Confidential draft
To Be or Not to Be for islet transplantation in the US
Reflection on the FDA review of the Biological License Application for human islets for transplantation

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Word limit: 500

Dear Editor:

Human islet regulated as biological drug in the US, requires the biological license application (BLA) approval before islets can be used for allotransplantation outside clinical trials (1). The goal of the BLA is to prove that the drug manufacturing procedures meet appropriate standards and provide consistently well-defined, high quality biological product, which characteristics reassures desired clinical effect. Such verification is essential for clinical safety and efficacy of the drug.

None, of the academic institutions has been able to submit BLA over last 20 years, which led to gradual demise of the field (1). Recently, private company has submitted BLA for human islets and FDA Advisory Committee members were asked to provide feedback regarding the application on April 15th, 2021 (2).
Herein, we share findings and conclusions from the meeting as they have major implications for the field of islet, cellular and organ transplantation as well as regenerative medicine in the US.

FDA Advisors voted and confirmed that human islets transplanted intraportally have favorable benefits to risk profile for some patients with type 1 diabetes. Such conclusion is not surprising to the transplant community, as clinical outcomes have been well documented and presented over the last 20 years (1).

However, the main question whether BLA should be approved, was not asked and remained unanswered. Moreover, during the same meeting, the FDA presented own analysis of the BLA data. FDA concluded that the quality and potency of the human islets may not be reliably defined, and critical quality attributes of the islets (islet characteristics based on the reported release criteria) did not correlate with islet function (2).

What does it practically mean?
Basically, it means that quality of human islets their potency to provide desired clinical effect cannot be reassured prior to transplantation. As the main goal of BLA was not achieved, the BLA approval has no merit. However, the final FDA decision is yet to be made and is not obvious.

Based on scientific evidence and own findings, we would hope that FDA would make the most rational decision allowing islets to be included into the definition of human organs under the

OPTN Final Rule resulting in islet regulation as any other organ for transplantation under the HRSA by the OPTN and UNOS. We have proposed it in recent publications and directly to the FDA and HHS on multiple occasion (3, 4). However, recent statement of the FDA spoke person indicates otherwise (5).

FDA decision to reject the BLA and hold the same drug related requirements would enviably prevent any clinical use of human islets indefinitely in the US.

As another option, an approval of clearly deficient BLA will also result in fatal consequences. BLA holding commercial entity would be authorized to sell human islets of unverifiable quality and potency. Transplant centers will have no choice and buy and use them in patients. Such situation clearly is morally and legally unacceptable.
Moreover, even when islet graft fails, the ultimate reason for the failure cannot be established so islet manufacturer performance still cannot be verified.

FDA new findings provide another strong scientific evidence that human islets do not fit into drug regulatory framework and should be included into organ for transplant regulations by the HHS Secretary.

Reference

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2. Cellular, Tissue, and Gene Therapies Advisory Committee April 15, 2021 Meeting Announcement. https://www.fda.gov/advisory-committees/advisory-committee-calendar/cellular-tissue-and-gene-therapies-advisory-committee-april-15-2021-meeting-announcement-04152021
3. Witkowski P, Barth RN, Japour AJ, et al. on behalf of the "Islet for US Collaborative". Regulatory updates are needed to prevent the commercialization of islet transplantation in the US. Am J Transplant, 2021, March 8, https://doi.org/10.1111/ajt.16555.
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5. https://www.medscape.com/viewarticle/951142#vp_2