



Our STN: BL 125734/0

COMPLETE RESPONSE

August 18, 2021

CellTrans Inc.

Attention: Jose Oberholzer, MD, MHCM, FACS

2201 W. Campbell Park Drive, Suite 23

Chicago, IL 60612

Dear Dr. Oberholzer:

Please refer to your Biologics License Application (BLA) submitted and received May 19, 2020, for Donislecel (Purified Allogeneic Islets of Langerhans for Transplant) manufactured at your Chicago, IL location and submitted under section 351(a) of the Public Health Service Act.

We have completed our review of all the submissions you have made relating to this BLA with the exception of the information in amendment 43 submitted and received July 27, 2021. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

Chemistry, Manufacturing, and Controls

1. Outstanding issues identified during the pre-license inspection (PLI) at the CellTrans Inc. manufacturing facility between June 7, 2021 to June 11, 2021, as detailed in Form FDA 483 issued to you on June 11, 2021, have yet to be resolved. Per your response dated June 28, 2021, (as per amendment 39) to the Form 483 Observations, change controls have been initiated; however, the data to confirm the adequacy of the changes have not been submitted. Please submit documentation with data that demonstrates that all outstanding inspectional issues identified during the PLI have been resolved.
2. The BLA submission lacks sufficient data to demonstrate operational proficiency. No clinical lots of donislecel were manufactured since 2016. Deviations occurred in two out of the three process validation runs performed between March 2019 and May 2019. Your root cause analysis identified that, among other findings, there was inadequate training of staff. Based on your lack of clinical manufacturing experience since 2016, the deviations documented during the process validation studies, and observations we noted during the June 7, 2021 to June 11, 2021 PLI, there are insufficient data to evaluate your operational proficiency to successfully manufacture, package, and release the commercial product. Further, you propose

additional manufacturing process changes such as the (b) (4) (b) (4) (see comment #3).

To address this issue, please manufacture at least three donislecel lots to demonstrate your operational proficiency, incorporating all manufacturing process changes made since your 2019 process validation runs. Operational proficiency should demonstrate that the product can be successfully manufactured, packaged, and released, and is consistent with the proposed labelling. If you choose to manufacture clinical donislecel lots, these may be administered to patients under an Expanded Access protocol per 21 CFR 312.320. You may seek additional advice from us to address this issue.

3. We are unable to determine if the (b) (4) (b) (4) is suitable for the (b) (4) of clinical grade islets. During your manufacturing process development and clinical trials, you used (b) (4) (b) (4) to (b) (4) (b) (4) (b) (4) (b) (4) (b) (4). You indicated in Amendment 35, dated May 25, 2021, that you intend to change from (b) (4) to (b) (4). You provided a risk assessment in which you compared the specifications of (b) (4) to that of (b) (4) and assessed that the (b) (4) were comparable. Further, in your process validation plan, you identified (b) (4) (b) (4) as a critical process parameter (CPP). A change in a reagent involved in a CPP is considered a high-risk change, and as such, the reagent requires additional qualification prior to being introduced into the manufacturing process.

Please qualify the (b) (4) (b) (4) in your manufacturing process to determine if this (b) (4) could adversely affect the quality of your product and evaluate if there are any changes in step times and or changes to the (b) (4). Please submit the qualification reports for (b) (4) (b) (4).

4. There is a lack of adequate quality control (QC) of excipients and reagents used in your manufacturing process. The excipients in the final product (e.g., transplant media, HEPES buffer) and reagents (e.g., (b) (4) (b) (4) (b) (4) CMRL 1066 (b) (4) used in manufacturing are (b) (4) with Certificates of Analysis (COAs) indicating that they are “not suitable for human use.” The (b) (4) reagents are not adequately qualified or controlled for use in donislecel manufacturing. Please source pharmaceutical grade or reagents manufactured under suitable conditions as they are available from your vendors, in order to control the manufacturing process and minimize lot-to-lot variability of donislecel. Alternatively, please provide qualification data and justification that may support the use of (b) (4) excipients and reagents.
5. You have not established independent identity verification of reagents that come in contact with the product during the manufacturing process. The identity testing

should be performed not only on the excipients used in final formulation and transplant media but should also include other reagents used during the manufacturing process, such as enzymes and other solutions. Please establish a reagent identity testing program per 21 CFR 211.84.

6. Your lot release specification includes visual inspection tests for “container closure integrity” and “appearance,” which involves checking the final container closure system for leaks and inspecting the final drug product bag and rinse transplant media bag for any visible foreign objects or turbidity. You have not provided sufficient information regarding how this testing is performed, including, but not limited to, the standard operating procedures (SOPs), controls, and operator training for these tests. Please establish and provide SOPs, controls, and operator training for objective visual inspection tests to demonstrate the testing is established and well-controlled.
7. The training program for QC operators who perform lot release testing (e.g., islet viability, yield, purity, and potency assays) is grossly deficient. The (b) (4) training entails the QC operator (b) (4)
(b) (4)
The QC operators are not trained to perform the actual testing, which involves steps such as (b) (4)
For example, for Glucose Static Index (GSI) potency assay training, operators use (b) (4) to perform the enzyme-linked immunosorbent assay (ELISA). Using (b) (4) for training is inadequate, as it does not cover the entire assay that includes challenging the islets with high and low glucose concentrations. Operator training for each of the lot release assays should include the operator performing all the steps of the assay in their entirety. Please update your training SOPs and provide training data and documentation qualifying the operators to perform all lot release testing.
8. The in-process pancreas digestion assessment SOP, MFG-SOP-212 Pancreas Digestion, lacks clear instructions to ensure accurate assessment and scoring of digested tissue samples from the pancreas. During the digestion phase using the Ricordi instrument, an operator takes a (b) (4) sample of the digested pancreas every (b) (4) from the sampling port, stains the sample with Dithizone, and microscopically evaluates the samples to determine the amount of tissue, size of tissue and percentage of free islets. These three parameters are each assessed and scored as (b) (4). Please update MFG-SOP-212 Pancreases Digestion with specific instructions on how to assess and score the digested tissue samples to enable operators to consistently score the digested tissue samples.

Labeling

9. We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval.

Please submit your meeting request as described in the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf>, and CBER's SOPP 8101.1 *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants* at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>.

We acknowledge receipt of your amendment 43 dated July 27, 2021. Please be aware that we have stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response. You may cross reference applicable sections of the amendment dated July 27, 2021, in your complete response to this letter and we will review those sections as a part of your complete response.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Rommel Maglalang, at Rommel.Maglalang@fda.hhs.gov.

Sincerely,

Raj K. Puri, MD, PhD
Director
Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research