U.S. FOOD & DRUG ADMINISTRATION

Preliminary Meeting Responses

Our Reference: PTS# PS004003
CRMTS # 11444

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SUBJECT: 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

PRODUCT: Allogeneic Islet Cells (human, NIAID/DAIT) Administered via Intraportal Infusion; and Immunosuppressive Therapy

PROPOSED INDICATION: Treatment of Type 1 diabetes mellitus

FDA Participants:
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This material consists of our preliminary meeting responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 20, 2018 at 12pm ET. We are sharing this material to promote a collaborative and successful discussion at the meeting.

Although we continue to reserve November 20, 2018, with you regarding this product, if you find that our attached responses and advice are sufficiently clear and complete to obviate the need for further discussion, please inform us in writing as soon as possible so that we may clear the meeting time. These responses would then become the official FDA responses to your questions.

If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from Face-to-Face to teleconference). If you have questions regarding specific responses or advice, please inform us so that the appropriate members of the Review Committee can provide clarification during the reserved meeting time.

The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting.

Contact the Regulatory Project Manager (RPM), Erica Giordano at (240) 402-8298 if there are any major changes to your development plan, including any [planned] Pediatric Studies (if subject to PREA), the purpose of the meeting, or the questions based on our preliminary meeting responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

If you choose to cancel the meeting, please be aware that your submission should include all components for a complete submission and should be in compliance with all appropriate statutes and regulations.

Please include a reference to SUBMISSION # PTS# PS004003 in your future submissions related to the subject product.

Preliminary Meeting Responses

Sponsor Question 1: *Does the FDA agree with our request to consider PHPI as "minimally manipulated" (21 CFR 1271.10(a)), thereby allowing PHPI to be regulated as HCT/P's under 21 CFR 1271.3(d)(1) and Section 361 of the PHS Act, similar to other products such as Hematopoietic Stem Cells Derived from Peripheral or Umbilical Cord Blood, Semen, Embryos and Oocytes?*

FDA Response to Question 1:
We disagree that your allogeneic islet cell product is regulated solely under section 361 of the Public Health Service Act.

Human cells, tissues, or cellular or tissue-based products (HCT/Ps) are defined in 21 CFR 1271.3(d) as articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

The regulations in 21 CFR Part 1271 identify the criteria for regulation solely under Section 361. If all criteria in §1271.10(a) are met, then the HCT/P is regulated solely under Section 361 of the PHS Act, and no pre-market review (application to FDA) is required. An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria (21 CFR 1271.10(a)):

1. The HCT/P is minimally manipulated;

2. The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;

3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

4. Either:

    a. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

    b. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

        - Is for autologous use;
        - Is for allogeneic use in a first-degree or second-degree blood relative; or
        - Is for reproductive use.

HCT/Ps that do not meet all the criteria in §1271.10(a) are also regulated under Section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act (FD&C) as drugs, devices and/or biological products, and require pre-market review and approval.

Allogeneic islet cells have a systemic effect, depend on the metabolic activity of living cells for their primary function, are not autologous, are not for use in a first-degree or second-degree blood relative, and are not for reproductive use. Therefore, your allogeneic islet cells do not meet the criterion in 21 CFR 1271.10(a)(4) and are regulated as drugs and biological products under Section 351 of the PHS Act.

As described in our final guidance, Regulatory Considerations for HCT/P Products: Minimal Manipulation and Homologous use, cell culture generally alters the relevant biological characteristics of cells or tissues. However, because HCT/Ps must meet all of the criteria in 1271.10(a) in order to be regulated solely under section 361 of the PHS

Act, your allogeneic islet cells are regulated as drugs and biological products regardless of whether they are minimally manipulated or more than minimally manipulated.

Therefore, a biologics license application (BLA) is required in order to lawfully market your product.

Sponsor Question 2: *Should the FDA determine that some form of BLA is required, does the FDA agree that multiple manufacturing facilities can submit the data for a single facilitated BLA submission?*

FDA Response to Question 2:
As noted above, an approved BLA is required to lawfully market your allogeneic islet cells for the treatment of Type I diabetes mellitus. In the context of a BLA submission, it is unclear what you mean by the term "facilitated" BLA submission.

Below are several possible approaches for seeking marketing approval of allogeneic islet cells:

1. Each participating center prepares and submits a separate BLA independently. Each BLA would include shared clinical data obtained by the consortium, the specific center's own clinical data that are not part of the shared data, and the specific center's chemistry, manufacturing and control (CMC) and manufacturing facility information.

2. To reduce/share the burden of writing a BLA application, the participating centers collaborate on the preparation of common sections of a BLA application to create a template. To prepare its own BLA for submission, each participating center would use the BLA template and insert its own clinical data and CMC and manufacturing facility information into the template.

3. The participating centers collaborate on a single BLA, which includes the shared clinical data obtained by the consortium, each specific center's own clinical data that are not part of the shared data, and each specific center's manufacturing information. This approach would require that all participating centers use the same manufacturing protocol. One single entity (e.g., one study center) would serve as the applicant and be responsible for the BLA, and upon licensure would have all the responsibilities of a license holder. The various centers would be manufacturing locations and be subject to facility inspections under the BLA.

As it appears that allogeneic islet cells would be subject to the Prescription Drug User Fee Act (section 736 of FD&C Act), you may want to consider potential user fees associated with these different scenarios, including any potential waivers of such fees that may be available for orphan designated products. For additional information, please refer to the *Guidance for Industry: User Fee Waivers, Reductions, and Refunds for Drug and Biological Products* (September 2011), available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079298.pdf .

As an alternative to submitting a BLA for marketing approval, participating centers may decide to continue to treat patients under an IND. Any participating center that sponsors an IND may apply for FDA permission to charge for the investigational allogeneic islet product for the purpose of either clinical trials or expanded access for treatment use (21 CFR 312.8). For more information, please refer to the *Guidance for Industry, Charging for Investigational Drugs Under an IND – Questions and Answers* (June 2016), available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351264.pdf

Sponsor Question 3: *Should a facilitated BLA submission be allowed, does the FDA agree that transient preservation of PHPI before the transplant, to prepare the recipient and perform quality controls, does not require a separate classification as PHPI substance and PHPI product?*

FDA Response to Question 3:
Please see our comment regarding "facilitated" BLA submission in our response to Question 2.

Regarding your question about a need for a separate classification of purified human pancreatic islets (PHPI) substance and PHPI product, it is not clear what you mean by "transient preservation of PHPI before the transplant……does not require a separate classification as PHPI substance and PHPI product". For your proposed cellular product, however, we strongly recommend that you distinguish Drug Substance (DS) and Drug Product (DP) in your description of the product, manufacturing process, and quality controls.

A DS is defined as an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure or any function of the human body (21 CFR 314.3(b)). A DP is a finished dosage form that contains an active ingredient (DS) (21 CFR 210.3). Like most biologics, cellular therapy products can be described in terms of DS and DP, though it may be less intuitive in certain cases. For the vast majority of cell therapies, patients are not directly administered the DS, but instead the product formulated in excipients and placed in the final container as DP.

FDA offers some flexibility on how each sponsor defines the DS and DP portions of their manufacturing process, but we recommend you adhere as closely to the established eCTD structure as possible. You may also discuss with FDA your proposed DS and DP and strategies for testing and release for your specific product.

Sponsor Question 4: *In case of facilitated BLA submission, does the FDA agree that PHPI would benefit from Regenerative Medicine Advanced Therapy (RMAT) designation aimed at the expedited approval of PHPI?*

FDA Response to Question 4:

One of the primary benefits of RMAT designation is that it allows sponsors to have early and increased interactions with FDA, to promote efficient product development. However, RMAT designation does not change the review times associated with a BLA submission, nor does it change the BLA approval standard.