleid%3AUSC-2014-title42-section274&num=0
10		Final rule	https://optn.transplant.hrsa.gov/governance/about-the-optn/final-rule/
11		Polices	https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf
12		Bylaws	https://optn.transplant.hrsa.gov/governance/bylaws Appendix G outlines the membership and personnel requirements for the transplant programs

Figure 1. Catastrophic decline of allo-ITx procedures in the US

NIH- National Institute of Health; JDRF- Juvenile Diabetes Research Foundation;

Catastrophic decline of new patients treated with islet allografts in USA



Graph courtesy of Dr. Franca Barton, Clinical Islet Transplantation Registry, USA

Figure 2. Status of islet transplantation in the US and worldwide proposed regulatory update

- Islet allograft regulated as a drug by FDA since 1993.

- 15 years of clinical research supported by over \$100M of US taxpayer funding did not benefit US patients, although benefits were enjoyed by other patients worldwide; islet allograft processing were recognized by regulatory agencies worldwide as minimal manipulation based on US trial results and islets were exempt from BLA and regulated as a tissue/organ transplantation instead of a drug or biologics.
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