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Regulatory updates are needed to prevent the commercialization of islet transplantation in the United States

To the Editor:

We are writing with great concern about the consequences of applying drug-related regulations to human allogeneic islets (allo-islets). Currently, the Food and Drug Administration (FDA) is reviewing a Biologics License Application (BLA) for the isolation of allogenic islets which, if approved, will effectively confer marketing rights to a private, for-profit company.[1] We believe this will lead to the commercialization of human pancreatic islets and limit access to islet transplantation for Americans with diabetes (Figure 1A). This scenario directly conflicts with the intent of the 1984 National Organ Transplantation Act (NOTA), under which human organs (e.g., pancreas) and their subparts (e.g., islets) are protected from commercialization.[2,3] Furthermore, this approach jeopardizes the public role of academic transplant programs, which as stewards of a donated public good (i.e., human organs), are entrusted with their safe, transparent, and just allocation. Lastly, regulating islets as biological drugs also removes them from the safeguards which help keep transplantation of all other organs safe, ethical, and fair.[1]

Human islets, just like the pancreas, are de facto treated as organs already, since both require the same procurement, allocation, and distribution framework in the United States. Given the organ-like structural and functional anatomy (including an internal vasculature), which remains preserved during the entirety of the transplantation process, islets should properly be classified and regulated as other vascularized organs for transplantation. Human organs, *other than islets*, are regulated by UNOS/OPTN in the United States. This list already includes vascularized composite tissue allografts which were added by the Secretary of the Department of Human Health Services (HHS) to the list of transplantable organs in 2013.[4]

As we recently reported in detail, we are not proposing the deregulation of islet transplantation; but rather, a scientifically justified update based on the current state-of-the-art in clinical practice.[1] We made three main recommendations: (1) allo-islets should be exempt from drug regulations, just as autologous islets already are, since both types of islets are processed exactly the same; (2) the current regulatory system for allo-islet transplantation is very effective and functions without BLA requirements and additional FDA drug manufacturing standards; and (3) islets are already regulated as organs for transplantation and are safely and effectively offered as a standard-of-care treatment option in developed nations- with the notable exception of the United States.[1]

For optimal regulatory oversight and in order to foster clinical islet transplantation in the United States, we strongly recommend that the Secretary of the Department of Health and Human Services with his/her legal authority urgently designate islets as human organs. This action will enable proper islet regulation under the robust OPTN/UNOS framework developed for organ transplantation and will prevent islet commercialization (Figure 1B). This regulatory action will help preserve human islets as a public resource and help make islet transplantation a safe, effective, accessible, and affordable standard-of-care procedure for diabetic care in the United States.

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(A)

Health and Human Services (HHS)	
Organs for Transplantation	Drugs (including islets):
HRSA OPTN/UNOS	FDA
• pancreas, liver, kidney, heart, etc. • blood vessels for transplant (added in 2007) • vascularized composite allografts (VCAs) (added in 2013) • *islets are not on the list of organs to be regulated*	Clinical trials for new drug (islets) under the Investigational New Drug (IND)
• **pancreas allocation based on waitlist** pancreas 1. as "material" for islets vs. 2. as organ	• study subject evaluation • UNOS wait-listing • cross-match, HLA matching • islet isolation (drug manufacturing) • islet transplantation (drug infusion) • study follow up
Clinical use & oversight: Transplant Program Accreditation by the OPTN/UNOS Regulatory oversight over: • recipient evaluation • pancreas procurement • pancreas preservation • pancreas preparation • pancreas transplantation • clinical follow-up	**After completion of new drug trials & clinical use:** • BLA preparation-> approval ($) • implementation of full GMP drug manufacturing standards ($) • marketing, standard-of-care use ($) • distribution of the islets (as drugs) by the manufacturer to selected Tx centers based on commercial contract and business decisions (commercialization) • only Tx centers, which accept conditions of a for-profit manufacturer will have access to islets and be eligible to list patients on the UNOS list for islet Tx
Safety and effectiveness monitoring based on: • transparent, publicly available reporting, • corrective action or loss of accreditation	**Safety and effectiveness monitoring:** • no clinical oversight for drugs by the FDA besides voluntary reporting (e.g., by patients or physicians)

(B)

Health and Human Services (HHS)		
Organs & Islets for Transplantation		Drugs
HRSA OPTN/UNOS		FDA
• pancreas, liver, kidney, heart, etc. • blood vessels for transplant (added in 2007) • vascularized composite allografts (VCAs) (added in 2013) • ***Add islets to list of organs regulated under OPTN/UNOS via decision of the HHS Secretary***		
• pancreas allocation based on waitlist for pancreas & islet transplantation		
pancreas as organ for transplant	pancreas as organ for islets transplant	
Clinical use & oversight: Transplant Program Accreditation by the OPTN/UNOS Regulatory oversight over: • recipient evaluation • pancreas procurement • pancreas preservation • pancreas preparation • pancreas transplantation • clinical follow-up	**Clinical use & oversight:** Transplant Program Accreditation by the OPTN/UNOS Regulatory oversight over: • recipient evaluation • pancreas procurement • pancreas preservation • **ISLET ISOLATION** • islets transplantation • clinical follow-up	• islet processing under Good Manufacture Practice (GTP) with special guidance from FDA with elements of the Good Manufacture Practice (GMP) • maintenance of the current level of regulation **To consider additional facility accreditation by:** • UNOS • American Association of Blood Banks (AABB) and/or • Foundation of Accreditation for Cellular Therapy (FACT)
Safety and effectiveness monitoring based on: • transparent, publicly available reporting • corrective action or loss of accreditation	**Safety and effectiveness monitoring based on:** • transparent, publicly available reporting • corrective action or loss of accreditation	It would allow : • islet processing by academic medical centers • healthy competition between institutions • stimulation of high quality and lower cost

FIGURE 1 (A) Current regulatory structure of organ versus islet transplantation (B) Proposed regulatory structure for islet transplantation

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