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The demise of islet allotransplantation in the United States: A call for an urgent regulatory update

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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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). In contrast, across the world, human islets are appropriately defined as "minimally manipulated tissue" and not regulated as a drug, which has led to islet allotransplantation (allo-ITx) becoming a standard-of-care procedure for selected patients with type 1 diabetes mellitus. This regulatory distinction impedes patient access to islets for transplantation in the US. As a result only 11 patients underwent allo-ITx in the US between 2016 and 2019, and all as investigational procedures in the settings of a clinical trials. 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.

Keywords

clinical research/practice; ethics and public policy; islet transplantation; islets of Langerhans; law/legislation; quality of care/care delivery

1 | INTRODUCTION

Human islets are considered as tissue for transplantation in many countries, which has contibuted to allogeneic islet transplantation (allo-ITx) becoming a standard-of-care procedure for selected patients with type 1 diabetes mellitus (T1DM) (Table S1B).[1] In contrast, in the United States (US), allogeneic islets (allo-islets) have been considered a biologic drug and despite the completion of federally funded clinical trials, allo-ITx have remained under development as investigational therapy for the last 20 years (Table 1;1–3,9,16,17).[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 allo-islets to be regulated solely under section 361 of the Public Health Act (PHA) and remain a public resource for transplantation with clinical oversight under the same regulatory framework as organ transplantation (Table 1; 1,2).

2 | 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 relevant biological characteristics are not 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 and relevant sections of the Federal, Food, Drug & Cosmetic Act (Table 1;3). 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.[3] The regulatory burden is progressive, with costs increasing dramatically as phases of development are completed.[4]

However, many HCT/Ps do not require such extensive regulatory oversight and are exempt from BLA approval based on criteria described in the Code of Federal Regulation (CRF) part 1271 and 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.

In contrast, the FDA regulates allo-islets 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 allo-islets and autologous islets.[5]

3 | WHY ARE ALLO-ISLETS AND AUTO-ISLETS REGULATED DIFFERENTLY DESPITE BEING PROCESSED IDENTICALLY?

1. Autologous islets are infused into the patient immediately following isolation.[5] 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 allo-islets do not meet the "minimal manipulation" standard met by autologous islets and thus to require BLA approval for allo-islets (Table 1;7,13,14).

Historically allo-islet cells were cultured for serveral days to limit acinar tissue in the islet preparation before transplantation. However, this practice was replaced by routine mechanical islet purification over 20 years ago.[6] For example, "fresh" (i.e., uncultured) islet infusions were utilized in a multicenter phase 1/2 clinical trial in the US (2001–2005).[7] In subsequent clinical trials, islets were maintained for up to 72 h prior to infusion for logistical reasons (to prepare the patient for the procedure).[8–11] 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).[8,9] 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).[8] 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.[8,9] 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" under CFR Part 1271 (Table 1;1,2,7).

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

Autologous islets meet criterion 4(ii) (a) for BLA exemption. Allo-islets 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 (HLAs) from the child or father during pregnancy and delivery. Thus, the safety and efficacy of allogenic transplants 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.[12,13] Additionally, rules of immunological matching might differ among various HCT/P therapies and treated diseases. For example, in type 1 diabetes mellitus we avoid HLA matching due to an increased risk of recurrent autoimmunity.[14] 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.

4 | 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 1 year post-procedure.[6] At that time, the FDA confirmed that islet allo-grafts needed to be regulated and tested as a New Investigational 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 $100 M (Table S1A). The results demonstrated by this collaborative effort 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]

5 | CONSEQUENCES OF THE CURRENT REGULATIONS ON THE STATUS OF ALLO-ITx IN THE US

5.1 | 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 generally reimbursed by medical insurance in the US. Additionally, limited research funding and the high procedural costs (>$138 000) are inherent constraints.[15] In the US, only 11 new patients received an allo-ITx in the past 4 years in contrast to 179 islet transplants performed between 1999–2005 (Figure 1).

5.2 | 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).[16] Most importantly, nearly 70 000 T1DM patients fail to improve despite structured education and advanced technologies for hypoglycemia avoidance.[17,18] 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.[18] 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.[19,20] Overall mortality rates remain at 4% for medically optimized patients in contrast to no deaths in those who underwent islet transplantation.[21,22] 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.[23] 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).[23,24] 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.

6 | OUTSIDE THE US ALLOGRAFTS ARE NOT REGULATED AS BIOLOGICAL PRODUCTS AND ALLO-ITX IS A STANDARD CLINICAL PROCEDURE (FIGURE 2B)

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;19).[1] Islets have not been classified as drugs (Advanced Technology Medicinal Products in Europe) and have not been subject to marketing authorization requirement (Figure 2B). Islets are still processed in special laboratories (i.e., GMP facilities) designed for aseptic cell product processing borrowed from the Good Manufacture Practice (GMP) regulations (Table 1; 20).[25] Clinical safety and efficacy outcomes have remained excellent for allo-ITx performed in accredited transplant centers worldwide (Table S1C).[21,26,27] Additionally, under the same conditions (i.e., facility meeting cGMP standards but without full implementation of cGMP requirements for biological product manufacturing, Table 1:12), islets were transplanted during clinical trials in the US. In the most experienced programs, 5-year insulin independence rates are ~50% and more importantly, allo-ITx confers complete protection from severe hypoglycemic episodes in ≥90% of patients (Table S1D).[26,28] Notably, countries outside of the US ensure access to human islets by limiting commercialization and providing financial support for programs by national health systems (Figure 2B, Table S1B).[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 allo-islet regulation. A comprehensive proposal including the data and rationale presented in this article was submitted and presented to the FDA in February 2020. However, the FDA has not pursued any updates to its regulations (Table 1;7).

7 | RECOMMENDATIONS FOR AN UPDATED REGULATORY FRAMEWORK FOR ALLO-ISLETS

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 allo-islet processing solely under Part 1271 and Organ Procurement and Transplantation Network (OPTN)/ United Network for Organ Sharing (UNOS) overseeing clinical islet transplantation (Table 1;2,21–24).

7.1 | Update current FDA regulations

We urge the FDA to update current regulations and allow allo-islets to be eligible regulation under Part 1271 to the same extent as autologous islets (Table 1; 1,2).

Specifically, we recommend that the FDA:

A) Confirm that islet allograft meets minimal manipulation criteria based on 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 alter relevant 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.

7.2 | 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, multi-disciplinary approach with properly structured medical and social support to achieve optimal clinical outcomes. Lack of clinical oversight, as would be provided by OPTN/UNOS, may lead to inadequate 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, monitoring of post-procedural outcomes following allo-ITx un-doubtedly is a better means of assessing 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; 21–24).[8,28,29]

8 | WHAT WILL HAPPEN IF WE DO NOT UPDATE ISLET ALLOGRAFT REGULATIONS?

Since not-for-profit organizations have not been able to offset the burden, liability, and costs related to BLA, only a for-profit entity with the 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.

Under the current regulations, the biologic drug designation for allo-islets has significant implications not least of which is the eligibility for Orphan Drug Designation (ODD) because brittle T1DM affects fewer than 200,000 people (Table 1;4–6). This confers 7 years of market exclusivity and currently only one entity, a for-profit company, CellTrans, has received an ODD. CellTrans has also submitted a BLA to the FDA in May 2020 with a user-

fee goal date for an action on the submission expected in 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]

Assurances of a waiver of exclusivity are insufficient given the commencial pressure 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 were to waive 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.

9 | WHAT WILL HAPPEN IF THE RECOMMENDED REGULATORY UPDATES FOR ALLO-IT X ARE ENACTED?

We anticipate several positive impacts of the proposed regulatory update (Table S2): (1) The human pancreas and isolated islets will be protected from unconstrained 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 regulation. (2) BLA related regulatory barriers will be removed, allowing allo-ITx to become a standard-of-care procedure as recommended by experts and professional societies. (3) Payors can be approached for reimbursement of a non-investigational procedure. (4) Not-for-profit academic centers will be able to process 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 repeat 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 will stimulate progress in regenerative medicine, cellular therapies, and organ bioengineering. Ultimately, this would benefit our patients and strengthen diabetic care across our health system.

10 | ADDITIONAL SAFETY AND QUALITY CONSIDERATIONS

If regulations are updated, we anticipate that: (1) high standards of allo-ITx will be reinforced by OPTN/UNOS via program accreditation and transparent surveillance of outcomes (Table 1; 21–24). Similar to pancreas transplant programs, outcome measures including waitlist mortality rates, transplantation rates, and 1- 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 remains vigilant and regularly updates polices and bylaws to ensure safety and efficacy. Islet graft failure criteria can be adopted from the experts' consensus.[30] (2) Islets would fall under Part 1271 and require compliance with current Good Tissue Practice (cGTP). However, the FDA should enhance cGTP requirements as needed to address specific issues related to islets, for example, by mandating islet processing in a proper "clean room" facility cGMP facility. There is precedent for this approach; in current cGTP guidance the FDA suggests to take into account cGMP guidance in determining appropriate environmental control during HCT/P processing (Table 1;8). Once regulations are updated, the FDA could issue new guidance specifically for human islet processing as has been done previously (Table 1;9) and by identifying critical elements for standards for aseptic HCT/P processing, which would be prerequisite for program accreditation by OPTN.

Each islet processing facility is also subject to FDA registration, certification, and unannounced visits/inspection as a tool to ensure and reinforce compliance with regulations. 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 overseen by the dual surveillance systems of OPTN/UNOS and specifically, the FDA's cGTP manufacturing control regulations. Additionally, ample scientific evidence from over 2000 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 (Table 2A).[9,28,29] 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 on observed advances in clinical outcomes. Programs will need to comply with requirements to obtain and maintain accreditation for allo-ITx and will need to demonstrate their capability and records. Experienced centers will drive clinical excellence while underperforming centers will be directed to make improvements supervised by the OPTN Membership and Professional Standards Committee, and if unsuccessful may lose OPTN accreditation and contracts for reimbursement.

11 | 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 US. We argue that allo-islets are minimally manipulated HCT/P and propose that the FDA revise its regulations to permit appropriately matched allo-islets to be regulated solely under Part 1271 of the Code of Federal Regulations. We call for additional clinical oversight for allo-ITx using the same framework as for organ transplantation. The US Department of Health and Human Services should promote these changes to improve and protect the public's health and strengthen the US health system.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

allo-islets	allogenic islets, islet allografts
allo-ITx	pancreatic islet allotransplantation
BLA	biologics license application
CFR	code of federal regulations
cGMP	current good manufacturing practice
CITC	Clinical Islet Transplantation Consortium
CMS	Centers for Medicare and Medicaid Services
FDA	Food and Drug Administration
GMP	good manufacturing practice
HCT/Ps	human cell and tissue products
HLA	human leukocyte antigen
HRSA	Human Resources Services and Administration
JDRF	Juvenile Diabetes Research Foundation
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.

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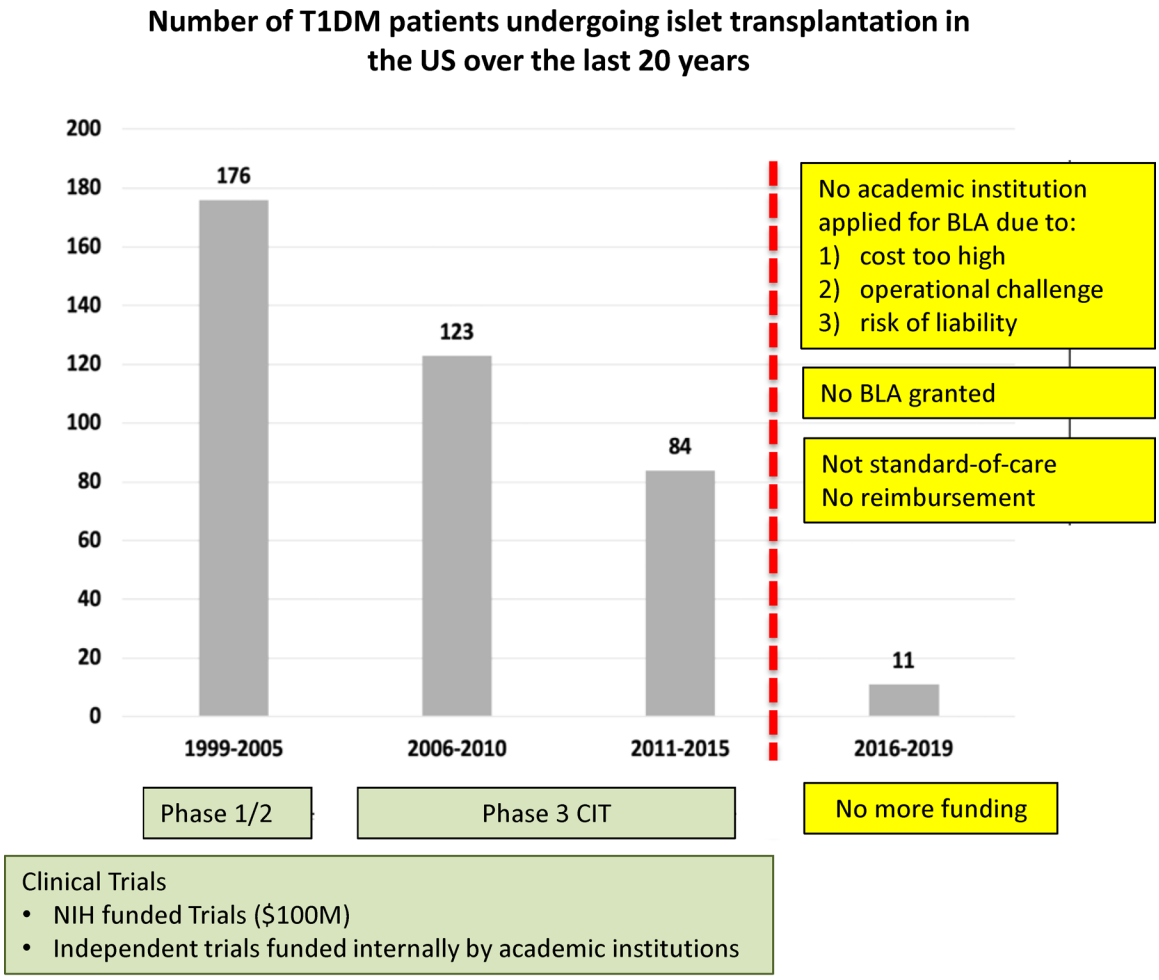

Graph courtesy of Dr. Franca Barton, Clinical Islet Transplantation Registry, USA

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

FDA				HRSA
Pharmacological drugs	Biological Drug Products (Biologics)			OPTN/UNOS
chemical synthesis	• produced from living organisms or • contain components of living organisms			
	non HCTP (animal and other live cell product)	human cells, tissues, or cellular or tissue-based products (HCT/Ps) not exempt do not meet criteria 21 CFR 1271 .10	HCT/Ps which meet exemption criteria 21 CFR 1271 .10	• human organs for Tx • bone marrow for Tx • blood vessels for organ Tx
FDC Act	PHS Act (351) and/or FDC Act	PHS Act (351) BLA required	PHS Act **(361)** **BLA exempt**	
		allogeneic Islets cultured cartilage cells cultured nerve cells lymphocyte immune therapy gene therapy products human cloning human cells used in therapy involving the transfer of genetic material (cell nuclei, oocyte nuclei, mitochondrial genetic material in ooplasm, genetic material contained in a genetic vector) unrelated allogeneic hematopoietic stem cells unrelated donor lymphocytes for infusion	**autologous islets** Bone Ligaments Tendons Fascia Ocular tissue Skin Vascular grafts Pericardium Dura matter Heart valve allografts Hematopoietic stem cells Semen Oocytes Embryos Autologous islets	

Proposed regulatory update → Allogenic Islet Regulation under FDA and HRSA

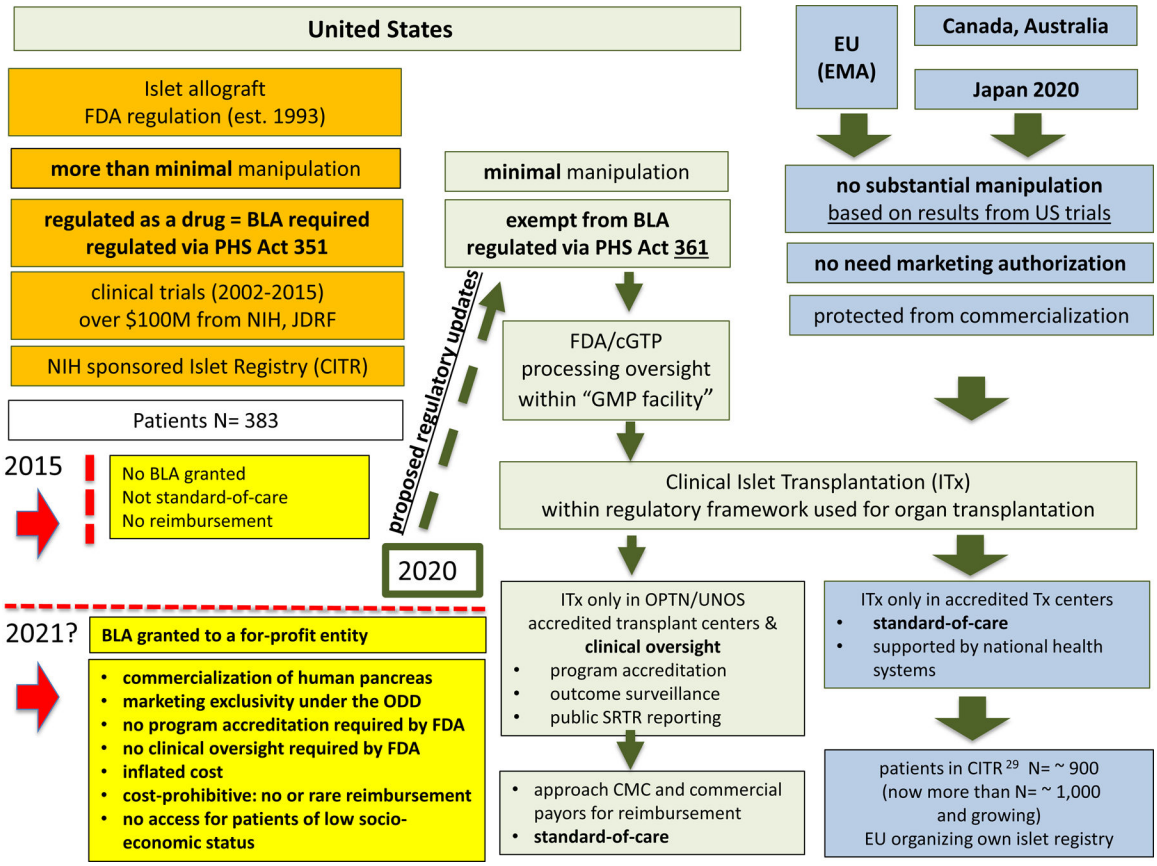

FIGURE 2.

Proposed regulatory updates related to allo-islets in the US. A) Details of the proposed regulatory framework. B) Status of islet transplantation in the US and worldwide & the impact of the proposed regulatory updates. 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 was recognized by regulatory agencies worldwide as not being "substantially manipulated" 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. Islet allograft regulation as a drug by FDA resulted in a series of negative consequences. Situation will worsen after BLA is granted to a for-profit entity (negative consequences marked with yellow color). Proposed solution: regulatory update based on current scientific data from US clinical trials and CITR, which would result in BLA exemption and the regulation of islets as organs with clinical oversight by OPTN/UNOS and islet processing according to specially tailored cGTP FDA regulations (dashed arrow). 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; cGTP, current Good Tissue Practice; FDA, Food and Drug Administration

Table 1

Selected regulations related to allo-ITx.

Regulatory agency	Title of the regulation	Source Link
Food and Drug Administration (FDA)	1 Human Tissue intended for Transplantation. 21CFR Part 1270. Public Health Service Act Section 361 (United States Code, Title 42, Section 264).	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1270
	2 Human cells, tissues, and cellular and tissue-based products. Code of Federal Regulations 21CFR Part 1271. Public Health Service Act Section 361 (United States Code, Title 42, Section 264	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=1271.10
	3 Regulation of biological products. Public Health Service Act Section 351 (United States Code, Title 42, Section 262) Food, Drug and Cosmetic Act, Section 301 et seq. (United States Code, Title 21, Section 321 et seq Code of Federal Regulations, Title 21 Parts 600, 610 Code of Federal Regulations, Title 21, Parts 210, 211	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=600https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=610 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=210 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211
	4 Orphan Drug Act Public Law 97–414 (enacted Jan. 4, 1983)	https://www.fda.gov/media/99546/download
	5 FDA Database of Orphan Drug Designations and Approvals	https://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm
	6 Developing Products for Rare Diseases & Conditions	https://www.fda.gov/industry/developing-products-rare-diseases-conditions#About%20OOPD
	7 Guidance for Industry and Food and Drug Administration Staff, Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use (2020)	https://www.fda.gov/media/109176/download
	8 Guidance for Industry Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)	https://www.fda.gov/media/82724/download
	9 Guidance for Industry Considerations for Allogeneic Pancreatic Islet Cell Products (2009)	https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Guidance-for-Industry--Considerations-for-Allogeneic-Pancreatic-Islet-Cell-Products-PDF.pdf
	10 FDA's lisitng of BLA approvals by year	https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biological-approvals-year
	11 Compliance Program Guidance Manual Chapter – 45 Biological Drug Products	https://www.fda.gov/media/73834/download#:~:text=Section%20501(a)(2,manufactured%20in%20compliance%20with%20CGMPs.&text=To%20help%20ensure%20the%20industry,each%20establishment%20at%20least%20biennially
	12 Facts About the Current Good Manufacturing Practices (cGMPs)	https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps
	13 FDA Type C Meeting Responses (Ref PTS#PS004003, CRMTS#11444), page 26. Type C Consortium Meeting to discuss and get FDA guidance about a possible facilitated path for islet transplantation by submitting one BLA to include five participating centers of the NIH CIT consortium	https://www.myast.org/sites/default/files/3-Islet%20Request-complete.pdf
	14 Letter to PW from Sheryl Lard-Whiteford, Ph.D. Associate Director for Quality Assurance, CBER Product Jurisdiction Officer Center for Biologics Evaluation and Research US FDA	https://ce31f435-fd7c-460d-ab8a-6527449851e8.filesusr.com/ugd/e04a06_8a179bb8ca7a4ad9bc0792ffc582837e.pdf

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Regulatory agency	Title of the regulation	Source Link
	15 Richard A. Merrill, Human Tissues and Reproductive Cloning: New Technologies Challenge FDA, Houston Journal of Health Law and Policy, Vol. 3, pp. 1–82	
	16 Weber DJ, Mcfarland R, Irony I. Selected Food And Drug Administration Review Issues For Regulation Of Allogeneic Islets Of Langerhans As Somatic Cell Therapy. Transplantation. 2002,74:1816–1820.	
	17 Weber DJ. FDA Regulation of Allogeneic Islets as a Biological Product Weber Cell Biochemistry and Biophysics, Supplement, 2004, 1085–9195/04/Supplement/40/19–22.	
	18 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
EMA –European Medicines Agency (EU) Committee for Advanced Therapies (CAT)	19 Reflexion paper on classification of advanced therapy products. 2015 May. EMA/CAT/600280/2010 rev.1	https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf
	20 Good Manufacture Practice	https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice
HRSA/ OPTN (Health Resources & Services Administration/Organ Procurement and Transplantation Network)	21 Federal law for organ transplantation, Charter	https://uscode.house.gov/view.xhtml?hl=false&edition=prelim&req=granuleid%3AUSC-2014-title42-section274&num=0
	22 Final rule	https://optn.transplant.hrsa.gov/governance/about-the-optn/final-rule/
	23 Polices	https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf
	24 Bylaws	https://optn.transplant.hrsa.gov/governance/bylaws Appendix G outlines the membership and personnel requirements for the transplant programs

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