

CBER CMC BLA Resubmission Review Memorandum

BLA STN 125734

**Purified Allogeneic Islets of Langerhans
(donislecel-jujn, LANTIDRA)**

CellTrans, Inc.

Reviewer/Title/Affiliation

Sukhanya Jayachandra, PhD, Biologist, OTP/OCTHT-CMC/DCT1/CTB1

Branch Chief Reviewer

Melanie Eacho, Ph.D.

CBER/Office of Therapeutic Products (OTP)/Office of Cellular Therapy and Human
Tissue CMC (OCTHT)/Division of Cell Therapy 1 (DCT1)/Cell Therapy Branch (CTB1)

1. **BLA#: STN 125734**
2. **APPLICANT NAME AND LICENSE NUMBER: CellTrans Inc. License #2213**
3. **PRODUCT NAME/PRODUCT TYPE**

Non-Proprietary/Proper/USAN: **Purified Allogeneic Islet of Langerhans, donislecel-jujn**

Proprietary Name: **LANTIDRA**

NDC: LANTIDRA Bag: **73539-001-01**
Rinse Bag: **73539-002-001**

UNII Code: **FW00DG4E3P** for donislecel active ingredient

RWW266YE9I for HEPES (2-[4-(2-hydroxyethyl)piperazin-1-yl] ethanesulfonic acid)-inactive ingredient

ZIF514RVZR for human serum albumin-inactive ingredient

UNII codes for inactive ingredients in the **Transplant /Rinse Media** are in **Appendix 1** at the end of this Review Memo

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

Pharmacological category: Purified Allogeneic Human Islets of Langerhans for Transplant

Dosage form: Cellular suspension

Strength/Potency: First Dose-5000EIN/Kg body weight of recipient,
Second and third Dose - 4500 EIN/Kg body weight of recipient
Note: Clinical review team, based on the pivotal trial data, recommend increasing the minimum for the second and third to 4500 EIN/Kg body weight from 4000 EIN/Kg body weight, during revision of the label in July 27, 2021 and June 21, 2023. CellTrans agreed with increasing the second and third dose recommendations.

Route of administration: Intravascular (hepatic portal vein)

Indication: For the treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education

5. MAJOR MILESTONES

Milestone	Date
BLA 125734 initial submission	May 19, 2020
BLA 125734 filed	July 16, 2020
BLA 125734 Proprietary name approval letter	September 25, 2020
BLA 125734 Major amendment	October 20, 2020
BLA 125734 Mid-cycle meeting	October 30, 2020
BLA 125734 Late-cycle meeting	April 01, 2021
BLA 125734 Advisory Committee Meeting	April 15, 2021
BLA 125734 Prelicensure inspection	June 07 - 11, 2021
BLA 125734 PDUFA action date	August 18, 2021
BLA 125734 Complete Response Letter (CRL) issued	August 18, 2021
BLA 125734 Type A meeting	September 27, 2021
BLA 125734 Resubmission	December 30, 2022
BLA 125734-Resubmission Midcycle Internal Meeting	April 10, 2023
BLA 125734 Resubmission PDUFA Action Date.	June 28, 2023

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Sukhanya Jayachandra, PhD BLA Chair; Product Office Reviewer CBER/OTP/OCTHT/DCT1/CTB-1	Reviewed Complete Response Letter (CRL) Comments 1 (Form 483 observation 3 and 9) and CRL comments 2 through 8 responses
Pankaj (Pete) Amin, Ph.D Facility Inspector/ DMPQ Reviewer CBER/OCBQ/DMPQ/MRB3	Reviewed CRL Comment 1 (Form 483 observations 1, 2, 4 through 8, 11, and 12) response
Andrey Sarafanov, OPPT Reviewer CBER/OTP/OPPT/DH/HB2	Reviewed CRL Comment 1 (Form 483 observation 10 on leachable and extractables of final container closure system) response

7. INTER-CENTER CONSULTS REQUESTED: N/A

8. SUBMISSION(S) REVIEWED

Date Received	Submission-STN	Comments/ Status
June 01, 2022	STN 125734/044	Applicant requested a six (6) month extension to respond to CR and resubmit. Extension granted on July 09, 2022.
BLA Resubmission		
Date Received	Submission (STN)	Comments/ Status
December 30, 2022	STN 125734/045	Resubmission to August 18, 2021 CRL
January 20, 2023	STN 125734/046	Response to information request (IR) dated January 18, 2023. The Applicant submitted a Revised Package Insert, Request for Proprietary Name Review and Proposed Suffix Review.
January 30, 2023	STN 125734/047	Response to IR dated January 26, 2023. The Applicant submitted revised tracked version of the package insert.
March 16, 2023	STN 125734/048	Response to IR dated March 6, 2023. The Applicant submitted complete Batch records for clinical H0603 and H0604 lots administered to subjects under the Expanded Access protocol in IND 11807.
April 19, 2023	STN 125734/049	Response to IR dated April 17, 2023. The Applicant submitted information on follow-up to 2 patients treated under the Expanded access protocol in IND 11807 with lot H0603 and H0604 in June/July 2022 and information on delivery device used to administer the H0603 and H0604 donislecel lots.
April 27, 2023	STN 125734/050	Response to Clinical IR dated April 24, 2023 regarding update on subjects from the September 20, 2018 date of data lock for BLA 125734 thru the December 30, 2022 Resubmission date.
May 02, 2023	STN 125734/051	Response to CMC IR dated May 01, 2023 regarding specific catheters used to administer lot H0603 and H0604.

May 08, 2023	STN 125734/052	Response to CMC IR dated May 05, 2023 regarding current carton and container labels.
May 19, 2023	STN 125734/053	Response to DMPQ IR dated May 10, 2023 regarding location of Form 483 response documents in the resubmission. The Applicant provided the Smoke study summary, facility diagrams, Certificate of analysis for (b) (4) and documentation of routine (b) (4) monitoring.
June 06, 2023	STN 125734/054	Response to CMC IR dated June 01, 2023 to revise MFG_FRM-307.01 Final Product Chain of Custody Form.
June 07, 2023	STN 125734/055	Response to CMC IR dated June 02, 2023 to revise the LANTIDRA CryoMACS bag and Rinse CryoMACS bag labels.
June 14, 2023	STN 125734/056	Response to CMC IR dated June 09, 2023 related to Extractable and Leachable Study report provided in response to Form 483 observation 10b.
June 15, 2023	STN 125734/057	Applicant provided an updated letter at the request of Office of Orphan Products Development confirming that, if eligible, CellTrans Inc. waives orphan drug exclusivity under section 527 of the FD&C Act.
June 21, 2023	STN 125734/058	Response to CMC IR dated June 16, 2023 for follow-up on Extractable and Leachable Study for final container closure system.
June 23, 2023	STN 125734/059	Response to Clinical IR dated June 19, 2023 regarding Package Insert (proposed labelling)
June 23, 2023	STN 125734/060	Response to CMC IR regarding concurrence and timeline for the proposed E & L PMC
June 21, 2023	CellTrans Inc confirmed via email dated June 21, 2023.	Agreement by CellTrans on E& L PMC with study report due date of February 29, 2024 Official eCTD load will occur as an amendment.

9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type and Number	Submission Holder name	Referenced Item	Letter of Cross Reference	Comments/Status
IND 11807	Dr. Jose Oberholzer, University of Illinois Hospital	Access to all the IND Information and Clinical trial data	Yes	File active. Clinical trials UIH-001 and UIH-002 were done under this IND. All rights of the IND 11807 transferred to CellTrans Inc in 2017
IND 9336	Division of Allergy, Immunology, and Transplantation. National Institute of Allergy and Infectious Diseases	To access all relevant information in BB-IND # 9336 for the purpose of review of BLA being submitted by CellTrans, Inc.	Yes	File active and current CellTrans Inc, participated in three studies (CIT-02, CIT-06, and CIT-07) performed under the purview of IND BB-9336 held by the Clinical Islet Transplantation (CIT) Consortium prior to 2016. The clinical studies and manufacturing information contained in IND 9336 were not considered as part of this BLA review. Clinical studies participated were CIT-02, CIT-06 and CIT-07. Reviewer Comment: CellTrans mentioned manufacturing experience in the introduction for process validation (STN 125734/0, Section 3.2.S.2.5). However, the manufacturing lot release information in IND 9336 was not used by CellTrans to set specifications for process validation.
(b) (4)	Division of Allergy, Immunology, and Transplantation.	To access all relevant information in (b) (4) for the purpose of review of BLA being submitted	Yes	File active and current. This Master File refers to the CMC information for the production of human allogeneic islets for transplantation at multiple processing facilities in the

	National Institute of Allergy and Infectious Diseases	by CellTrans, Inc.		<p>Clinical Islet Transplantation (CIT) Consortium trials and cross references IND 9336.</p> <p>Reviewer Comment: The Applicant does not directly reference (b) (4) for manufacturing of islets lot to support UIH-001 and UIH-002 clinical trials (BLA was supported by data from these trials). The Applicant, however, refers to the CIT manufacturing procedures to justify specifications and used CIT manufacturing procedures to support the CIT trials they participated in (BLA was not supported by data from CIT trials). BLA 125734 will not be affected, if IND 9336 or (b) (4) were withdrawn.</p>
IND 11228	University of Chicago	To access all relevant information in BB-IND # 11228 for the purpose of review of BLA being submitted by CellTrans, Inc.	Yes, Letter dated January 10, 2017	<p>File active and current. CellTrans Inc., participated in an additional Islet study performed at the University of Chicago under BB-IND-11228.</p> <p>Reviewer Comment: These studies were not considered as part of this BLA review. CellTrans mentioned manufacturing experience in the introduction for process validation (STN 125734/0, Section 3.2.S.2.5).</p>
(b) (4)	(b) (4)	<p>(b) (4)</p> <p>Product code (b) (4)</p>	Not needed; marketed product. Applicant noted the cross reference in Form 356hSN0 001May19, 2020	<p>The introducer is cleared under 21 CFR 870.1340 classification: introducer, catheter. The cleared use of the introducer is for catheter placement. In this BLA, applicant used it to deliver the donislecel, finished drug product.</p> <p>Reviewer Comment: Use of this device for administration</p>

				of a therapeutic agent/fluid is considered off-label use of the device. Please refer to Draft Labelling section 2.4 submitted by the applicant in Amendment STN125734/036, dated May 27, 2021
(b) (4)	(b) (4)	(b) (4) Product Code (b) (4)	Not needed; marketed product. Applicant noted the cross reference in Form 356h SN0001 May19, 2020	Reviewer Comment: The catheter is cleared under 21 CFR 870.1200 classification: catheter, intravascular, diagnostic. It is an Rx device and intended for use in angiographic procedures to deliver radiopaque media and therapeutic agents to selected sites in the vascular system. It is also used to lead a guide wire or a catheter into the target site.
BK090020	Miltenyi Biotec, Inc	CryoMACS Freezing Bag	No, this is marketed product	Reviewer Comment: Container, Empty, For The Collection ' & Processing Of Blood/Blood Component. CellTrans utilizes the CryoMACS bags for container closure of the LANTIDRA drug product and transplant solution

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

CellTrans, Inc. (“the Applicant”) has submitted a response dated December 30, 2022 to our complete response letter (CRL) dated August 12, 2021 referencing the Applicant’s biologics license application (BLA) 125734 seeking to market donislecel-jujn (LANTIDRA). LANTIDRA is an allogeneic pancreatic islet cellular therapy derived from deceased donor pancreases, indicated for the treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education. T1D is an autoimmune disease marked by destruction of insulin-producing beta cells, which leads to inadequate production of hormones in response to glucose stimulation and thus inadequate control of blood glucose levels. Each lot of donislecel is manufactured from a deceased donor pancreas procured via the Organ Procurement and Transplantation

Network (OPTN), and is used to manufacture one dose, but patients may receive up to three doses over the course of treatment (i.e., different donors for each of the doses).

Islets of Langerhans are composed of mixed populations of endocrine and exocrine cells, the major cell type being insulin producing beta cells. The proposed mechanism of action for LANTIDRA is regulation of blood glucose levels through LANTIDRA's secretion of insulin in response to exogenous glucose stimulation.

The manufacture of each LANTIDRA lot involves enzymatic and mechanical digestion steps using the Ricordi chamber. The (b) (4) islet preparation is purified by a (b) (4) (b) (4) (b) (4) step to isolate islet fractions, which are segregated and pooled as top, middle and bottom fractions based on islet purity. The islet fractions are incubated up to 48 hours. After incubation, the islets are harvested from the cell culture flasks for final formulation in buffered transplant media containing sodium chloride, dextrose, minerals, amino acids, vitamins, and other compounds supplemented with HEPES (2-[4-(2-hydroxyethyl)piperazin-1-yl] ethanesulfonic acid; 10 mM final concentration) and human serum albumin (0.5% final concentration). LANTIDRA is packaged into a CryoMACS infusion bag and is aseptically connected to another smaller CryoMACS Rinse bag containing 200ml transplant media, used to rinse the LANTIDRA bag and the infusion line. The filled CryoMACS bags containing LANTIDRA and rinse transplant media are labelled, packaged within two sterile overwraps, placed in a sterile temperature monitored carrier, and hand carried by walking it to the Radiology unit that is five minutes away within University of Illinois (UI) Health campus. The final drug product is administered via catheters into the liver via the portal vein by gravity flow over a 30 minute period.

We identified several Chemistry, Manufacturing and Controls (CMC) review issues and pre-license inspection observations that resulted in a Complete Response letter issued on August 18, 2021. On December 30, 2022, the Applicant provided a Resubmission with responses to the deficiencies.

In this Resubmission, the Applicant addressed all the facility related observations that were issued for the CellTrans manufacturing facility during the pre-license inspection (PLI) conducted between June 7 and 11, 2021. Another PLI did not occur during the Resubmission review cycle, instead DMPQ recommended a detailed review of all Form 483 corrective actions during the next routine FDA manufacturing site inspection.

In addition, the Applicant addressed the CMC review issues related to quality control personnel training, lot release testing standard operating procedures (SOPs), reagent qualification, process validation, and lack of clinical lot manufacturing since 2017. The Applicant demonstrated manufacturing proficiency by manufacturing (b) (4) additional lots of donislecel.

We issued multiple IRs between January and June 2023 to attempt to resolve the following:

1. For the (b) (4) donislecel clinical lots manufactured and administered in 2022 under an expanded access protocol in support of the Resubmission, the Applicant indicated that they were administered using only a sheath/introducer system and not catheters. As sheath/introducer systems are not FDA cleared for administration of drugs, and only catheters of specific dimensions should be used to deliver donislecel per clinical study experience, the Applicant obliged to take several actions. The Applicant revised the final “MFG-FRM-307.01 Final Product Chain of Custody Form” to inform the UI Health Radiology to administer all commercial lots of donislecel in accordance with the package insert (PI) instructions and to record the make and model of the catheters used to administer donislecel. We also worked with the Applicant to update the PI to include compatible catheter specifications and warnings to only use catheters to deliver donislecel. The delivery device issues have been resolved and no further action is required.
2. The Applicant in the Resubmission provided an extractables and leachables (E&L) study report to address PLI Form 483 observation 10. The E&L study pertains to the final containers closure systems that consist of two 510(k) cleared Miltenyi CryoMACS bags, one containing LANTIDRA and the second containing transplant media used to rinse the LANTIDRA bag and the infusion line post infusion to ensure LANTIDRA delivery. The leachables analytical study lacked a validated limit of quantification (LOQ) below the reporting level, above which a toxicological assessment for leachables would be needed. However, we determined that the analytical reassessment of leachables and toxicological assessment of leachables above the reporting level could be addressed in a postmarketing commitment (PMC) as these bags are 510(k) cleared and the drug product is stored for a relatively short time (six hours) compared to other approved products that use these CryoMACS bags. In addition, according to the E&L study reviewer, Dr. Sarafanov, the request for proper analytical reassessment and toxicological assessment is more a formality for completeness rather than a true safety concern.

As summarized above, all issues have been addressed, except the E&L study report and leachables toxicological assessment, which can be addressed via a PMC.

B. RECOMMENDATION

- C. APPROVAL: The CMC team recommends approval of BLA 125734 with a PMC on E&L.**

Manufacturing Facility

The following manufacturing and testing facilities are used for manufacturing LANTIDRA:

Facility and Address	Responsibility	Credentials
Islet Isolation Facility CellTrans Inc. 1740 West Taylor Street, Building 949, Suite C200, University of Illinois Hospital, Chicago, IL, 60612	Primary Manufacturing Facility: Donor Screening Islet Isolation and Purification Islet In- Process and Release Testing	
(b) (4)	Donor Testing	CLIA# (b) (4) FDA FEI# (b) (4)
(b) (4) University of Illinois Hospital & Health Science System (UI Hospital) (b) (4) (b) (4)	Gram Stain Testing	CLIA# (b) (4)
(b) (4)	Mycology Testing, sterility and identity testing of reagents	CLIA# (b) (4) FDA FEI# (b) (4)
(b) (4) University of Illinois Hospital, Sterile (b) (4) 1740 West Taylor Street, Suite (b) (4) Chicago, IL, 60612	Cleaning and Sterilization of Processing Equipment	
(b) (4)	Dynamic (b) (4) and Static Environmental Monitoring Facility Certification Cleaning and Sanitization of Facility	(b) (4) Accredited Accredited by the AIHA Laboratory Accreditation Program

(b) (4)	Testing of Facility Microbial and Fungal Samples	(b) (4) Accredited Accredited by the AIHA Laboratory Accreditation
(b) (4)	Gowning Qualification	(b) (4) Accredited Accredited by the AIHA Laboratory Accreditation

Postmarketing Commitment:

CellTrans, Inc. commits to reassess the analytical levels of organic leachables from the container closure system (two units, 750- and 1000-mL bags) using a methodology with validated limit of quantification (LOQ) values that are reliably below the reporting limit of (b) (4) (monitoring level, calculated based on the toxicological concern threshold). Based on this analytical reassessment, for compounds found above the reporting limit, CellTrans, Inc. also commits to perform a toxicological assessment and will submit the final reassessment of the organic leachables analytical levels and their toxicological assessment as a Post Marketing Commitment – Final Study Report by February 29, 2024.

Final Study Report Submission: February 29, 2024.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Sukhanya Jayachandra, PhD BLA Chair CBER/OTP/ OCTHT/DCT1/CTB1	Concur	
Irina Tiper, PhD Team Lead CBER/OTP/ OCTHT/DCT1/CTB1	Concur	
Melanie Eacho, PhD Branch Chief CBER/OTP/OCTHT/DCT1/CTB1	Concur	
Steven Oh, PhD Acting Division Director CBER/OTP/OCTHT/DCT1	Concur	

Heather Lombardi, PhD Office Director CBER/OTP/OCTHT	Concur	
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11. COMPLETE RESPONSE Letter (CRL) ITEMS

Below are the Chemistry, Manufacturing and Controls related deficiencies in the CRL letter repeated in **bold**, followed by a summary of the Applicant's response, where applicable, and the reviewer's assessment in *italics*.

CRL Comment 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.

Observation 1: Your firm's Quality Unit lacks a procedure/policy that details requirements for the following:

- a. **A local academic medical center is used for receipt of, for example, deliveries of your firm 's critical media or components. There is no procedure or policy in place that addresses the potential for deliveries that may be held at a receiving dock or where possible storage in dock refrigerators may occur.**
- b. **Lack of oversight of a sterilization firm:**
 - **Sterilization of CellTrans equipment is not performed according to the validated process. Specifically, it was found that the vendor fills autoclave cart with CellTrans equipment and other hospital equipment based on weight and available space. The autoclave validation report only describes load items from CellTrans.**
 - **Sterilization load can be re-sterilized. However, only documented final sterilization information is forwarded to CellTrans, initial failed or incomplete runs are not required to be reported to CellTrans as of this inspection.**

DMPQ Reviewer Assessment Summary: The Applicant's response is acceptable based on implementing corrective actions related to Procedure for Deliveries to CellTrans from UI Health Receiving Dock, Standard Operating Procedures (SOPs) implemented by the sterilization Vendors (b) (4) for

loading and unloading sterile equipment and updating reporting requirements of any failed or incomplete runs to CellTrans and updating SOPs for cleaning and sterilization of Islet isolation equipment.

DMPQ recommended a detail review of all Form 483 corrective actions during the next FDA manufacturing site inspection.

Observation 2: The current deviation reporting procedure was found deficient, for example:

- a. During review of the (b) (4) system for monitoring of incubators, (b) (4) and cleanroom temperature and humidity, it was found that temperature excursions are not properly documented and reported as deviations.
- b. Two HEPA filters were found to have leaks during routine (b) (4) HEPA filter certification. However, there is no documentation that a vendor performed leak sealing using (b) (4) whether the percentage of area sealed was within an allowable limit or any impact on room environmental quality.

***DMPQ Reviewer Assessment Summary:** The Applicants' response appears acceptable based on implementing corrective actions that includes updating SOPs and related Forms, installation of new qualified environmental monitoring systems and the HEPA filter integrity testing studies.*

DMPQ recommended a detail review of all Form 483 corrective actions during the next FDA manufacturing site inspection

Observation 3: Final product lots were released with incomplete batch record or failed lot release specifications. The batch records for these lots were part of your BLA submission. Specifically, Lots (b) (4) (b) (4) were released for transplant with incomplete information of purity tests in the batch record. Lot (b) (4) was released for transplant with failed potency test.

***Product Office Reviewer Assessment:** The Applicant indicated that donislecel lots (b) (4) were manufactured early in their clinical trials, prior to the establishment of CellTrans, Inc. With the establishment of CellTrans, Inc. in 2017, the Applicant implemented a Quality Control (QC) Unit with numerous standard operating procedures(SOPs) including SOP, MFG-SOP-500, Final Product Release, and related form, MFG-FRM-500.01, Final Islet Product Certificate of Analysis, in order to ensure that all required release specifications are met prior to final release of the final product. The Applicant submitted SOP: MFG-SOP-500 and MFG-FRM-500.01 in section 3.2.S.2.2-40 and 3.2.S.2.2-41 respectively that ensures the final islet product Certificate of Analysis must be*

reviewed and approved by the lead QC Unit personnel prior to release for transplantation.

DMPQ Reviewer Assessment Summary: The SOPs and forms were reviewed. In addition, the Applicant manufactured three lots, (b) (4)

The Applicant provided the batch records for (b) (4) of the lots that were administered to patients under the expanded access protocol. The review of the batch records indicated that the SOP MFG-SOP-500, Final Product Release, and related form, MFG-FRM-500.01 were followed and reviewed prior to release.

Overall Assessment: The Applicant's response is acceptable. No additional corrective action is required. DMPQ recommended a detail review of all Form 483 corrective actions during the next FDA manufacturing site inspection.

Observation 4: Regarding your firm's current aseptic process observed during inspection we noted the following deficiencies:

- a. Sterile equipment was exposed to ISO 7 clean room (a less clean area) before transferring into the biological safety cabinets (ISO 5) for use in your firm's aseptic process.
- b. An operator's hand repeatedly broke first air over exposed sterile equipment during a process performed within a BSC (ISO 5 condition).
- c. A smoke study was not performed for any of the (b) (4) BSC hoods that are used for aseptic processing study performed for the ISO 7 clean room failed to include dynamic conditions.
- d. Equipment and other items were observed in the clean room partially blocking the ISO 7 cleanroom air return vents.
- e. The ISO 7 clean room contains equipment that are not used for processing that may interfere with room cleaning and impact room quality such as the following: (b) (4) large wall mounted video cameras that have not functioned for many years, desktop computer not used for processing, and exposed wiring on a wall.
- f. A pressure differential between rooms of different classifications is not continuously monitored; it is only monitored during processing and weekly using handheld manometer.

DMPQ Reviewer Assessment Summary: The Applicants' response appears acceptable based on implementation of corrective actions, including revised SOPs, (b) (4) Air Pattern Testing (b) (4) report for the Processing Suite Biological Safety Cabinets under dynamic conditions, removal of unused equipment from clean room, media fill study reports, upgrading the Environmental Monitoring system (b) (4) to the (b) (4) (b) (4) Monitoring system and providing (b) (4) qualification reports.

All study reports are recommended to be verified in detail during next cGMP inspection.

DMPQ recommended a detail review of all Form 483 corrective actions during the next FDA manufacturing site inspection.

Observation 5: Your gowning procedures are deficient. Specifically,

- a. **The SOP, Gowning: Entering and Exiting Procedures for the Islet Isolation Facility, MFG-SOP- 201, section 8.1 "Gowning Process: Preparation Step," requires changing from street clothes to scrubs in restrooms, including the washing of hands as part of the preparation. The restrooms include one toilet and one sink and towel dispenser. There is no assurance that scrubs have not been contaminated by the restroom environment. The SOP also requires that street clothes be stored in an office space, which is done after scrubs are donned.**
- b. **Additional gowning is necessary to work in ISO (b) (4) environments to perform aseptic manufacturing steps, as per the SOP, Sterile Gowning Technique, MFGSOP- 221. Your firm does not conduct training in, nor have a gowning qualification program for, such sterile gowning of personnel as described by the SOP.**

DMPQ Reviewer Assessment Summary:

CellTrans updated and revised SOPs related to Gowning: Entering and Exiting Procedures for the Islet Isolation Facility to remove the use of restrooms and office space during the gowning procedure. Further, the Applicant established a dedicated locker room solely for changing from street clothes to scrubs and hand washing. The restrooms will no longer be used during gowning procedures and street clothes will not be stored in office. The new facility layout allows for storage of street clothes in a dedicated locker located beside the entrance of the islet isolation facility. Applicant revised training SOPs to include Surgical Gowning Techniques, and now conducts training and annual surgical gowning qualification.

The Applicant's response is acceptable, and details will be reviewed during the next FDA inspection.

Observation 6: Tube sealer equipment qualification is deficient.

Specifically, the qualification was not performed under the conditions of use (tubing internals exposed to moisture) and the verification of seal integrity was limited to (b) (4) of the seal.

DMPQ Reviewer Assessment Summary:

CellTrans performed a re-qualification of the tube sealer equipment to verify sealing integrity by (b) (4) of the seal under the conditions of use and found acceptable. This study concluded that tubing on the final container closure was sealed, with no leakage or damage present.

The Applicant's response is acceptable, and details will be reviewed during the next FDA inspection.

Observation 7: Effectiveness of the disinfectants used for facility and BSC cleaning was not demonstrated. Disinfectant effectiveness study design did not include acceptance criteria to demonstrate required log reduction, did not specify challenge organisms used or their concentration, and calculated log reduction is unknown.

DMPQ Reviewer Assessment Summary:

CellTrans outsourced the disinfectant effectiveness study and performed a new Effectiveness study of the disinfectants used for the Islet isolation facility and Biosafety Cabinets (BSCs). The revised study design included acceptance criteria to demonstrate required log reduction. The new Effectiveness study of the disinfectants report was acceptable. Further, CellTrans has replaced the use of (b) (4) in the cleaning of the Islet Isolation Facility with the sporicidal agent (b) (4)

Additionally, the facility underwent (b) (4) decontamination, and all Environmental Monitoring sample results met the acceptance criteria for the Islet Manufacture Facility.

The Applicant's response is acceptable, and details will be reviewed during the next FDA inspection.

Observation 8: CellTrans does not require periodic verification of manual cleaning used for product contact equipment. No such verification has been performed since 2018 when the initial cleaning validation was completed.

DMPQ Reviewer Assessment Summary:

CellTrans revised SOP, FAC-SOP-001, Cleaning and Sterilization of Human Islet Cell Isolation and Equipment and performed a cleaning study.

The Applicant's response is acceptable, and SOP and the cleaning verification results are recommended to be reviewed in detail during next FDA inspection

Observation 9:

- a. The Quality Unit oversight of raw materials is deficient. Specifically,**
 - i. Certificates of Analysis from a manufacturer of media/components that are used in the production of the product (b) (4) CMRL 1066 (b) (4) and (b) (4) and who also manufactures excipients/components (HEPES and CMRL 1066 Transplant**

Solution), state that these solutions are not sterile [Sterility Assurance Level (SAL) of (b) (4) All such components specifications have been approved by your firm's Quality Unit and raw materials were released for use in aseptic operations.

Applicant response: The Applicant has outsourced the testing to qualified laboratories (b) (4) who will be performing the (b) (4) sterility standard testing for media components and reagents used in the manufacturing of the drug substance and drug product, prior to the release of these reagents for islet manufacturing.

The following media components were identified to be tested.

- CMRL 1066 (Transplant Solution)
- HEPES
- (b) (4)
- (b) (4)
- (b) (4)
- CMRL 1066 (b) (4)
- (b) (4)
- (b) (4)

1. Change control CC-00064 establishing all media and media components undergo (b) (4) testing prior to introduction into manufacturing was implemented and provided for review.
2. The Applicant in Attachment 3.2.S.3-4.1 provided Method Suitability test (also known as Bacteriostasis/Fungistasis test) validation report date June 13, 2022 from (b) (4) The test was performed for CellTrans, Inc. using (b) (4)

. The results were acceptable. This Method Suitability test passed.

3. The Applicant in Attachment 3.2.S.3-42 provided Method Suitability or Bacteriostasis/Fungistasis test results and validation report dated June 14, 2022 for the CMRL 1066 (b) (4) (b) (4) (b) (4)

(b) (4)

4. The Applicant in Attachment 3.2.P.5.3-1 provided Method Suitability test (also known as Bacteriostasis/Fungistasis test) validation report date October 31, 2022 from (b) (4)

Product Office Reviewer Assessment:

1. *The Applicant provided the change control forms and documents that were established to ensure all media and media components undergo sterility testing prior to release into the LANTIDRA manufacturing process. **The change control data per the established procedures will be reviewed during the next cGMP inspection of the facility. DMPQ determined a re-inspection of the facility prior to licensure is not warranted.***
2. *The Applicant also provided Method Suitability test for media CMRL 1066 and manufacturing components used in the manufacture of LANTIDRA that was reviewed and is acceptable. **No CMC concerns.***
3. *The Applicant also provided Method Suitability test for CMRL 1066 (b) (4) The reports were reviewed and is acceptable. **No CMC concerns.***
4. *The Applicant also provided Method Suitability test for (b) (4) test samples for (b) (4) lots manufactured post facility changes and part of establishing clinical manufacturing consistency. Each (b) (4) containing approximately (b) (4) of sample for qualitative method suitability testing. CellTrans, Inc. also provided (b) (4) samples of Final Product Human Islet samples from (b) (4) lots (b) (4) with each (b) (4) containing approximately (b) (4) of sample for Method Suitability testing. The reports were reviewed and are acceptable. **No CMC concerns.***

Overall Product Office Reviewer Assessment: The Applicant has addressed observation 9a. No additional corrective action is required.

- ii. Your firm uses the SOP, Material Management Program, QAL-SOP-402, to manage the acceptance of raw materials, such as components/excipients. This SOP is linked to specifications that require (b) (4) testing of (b) (4) components. Both the material management SOP and specifications are approved by your firm's Quality Unit. An (b) (4) (b) (4) method is used as part of acceptance of raw material components (production media & excipients). The related (b) (4) method validation only addressed (b) (4) media components and (b) (4) excipient. However, the validation is also used to support the (b) (4) testing of other excipients/components and media that are used in production or are part of the final product.

Applicant Response:

1. The Applicant in Attachment 3.2.A.1.46, provided the QAL-SOP-402 with an effective date of September 20, 2022 to provide instructions for the management of receiving and storage of material at CellTrans, Inc. The SOP covers specific instructions for receipt, quarantine, acceptance, release and storage of incoming materials.
2. The Applicant in Attachment 3.2. A.1.47, provided the QAL-FRM - 404.02 Media Release Form. Sample form as supportive documentation for release of media from quarantine was provided. The form included addition information as update to release criteria testing requesting prior to QC release and addition of (b) (4) testing release criteria.

Product Office Reviewer Assessment:

The revised SOP (document number QAL-SOP-402) and revised Media Release Form were reviewed and are acceptable. No CMC concerns.

- b. Establishment of the reliability of the container and component suppliers' report of analysis is deficient in that the test results are not appropriately validated at appropriate intervals. Specifically:
- i. Your firm has not established the reliability of suppliers' Certificate of Analysis for, but not necessarily limited to, the following excipients/components: (1) CMRL 1066 (Transplant Solution) and (2) HEPES, specification FAC-SPC-017 and FAC-SPC-008, respectively. For CMRL 1066, tests include (b) (4) (b) (4) For HEPES, tests include (b) (4) (b) (4)

Applicant Response: The Applicant has addressed this observation by implementing a process to independently verify the Certificate of Analysis (CoA) through outsourcing some of the quality control (QC) testing activities to a qualified contract testing laboratory. The testing of each reagent is based on the specific CoA for each reagent. Testing includes (b) (4) (for the HEPES buffer). Further CellTrans also performs in-house (b) (4) (b) (4) QC testing for each excipient and reagent based on the specific CoA. Lastly, QC testing for each excipient and reagent lot is performed to determine the reliability of the suppliers' CoA prior to lot release.

CellTrans provided the following change controls documents and SOPs for review:

(b) (4)

- The Applicant provided the following:

(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)

Product Office Reviewer Assessment: The Applicant has addressed observation 9.b.i. No additional corrective action is required.

- ii. Your firm has not established the reliability of suppliers' Certificate of Analysis for the following containers: CryoMACS Freezing Bag 1000 (Specification FAC-SPC-029) and CryoMACS Freezing Bag 750 (Specification FAC-SPC-030). For both bags, tests include: (b) (4)

Applicant Response: In the Change Control form CC-00070, the Applicant included independent verification of (b) (4) for the CryoMACs Freezing Bag 1000 and Freezing Bag 750. (b) (4) performed the (b) (4) Validation and (b) (4) Validation for CryoMACS Freezing Bag 1000 and CryoMACS Freezing Bag 750. The Change Control and Validation was previously reviewed in the Applicant response to Observation 9a. Further, the Applicant provided the following documents:

- a. Attachment 3.2.A.1-48: Form: QALFRM- 402.05, Material Release Form
- b. Attachment 3.2.S.2.3-14: Specification FAC-SPC-029 CryoMACS Freezing Bag 1000 where the testing requirements prior to QC release was updated.
- c. Attachment 3.2.S.2.3-15: Specification FAC-SPC-030 CryoMACS Freezing Bag 750 where the testing requirements prior to QC release was updated.
- d. Attachment 3.2.P.7-4: Final Report for the (b) (4) by (b) (4) Method Suitability (b) (4) Test) of CryoMACs Freezing Bag 1000
- e. Attachment 3.2.P.7-5: Final Report for the Method Suitability (b) (4) Testing for (b) (4) for CryoMACs Freezing Bag 1000
- f. Attachment 3.2.P.7-6: Final Report for the (b) (4) by (b) (4) Method Suitability (b) (4) Test) of CryoMACs Freezing Bag 750.
- g. Attachment 3.2.P.7-7: Final Report for the Method Suitability (b) (4) Testing for (b) (4) for CryoMACs Freezing Bag 750

***Product Office Reviewer Assessment:** The Applicant has addressed observation 9.b.ii, by establishing procedures to verify the reliability of the manufactures certificate of analysis for components that come in direct contact with the product. No additional corrective action is required.*

- c. **Drug product component testing is deficient in that at least one specific test to verify the identity of each component is not performed. Specifically, your firm does not conduct identity testing for, but not necessarily limited to, the following excipients that are included in the final product: (1) CMRL 1066 (Transplant Solution) and (2) HEPES, specification FAC SPC-017 and FAC-SPC-008, respectively.**

Applicant Response: CellTrans outsourced the identity testing to (b) (4) laboratories. In the Change Control form CC-00071 the Applicant included independent verification of identity testing of the drug product components namely CMRL 1066 (Transplant solution), HEPES, (b) (4) (b) (4) (b) (4)

(b) (4) (b) (4) The Application specified the identity test for each reagent. CellTrans also provided the following documents for review:

(b) (4)

Product Office Reviewer Assessment: *The Applicant addressed observation 9c. The Applicant is independently verifying the identity of the excipients by outsourcing testing to a contract testing lab. Specifically, the following identity testing is being performed by (b) (4)*

(b) (4)

(b) (4)

Observation 10: Lack of assessment of extractable and leachable impurities. Specifically,

- a. Your firm has not assessed for extractable and leachable impurities regarding single use/consumable equipment/parts (e.g., polymeric materials) and sterilized re-usable equipment that are used in manufacturing of the product.**

Applicant Response: CellTrans performed a risk assessment for extractables and leachables (E&L) regarding single use/consumable equipment/parts and sterilized re-usable equipment that are used in manufacturing of the product. The information was presented in:

- Risk Assessment, RA-0004 (Appendix 9, page 83-163).

The assessment included (b) (4) process components (most of them are single-use) such as (b) (4)

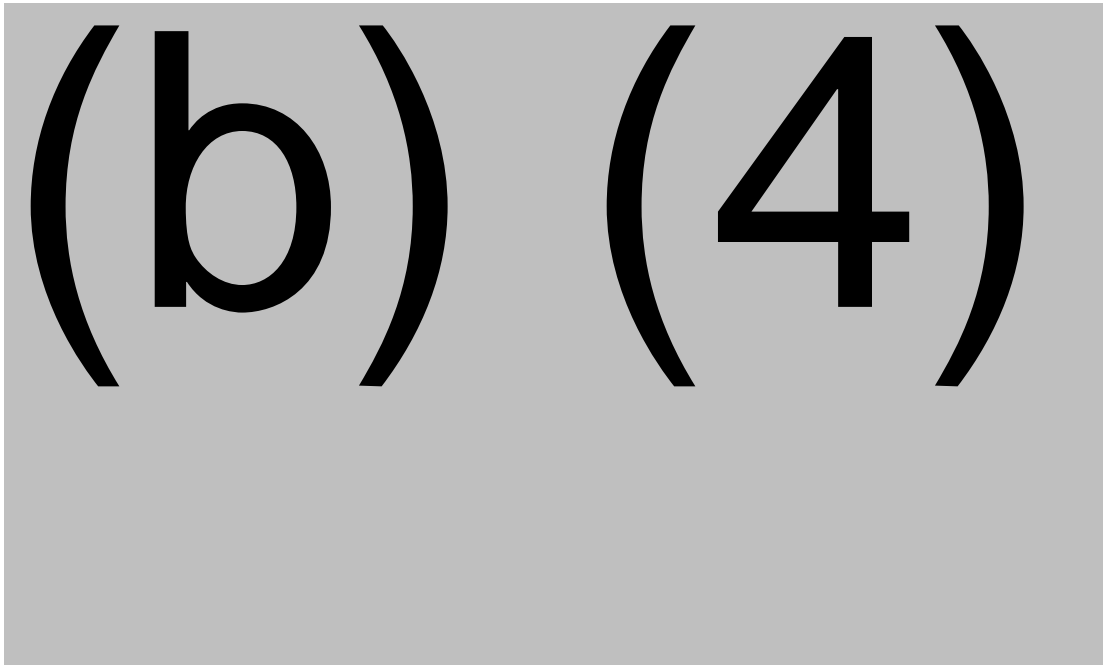
considering such process parameters related leachables appearance as material contact surface, dimensions, instructions for use, sterilization, and application-specific parameters (contact time, temperature, surface area/volume, and solution properties). The assessment concluded that each of components has a low risk for leachables in donislecel .

OPPT Reviewer Assessment: *The data provided is acceptable. The Applicant has addressed Observation 10a satisfactorily. No additional corrective actions will be required.*

- b. Your firm has not assessed for extractable and leachable impurities for your drug product containers: CryoMACS Freezing Bag 1000 (Specification FACSPC-029) and CryoMACS Freezing Bag 750 (Specification FAC-SPC-030).

OPPT Reviewer Assessment Summary: *The Applicant outsourced to a qualified contract testing laboratory (b) (4) extractable and leachable impurities testing for the drug product container. The information is presented in:*

- *Change Control, CC-00071 (Appendix 9, page 164-169)
The data is acceptable however, its relevancy to the Extractable and Leachable (E&L) assessment was not clear.*



An IR was issued on June 9, 2023 to ask the Applicant to provide clarification on the Simulated Leachables study. Although the AET were calculated, no Limits of Quantification (LOQ) for the respective analytical methods were provided. Further, it was unclear if the compounds detected above the reporting limits present a risk concern, as no toxicological analysis was provided. Lastly, in the Simulated Leachables study, the results were underestimated as the leachable from the additional bag (750 mL Rinse) used for to rinse the LANTIDRA Bag and infusion line was not included in the assessment. These issues were raised because (i) the upstream process may affect the leachables profile, and (ii) in this specific product, two bags

are used for DP in use presentation that results in leachables cumulative effect. CellTrans has missed considering both conditions in their study.

In response dated June 12, 2023, to our IR dated June 9, 2023 regarding LOQ values in the respective analytical methods, the Applicant did not provide the requested information. The Applicant instead provided the following:

1. Lowest levels of used surrogate standards, which are (b) (4) for organic compounds (by the (b) (4) and (b) (4) (b) (4) for elemental compounds by (b) (4)
2. Assessment of feasibility to detect respective (organic) standards for the (b) (4) methods (b) (4) at level of (b) (4)

The Applicant did not provide a toxicological assessment report because, per their evaluation, “given the extremely low levels of extractable and leachables detected in the study, no toxicology study was performed.”

We disagree with the Applicant’s assessment, because the ML based on AET was (b) (4) for organic compounds, and (b) (4) for elemental compounds. These data indicate that they were able to assess the levels of organic leachables only at (b) (4) times higher the ML, and with higher analytical uncertainty (not validated quantitation) at (b) (4) higher than ML. They could have missed some organic leachables at levels below lowest concentration of surrogate standards or performed quantitation of such compounds with significant error. Furthermore, the results obtained in the Applicant’s Simulated Leachable study may represent toxicological concern.

An IR was issued on June 16, 2023 to ask the Applicant to provide details on the reassessment of the analytical levels of organic leachables from the container closure system (two units, 750- and 1000-mL bags) using a methodology with validated LOQ values and if they can provide a toxicological assessment of the revised analytical data.

In their June 20, 2023 response, they indicated they may not be able to provide the above information prior to the Action Due Date.

The Miltenyi 1000 ml and 750 ml CryoMACS bags are 510(k) approved by the FDA. The 510(k) number is BK090020. The bags are tested by the manufacturer (Miltenyi Biotec) for bacterial endotoxin,

sterility, biocompatibility, and mechanical integrity at extreme low temperature, leachable and extractable.

The approved bags are used in multiple different approved BLAs as the final container closure system. For example, in a recently-approved BLA, the Miltenyi bags contains the final drug product and the infusion solution, which are cryopreserved for shipment and thawed at the clinical sites. In the current BLA, there are 2 bags, one containing the LANTIDRA drug product in transplant media and the second Rinse bag containing transplant media used to rinse the LANTIDRA bag and infusion line. Post final packaging, the bags are NOT frozen and are held at room temperature for a maximum of 6 hours. The risk to patient safety is low.

We acknowledge the Applicant may need to reanalyze the E&L study report data, taking into consideration validated limits of quantification (LOQ) of the analytical assays and the leachable data that also takes the second rinse bag into account. Further, the data may indicate the Applicant may need to perform a toxicological assessment. Dr. Sarafanov recommended a PMC that asks the Applicant to reassess the analytical levels of organic leachables using a methodology with a validated LOQ and to evaluate whether a toxicological reassessment is warranted.

We issued an IR on June 20, 2023 to the Applicant to commit to reanalyze the E&L study report data and conduct a toxicological assessment based on the analytical reassessment, as indicated above in the context of a PMC and to provide a timeline when study would be completed. The Applicant in their response on June 21, 2023 agreed to the PMC and indicated they can provide the report by February 29, 2024. We agree with the timeline and recommend a PMC be issued in the approval order. Please see finalized PMC language in this memo under section 10.B Recommendation.

Observation 11: Your firm failed to establish a reserve sample program and did not retain reserve samples for drug products for one year after the expiration dates.

Applicant Response: CellTrans implemented a reserve sample program for the retention of reserve samples for drug products for (b) (4) after the expiration date. Further, CellTrans established Change Control CC-00065 describing procedures for retention of reserve sample for drug product for (b) (4) after the drug product expiration date and established a Standard Operating Procedure for retention of a drug product reserve sample.

Applicant provided for review Attachment 3.2.S.2.2-30: SOP: MFGSOP- 308, Drug Product Reserve Sample.

DMPQ Reviewer Assessment: *The Applicant addressed observation 11. The change control and sample storage procedures were updated and provided for review. The Applicant's response is acceptable. No additional corrective action is needed.*

Observation 12: (b) (4) used in incubator is not routinely monitored for chemical quality, oil, or particulate levels and no COA is available to describe (b) (4) quality.

DMPQ Reviewer Assessment: *Cell Trans established corrective actions that includes revised SOPs for the Operation and Maintenance of (b) (4) incubators, to include the replacement of the use of (b) (4) (b) (4) with the use of (b) (4) (b) (4) (b) (4) for incubators and the requirement for a CoA.*

The Applicant's response is acceptable, and DMPQ recommend that SOPs and the cleaning verification results should be reviewed in detail during next FDA inspection.

CRL Comment 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 (b) (4) (see comment #3).

Applicant Response: CellTrans manufactured (b) (4) donislecel lots to demonstrate operational proficiency. All (b) (4) lots were manufactured between (b) (4) (b) (4). All (b) (4) lots were made post implementation of facility changes and in response to pre-license inspection observations. All donislecel final product lots met all release specifications. Additionally, (b) (4) of the donislecel lots, lot (b) (4) manufactured on (b) (4) and lot (b) (4) manufactured on (b) (4) were administered to patients under an Expanded Access protocol under IND (b) (4) per 21 CFR 312.320. CellTrans provided Attachment 3.2.S.2.5-2 VAL-008, that includes the document VAL-PLN-008- Process Validation Plan and document VAL-RPT-008- Process Validation Report for review.

The Process Validation Plan dated April 05, 2022 outlined the validation requirements and procedures to validate the islet manufacture process for transplantation and included procedures and acceptance criteria to qualify all critical processing

parameters (CPPs) and the islet manufacturing process to ensure that the manufacture method, from the time of arrival of the donor pancreases to the manufacturing facility to release the donislecel final drug product, is suitable for the isolation of islets and produces safe and potent islet product for transplantation. Donor eligibility and organ procurement were not part of the scope of this study.

Product Office Reviewer Note: Donor pancreases procurement and donor eligibility was reviewed previously during the original BLA submission and no concerns were raised.

The Process Validation Report Date October 10, 2022 indicated that (b) (4) (b) (4) process validation runs were performed between June 24, 2022 and August 13, 2022.

The islets products lots (b) (4) (Manufactured (b) (4)), (b) (4) (manufactured date (b) (4)) and (b) (4) (manufactured on (b) (4)) were manufactured and tested as outlined in the Process Validation of Islet Manufacture for Transplantation Plan (VAL-PLN-008). All acceptance criteria were met for the Process Validation. Briefly, the (b) (4) Islet products were manufactured in a series of manufacturing steps that began with

(b) (4)

The Applicant provided tables for each lot manufactured indicating the process parameter evaluated, if the process parameter was a CPP, processing step, processing evaluation methods, acceptance criteria and results. Additionally, The Validation report included the lot release table with acceptance criteria and test results.

Product Office Reviewer Assessment: All (b) (4) lots met the acceptance criteria, for in-process testing and final lot release.

The Applicant indicated no deviations occurred during the islet manufacturing procedure for the (b) (4) lots.

The Applicant indicated that (b) (4) of the (b) (4) lots (b) (4) were clinical lots that were transplanted into patients as part of an expanded access protocol based on the prospective label.

We issued an IR to the Applicant on March 06, 2023 to request complete batch records for the clinical lots (b) (4). The Applicant submitted for review the requested batch records in amendment 48 on March 16, 2023.

The Batch Records were reviewed and no concerns were noted. Briefly, below is the summary of the lot release information.

Lots administered to 2 subjects under expanded access:

(b) (4)

The Applicant has addressed the CRL comment 2 and the Applicant's response is acceptable.

CRL Comment 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) (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) 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) process. Please submit the qualification reports for (b) (4) solution.

Applicant Response: The (b) (4) was qualified in a new islet manufacture process validation (refer to report VAL-008, Process Validation). The use of (b) (4) in the islet purification steps during the islet manufacture procedure did not adversely affect the quality of the final product and the final product for all (b) (4) islet manufacture process runs met all release specifications. Furthermore, there were no changes in step times or changes to the islet purification process (refer to Summary Report for Qualification of (b) (4) During Islet Manufacture).

***Product Office Reviewer Assessment:** The (b) (4) (b) (4) qualification was provided in attachment 3.2.S.2.5. The change from (b) (4) to (b) (4) (b) (4) for the (b) (4) separation of islets cells did not adversely affect the manufacturing process. The Applicant has qualified this new reagent by manufacturing (b) (4) donislecel lots.*

Further as noted previously in this review the (b) (4) (b) (4) undergoes independent verification for (b) (4) confirmation as part of reagent qualification prior to introduction into the manufacturing process. No additional qualification of the reagent is required.

The Applicant response is acceptable.

CRL Comment 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) (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 (b) (4) 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.

Applicant Response: The Applicant indicated they continue to use the excipients and reagents used for the Phase 1/2, 3 clinical trials as there are no pharmaceutical grade reagents that exist that could be used as replacement. Further, the excipients and reagents listed below cannot be terminally sterilized as sterilization has negative effects on the media/reagent composition, amino acids, glucose etc. However, all reagents and excipients are (b) (4) (b) (4)

Applicant provided Change control forms CC-00064 and attachment, which are reviewed under CRL Comment 1, Observation 9.

Product Office Reviewer Assessment: *The Applicant is unable to source reagents and excipients used in their manufacturing that are of higher quality as they are not available by vendors. Where possible the Applicant is using the highest quality reagent available. The Applicant assures the quality of these reagents through additional qualification, (b) (4) sterility testing and identity verification to ensure the reagents are acceptable for clinical and commercial manufacturing. Further, the Applicant has established the reliability of the suppliers' Certificate of Analysis, for each research grade excipient and reagent used in islet manufacture. CellTrans has outsourced to qualified contract laboratories to perform Quality Control Testing for each reagent, based on the specific Certificate of Analysis tests performed for each reagent. Testing includes (b) (4). Further the Applicant is also performing (b) (4) testing in-house as part of quality control of these reagents.*

The Applicant has introduced steps to adequately control the reagents used in the manufacturing. Further, they used these qualified reagents in the manufacture of the additional donislecel product lots (b) (4). These lots all passed acceptance criteria.

Applicant's response is acceptable.

CRL Comment 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.

Applicant Response: CellTrans outsourced to two qualified contract test laboratories (b) (4) to perform validated identity testing on the excipients used in final formulation and transplant media and the reagents used in manufacture prior to release by the CellTrans Quality Control Unit.

The list of identity testing performed for each reagent was provided in the response to CRL 1, Observation 9.

Product Office Reviewer Assessment: *The list of identity tests for the reagents and excipients were reviewed under the CRL comment 1, Observation 9.*

The Applicant's establishment and implementation of identity verification is acceptable. The Applicant has adequately addressed this deficiency.

CRL Comment 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.

Applicant Response: The Applicant established SOP, MFG-SOP- 309 Attachment 3.2.S.2.2-31, Visual Inspection Tests for Final Container Closure, to provide all the required information in relation visual inspection testing for container closure integrity and appearance.

To demonstrate that the testing is established and well controlled, the Applicant provided the Change Control form CC-00080. Further, Applicant provided the SOP and an example of the operator training for visual inspection testing performed on the Final Container Closure.

The SOP provides detailed instructions and pictures of bags before and after they are heat sealed. The SOP also covers the training provided to quality control analysts. The Applicant provided the visual inspection re-training log TRN-FRM-100.06 dated February 11, 2022.

The visual inspection test results are recorder on Form MFG-FRM-309-01- Visual Inspection Tests for Final Container Closure.

***Reviewers Assessment:** The Applicant established formal SOPs for the visual inspection of the final container closure lot release test. Further, the Applicant provided the re-training records for this test indicating the operators were qualified to perform the test. The test was employed for the (b) (4) donislecel lots that were manufactured as part of manufacturing proficiency.*

The Applicant has addressed this deficiency and the response is acceptable.

CRL Comment 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)

(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.

Applicant Response: The Applicant provided TRN-SOP-101 Quality Control Release Testing Training, which includes the procedure to establish and define an internal training program for Quality Control release testing and to ensure the competency of QC operators at CellTrans Inc. Further, the Applicant also provided the QC Operators Training documentation in Appendix 3 (TRN-FRM-100.5) that included the following training documentation: cGMP and equipment training. Equipment training included gowning qualification information. The equipment training also included training on using equipment necessary for performing release testing. The Training records for (b) (4) QC analysts were provided.

***Product Office Reviewer Assessment:** The QC analysts performed all aspects of the assay using islets and included the sampling, dilution and microscopy. Training documents for (b) (4) analysts who will be performing the QC testing were provided. The training was performed at various times in fiscal year 2022.*

The Applicant has addressed this deficiency and the response is acceptable.

CRL Comment 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 (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.

Applicant Response: The Applicant provided SOP, MFG-SOP-212, in Attachment 3.2.S.2.2-8, Pancreas DigestionV2, which includes instructions for accurate assessment of digested tissue samples and (b) (4) The updated the SOP includes clear instructions for stopping the digestion based on the percentage of free islets present in the sample. The SOP further includes representative images for (b) (4) (b) (4) Free Islets as reference. and a Table with Description of Range to Stop Tissue Digestion.

***Product Office Reviewer Assessment:** The Applicant updated MFG_SOP-212 with clear instructions for when to stop the pancreas digestion procedure through sampling and microscopic evaluation of the free islets.*

The Applicant has addressed this deficiency and the response is acceptable.

12. LABELING

This section provides a summary of labeling revisions and interactive review performed by the CMC (Product Office) Reviewer for the Package Insert and the primary and secondary package labels. Please also refer to the Clinical Reviewer's assessment of the Package Insert and Regulatory Project Manager's assessment of the package labels, and Advertising and Promotional Labeling Branch's (APLB) review of all labeling for additional assessments.

- A. **PACKAGE INSERT:** During the review of the Package Insert (PI), in Section 2.4-Instructions for Infusion, Subsection 2.4.1, the Applicant indicated, "LANTIDRA is to be delivered through a 5 or 6 French angiographic catheter indicated for the delivery of drugs or other therapeutic fluids. The catheter length should be (b) (4) The internal diameter of the catheter should be of 0.97mm / 0.038 inches or less."

In the original submission, compatibility studies indicated the Applicant had used catheters in conjunction with sheaths/introducer systems. FDA revised the PI to reflect catheter specifications based on the compatibility studies to, "*LANTIDRA is to be delivered through a 5 or 6 French IV (intravascular or interventional) catheter indicated for the delivery of drugs or other therapeutic fluids. The catheter length should be 65 cm or less.*"

In the response to CRL Comment 2, the Applicant further indicated that two of the lots the Applicant manufactured as part of process validation studies performed in June/July 2023 were administered to patients under an expanded access protocol under IND 11807 based on the prospective label.

On April 17, 2023, an IR was issued to the Applicant to clarify and identify the delivery devices used to administer the clinical lots H0603 and H0604.

Applicant Response: The Applicant, in the response dated April 19, 2023, to IR dated April 17, 2023 provided the following:

Table 2: Specific delivery device used for administration of donislecel for islet intraportal infusion for clinical lots H0603 and H0604.

	Manufacturer	Delivery Device Name	Catalog #	Length
H0603	(b) (4)			

	(b) (4)
H0604	

Reviewers Assessment: The Applicant used (b) (4)

(b) (4)

A web search for the (b) (4) catalog number (b) (4) indicated that this is a sheath set that is not packaged with a catheter.

An additional IR was sent on May 1, 2023 to request details on the specific catheter used with the sheath introducer system. The Applicant in the response dated May 2, 2023 to the IR dated May 1, 2023 confirmed that H0603 and H604 lots were administered using only the sheath introducer system, which is not as previously discussed. The Applicant indicated, "No catheter was used for the infusions of lots H0603 and H0604."

As a result, the Applicant further indicated they have revised form MFG_FRM-307.01 effective date May 1, 2023-Final Product Chain of Custody Form to ensure that all future lots of donislecel will be administered by UI Health Radiology in accordance with the instructions for infusion present in the draft package insert and the Physician to fill out the following information:

Figure 1: Addition of section to be signed indicating the catheters to be used and appropriate sign off.

To be completed by CellTrans Inc. Staff Member and UIH Staff Member during transfer of Final Product (Human Islet Cells) for Transplantation.

UIH Staff Member confirms the use of "a 5 or 6 French angiographic catheter between (b) (4) in length, with an internal diameter of 0.97mm / 0.038 inches or less":	Name (print): _____
	Signature: _____
	Title: _____
	Date: _____ Time: _____

We do not agree with the catheter dimensions listed in the revised MFG_FRM-307.01.

As we previously communicated to the Applicant, LANTIDRA should be delivered using a 5 or 6 French angiographic catheter indicated for the delivery of drugs or

other therapeutic fluids. The catheter length should be 65 cm or less. The internal diameter of the catheter should be of 0.97mm / 0.038 inches or greater. This was based on the compatibility bench testing that was performed and catheters used in the Applicants clinical studies. Further, Sheath/Introducers should ONLY be used in combination with a catheter with dimensions listed above to deliver LANTIDRA. Sheath/Introducers alone are not indicated for the delivery of drugs or therapeutic fluids.

To ensure patient safety, it is important that only catheters meeting the above specifications be used in conjunction with sheaths /introducers to deliver LANTIDRA. An IR was issued to the applicant to amend the Final Chain of Custody form (MFG_FRM-307.01) to reflect the above catheter dimensions, and for the form to include space for the treating radiologist to record the name of the sheath/introducer system (i.e., catalog number and manufacturer) and the Name of the Catheter (i.e., catalog number and manufacturer).

The Applicant in the response dated June 5, 2023 to an IR dated June 1, 2023 provided the updated MFG-FRM-307-01 revision 3-Final Product: Chain of Custody Form. The change history indicates a new section was added to the form to update the use of a 5 or 6 French angiographic catheter, with a catheter length of 65 cm or less, with an internal diameter of 0.97mm I 0.038 inches or greater.

The Applicant also added a section for the treating radiologist to record the specific angiographic catheter and sheaths and introducers used for transplantation.

The Chain of custody forms upon completion is returned to CellTrans and is added to the Batch Record.

Figure 2: Picture of section taken form updated MFG-FRM-307.01

<p>Treating Radiologist confirms the use of “a 5 or 6 French angiographic catheter, indicated for the delivery of drugs or other therapeutic fluids, of 65cm in length or less, with an internal diameter of 0.97mm / 0.038 inches or greater”:</p>	Information for Angiographic Catheter Used	
	Name:	
	Manufacturer:	
	Catalog number:	
	Information for Sheath/Introducer System Used	
	Name:	
	Manufacturer:	
	Catalog number:	
	Radiologist Name (print): _____	
	Radiologist Signature: _____	
Title: _____ Date: _____		

The dimensions of angiocatheters were updated based on the Applicant compatibility bench testing and the catheters used in their clinical trials.

The Applicant will capture details of the angiocatheters and sheaths that were used to transplant LANTIDRA.

The Applicant has addressed the safety concerns. No further action is required.

Lastly, the package insert (label) was modified to contain statements under Section 2.1 Instruction for Infusion” to contain the following statements to emphasize compatible delivery devices that should be used per known compatibility data:

- LANTIDRA is to be delivered through a 5 or 6 French angiographic catheter indicated for the delivery of drugs or other therapeutic fluids. The catheter length should be 65 cm or less. The internal diameter of the catheter should be of 0.97mm / 0.038 inches or greater. Sheath/Introducers should ONLY be used in combination with a catheter with dimensions listed above to deliver LANTIDRA.*
- Sheath/Introducers alone are not indicated for the delivery of drugs or therapeutic fluids. Therefore, Sheath/Introducers alone cannot be used for the delivery of LANTIDRA into the hepatic portal vein.*

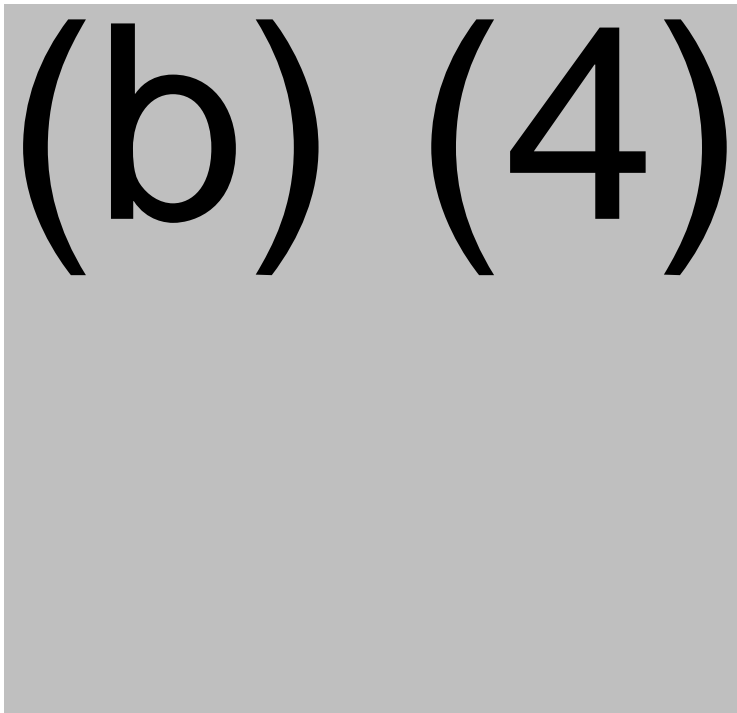
B. PRIMARY AND SECONDARY PACKAGE LABELS.

We reviewed the primary (affixed to the product and rinse bags) and secondary (affixed on the bag overwrap and transport cooler) package labels in conjunction with the APLB reviewer and RPM. Overall, the Applicant provided adequate labels after several rounds of IRs as noted below.

During the review of the Resubmission and the review of the Package Insert, we identified discrepancies in the dose of the second LANTIDRA transplantation. We issued an IR to the Applicant on May 05, 2023 to ensure there were no additional changes to the carton (the primary label that is affixed to the LANTIDRA and Rinse bags), the respective secondary overwraps and transport container (carrier) labels. The Applicant in their response dated May 08, 2023 provided updated labels that will be attached to the LANTIDRA CryoMACS bags, the Rinse CryoMACs bag, the secondary overwraps and the cooler for transport of the drug product from the manufacturing facility to UI Health, Department of Radiology. The Department of Radiology is located on the second floor of the same building where CellTrans is located.

Figure 3: Applicant provided the following LANTIDRA CryoMACS bags in Amendment 53 dated May 08, 2023.

This label will be affixed to the CryoMACS bag that contains donislecel/LANTIDRA



Line 2: LANTIDRA (i.e., Proprietary Name)

Line 3: Allogeneic Pancreatic Islets, Cellular Suspension for Hepatic Portal Infusion.

Line 4: Dose: One Sterile Bag of LANTIDRA for Primary Infusion followed by One Sterile bag (Rinse) for secondary infusion. (increase the font size)

At the request by the Applicant, we held an informal teleconference on June 05, 2023, where the Applicant asked about the box outline and we noted in general the Name does not have a box outline. APLB indicated boxes are used to draw attention to important information.

Position 2: on the Right Side top line 1: Rx Only

Position 3: Lot Number Box, Manufactured date and Time remains. Add the following Statement "Product needs to be administered within 6 hours of product release time". Remove Expiration date and (24 hours).

Regarding the information in position 3, further discussion was held with the Applicant during an informal teleconference held on June 5, 2023. The Applicant indicated the 24 hours depicted military time. We noted that military time is not normally used in the University/Hospital settings and could add to confusion. We noted the package insert, Section 16 "How supplied /storage and handling" and Applicant's stability studies indicate that LANTIDRA is stable for 6 hours at 15°-25°C post final packing into the CryoMACS bags and the transport carrier for transplantation to patients. If time (24hours) is included it may be confusing as it could imply the product could be administered up to 24 hours post final packaging. The Applicant agreed this could be confusing and indicated they will make the recommended changes to the LANTIDRA CryoMACS label. The Applicant also inquired if Total EIN should be included in this box. We indicated that information indicates the dose that was given to the patient based on their total body weight, and that information is not present in the any other place.

Position 4: For Use by Intended Recipient Only (Information is OK). Move to where the current target dose box. Can be in a box.

Position 5: Remove the word "Warning" the other lines should not be in a box. Remove the box outline

Bold the following

Do Not Use a Leukodepleting Filter

Do Not Irradiate

Storage at Room temperature (15°-25°C)

Transplant within time, LANTIDRA bag primary infusion (Increase font size and make consistent)

Position 6:

Donor Identifier (Information is ok) The box can remain move to left below : for intended Recipient Only box).

Position 7: Dispose of Used Material that comes in contact with LANTIDRA as biohazards waste in accordance with local requirements (increase the font size)

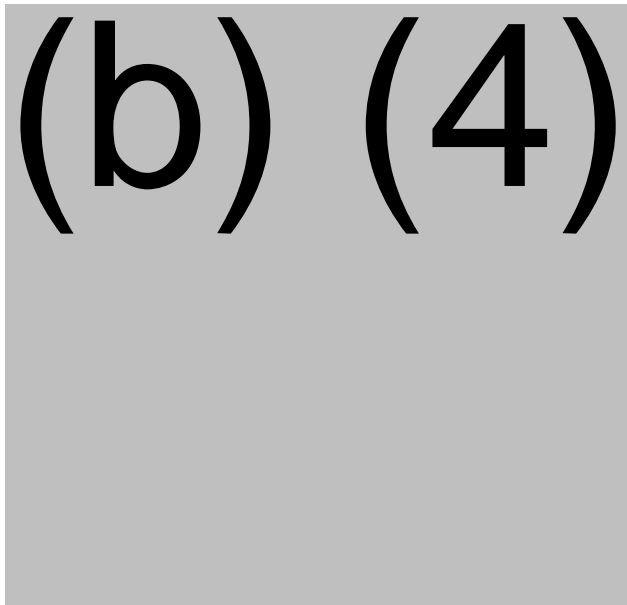
Position 8: Target dose is 5000EIN etc...up to 4000EIN/kg (number should be changed to **4500 EIN/kg**) for subsequent transplants. LANTIDRA is a cellular suspension of allogeneic pancreatic islets (Islets of Langerhans) in buffered transplant media. (See package insert for complete list of transplant medium ingredients). Increase the font size. Delete the rest of the sentences in the box. Remove the box outline.

Position 9: Manufacturer information (OK)

Position 10: NDC Code: Unique for LANTIDRA. The middle segment of the NDC code should be unique for the LANTIDRA and Rinse bags. (73539-XXX-01). Barcode and Barcode number should be reduced in size

Rinse CryoBag Label:

Figure 5: Copy of Label for the Rinse CryoMACS bag provided Amendment 53 date May 08, 2023.



Reviewer Assessment: *We did not agree with the Rinse CryoMACS Bag label. Based on APLB recommendation, there was a concern that the label as presented is crowded and may not allow for easy identification of critical information. We issued an IR on June 02, 2023 to the Applicant to request that they move the location of some of the information, increase or decrease font sizes and ensure readability.*

Line 2: **Do Not Irradiate**

Line 3: **Storage at Room temperature (15°-25°C)**

Line 4: **Transplant within expiration date and time**

Line 5: **Rinse bag infused after the primary LANTIDRA bag infusion and rinse goes through the LANTIRIDA CryoMACS bag. (Increase font size and make consistent)**

Position 6: Target total volume of Rinse : 200 ml per bag. Transplant media used for rinsing LANTIDRA CryoMacs bag to ensure all islets are transfused.

Rinse/Transplant media ingredient list. (See package insert for complete list of transplant medium ingredients). Increase the font size. Delete the rest of the text in the box. Not necessary to be in a box.

Position 7:

Dispose of Used Material that comes in contact with LANTIDRA as biohazards waste in accordance with local requirements (Increase the font size.)

Position 8: Manufacturer Information is OK

Position 9: NDC Code: Unique for Rinse Bag has to be a different NDC Code (Middle segment, 73539-XXX-01) from LANTIDRA Bag;


Barcode and Barcode number should be smaller

The Applicant during an in formal teleconference held on June 05, 2023 indicated there may be difficulties is getting unique NDCC codes. Lisa Stockbridge (APLB) and Rommel Maglalang (RPM) recommended the Applicant can list the transplant medium (rinse) as a second component of the donislecel /LANTIDRA product in the Structured Product Label (SPL) database that generates the unique NDCC codes. The Applicant indicated they will reach out to the FDA if they run in to issues creating a unique NDCC code for the Rinse CryoMACS bag.

The Applicant in the response dated June 07, 2023 to an IR dated June 2, 2023 updated the LANTIDRA CryoMACS bag label and the RINSE CryoMACS bag labels. The dimensions of the label are 4 inches in width by 4 inches in length.

Revised LANTIDRA CryoMACS Bag Label

Figure 7: Revised LANTIDRA CryoMACS Bag label provided in the Applicant response dated June 7, 2023

donislecel – jujn LANTIDRA		Rx Only	
Allogeneic Pancreatic Islets, Cellular Suspension for Hepatic Portal Infusion. Dose: One Sterile Bag of LANTIDRA for Primary Infusion followed by One Sterile bag (Rinse) for secondary infusion			
Lot Number: _____ Total EIN: _____ Manufactured Date: _____ Time _____ YYYY – MMM – DD _____ : _____ Product needs to be administered within 6 hours of product release time		For Use by Intended Recipient Only Recipient Name: _____ Recipient ID: _____ DOB: YYYY – MMM – DD _____ Recipient ABO/Rh: ____ / ____	
Do Not Use a Leukodepleting Filter Do Not Irradiate Storage at Room Temperature (15° – 25°C) Transplant within expiration date and time, LANTIDRA bag primary infusion Target dose is 5,000 EIN/kg for initial transplant and 4,500 EIN/kg for subsequent transplants. LANTIDRA is a cellular suspension of allogeneic pancreatic islets (Islets of Langerhans) in buffered transplant media (See package insert for complete list of transplant medium ingredients).		<div style="border: 1px solid black; padding: 5px; margin-bottom: 10px;"> Donor Identifier Donor ID: _____ DOB: YYYY – MMM – DD _____ Donor ABO/Rh: ____ / ____ </div> Dispose of Used Material that comes in contact with LANTIDRA as biohazard waste in accordance with local requirements NDC 73539 – 001 – 01  (10)H0000(17)230606(240)73539-001-01	
Manufactured by: CellTrans Inc. 1740 W. Taylor St., STE C200, Chicago, IL, 60612 (P: +1 312 413 3507)			

Reviewers Assessment: The revised LANTIDRA Label addresses APLB concerns regarding readability. The Applicant has also increased the font size. Further, the product label includes both the proper name, donislecel-jujn and the Proprietary name: LANTIDRA. The label captures the manufactured date and time. The expiration date has been removed, however a statement indicating the product has to be administered within 6 hours of the time when the product is released. Information on transplant media ingredients is captured in the package insert. The label is compliant with 21 CFR 610 subpart G. The Applicant has addressed all package label concerns.

Revised Rinse Bag Label:

Figure 8: Revised Rinse CryoMACS Bag label provided in the Applicant response dated June 7, 2023

Rinse Bag for Infusion following hepatic portal infusion of LANTIDRA (Allogeneic Pancreatic Islets for hepatic portal infusion)
Dose: One Sterile Bag of Rinse for Secondary Infusion after primary infusion of LANTIDRA.

Rx Only

Lot Number: _____	Total EIN: _____
Manufactured Date: _____	Time _____
YYYY – MMM – DD	: _____

Product needs to be administered within 6 hours of product release time

Rinse Bag For Intended Recipient Only
(ONLY FOR USE WITH LANTIDRA)

Recipient Name: _____
Recipient ID: _____
DOB: YYYY – MMM – DD
Recipient ABO/Rh: ____ / ____

Do Not Use a Leukodepleting Filter

Do Not Irradiate

Storage at Room Temperature (15° – 25°C)

Transplant within expiration date and time

Rinse bag infused after the primary LANTIDRA bag infusion and rinse goes through the LANTIDRA CryoMACS bag

Target total volume of Rinse: 200 ml per bag. Transplant media used for rinsing LANTIDRA CryoMACS bag to ensure all islets are transfused. Rinse/Transplant media ingredient list (See package insert for complete list of transplant medium ingredients).

Manufactured by: CellTrans Inc.
1740 W. Taylor St., STE C200,
Chicago, IL, 60612 (P: +1 312 413 3507)

Dispose of Used Material that comes in contact with LANTIDRA as biohazard waste in accordance with local requirements

NDC 73539 – 002 – 01



(10)H0000(17)230608(240)73539-002-01

Reviewers Assessment: The revised Rinse Bag Label addresses APLB concerns regarding readability. The Applicant moved information around and increased the font size. The Rinse Bag Label is a second component of the LANTIDRA and now has a unique NDC code where the last five (5) numbers are different from the LANTIDRA bag NDC code.
Information on transplant media ingredients is captured in the package insert.
The label is compliant with 21 CFR 610 subpart G.
The Applicant has addressed all concerns.

The Applicant also provided the image in Figure 9 below, indicating the placement of the LANTIDRA bag and Rinse bag labels on the respective bags.

Figure 9: LANTIDRA CryoMACS Bag Label and Rinse CryoMACS Bag Labels attached to the final container Closure CryoMACS bags.



Reviewers Assessment: The placement of the labels on the CryoMACS LANTIDRA and CryoMACS Rinse bags is acceptable and is in compliance with 21 CFR 610 subpart G. No CMC concerns.

Appendix 1: UNII Codes for Ingredients in the Transplant/Rinse Media

Ingredient Name	Complete Name	UNII code
CaCl ₂ anhydrous	CALCIUM CHLORIDE ANHYDROUS	OFM21057LP
biotin	BIOTIN	6SO6U10H04
MgSO ₄ anhydrous	MAGNESIUM SULFATE ANHYDROUS	ML30MJ2U7I
folic acid	Folic acid	935E97BOY8
Na acetate anhydrous	SODIUM ACETATE ANHYDROUS	NVG71ZZ7P0
riboflavin	RIBOFLAVIN	TLM2976OFR
NaH ₂ PO ₄ H ₂ O	SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE	593YOG76RN
coccarboxylase	COCARBOXYLASE	Q57971654Y
dextrose	ANHYDROUS DEXTROSE	5SL0G7R0OK
Li ₃ coenzyme A 2H ₂ O	COENZYME A TRILITHIUM DIHYDRATE	6GHL9SC2QT
KCl	Potassium chloride	660YQ98I10
cozymase	NADIDE	0U46U6E8UK
NaCl	Sodium chloride	451W47IQ8X
Na ₂ flavin adenine dinucleotide	FLAVIN ADENINE DINUCLEOTIDE DISODIUM	67U7UHJ04C
Na gluconate H ₂ O	SODIUM GLUCONATE	R6Q3791S76
Na triphosphopyridine nucleotide	NADIDE PHOSPHATE MONOSODIUM	NR2O7P57YA
L-alanine	ALANINE	OF5P57N2ZX
Na ₃ uridine 5'-triphosphoric acid H ₂ O	TRISODIUM URIDINE 5'-TRIPHOSPHATE DIHYDRATE	05161190OB
L-arginine HCl	ARGININE HYDROCHLORIDE	F7LTH1E20Y
ascorbic acid	ASCORBIC ACID	PQ6CK8PD0R
L-aspartic acid	ASPARTIC ACID	30KYC7MIAI
D-Ca-pantothenate	CALCIUM PANTOTHENATE	568ET80C3D
L-cysteine HCl H ₂ O	CYSTEINE HYDROCHLORIDE	ZT934N0X4W
choline chloride	CHOLINE CHLORIDE	45I14D8O27
L-cystine 2 HCl	CYSTINE DIHYDROCHLORIDE	WFN1A47EIG
i-inositol	INOSITOL	4L6452S749
L-glutamic acid	GLUTAMIC ACID	3KX376GY7L
nicotinic acid	NIACIN	2679MF687A
glycine	Glycine	TE7660XO1C
nicotinamide	NIACINAMIDE	25X51I8RD4
L-histidine HCl H ₂ O	HISTIDINE MONOHYDROCHLORIDE MONOHYDRATE	X573657P6P
para-aminobenzoic acid	AMINOBENZOIC ACID	TL2TJE8QTX
hydroxy-L-proline	HYDROXYPROLINE	RMB44WO89X
pyridoxine HCl	PYRIDOXINE HYDROCHLORIDE	68Y4CF58BV

L-isoleucine	ISOLEUCINE	04Y7590D77
thiamine HCl	THIAMINE HYDROCHLORIDE	M572600E5P
L-leucine	LEUCINE	GMW67QNF9C
glutathione (reduced)	GLUTATHIONE	GAN16C9B8O
L-lysine HCl	LYSINE HYDROCHLORIDE	JNJ23Q2COM
thymidine	Doxribtamine	VC2W18DGKR
L-methionine	METHIONINE	AE28F7PNPL
2D-adenosine	2'-DEOXYADENOSINE	P582C98ULC
L-phenylalanine	PHENYLALANINE	47E5O17Y3R
2D-cytidine HCl	DEOXYCYTIDINE HYDROCHLORIDE	X8FX60E66D
L-proline	PROLINE	9DLQ4CIU6V
2D-guanosine	2'-DEOXYGUANOSINE	G9481N71RO
L-serine	SERINE	452VLY9402
5-methyl-2'-deoxycytidine	5-METHYLDEOXYCYTIDINE	B200GV71QM
L-threonine	THREONINE	2ZD004190S
cholesterol	CHOLESTEROL	97C5T2UQ7J
L-tryptophan	TRYPTOPHAN	8DUH1N11BX
Tween 80	POLYSORBATE 80	6OZP39ZG8H
L-valine	VALINE	HG18B9YRS7
L-alanyl-L-glutamine	ALANYL GLUTAMINE	U5JDO2770Z
L-tyrosine 2 Na ₂ H ₂ O	TYROSINE DISODIUM DIHYDRATE	5RFD27DQ22

Appendix 2: Abbreviations.

Abbreviation	Detail
510 (k)	Premarket Notification
AET	Analytical evaluation threshold
APLB	Advertising and Promotional Labeling Branch
BLA	Biologics License Application
B and F	Bacteriostasis and Fungistasis
BSC	Biosafety cabinet
CAPAs	Corrective and Preventive Actions
CBER	Center of Biologics Evaluation and Research
CC	Change Control
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
cGMP	Current Good Manufacturing Practices
CMC	Chemistry, Manufacturing and Controls
CMRL	Connaught Medical Research Laboratories
(b) (4)	(b) (4)

CoA	Certificate of Analysis
CPPs	Critical Process Parameters
CQAs	Critical Quality Attributes
CTB	Cell Therapy Branch
CR	Complete Response
CRL	Complete Response Letter
DCT	Division of Cellular Therapies
DCM	Division of Case Management
DHT	Division of Human Tissues
DMPQ	Division of Manufacturing and Product Quality
DP	Drug Product
DS	Drug Substance
DTZ	Dithizone stain
EIN	Equivalent Islet Number also refereed to IE
EIR	Establishment Inspection Report
E/L	Extractables and Leachables
ELISA	Enzyme-linked immunosorbent assay
EU/kg	Endotoxin Unit per Kilogram
FAC	Facilities
FDA	United States Food and Drug Administration
FRM	Form
G	Gauge
(b) (4)	(b) (4)
GSI	Glucose Static Index or Glucose Static Incubation or Glucose Stimulation Index
(b) (4)	(b) (4)
ID	Identity
IE	Islet Equivalent also referred to as EIN
IR	Informational Request
ISO	International Organization for Standardization
HbA1c	Hemoglobin A1C
(b) (4)	(b) (4)
HEPES	2-[4(2-hydroxyethyl)piperazin-1-yl] ethanesulfonic acid
(b) (4)	(b) (4)
HSA	Human Serum Albumin
(b) (4)	(b) (4)
IND	Investigational New Drug
kg	Kilogram
L and E	Leachables and Extractables
(b) (4)	(b) (4)
LOQ	limit of quantification
mL	Milliliter
ML	Monitoring Level
mM	Milli Molar

MFG	Manufacturing
MSDS	Material safety data sheet
NDC	New Drug Code
(b) (4)	(b) (4)
OCBQ	Office of Compliance and Biologics Quality
OCTHT	Office of Cellular Therapy and Human Tissue CMC
OPO	Organ Procurement Organization
OPPT	Office of Protein and Plasma Therapeutics
OPTN	Organ Procurement and Transplantation Network
OTP	Office of Therapeutic Products
PDUFA	Prescription Drug User Fee Agreement
PI	Package Insert
PLI	Pre-license Inspection
PMC	Post Marketing Commitment
PNR	Proprietary Name Review
QC	Quality Control
RCDADs	Relevant Communicable Disease Agents or Diseases
SAL	Sterility Assurance Level
SOP	Standard Operating Procedure
T1D	Type 1 diabetes
UI	University of Illinois
UIH	University of Illinois Health
UNII	Unique Ingredient Identifier
UNOS	United Network of Organ Sharing
(b) (4)	(b) (4)
(b) (4)	(b) (4)
USP	United States Pharmacopeia
USAN	United States Accepted Name
(b) (4)	(b) (4)