

CBER CMC BLA Review Memorandum

BLA STN 125734/0

**LANTIDRA (proposed proprietary name)
Donislecel (USAN)**

Timothy Martin / Regulatory Officer / CBER/OCBQ/DMPQ

1. BLA#: STN 125734/0

2. APPLICANT NAME AND LICENSE NUMBER

CellTrans Inc, license # 2213

3. PRODUCT NAME/PRODUCT TYPE

Purified islets of Langerhans for transplant (common name)
Donislecel (USAN)
LANTIDRA (proposed proprietary name)

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

- a. Pharmacological category: Cellular Therapy.
- b. Dosage form: cellular suspension.
- c. Strength/Potency: minimum dose of 5,000 equivalent islet number per kg patient body weight; infusion rate should not exceed 25 mL/kg/h.
- d. Route of administration: administered by infusion into the hepatic portal vein.
- e. Indication: Brittle Type 1 Diabetes (labile diabetes) in adults whose symptoms are not well controlled despite intensive insulin therapy.

5. MAJOR MILESTONES

7/2/2020	Filing Meeting
10/30/2020	Major Amendment filed.
11/18/2020	Mid-cycle communication
4/1/2021	Late-cycle meeting
4/15/2021	Advisory Committee Meeting
4/30/2021	Late-cycle communication
6/7-6/11/2021	Pre-License Inspection (PLI)
8/18/2021	Action Due Date

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Timothy Martin, OCBQ/DMPQ/MRBII	3.2.S Drug Substance 3.2.P Drug Product 3.2.A.1 Facilities and Equipment

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No ¹)
N/A	N/A	N/A

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
5/19/2020	STN 125734/0/0	Original Submission
9/10/2020	STN 125734/0/8	Applicant Response to DMPQ IRs related to additional details for APV, process development, line clearance, shipping, and facilities and equipment (list, qualification, cleaning, sterilization, and flows).
10/26/2020	STN 125734/0/15	Applicant Response to DMPQ/CMC Records Request
12/30/2020	STN 125734/0/19	Applicant Response to DMPQ IRs related to additional details for organ decontamination validation, APS, cleaning validation, equipment qualifications, and HVAC.
2/19/2021	STN 125734/0/28	Response to IR for details of bioburden assessment for the organ decontamination manufacturing step

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

Submission	Holder	Ref. Item	Letter of Ref.	Comments/Status
125651/0	CellTrans, Inc.	Donislecel	N/A	Original submission for licensure of donislecel. Sponsor withdrew submission on July 14, 2017.
IND BB-11807	University of Illinois Hospital	Clinical trial data.	yes	Transfer of ownership of data in IND BB-11807 to CellTrans for use in this BLA.
IND BB-9336	NIAD, NIH	Clinical trial data.	yes	Right of Reference or Letter of Authorization was provided for CBER to access IND.
IND BB-11228	University of Chicago	Clinical trial data.	yes	Right of Reference or Letter of Authorization was provided for CBER to access IND.
BK090020	Miltenyi Biotec	CryoMACS Freezing Bag	No	CryoMACS cell bag used in the container closure system, 510k cleared under 21 CFR 864.9100 classification for freezing, storage (-196 °C), and subsequent thawing (at 37°C) of hematopoietic progenitor cells.

Submission	Holder	Ref. Item	Letter of Ref.	Comments/Status
(b) (4)	(b) (4)	(b) (4)	No	(b) (4)
(b) (4)	(b) (4)	(b) (4)	No	(b) (4)

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

The applicant, CellTrans, Inc., submitted this original BLA, standard 12-month review, for licensure of their cellular product, donislecel (orphan drug designation). The drug product is a sterile cellular suspension of allogeneic pancreatic islets that is intravascularly administered to the patient's liver via the portal vein for the treatment of brittle type I diabetes mellitus. The drug product is a tissue that cannot undergo terminal sterilization; sterility assurance is achieved using process and engineering controls. The product is conditionally released based on gram stain and endotoxin testing and transplanted into the patient before the product expiration of 6 hours and before sterility test results can be completed. The drug product is stored in cell bags and transported by hand courier at room temperature to the adjacent hospital transplant suite.

Manufacture of Donislecel drug substance and drug product is dedicated to the CellTrans Islet Isolation Facility in Chicago, IL. The manufacture of Donislecel drug substance (islet isolation and purification) and drug product (islet formulation and fill) is performed at CellTrans Islet Isolation Facility in Chicago, Illinois, USA. To support this BLA, the firm provided facility information and containment strategies, equipment description and qualifications, cleaning validations, computer systems, container closure and container closure integrity, manufacturing process description and process validation to include aseptic process simulations and three conformance lots and

transport validation. The product does not undergo storage and the submission included stability study up to the 6-hour expiry.

The reviewed and evaluated information under DMPQ purview (as per CBER SOPP 8404.1) appears acceptable. All the identified deficiencies were addressed with the amendments in response to information requests. The review of the records provided in response to the pre-inspection records requests (as per 704(a)(4) in advance of an on-site inspection) was also performed and this review was documented in a separate records review memo uploaded to this file as well as CM Work Activity 401420. However, due to the COVID-19 pandemic travel restrictions, the CellTrans pre-license inspection was delayed to June 7 through June 11, 2021 with inspection results pending at the time of writing this memo. The final recommended action for this BLA will be documented in an addendum memo.

In a separate memo, the decision was made to waive pre-license inspection of release testing facility (b) (4), which conducts release testing on the final drug product. The facility was last inspected by Team Biologics from (b) (4) and classified as VAI.

B. RECOMMENDATION

A final recommendation cannot yet be determined as the results of the inspection are still pending at the time of preparation of this memo. The final recommendation will be made in an addendum memo(s) once the impact of the BLA can be assessed from the 483 observations and applicant responses. The original BLA and amendments were reviewed, and the following items were identified for potential inspectional follow-up:

3.2.S Drug Substance Manufacturing:

- 3.2.S.2.3. If complete analyses on all materials/reagents that are used in the manufacturing process were conducted on at least (b) (4) batches before reducing in-house testing.

3.2.A Facilities and Equipment:

- Classified areas. If there is adequate space in the classified areas.
- Product flow. If there are procedures for receipt of donor pancreas and critical reagents by UIH personnel.
- Equipment flow. If there is segregation of CellTrans equipment from UIH equipment.
- Personnel flow. If there is adequate space for gowning and doffing scrubs.
- Waste flow. If waste existing (b) (4) may cross contaminate personnel entering the pre-gowning room.
- HVAC. Adequacy of (b) (4) pressure monitoring.
- Facility Cleaning. If the disinfectant effectiveness study is adequately validated to reduce (b) (4) and facility isolates.
- EM. Review of the most recent EM trend data.
- Critical Utilities. Door interlock or procedures ensuring HVAC room recovery to the classified state.

- Computer Systems. Data integrity and audit trail of the electronic EM system.
- Equipment Qualification. Verify adequacy of equipment qualifications for the COBE cell processor, BSCs, incubators, tube sealers, and refrigerators.
- Equipment Cleaning Validation. If equipment cleaning includes routine rinse sampling to verify (b) (4) how effective training is achieved/maintained; if SOP is available during cleaning; if CellTrans equipment loads are dedicated and fixed or if they are mixed with UIH loads; if equipment are inspected for damage; if equipment undergo final WFI rinse after being cleaned.
- Equipment Sterilization Validation. If IQ and OQ were conducted on (b) (4) and (b) (4) equipment and procedures for re-qualification.

I. APPROVAL

Decision is deferred; see above comment.

II. COMPLETE RESPONSE (CR)

Decision is deferred; see above comment.

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Timothy Martin, Regulatory Officer OCBQ/DMPQ/MRBII		
Anthony Lorenzo, Branch Chief OCBQ/DMPQ/MRBII	Concur	
John Eltermann, Director OCBQ/DMPQ	Concur	

Review of CTD
Module 3

3.2.S DRUG SUBSTANCE²

(b) (4)

3 pages have been determined to be not releasable: (b)(4)

(b) (4)

3.2.S.2.3 Control of Materials

(b) (4)

Reagent	Use
HEPES Buffer	Perfusion solution; Transplant solution
(b) (4)	(b) (4)
Human Serum Albumin	Wash solution; Dilution solution; Culture medium Transplant solution
CMRL Culture Media	Cell Culture
CMRL Culture Media, (b) (4)	Transplant media

(b) (4)

9 pages have been determined to be not releasable: (b)(4)

3.2.P DRUG PRODUCT³

3.2.P.1 Description and Composition of the Drug Product

The drug product, Purified Allogeneic Human Islets of Langerhans for Transplant, is a cellular therapy derived from the pancreas of a deceased donor. The dosage form is a suspension of viable islet tissue. The product is formulated in supplemented serum-free transplant medium (indicator-free Connaught Medical Research Laboratories (CMRL) 1066 medium) supplemented with HEPES and HSA. The resulting islet suspension is delivered into the portal vein. The components and their function, quantity, and quality standards are summarized in below **Table 5**.

Table 5. Composition of the Drug Product.

Component	Function	Quantity	Quality Standard
Purified Allogeneic Human Islets of Langerhans	Transplant Tissue (Drug Substance)	≤10 cc estimated packed cell tissue volume ≥5000 IE/kg (1st dose) ≥4000 IE/kg (2nd, 3rd dose)	CellTrans
CMRL 1066 Transplant Medium	Excipient	400 mL in drug product bag and 200 mL in separate rinse bag	Research
HEPES	Excipient	10 mM	Research
Human Serum Albumin	Excipient	0.5%	USP

The final drug product is stored in a CryoMACS Bag 1000 mL. Each bag is filled with 400 mL of Transplant Media containing not more than 10 cc of estimated packed islet tissue. The CryoMACS Bag 1000 mL, containing the final product, is aseptically connected to a smaller CryoMACS Bag 750 mL containing 200 mL of CMRL transplant media for use in rinsing the CryoMACS Bag 1000 mL with final product and line following transplant to assure complete transfer of islets to the patient.

The 1000 mL Bag containing the Islet Suspension and the connected 750 mL bag containing the transplant media for rinsing are stored in a flexible sterile outer package and placed in an insulated cooler to avoid temperature extremes during transport to the radiology department where transplant takes place. The entire contents of the drug product are administered with no proposed excess volume. A more detailed description of the container closure system is provided in 3.2.P.7 Container Closure System.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

The pharmaceutical development information of both drug substance and drug product is provided in Section 3.2.S.2.6 Manufacturing Process Development.

3.2.P.2.1.2 Excipients

The drug product contains excipients of HAS, HEPES, and CMRL. No excipients are of animal origin.

HSA is of human origin, labeled as (b) (4) and is a sterile aqueous solution of albumin (b) (4) obtained from (b) (4) (b) (4)

The product contains no preservatives.

HEPES, 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid, is a (b) (4) prepared solution used to (b) (4) of the transplant medium Connaught Medical Research Laboratories 1066 (CMRL).

CMRL 1066 is a novel excipient in the finished drug product. CMRL 1066 medium is a sterile, chemically-defined, complex solution that is used to suspend the islets prior to transplantation and acts as the primary vehicle for delivery of the islets into the recipient. In addition the medium contains (b) (4)

➤ **Reviewer Comment:** Evaluation of excipients is deferred to PO.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

The pharmaceutical development information of both drug substance and drug product is provided in Section 3.2.S.2.6 Manufacturing Process Development.

3.2.P.2.2.2 Overages

This section is not applicable as no overages are packaged into the final cell bag.

3.2.P.2.2.3 Physicochemical and Biological Properties

The firm established parameters to characterize the drug substance and product for islet shape, size, and biological activity, as specified above in 3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties.

3.2.P.2.3 Manufacturing Process Development

No significant changes in the process were reported for manufacturing process development, other than for drug substance manufacture; refer to above Section 3.2.S.2.6 Manufacturing Process Development. The manufacturing process was the same for clinical and commercial-scale batches, i.e. process validation batches.

3.2.P.2.4 Container Closure System

The container closure system was the same for clinical and commercial-scale batches, i.e. process validation batches. For details of the closure system, refer to 3.2.P.7 Container Closure System.

3.2.P.2.5 Microbiological Attributes

The drug product is a sterile cellular suspension manufactured by aseptic processing and filling. For batch specifications refer to 3.2.P.5.4 Batch Analyses.

3.2.P.2.6 Compatibility

(b) (4)

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Table 6. Facilities and responsibilities for manufacture and testing of the drug product.

Facility	Responsibility
CellTrans Islet Isolation Facility, 1740 W. Taylor St., Chicago, IL 60612 FEI#: 3010872260	<ul style="list-style-type: none">• Production of drug substance and product• In-process and final release testing (endotoxin; bacterial culture) of drug substance and product• Drug product primary packaging and labeling.• Drug product final packaging.• Logistic operations (receiving and shipping).
University of Illinois Hospital & Health Science System, (b) (4) Chicago, IL 60612 FEI#: None CLIA# (b) (4) (b) (4)	<ul style="list-style-type: none">• Conditional release testing (gram stain) of drug product
(b) (4)	<ul style="list-style-type: none">• Release testing (fungal culture) of drug product

CellTrans Islet Isolation Facility is a new facility for dedicated manufacture of the subject product. A pre-license inspection (PLI) of the facility was conducted from June 7, 2021 through June 11, 2021. Inspectional findings, form 483 observations, and establishment inspection report are documented in separate documents uploaded in CBER connect. Facilities and responsibilities involved in the manufacturing and testing of the drug product are in the above **Table 6**.

PLI is waived for release testing facility (b) (4) which is communicated in a separate Inspection Waiver Memo uploaded in CBER Connect.

3.2.P.3.2 Batch Formula

The composition of an islet batch for transplantation is summarized in the below **Table 7**.

Table 7. Batch Formula.

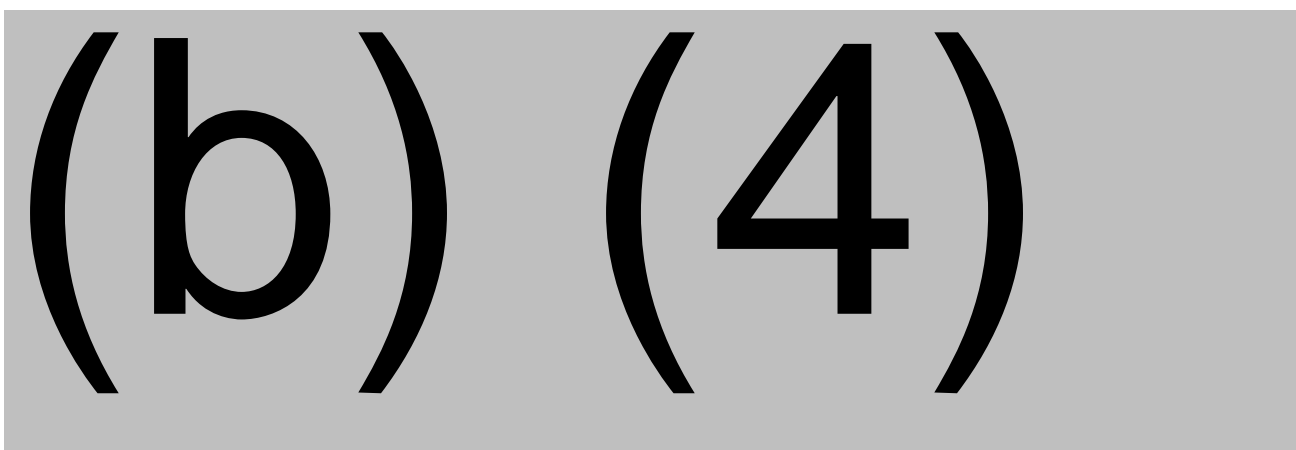
Component	Purpose	Amount per Batch
Purified Allogeneic Human Islets of Langerhans	Transplant Tissue (Drug Substance)	≤ 10 cc estimated packed cell volume ≥ 5,000 IE/kg (1st dose)
CMRL 1066 Transplant Solution	Excipient	400 mL in drug product bag and 200 mL in separate rinse bag.

Component	Purpose	Amount per Batch
HEPES	Excipient	10 mM
Human Albumin 25%, USP	Excipient	0.5%

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:

The information provided is acceptable as submitted.

3.2.P.3.3 Description of Manufacturing Process



Step 7. The purified islets are aseptically transferred from the (b) (4) into a sterile 1000 mL CyroMACS infusion bag. The finished drug product is labeled and packed into a sterile outer bag intended to protect the final product during transport to the clinic.

There are no sterilizing operations as the cell product is not amenable to sterilization, either by filtration or energy; therefore, the entire manufacturing process is aseptic.

Description and assessment of controls associated with critical steps and intermediates including operating and performance parameters, in-process controls and hold-times are provided in 3.2.P.3.4 Controls of Critical Steps and Intermediates and 3.2.P.3.5 Process Validation and/or Evaluation.

Overall Reviewer's Assessment of Section 3.2.P.3.3:

The information provided is acceptable as submitted.

3.2.P.3.4 Controls of Critical Steps and Intermediates

The critical steps for manufacture of the drug product include islet harvest and formulation (step 6) and packaging, labeling, and release (step 7); refer to above **Figure 1** located in 3.2.S.2.2 Description of Manufacturing Process. The acceptance criteria

and tests are summarized in the below **Table 8**. The process is continuous manufacture and there are no intermediates. Post-formulation hold time to transplantation < 6 hours. Samples are taken as per SOPs, documented on worksheets, and attached to the batch record.

Table 8. Controls for the Drug Product Manufacturing Process.

Critical Step and Critical Process Parameter(s)	Acceptance Criteria	In Process Test/Control
(b)	(4)	

Overall Reviewer's Assessment of Section 3.2.P.3.4:

The information provided is acceptable as submitted. The controls appear adequate for the drug product manufacturing process, including the critical steps and corresponding CPPs, operating ranges, in-process tests and acceptance criteria.

The assessments used to identify CPPs, corresponding strategy in ranking severity, and critical ranges were mostly provided in BLA submission Section 3.2.P.3.3 and the remainder in this section 3.2.P.3.4.

3.2.P.3.5 Process Validation and/or Evaluation

Process validation information is provided in 3.2.S.2.5 Process Validation and/or Evaluation of this submission because the manufacturing is a continuous process from drug substance to drug product. Validation of sterilization and aseptic processing is documented in section 3.2.A.1 Facilities and Equipment, Aseptic Process Simulation.

Overall Reviewer's Assessment of Section 3.2.P.3.5:

Refer to reviewer's assessments in 3.2.S.2.5 Process Validation and/or Evaluation and 3.2.A.1 Facilities and Equipment, Aseptic Process Simulation.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

The firm stated the excipients were CMRL 1066 Transplant Medium, HEPES, and Human Serum Albumin (HSA). The quality specifications for Transplant Medium and HEPES are controlled through CoA and conformity testing. The HSA is accepted on CoA. Specifications are summarized below (**Table 9**). The firm provided sample CoA's for HSA.

Table 9. Testing, Specifications, and Verification of CMRL 1066 Transplant Medium and HEPES.

Testing Performed by Manufacturer	Testing Method	Specifications	Testing Lab
(b) (4)			CellTrans
			CellTrans
			CellTrans

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

Excipients used in the final Drug Product formulation (i.e., CMRL 1066 medium and 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid [HEPES]) are described in 3.2.S.2.3 Control of Materials. The HSA used in the formulation is (b) (4) grade and is accepted on the manufacturer's Certificate of Analysis, as described in 3.2.P.4.1 Specifications.

Analytical procedures include (b) (4)

3.2.P.4.4 Justification of Specifications

The firm provided the following justification of specifications (**Table 10**).

Table 10. Testing, Specifications, and Justifications for CMRL 1066 Transplant Medium and HEPES

(b) (4)

(b) (4)

3.2.P.4.5 Excipients of Human or Animal Origin

Excipients are described in above Section 3.2.P.2.1.2 Excipients, and evaluation is deferred to PO. Control of excipients are described in above Section 3.2.S.2.3 Control of Materials.

3.2.P.4.6 Novel Excipient

CMRL 1066 Transplant Medium is a novel excipient in the finished drug product, Purified Allogeneic Human Islets of Langerhans for Transplant, and is described in 3.2.A.3 Novel Excipients.

Overall Reviewer's Assessment of Section 3.2.P.4:

The information provided is acceptable as submitted. The applicant appears to have control of excipients. Under DMPQ purview, the testing, specifications, and justifications are adequate for (b) (4)

Defer to DBQSC for assessment of validation of analytical procedures. Defer to PO for testing, specifications, and justifications under PO purview.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

The quality control specifications for the drug product, referred to the firm as Purified Allogeneic Human Islets of Langerhans for Transplant, are provided in the below **Table 11**.

Table 11. Quality Control Specifications for final drug product.

Quality Parameter	Test Method	Acceptance Criteria	Justification
Container Closure Integrity	Visual Inspection	No evidence of tampering or damage to drug product container	Visual assurance of container closure integrity

Quality Parameter		Test Method	Acceptance Criteria	Justification
Appearance		Visual Inspection	No visible foreign objects or turbidity	Visual assurance of quality
Safety	Sterility	(b) (4)	No growth in 14 days	Assures Sterility of the Transplanted Tissue and compliance with regulatory standards
	Fungal	Culture	No growth in 28 days	Assures Sterility of the Transplanted Tissue and compliance with regulatory standards
	Gram stain	Gram Stain and Microscopic Evaluation	Negative for presence of contamination	Visual assurance of freedom from microbial contamination
	Endotoxin	Endotoxin (Limulus Amebocyte Lysate), EndoSafe	Each transplant will contain ≤ 5 EU/kg of patient weight/Hour	Limit based on compendial requirements
Identity	Estimated Tissue volume	Visual Quantification of Pelleted Islets (packed tissue volume)	≤ 10 cc	Packed tissue volume is limited based on anticipated risks of portal pressure increase during infusion
	Islet morphology	DTZ Stain and Microscopic	Islet Present	Assurance of islets presence
Potency	Glucose Static Incubation (GSI)	ELISA Quantification of Glucose Stimulated Islets	Ratio of insulin secretion under high glucose stimulation to that under low glucose stimulation ≥ 1	The glucose stimulation index is defined based on minimal values that correlate with clinical outcome

Quality Parameter		Test Method	Acceptance Criteria	Justification
	Islet yield	Dithizone (DTZ) Stain and Microscopic Quantification (Islet Yield)	$\geq 5,000$ EIN per kg for initial transplant. $\geq 4,000$ EIN per kg for subsequent transplants (same recipient)	Minimal EIN limits are based upon the Edmonton Protocol and standards established by independent groups
	Viability	SYTO 13 Green/Ethidium Bromide Staining and Microscopic Evaluation	$\geq 70\%$ viable islets	Limit based on industry standard for cellular products for human transplant
Purity	Endotoxin	Endotoxin (Limulus Amebocyte Lysate), EndoSafe	Each transplant will contain ≤ 5 EU/kg of patient weight	Limit based on compendial requirements
	Islet purity	Dithizone (DTZ) Stain and Microscopic Quantification	$\geq 30\%$	Limit based on industry standard for islet products for human transplant

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:

The information provided is acceptable as submitted.

Under DMPQ purview, there were no changes in release specifications for safety or closure integrity during product development (e.g., no tightening or shifting of acceptance criteria, replacing a method) compared to those used for clinical batches and process validation batches, both at commercial scale, to support licensure.

Defer to PO on specifications under PO purview for the evaluation of approaches and data used to establish the acceptance criteria, statistical analysis, and clinical experience.

The overall control strategy using in-process controls/testing and release testing appear appropriate to assure Drug Product quality. Additional refer to reviewer comments in 3.2.P.3.4 Controls of Critical Steps and Intermediates.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Under DMPQ purview, analytical procedures used to test the drug product include: container closure integrity and appearance; sterility; fungal; gram stain; and endotoxin. Under PO purview, analytical procedures include estimated packed cell volume; morphology; glucose static incubation; yield; viability; and islet purity. Below, procedures under DMPQ purview are further described. Defer the review of the method validation of the microbial testing to DBSQC.

Container closure integrity and appearance. The drug product in its final container closure system is visually inspected for no evidence of tampering or damage and no visible foreign objects or turbidity. Any product that is cloudy and turbid, is not released. Any product in which the container closure appears to be damaged is not released. Cloudiness and turbidity are indicators of potential contamination. Presence of visible foreign objects raises safety concerns.

Sterility. The drug product must be free from evidence of viable microbial contamination to assure that culture and subsequent formulation and filling of the drug product is sterile. The (b) (4) is used to test (b) (4) final product samples for bacterial growth. All (b) (4) final product cultures are incubated for 14 days or reported immediately if the sample becomes positive.

Fungal. The drug product must be free from evidence of viable microbial contamination. Sterility testing for fungal contamination is performed on samples submitted to the CLIA-certified and FDA registered (b) (4) by (b) (4) culture method. Specimens are (b) (4).

Gram stain. The drug product must be free from evidence of viable microbial contamination. The (b) (4) University of Illinois Hospital & Health Science System (UI Hospital) performs a Gram stain on the drug product via (b) (4).

Endotoxin. Testing is per (b) (4) and is performed by CellTrans using the (b) (4) (b) (4) and the FDA-cleared Limulus Amebocyte Lysate (LAL) (b) (4). The endotoxin limit for the drug product is established based on (b) (4) limits for endotoxin exposure for infusions/injections of one hour or less in duration.

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

The information provided is acceptable as submitted. Defer to DBQSC for evaluation of validation performed to assure that methods are suitable for their intended purpose (i.e., assurance of product identity, purity, potency). Defer to PO for procedures used to evaluate product characteristics under PO purview.

3.2.P.5.4 Batch Analyses

A manufactured batch is defined as the isolated and purified islets from a single cadaveric pancreas. Each lot is made up of a single batch. Each batch is always a single unit and assigned a unique ID number. Each lot is intended for a single matched transplant recipient.

In support of this BLA, (b) (4) GMP clinical study batches (b) (4) (b) (4) and (b) (4) GMP process validation batches (b) (4) (b) (4) of drug product were manufactured in the GMP Islet Isolation Facility. Clinical study batches were transplanted to patients under clinical investigation IND BB-11807. The clinical batches were manufactured between (b) (4) the validation batches were manufactured between (b) (4) All batches were negative for gram stain and no bacterial or fungal growth was detected. All batches passed acceptance criteria for endotoxin levels ≤ 5 EU/kg.

3.2.P.5.5 Characterization of Impurities

The manufacturing is a continuous process from drug substance to drug product. The characterization of impurities is described in 3.2.S.3.2 Impurities.

Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:

Defer to PO.

3.2.P.6 Reference Standards or Materials

Given the nature of the drug product, no reference standards or materials are utilized as part of the drug product manufacturing process.

➤ **Reviewer Comment:** Not under DMPQ purview.

3.2.P.7 Container Closure System

The original submission was not clear on any changes to closure system between clinical and production batches used to support the BLA. The details were requested in IR on 8/28/2020. The applicant responded in amendment 125734/0/8 on 9/10/2020 and clarified there were no changes to the changes to closure system between clinical and production batches used to support the BLA.

The drug product is a suspension of the purified islet culture in final excipient in CryoMACS bags (**Figure 3**). The total suspension of 400 mL is filled in a single 1000 mL infusion bag (BK090020 CryoMACS Catalog # 200-074-404; <https://www.miltenyibiotec.com/US-en/products/cryomacs-freezing-bags.html#200-074-400>), containing not more than 10 cc of estimated packed islet tissue and not more than 1×10^6 EIN (equivalent islet number). The 1000 mL infusion bag is aseptically connected to a smaller CryoMACS 750 mL bag containing 200 mL of final excipient volume for use in rinsing of the 1000 mL bag and catheter following transplant procedure to ensure complete transfer of islets to the patient.

Each CryoMACS bag is made of ethylene vinyl acetate (EVA) sealed tubular film, with tubing, luer connectors, roller clamps, an injection port, and two ports with sealed twist-off protective caps. Each bag is contained within an overwrap bag and sterilized by (b) (4) at the supplier. The bags are received and accepted by CellTrans on CoA indicating sterile and endotoxin (b) (4)

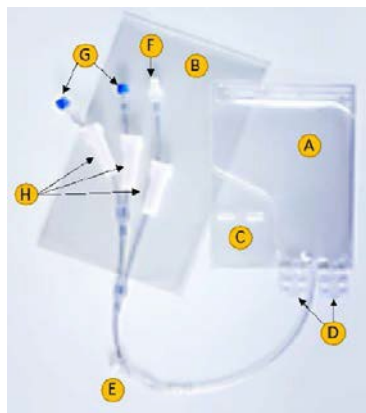


Figure 3. Picture of final closure system.

A. Primary Containment (CryoMACS Freezing bag); B. Overwrap Bag; C. Label Pocket; D. Membrane Ports; E. Injection Site; F. Male (b) (4) Adapter; G. Female (b) (4) Adapter; H. Roller Clamps. Image source BLA 125734/0/8 Section 1.11.

After the bags are filled, the bags are labeled with product information, including manufacturer, lot number, total EIN, expiration date and time, storage conditions, and donor and matched recipient information. The final drug product and rinsing solution bags are placed into a sterile outer bag and then stored in an insulated container at 15°C – 25°C. The drug product is not stored in the final container closure system, as the product expiry is 6 hours.

To use the drug product, the hospital uses delivery systems, which are not kitted with the drug product or part of this BLA submission. The final container closure is spiked with an intravenous tubing set which in turn is connected to the catheter to deliver the drug product to the portal vein. Images of the setup are available in the BLA 125734/0/8 Section 1.11.

Transport.

In the original submission it was not clear if the drug product was shipped. IR was sent 8/28/2020 to request clarification; the applicant provided additional information on 9/10/2020 in amendment 125734/0/8 as next reviewed. The final drug product is not shipped but rather loaded into a transporter and then hand carried from the manufacturing suite to the UIH transplant room. The transporter configuration consists of the final drug product cell bag configuration, wrapped in sterile drape covers, and placed within a Styrofoam container with lid.

CellTrans conducted (b) (4) qualification runs of the carrier transporter as part of (b) (4) Process Validation runs. The transporter was validated for maintaining temperature. (b) (4) temperature thermometer was placed inside the packed transporter. The temperature was measured at (b) (4) intervals from (b) (4). The transporter remained in the CellTrans (b) (4) lab during the first (b) (4) and then was transported to the UIH Radiology Department for the last temperature measurement at the (b) (4) timepoint. During commercial production, transport typically takes (b) (4). The acceptance criterion was temperature maintained within 15 – 25 C. All results met the acceptance criteria for all (b) (4) qualification runs with no deviations reported.

The manufactured product will only be used at University of Illinois Hospital under this license application.

Overall Reviewer's Assessment of Section 3.2.P.7:

The information provided is acceptable. The bags and assembled container closure system appear suitable with respect to materials of construction, protection from moisture, microbial ingress, and adsorption of the drug product.

CellTrans is using the CryoMACS devices like the intended use as the 510k clearance. The bag is 510k cleared under BK090020 with 21 CFR 864.9100 classification, and intended for a single cycle of freezing, storage (down to -196°C), and subsequent thawing (at 37°C) of hematopoietic progenitor cells. CellTrans does fill the bags beyond the recommended volume, but the bags are not being frozen eliminating the concern of bag rupture as freezing the filled volume would cause expansion. Although the supplier of the bag demonstrated bag integrity performance in the 510k clearance, CellTrans conducted APS studies to verify integrity both during manufacturing process and transport; refer to below section 3.2.A.1 Facilities and Equipment, Aseptic Process Simulation.

The results of the transporter qualification met the acceptance criteria, demonstrating the temperature of the final drug product can be maintained within the transporter system. The temperature was measured using (b) (4) this is acceptable since the transport environment is maintained at room temperature and the temperature specification includes room temperature (15 – 25 C). The transporter appears to act more as a convenience packaging for handling, protection of the cell bags during transport, with (b) (4) to facilitate transfer into the sterile boundary of the clinical transport suite. Protection of the cell bag during transport was demonstrated during process validation in above section 3.2.P.3.5 Process Validation and/or Evaluation and in APS in below section 3.2.A.1 Facilities and Equipment, Aseptic Process Simulation.

Defer to Product Office for assessment of the container closure system and transporter on the drug product characteristics under PO purview. The firm is relying on the 510k clearance performance data for E&L studies and data as it pertains to safety and product quality. The data were not provided in this BLA.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

The product undergoes final release testing, to include visual inspection of product appearance and container integrity; gram stain; endotoxin testing; and sterility testing (bacterial and fungal cultures). The product expiration is 6 hours from time of product release, based on stability test results from (b) (4) batches (b) (4) where islets met viability, functionality, endotoxin, and gram stain specifications. It is not possible to prospectively report results from sterility testing for each batch before the drug product is transplanted into the patient. The drug product is conditionally released and transplanted based on gram stain, endotoxin testing, and visual inspection. A sample of the drug product undergoes sterility testing. Once sterility testing (14 day bacterial culture (b) (4) 28 day fungal culture (b) (4) are complete, the results of the sterility tests are documented on a Final Islet Product Certificate of Analysis and forwarded to the medical staff for inclusion in the patient's medical record. Although the stability data supports at least 6 hours of holding post formulation, CellTrans will continue to transplant the islet products immediately after formulation without holding.

Batch#	Sample#	Islet recovery (%)		Viability (%)		GSI		Gram Stain		Endotoxin	
		0hr	6hr	0hr	6hr	0hr	6hr	0hr	6hr	0hr	6hr

(b) (4)

Additional stability data: Drug Product batch is comprised of a single unit and is not stored or maintained for a period greater than 6 hours. Each batch is packaged in one infusion bag for transplant. Of the most recent (b) (4) batches, the average hold time was (b) (4) with a standard deviation of (b) (4). In addition to these data, islets have been held at ambient temperature during shipment for as long as 48 hours[1] Kaddis, J.S., et al., Standardized transportation of human islets: an islet cell resource center study of more than 2,000 shipments. Cell Transplant, 2013. 22(7): p. 1101-11. While these islet batches were not used for human transplant, the islets were shown to retain biological activity and viability comparable to islet tissue prior to shipment.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

Not applicable as product is used immediately after formulation.

Overall Reviewer's Assessment of Section 3.2.P.8:

The results of the gram stain and endotoxin support product stability for 6 hours. Defer to PO for characteristics under PO purview regarding stability. The product is used immediately after formulation and is not stored.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Several details were missing, incomplete, or unclear in the original submission regarding Facilities and Equipment. Additional information was requested in IRs; the details of this information are integrated into the review memo:

- DMPQ IR Sent 8/28/2020 with applicant response on 9/10/2020 in amendment 125734/0/8: additional information included Aseptic Process Simulation (APS); Container Closure System (CCS) information; line clearance; transport validation; facilities & equipment list, qualification, cleaning, sterilization, and flows.
- DMPQ IR Sent 12/3/2020 with applicant response on 10/26/2020 in amendment 125734/0/19: additional information included organ decontamination validation; additional APS details; cleaning validation details; equipment qualifications; and HVAC
- DMPQ IR Sent 1/27/2021 with applicant response on 2/19/2021 in amendment 125734/0/28: additional details provided for organ decontamination development and assessment summary.

Manufacture of the drug substance and drug product are conducted at the CellTrans Islet Isolation Facility, located in Chicago, IL (below **Table 12**). For the subject facility, the firm provided information about procedures and design features used to prevent contamination and cross-contamination: classified areas and facility flow; facility cleaning and disinfection; environmental monitoring; critical utilities; computer systems; equipment qualification, cleaning and sterilization; and aseptic process simulations. These features are reviewed below in the ensuing sections.

Table 12. Facilities Table.

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS- BLA entry required?	Comments
<ul style="list-style-type: none"> - Production of drug substance and product - (b) (4) final release testing (endotoxin; bacterial culture) of (b) (4) product - Drug product primary packaging and labeling. - Drug product final packaging. - Logistic operations (receiving and shipping). <p>Facility: CellTrans, Inc. Islet Isolation Facility, 1740 W. Taylor St., Chicago, IL 60612 FEI#: 3010872260</p>	Inspection	Yes	Yes	<p>New Facility.</p> <p>The applicant stated the facility is ready for PLI.</p>
<p>Conditional release testing (gram stain) of drug product</p> <p>Facility: University of Illinois Hospital & Health Science System</p> <p>(b) (4)</p> <p>FEI#: None CLIA# (b) (4)</p>	Not required.	No	Yes	

(b) (4)

Classified areas and facility flows

Summary. Personnel utilize gowning qualification and GMP training and (b) (4) aseptic training/re-certification. Personnel and product flow is primarily unidirectional. Materials

are stored throughout the manufacturing areas and adjacent areas. Waste flow is unidirectional and exits through the exit vestibule, opposite of the gowning area. All (b) (4) manipulations involving the pancreas are performed in a BSC (ISO 5) with (b) (4) procedures being conducted in the surrounding ISO 7 clean room suite. (b) (4) is manufactured during (b) (4) shift, therefore production scheduling and changeover and are not part of current procedures. Changeover procedures were clarified in IR sent on 8/28/2020 with applicant clarification on 9/10/2020 in amendment 125734/0/8 that there is not a changeover procedure, but that changeover is included in the equipment cleaning and facility cleaning SOPs. In the same IR request, additional details were requested for flows and security access. Refer to below for details.

Substantive. GMP manufacturing and testing activities are conducted at the Islet Isolation Facility (FEI 3010872260) in Chicago, IL. The facility is a (b) (4) complex located in the (b) (4) University Hospital on the University of Illinois medical campus. (b) (4) The Quality Control Unit has an approved list of individuals authorized to enter the cleanroom space, which has a single entrance with controlled access (entrance vestibule room (b) (4); **Figure 4**). The facility has (b) (4) classified areas (ISO 5 BSCs with ISO 7 background; ISO (b) (4) entrance and gowning) and (b) (4) of CNC support space (QC labs, storage, observation room); refer to **Figure 4**.

- **Reviewer Comment:** The area classifications appear adequate to prevent contamination or cross-contamination. The manufacture suite may be inadequate depending on number of manufacturing personnel occupying the space at the same time; the adequacy of the space should be followed up on during the PLI.

(b) (4)

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

(b) (4)

Equipment.

The original submission did not contain details or procedures describing which equipment/utensils are labeled for unique identification; and how equipment will not be mixed with the nearby hospital equipment and supplies. An IR was sent to the firm on 8/28/2020 for the applicant to describe and provide the procedures for how equipment is labeled, which equipment are labeled, how equipment is taken in or out of service, and how equipment is tracked. The applicant responded on 9/10/2020 with the requested details amended to the BLA in 125734/0/8. The applicant indicated there is (b) (4) flow of equipment throughout the cleaning and sterilization process at (b) (4) (from (b) (4)

(b) (4)

- **Reviewer Comment:** Equipment flows appears to be procedural and physically separated from UIH equipment; adherence to the procedure should be followed up on during the PLI.

Personnel.

Personnel flow is (b) (4) within the islet isolation facility. Once (b) (4) (b) (4) and (b) (4), authorized personnel enter the gowning room through a (b) (4). Per procedure MFG-SOP-201, (b) (4)

- **Reviewer Comment:** There appears to be inadequate space for gowning and doffing scrubs; the areas and procedures for gowning/doffing should be followed up on during the PLI.

Materials.

New production supplies enter through the (b) (4) and are retrieved by a staff member inside of the processing room. Supplies are stored in (b) (4)

New QC supplies are stored in the clean storage room and are taken to the QC lab as needed. Production media and reagents are prepared when required for islet manufacture. The reagents are stored in (b) (4) then formulated in BSC^{(b) (4)} of the cleanroom suite, and followed by storage in room (b) (4) until needed for production (**Figure 4**).

Waste.

As per FAC-SOP-001, flow of waste materials is (b) (4). All waste exits through the exit vestibule at the opposite end from the gowning room. No waste transits the airlock used for entry of new production supplies. Tissue waste from initial dissection of the donor pancreas as well as used material, including disposable pipettes and tubes, are discarded in biohazard bins and bags that are (b) (4). Once outside of the classified space, all biohazard waste is picked up and disposed of by (b) (4).

- **Reviewer Comment:** The waste exit the (b) (4) which may cross paths with manufacturing employees as they enter the pre-gowning room; the potential for cross-contamination should be followed up on during the PLI.

HVAC.

In the original submission several details of the HVAC equipment were unclear, insufficient, or missing for: differential pressure, air change rate, and room recovery between area classifications; owner/maintenance of HVAC system; and airflow diagram. An IR was sent to the applicant on 12/3/2020 with a response provided on 12/30/2020 in amendment 125734/0/19. The facility is maintained with a cascading pressure differential with the highest pressure in the critical areas, cascading outward to the less critical areas. The processing room is maintained at a higher pressure than the gowning and egress rooms, which are at higher pressure than the airlocks. The minimum acceptable differential pressure reading limit between (b) (4) rooms is (b) (4) (b) (4) The entire facility is at positive pressure to surrounding building space. Differential pressure is monitored by (b) (4) during Static and Dynamic Environmental Monitoring and (b) (4) by CellTrans. HEPA filters are placed throughout the manufacturing suite, contained within the ceiling at the numbers and locations depicted in **Figure 7**. Additional details of the HVAC unit specifications are in below section "Critical utilities"; meanwhile performance qualification and monitoring are provided in below section "Environmental Monitoring".

- **Reviewer Comment:** The HVAC differential pressure is very low. The pressure monitoring may be inadequate as it is manually monitored (b) (4) by CellTrans and contracted out to (b) (4) during production. The pressure monitoring should be followed up on during the PLI.

(b) (4)

Other Products in Facility

The applicant indicated the facility is dedicated to the subject product and no other products are manufactured in the Islet Isolation Facility.

Facility cleaning and disinfection

Summary. The facility is routinely cleaned using a validated cleaning procedure. Cleaning and sanitization procedure for the islet isolation facility has been validated and the facility is cleaned on a standardized schedule, as well as (b) (4) every islet isolation. In the original submission there was no disinfectant effectiveness study. The information was requested in IR on 8/28/2020 with the applicant providing the details on 9/10/2020 in amendment 125734/0/8.

Substantive.

A cleaning procedure and disinfectant effectiveness study was conducted by

(b) (4)

Cleaning frequency, solutions, and technique. All rooms are cleaned in the same manner, on a (b) (4) basis, (b) (4) an isolation procedure, or if deemed necessary. The cleaning solutions include (b) (4) The (b) (4) (b) (4) are cleaned similarly by using a (b) (4)

The entirety of all surfaces are cleaned, including (b) (4)

are used for the separate surfaces and discarded after use. The furniture and laboratory equipment are cleaned using a (b) (4) cleaning solution, and (b) (4),

(b) (4)

(b) (4) Rooms are inspected after every cleaning or disinfection. If rooms do not pass a visual inspection, they are re-cleaned.

(b) (4)

(b) (4)

Environmental Monitoring

Summary. The performance of the Environmental Monitoring (EM) was qualified (EMPQ) for routine monitoring to ensure control (b) (4)

(b) (4)

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

(b) (4)

Critical utilities

The only critical utility are the HVAC units; in the original submission there were missing HVAC unit details, qualification, and oversight. The information was requested in IRs on 8/28/2020 and 12/3/2020. CellTrans provided additional information on 9/10/2020 (amendment 125734/0/8) and 12/30/2020 (amendment 125734/0/19). There are (b) (4) dedicated HVAC units supplying (b) (4) recirculated HEPA filtered air to the classified areas, with exhaust air into the Hospital area and (b) (4) fresh air make-up (**Figure 8**). The HVAC unit controls for particulate, temperature, humidity, and pressure differential, which were qualified for performance and are monitored to action limits as described above section Environmental Monitoring. The HVAC unit provide up to (b) (4) air changes per (b) (4) Each air handling unit has (b) (4) There are (b) (4) HEPA filters in the islet isolation facility rated at (b) (4) efficiency (refer to **Figure 7**).

(b) (4)

- **Reviewer Comment:** The HVAC appears adequate to prevent contamination or cross-contamination with air from the surrounding UIH infrastructure. The HVAC units are dedicated with (b) (4) fresh air make-up. The HVAC unit was not separately qualified for IQ, OQ, or PQ; the performance was conducted in conjunction with EMPQ. The firm did not provide a room recovery study for the length of time needed for the room to recover. The door interlocks or procedures ensuring room recovery should be followed up on during the PLI.

Computer systems

CellTrans uses an electronic environmental monitoring system; there are no automated process control systems. In the original submission, limited details of the system were provided, and therefore requested in IR on 8/28/2020. The applicant provided the additional details on 9/10/2020 in amendment 125734/0/8. CellTrans uses (b) (4) (b) (4) for collection and storage of EM data. (b) (4) is a networked system that (b) (4) collects wireless readings from probes installed in the classified areas of the manufacturing suite. (b) (4) is configured to send remote notification via telephone for of out of range conditions. (b) (4) can be remotely accessed and is password protected and only accessible by authorized personnel. The system was qualified to perform (b) (4) monitoring of temperature, CO₂, and relative humidity. The IQ included verifications of equipment hardware specifications as compared to design specifications, installation of network elements, utility verification, spare parts, and system documentation. The OQ included verifications of system programming, server information, network paths, dependencies, port details, versions, post-installation support, telephone testing, sensor input calibrations and placement

verifications, sensor operation, alarm testing, and system reporting. All elements were verified to adhere to each design and user specifications or requirements. No deviations were reported.

- **Reviewer Comment:** The IQ/PQ protocol stated the procedure was conducted to meet GLP and GCP. While the system appears to meet CGMP requirements, the (b) (4) computer system should be followed up on during the PLI to verify data integrity and audit trail.

Equipment Qualification

Summary. In the original submission, equipment details were missing or incomplete (equipment list; labeling/control; cleaning/sterilization; and qualification). The details were requested in IR on 8/28/2020 with applicant response on 9/10/2020 in amendment 125734/0/8. After review of the information, not all of the major equipment appeared to be validated or qualified. Likewise, the validation of equipment used for sterilization, i.e. (b) (4) did not appear to be validated or qualified. Below, these items are explained in further detail with recommendation for follow-up on inspection.

Substantive. The equipment used in the manufacture of the drug substance and drug product is summarized in the below **Table 14**. BSCs are recertified (b) (4) Centrifuges, CO₂ incubators, the COBE cell processors and all major pieces of equipment are under yearly preventive maintenance contract with their respective manufacturers. Major equipment used for islet isolation were qualified in conjunction with the Process validation as described in 3.2.S.2.5 Process Validation and/or Evaluation.

Table 14. Equipment list.

A large rectangular area of the document is redacted with a solid grey background. In the center of this redacted area, the text "(b) (4)" is written in a large, bold, black font. This indicates that the entire table content has been withheld for public release.

3 pages have been determined to be not releasable: (b)(4)

(b) (4)

Equipment Cleaning Validation

The original submission was unclear for several details about cleaning of reusable equipment, including the cleaning procedure used (b) (4) source of water for cleaning and final rinse, and if cleaning operations were contracted to (b) (4). Details regarding the cleaning were requested in IR on 8/28/2020; the applicant provided a response on 9/10/2020 in amendment 125734/0/8. The cleaning validation was reviewed, but details were unclear for acceptance criteria, lifetime cycle assessment on the (b) (4) frequency of requalification, and how/if repeated cleaning steps are documented.

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

(b) (4)

Equipment Sterilization Validation

The original submission was missing details of equipment sterilization for the (b) (4) qualification, (b) (4) from (b) (4) and sterile hold times. These details were requested in an IR on 8/28/2020 with the applicant response provided on 9/10/2020 in amendment 125734/0/8. The firm uses contracted services from (b) (4) for sterilization of re-usable equipment by (b) (4) (b) (4) Validation of (b) (4) were conducted by (b) (4) and next reviewed. Only PQ was provided in the submission.

(b) (4)

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

Aseptic Process Simulation

Summary. Details of APS were missing, incomplete, or unclear in the original submission regarding the APS summary, use of a phantom, and comparison to routine production. The information was requested in IRs sent 8/28/2020 and 12/3/2020 with applicant responses provided on 9/10/2020 (amendment 125734/0/8) and 10/26/2020 (amendment 125734/0/19). In summary, (b) (4) APS runs were conducted using (b) (4) in place of all reagents and pancreas to simulate manufacture of (b) (4) simulated batches. Per simulated batch manufacture, there were (b) (4) samples taken during simulated aseptic manufacturing steps. Additionally, (b) (4) (b) (4) were included per APS run. The manufacturing processes were simulated as comparable to routine production and SOPs and involved worst-case conditions. The simulated aseptic processing included (b) (4)

And additionally, the APS included simulations of (b) (4) process steps, which included (b) (4)

All (b) (4) APS runs showed no contamination of simulation samples or negative control; positive controls demonstrated growth promoting media. Deviations were reported but did not affect the validity of the APS runs.

Substantive. The media simulations occurred on (b) (4) Details for the aseptic process simulations are next described and include study design, environmental conditions, run details (frequency, number, duration, size), and growth details (media, incubation, examination, results). The firm conducted media simulation studies to validate aseptic processing according to VAL-PLN-002 Validation Plan: Aseptic Process Validation. Per the firm, the study was conducted according to “Sterile Drug Products Produced by Aseptic Processing CGMP” issued on September 2004.

(b) (4)

2 pages have been determined to be not releasable: (b)(4)

(b) (4)

Overall Reviewer's Assessment of Section 3.2.A.1:

The information as originally submitted and amended is acceptable for most elements to prevent contamination and cross-contamination, including classified areas and facility flow; HVAC; facility cleaning and disinfection; critical utilities; computer systems; equipment cleaning; and APS runs. Refer to the above Reviewer Comments associated with each element.

There are a few elements that should be followed up on during the PLI, which are explained in the above **Reviewer Comments** and briefly listed here: HVAC pressure differential is low (b) (4) computer system should be verified for audit trail; several pieces of equipment do not appear to be qualified adequately; and (b) (4) do not appear to use a validated sterilization (b) (4) (b) (4)

3.2.A.2 Adventitious Agents Safety Evaluation

Not under DMPQ purview.

□ **Viral Clearance Studies**

Not under DMPQ purview.

Overall Reviewer's Assessment of Section 3.2.A.2:

Not under DMPQ purview. Deferred to PO.

3.2.A.3 Novel Excipients

Not under DMPQ purview.

3.2.R Regional Information (USA)

❑ Executed Batch Records

The submission includes the master batch record and one executed batch record from the Process Validation Batch.

❑ Method Validation Package

Not under DMPQ purview.

❑ Combination Products

The BLA was not reviewed as a combination product.

Overall Reviewer's Assessment of Combination Products Section:

The submission was not reviewed as a combination product.

❑ Comparability Protocols

No comparability protocols were submitted.

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

Not under DMPQ purview; defer to PO.

B. Labeling Review

Full Prescribing Information (PI):

Not under DMPQ purview; defer to appropriate office/division.

Carton and Container Label:

Not under DMPQ purview; defer to appropriate office/division.