

**CBER DMPQ CMC/Facility BLA Review Memorandum**

**BLA STN 125812/0**

**Acellular tissue engineered vessel - SYMVESS**

**Zainab Mansaray-Storms  
CMC/Facility Reviewer  
CBER/OCBQ/DMPQ/MRB2**

1. **BLA#:** STN 125812/0

2. **APPLICANT NAME AND LICENSE NUMBER:** Humacyte Global, Inc. (Lic # 2336)

3. **PRODUCT NAME/PRODUCT TYPE**

Non-Proprietary/Proper/USAN: acellular tissue engineered vessel

Proprietary Name: SYMVESS

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

- a. Pharmacological category : Tissue Therapy
- b. Dosage form: 6mm inner diameter x 42cm acellular tissue engineered vessel
- c. Strength/Potency: 6mm inner diameter x 42cm Vascular Implant
- d. Route of administration: surgical implantation
- e. Indication(s): Urgent arterial repair following extremity vascular trauma (b) (4)  
(b) (4) when autologous vein is not feasible

5. **MAJOR MILESTONES**

Original Submission: 12 December 2023

Internal Filing Meeting: 19 January 2024

Internal Mid-cycle Meeting: 26 March 2024

Pre-License inspection (Humacyte Global, Inc.): 01 – 05 April 2024

Internal Late-Cycle Meeting: 10 May 2024

Action Due Date: 09 August 2024

6. **DMPQ CMC/FACILITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Zainab Mansaray-Storms, OCBQ/DMPQ/MRB2	Drug Product, Facilities & Equipment

7. **SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
11 December 2023	STN 125812/0	Original submission
12 January 2024	Amendment STN 125812/0/1 (response to DMPQ IR #1 sent 05 January 2024)	356h form update to provide complete establishment information
22 January 2024	Amendment STN 125812/0/6 (response to DMPQ Inspection Notification Email)	Production schedule at Humacyte Global Inc., Durham NC
01 February 2024	Amendment STN 125812/0/8 (response to DMPQ IR #2 sent 23 January 2024)	Information on other products, cross- contamination measures and equipment cleaning procedures

<b>Date Received</b>	<b>Submission</b>	<b>Comments/ Status</b>
01 May 2024	Amendment STN 125812/0/26	Response to FDA Form 483 issued on 05 April 2024 at Humacyte Global Inc. PLI
10 May 2024	Amendment STN 125812/0/30 (response to Product Office IR#21 sent 26 April 2024)	Information on sterilization validation of the bioreactor disposable set
23 May 2024	Amendment STN 125812/0/34 (response to DMPQ IR #3 sent 09 May 2024)	Information on (b) (4) validation, gas system qualification and disinfectant efficacy study.
23 May 2024	Amendment STN 125812/0/35 (response to commitment from Late Cycle meeting on 20 May 2024)	Comparison of Humacyte Assembly to Sterilization Validation simulated products by (b) (4)
26 June 2024	Amendment STN 125812/0/48 (response to DMPQ IR #5 sent 18 June 2024)	Confirmation of CCIT testing used for future commercial lots
27 June 2024	Amendment STN 125812/0/49 (response to DMPQ IR #4 sent 13 June 2024)	Piping and instrument diagrams of the flow paths for gas, media and buffers.
27 June 2024	Amendment STN 125812/0/50 (response to Product Office IR sent 20 May 2024)	Additional shipping validation study submitted
02 July 2024	Amendment STN 125812/0/51 (response to DMPQ IR #6 sent 26 June 2024)	Initial EMPQ of HVAC system
17 July 2024	Amendment STN 125812/0/55 (response to Product Office IR #35 sent on 12 June 2024)	PMC to perform sterilization validation of the commercial bioreactor disposable set

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
(b) (4)	(b) (4)	Container closure information	Yes	No DMF review required, information pertinent to container closure is provided in the BLA

**9. REVIEWER SUMMARY AND RECOMMENDATION****A. EXECUTIVE SUMMARY**

Humacyte Global Inc., (Humacyte) submitted BLA 125812/0 for a novel acellular tubular implant composed of human extracellular matrix (ECM) proteins typically found in human blood vessels, acellular tissue engineered vessel for the treatment of urgent arterial repair following extremity vascular trauma (b) (4) (b) (4) when autologous vein is not feasible.

There is no drug substance (DS) for this product. The drug product (DP) is manufactured at the Humacyte facility in Durham, NC (FEI # 3014294024).

DMPQ conducted a pre-license inspection (PLI) of the Humacyte facility in April 2024 for acellular tissue engineered vessel manufacturing and packaging activities. A Form FDA 483 was issued at the end of the inspection. The firm adequately responded to the observations and review of Humacyte's response is documented in a separate Form FDA 483 response review memo. All inspectional issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

This review memo covers the Chemistry and Manufacturing Controls (CMC) with focus on microbial controls, and facilities with focus on facility and major equipment qualification, cleaning, environmental monitoring (EM), utilities and controls of cross-contamination.

Based on review of this BLA submission and amendments which addressed DMPQ information requests, and the outcome of the manufacturing facility inspection, approval of this BLA is recommended.

**B. RECOMMENDATION****I. APPROVAL**

Based on information reviewed in this submission and the outcome of the manufacturing facility inspections, approval is recommended with the following post-marketing commitment (PMC) and inspectional recommendation for the

next surveillance inspection. CBER understands that the recommendations may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.:

- PMC: Humacyte commits to perform sterilization validation of the commercial bioreactor disposable set and provide the final report, including a summary of the dose verification study and the applicable data. Humacyte commits to continue performing aseptic process simulation of the full manufacturing process (b) (4) every (b) (4) until this post-marketing commitment is fulfilled. Humacyte will submit the final study report by September 30, 2024.
- Inspectional Recommendation: Review of the environmental monitoring trending data and the contamination recovery rate of the (existing and new) (b) (4) areas in the Humacyte Global Inc. facility.

## II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Zainab Mansaray-Storms Facility/CMC Reviewer OCBQ/DMPQ/MRB2	Concur	
Anthony Lorenzo Branch Chief OCBQ/DMPQ/MRB2	Concur	
Carolyn Renshaw Division Director OCBQ/DMPQ	Concur	

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## Module 3

### 3.2.S DRUG SUBSTANCE

Acellular tissue engineered vessel does not contain a Drug Substance. Module 3.2.S is not applicable and is therefore not included in the BLA submission.

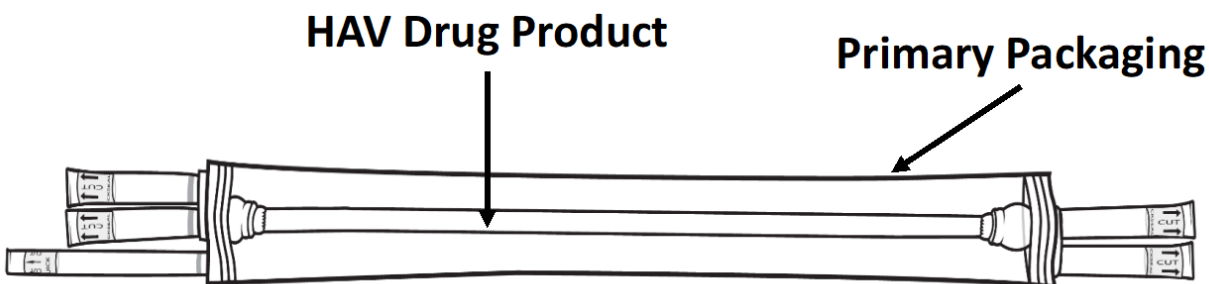
### 3.2.P DRUG PRODUCT

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

The acellular tissue engineered vessel drug product (DP) is a tissue-engineered, acellular, flexible tube composed of organized extracellular matrix (ECM) proteins. The acellular tissue engineered vessel DP is implanted using standard surgical techniques as a vascular conduit used to replace a patient's damaged blood vessels after sustaining trauma. The acellular tissue engineered vessel has dimensions of approximately 6 mm in inner diameter and 42 cm in length. Since the length of the acellular tissue engineered vessel to be implanted is dependent on the surgical needs, the acellular tissue engineered vessel is cut to length by the surgeon in the operating room.

The acellular tissue engineered vessel DP is manufactured within a custom bioreactor bag that, after being aseptically sealed at the end of the manufacturing process, serves as the primary packaging (see figure below). The acellular tissue engineered vessel DP is immersed within the primary packaging in (b) (4) Phosphate Buffered Saline (b) (4) which is the only excipient. (b) (4) keeps acellular tissue engineered vessel hydrated prior to implantation.

*Figure 1: Acellular tissue engineered vessel Drug Product in Primary Packaging*



#### 3.2.P.2.5 Microbiological Attributes

The acellular tissue engineered vessel DP and the (b) (4) excipient solution within the primary packaging are sterile. After the primary packaging is placed within a thermoformed (b) (4) tray that is sealed with a Tyvek lid, the exterior surfaces of the primary packaging are sterilized by a validated (b) (4) process. During the (b) (4) process, (b) (4) diffuses through the Tyvek lid of the tray and sterilizes the outer surface of the primary packaging. Validation of the (b) (4) process is reviewed in *Section 3.2.P.3.5 Process Validation* below.

Description and review of the container closure and container closure integrity testing (CCIT) can be found in *Section 3.2.P.7 Container Closure System* below.

### 3.2.P.3 Manufacture

#### 3.2.P.3.1 Manufacturer(s)

Refer to section 3.2.A.1 for a complete list of all manufacturing facilities.

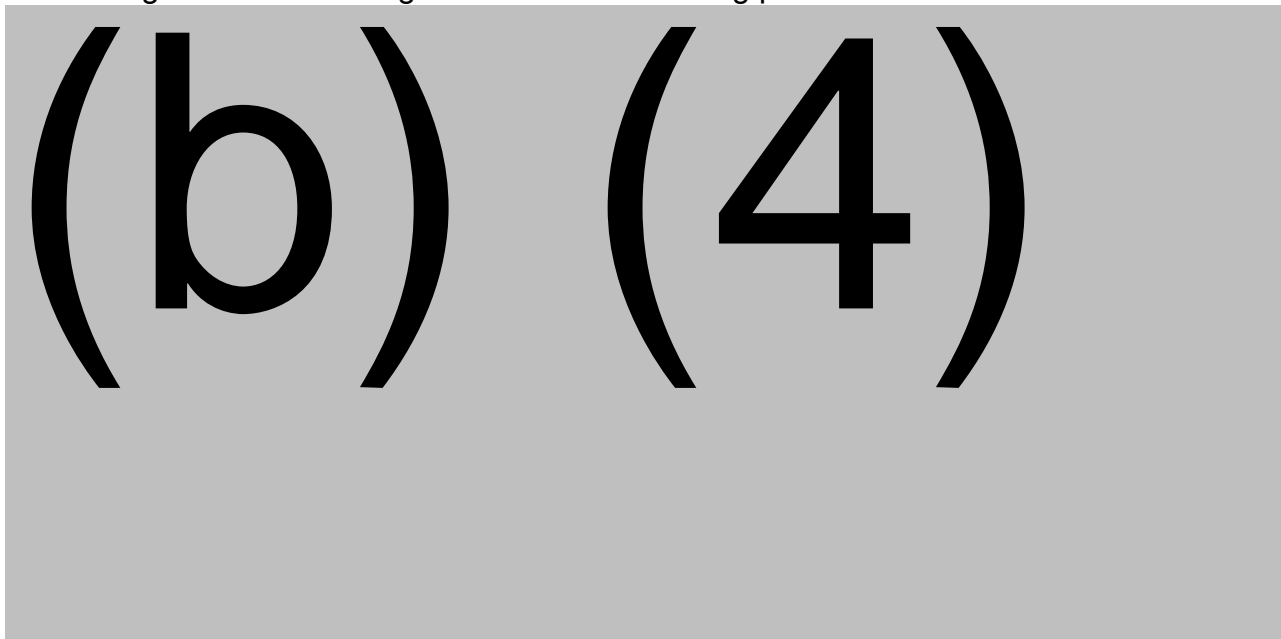
Facility	FEI/DUNS Numbers	Responsibility
Humacyte Global, Inc. 2525 E Highway 54 Durham, NC 27713, USA	FEI: 3014294024 DUNS: 557190449	Drug product manufacturing, quality control testing, packaging, labeling, and distribution, Storage of working cell bank, Drug Product stability storage

#### 3.2.P.3.3 Description of Manufacturing Process

Acellular tissue engineered vessel is manufactured using an aseptic bioreactor cell culture process. Briefly, primary human aortic cells, expanded from a working cell bank (WCB), are inoculated onto a (b) (4) mesh scaffold that is housed within a flexible plastic bioreactor bag. After inoculation onto the (b) (4) (b) (4)

and deposit ECM components forming a tubular construct, or acellular tissue engineered vessel. At the conclusion of the growth process, a (b) (4) decellularization process removes cellular components from the acellular tissue engineered vessel. The (b) (4) of this decellularization process fills the flexible plastic bioreactor with (b) (4) (b) (4) bioreactors are inoculated, grown, and decellularized (b) (4) The (b) (4) bioreactors are then individually sealed becoming the sterile primary package for each product unit.

The following are the main stages of the manufacturing process:





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

(b) (4)

**Reviewer Comments:** The submission contains detailed descriptions of each acellular tissue engineered vessel DP manufacturing process including general information regarding equipment used during the manufacturing process. Process parameters and in-process controls, including microbial control, are in place for the manufacturing process during key process steps. The information provided appears appropriate.

In a PMC from the product office, Humacyte committed to implement a validated sterility assurance strategy on the (b) (4) based on their proposed feasibility study for a sterile filtration procedure in (b) (4) preparation process.

### 3.2.P.3.4 Controls of Critical Steps and Intermediates

During acellular tissue engineered vessel manufacturing process, (b) (4) controls performed include bioburden, sterility and endotoxins. Bioburden samples are retrieved from the (b) (4) (b) (4) after (b) (4) of the (b) (4) decellularization process. Sterility and endotoxin samples are collected from the excipient (b) (4) fill in the (b) (4) after circulating for (b) (4). Per the firm, this fluid sample is representative of the (b) (4)

(b) (4) throughout the bioreactor system. The (b) (4) within the (b) (4) from each (b) (4) is also collected and tested for sterility and endotoxins.

The in-process control (IPC) parameters under DMPQ purview are summarized below.

Process Step	Description	In-Process Control	Acceptance Criteria
(b) (4)			

In response to an Information Request (IR) sent by the Office of Therapeutic Proteins (OTP) on February 2, 2024, the firm provided a description of the in-process bioburden testing method in amendment BLA125812/0/10. Bioburden testing is performed, at a contract manufacturing lab, using the (b) (4) method in accordance with (b) (4)

**Reviewer Comments:** *Microbial in-process control parameters are in place, and the acceptance criteria appear appropriate. There are (b) (4) during the manufacturing process of acellular tissue engineered vessel. The information appears acceptable.*

### 3.2.P.3.5 Process Validation and/or Evaluation

(b) (4)

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

(b) (4)

### **Packaging Process Validation**

Packaging stage consists of (b) (4)

The PPQ for the packaging process validation was executed discontinuously from the (b) (4)

The firm stated that since there are no CQAs directly linked to the packaging stage, no final product testing is in scope of Packaging PPQ and the goal of the PPQ is to demonstrate reliability and control of the packaging process.

(b) (4) batches were executed consecutively and met the established acceptance criteria as follows:

(b) (4)

(b) (4)

The sample size and number of passing/rejected for AQL Tray seal is determined using (b) (4) with a general inspection (b) (4). If the initial AQL Tray seal fails, a deviation investigation is initiated and reinforced sampling is performed. The sample number is determined at a (b) (4) or a 100% re-inspection of the batch will be performed.

Batch sizes used for the validation were (b) (4) acellular tissue engineered vessels for maximum batch size, (b) (4) acellular tissue engineered vessels for near-maximum batch size and (b) (4) acellular tissue engineered vessels. The (b) (4) batches and the AQL results are summarized below.

(b) (4)

Overall, the results for all (b) (4) batches met the predefined acceptance as well as the AQL acceptance criteria for the Packaging processing stage PPQ. There were no protocol deviations.

#### *Hold Times*

(b) (4)

**Reviewer's Comment:** Results from packaging testing from (b) (4) scale lots for acellular tissue engineered vessels were provided. All results met the predetermined acceptance criteria. The packaging process validation appear appropriate.

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

(b) (4)

**Reviewer's Comment:** Results from (b) (4) qualification were provided. All results met the predetermined acceptance criteria. The maximum packaging-specific TOR and (b) (4) temperature equilibration time were established. The (b) (4) validation appears acceptable. During the PLI of Humacyte, (b) (4) PQ and the most recent requalification in December 2023 were reviewed. No objectionable findings were noted.

### Shipping Validation

The processed acellular tissue engineered vessel units are inserted into a (b) (4) (b) (4) for each individual acellular tissue engineered vessel, forming the market package. (b) (4)



(b) (4)

The shippers include temperature monitoring devices and security seals to demonstrate environmental control and to assure security of the shipment.

Humacyte uses (b) (4) to transport the final packaged acellular tissue engineered vessel units direct to hospitals (b) (4). The larger outer shipping box contains an insulated inner box. Within the insulated box is one “payload” box with up to three acellular tissue engineered vessels per box. (b) (4)

to (b) (4) temperature monitors; (b) (4) is placed in the shipper and (b) (4) (b) (4) is placed on the secondary package).

The shipper is designed for shipment of (b) (4). Both minimum load (b) (4) and maximum load (b) (4) were evaluated in the study. Results provided of the shipping validation temperature summary demonstrated controlled (b) (4) environmental conditions for at least (b) (4) under (b) (4) simulated summer and winter shipping conditions.

In addition, a shipping simulation study was performed. The shipping of packaged acellular tissue engineered vessels was simulated by exposing the shipping system to a sequence of (b) (4) tests as outlined in the (b) (4)

(b) (4) (b) (4)  
(b) (4) (b) (4) (b) (4)  
(b) (4)

Both minimum load (b) (4) and maximum load (b) (4) were evaluated in the study.

Per the firm, through both the (b) (4) tests and (b) (4) tests no damage to the packaging system, including the outer corrugate shipper, (b) (4) (b) (4) was observed beyond normal fatigue.

To ensure that the Tyvek lids stay affixed to the trays during shipment, seal integrity testing was performed using a (b) (4) test following a shipping simulation. According to the firm, no evidence of (b) (4) was observed following the shipping simulation indicating the tray seal was not impacted by the shipping and remained integral.

During the PLI of Humacyte, the product office reviewer noted that there was no evaluation of drug product critical quality attributes (CQAs) included in the shipping study. Humacyte provided an additional shipping validation study in amendment BLA 125812/0/50 (received 26 June 2024) evaluating the impact of a worst-case shipping route on drug product CQAs and primary container CCIT.

In this additional shipping validation study, (b) (4) were executed with (b) (4) (b) (4) acellular tissue engineered vessels using the validated (b) (4)

shippers. Shipments were sent using (b) (4) from Durham, NC to (b) (4) and back to Durham, NC (b) (4). Per the firm, this route served as a worst-case transit path as it captures (b) (4) modes and (b) (4) that of a typical acellular tissue engineered vessels domestic shipment. The shipped acellular tissue engineered vessels were then subjected to CCIT (b) (4) of the primary packaging (BDS) and QC testing of several DP CQAs.

The maximum shipment duration in the worst-case study was (b) (4) at (b) (4). The shippers maintained the desired shipping temperature throughout for all shipments. All results from CCIT passed, meeting the acceptance criteria. In addition, all QC testing of DP CQAs met the acceptance criteria. There were five deviations during the study, all were investigated, resolved, and closed.

**Reviewer's Comments:** Shipping validation studies were performed. The shipper validation results demonstrated controlled (b) (4) for at (b) (4) (b) (4). The CCIT testing following the shipping simulation and the additional worst-case transportation study met all acceptance criteria. The shipping validation appear acceptable. CCIT appears acceptable and is reviewed below in section 3.2.P.7 Container Closure System.

During the PLI of Humacyte, shipping validation studies were discussed with the SME. Deviations associated with the validation were also reviewed and appear acceptable. No objectionable findings were noted.

### Aseptic Process Qualification

The firm states that the aseptic processing steps in the acellular tissue engineered vessel manufacturing process have been validated and is routinely challenged through Aseptic Process Simulations (APS).

Per the firm, an APS master plan was developed after risk assessments of the full manufacturing process and facility design. Below is a summary of the operations included in the aseptic simulation.

(b) (4)

(b) (4)

The figure below illustrates the acellular tissue engineered vessel aseptic process simulation summary from the risk assessment.

*Figure 4: Acellular tissue engineered vessel Aseptic Process Simulation Summary*

(b) (4)

The initial APS validation evaluated all open and closed process operations throughout the (b) (4) and decellularization steps. These were validated through representative APS operations utilizing (b) (4) (b) (4) to assess the potential for contamination during routine operations. APS was

performed through a series of (b) (4) simulated batches using (b) (4) instead of acellular tissue engineered vessel product.

For each simulation, the firm stated that the following principles apply:

- Representative batch sizes, media volumes, materials, equipment, operations, durations, and personnel were utilized to challenge all aspects of aseptic control during routine manufacturing.
- Following the manufacture for each batch, microbial testing is performed on (b) (4) from each batch.
- All growth media utilized during initial APS is (b) (4) for signs of contamination. (b) (4) was (b) (4) followed by (b) (4) for total of (b) (4)

The firm noted that it used a family approach for the APS studies. In such, any duplicate equipment such as the (b) (4) equivalent (b) (4) were validated to identical IOQ requirements for equipment and controls. All product contact components are single-use; therefore, the APS challenges the (b) (4) used in the process, as well as the process of (b) (4) during the manufacturing process. The APS included an assessment of (b) (4) (b) (4) (b) (4)

During the APS of the (b) (4) steps, the (b) (4) (b) (4) collected were from the following process steps (b) (4)

These samples cover the entirety of the (b) (4)

During the APS of the (b) (4) process steps, the (b) (4)

The aseptic connections used (b) (4)

For all APS execution runs, the predefined acceptance criteria included “no contaminated units should be detected” and “All growth promotion tests must demonstrate adequate growth promoting capabilities”. All (b) (4)

(b) (4)

In addition, the environmental monitoring (EM) of rooms used in the APS met all acceptance criteria for the room classification. This includes pre-activity, in-operation and post-activity personnel EM results. Pre-activity EM includes (b) (4)

In-operation EM includes (b) (4)

Post-process EM of personnel occurred following each (b) (4)

(b) (4)

A summary of the (b) (4) is provided in the table below.

(b) (4)

(b) (4)

**Reviewer's Comments:** The (b) (4) simulated APS runs conducted had no positive growth units detected and all growth promotions met the acceptance criteria. Deviations were reviewed and found to be resolved acceptably. The (b) (4) steps were initially validated during the initial APS and will not be requalified (b) (4) Review of the aseptic connections used in the closed processing steps appear acceptable. The (b) (4) steps have been requalified (b) (4) since 2020 and the results meet the acceptance criteria. The APS appears appropriate.

During the PLI of Humacyte, APS initial qualification was reviewed, and the associated deviations were discussed with Subject Matter Experts (SMEs). There were no objectionable findings noted with APS and the handling of the deviations. The most recent requalification in January 2024 was also reviewed and appeared acceptable.

#### **Sterilization Validation of Bioreactor Disposable Set**

Sterilization validation of the bioreactor disposable set (BDS) was not provided in the original submission.

In response to an IR sent on 26 April 2024 (STN 125812/0/30; received 10 May 2024), Humacyte informed the agency of a technical issue that will delay the submission of the sterilization validation report. During the study, the bioburden level (b) (4) requirement of (b) (4) on at least (b) (4) of the assemblies was not met, as required per (b) (4) Of the (b) (4) non-sterile assemblies tested in the study, (b) (4) were found to

contain (b) (4) and (b) (4) were found to contain (b) (4). According to the firm, the assemblies used to perform the initial sterilization validation study consisted of (b) (4) or (b) (4) design of the full BDS assembly, meaning it did not contain a full tray of (b) (4) individual BDS assemblies. Per the firm, to greatly increase the likelihood of recovering bioburden on (b) (4) of the assemblies, the study will be repeated with a (b) (4) design of the full BDS assembly.

In STN 125812/0/35 (received 23 May 2024), the firm submitted a summary report of the comparative analysis between the Humacyte assembly used during routine production and (b) (4) simulated products used for sterilization validation. Per the report, the Humacyte simulated product is considered covered within the product family supported via the (b) (4) based on the following rationale. The additional componentry of the Humacyte (b) (4) product add marginal additional (b) (4) (b) (4) on Humacyte (b) (4) product yielded an average (b) (4) of (b) (4). In addition, the additional components of the Humacyte product are (b) (4) in nature, composed of materials of construction similar in both design and size to items already included in the (b) (4) product and they do not represent a greater challenge to the sterilization process. However, the firm states that out of an abundance of caution, an additional dose verification study is currently being performed.

During the Late Cycle meeting with the applicant on 20 May 2024, Humacyte committed to provide the sterilization validation of the bioreactor disposable set by 25 July 2024.

**Reviewer Comments:** *The applicant did not provide a sterilization validation of the complete BDS, and the study is ongoing. They provided a comparative analysis between Humacyte BDS, and other simulated products used in the vendor's sterilization validation which indicates the Humacyte BDS is considered covered within the product family.*

*A post-marketing commitment was made with the applicant to provide the sterilization validation when available. In the meantime, the firm commits to continue performing aseptic process simulation of the full manufacturing process (b) (4) process steps) until this post-marketing commitment is resolved.*

### 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)

Humacyte lists (b) (4) as specifications for acellular tissue engineered vessel DP tested at release and throughout shelf-life. Acellular tissue engineered vessel DP bacterial endotoxins and sterility methods are (b) (4) validated and specification is set at (b) (4) and "no growth" respectively. Both tests are performed at release and at the end of shelf life.

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

Sterility testing is performed at release and end of shelf-life. CCIT is performed at release and (b) (4) during stability testing to demonstrate the integrity of the container closure over product shelf life. The review of CCIT can be found in section 3.2.P.7 *Container Closure System* of this review memo.

### 3.2.P.5.4 Batch Analyses

A total of (b) (4) (using (b) (4) to support clinical studies) and (b) (4) batches (b) (4) system to support comparability, PPQ and stability studies) of acellular tissue engineered vessel were manufactured at Humacyte including (b) (4) batches to support PPQ. All PPQ batches were tested against the commercial release and stability specifications, including those tests under DMPQ purview with acceptance criteria defined the same as in 3.2.P.5.1. *Specification* above met acceptance criteria.

**Reviewer Comment:** *Humacyte reports no out-of-specification (OOS) results for bacterial endotoxins or sterility at release for any of the PPQ batches. The acceptance criteria for the quality attributes under DMPQ purview did not change from the reported commercial acceptance criteria. This information appears acceptable.*

### 3.2.P.7 Container Closure System

The acellular tissue engineered vessel drug product is manufactured within a custom bioreactor bag that, after being aseptically sealed at the end of the manufacturing process, serves as the primary Container Closure System (CCS). The acellular tissue engineered vessel packaging consists of:

- The primary bioreactor containing the sterile acellular tissue engineered vessel drug product.
- Secondary packaging comprised of a plastic thermoform tray, which securely holds the primary packaging, sealed with a Tyvek lid.
- Outer moisture resistant, printed box, which holds the secondary packaging, onto which the product label is applied (which is the market package).

#### Primary Packaging

The 42cm acellular tissue engineered vessel primary packaging is composed of a clear, flexible, film bioreactor bags made of (b) (4) (b) (4) filled with (b) (4) with acellular tissue engineered vessel present. Segments of (b) (4) tubing (b) (4) and (b) (4) silicone tubing (b) (4) are attached to the end caps of the bioreactor bag and sealed with (b) (4)

There are two differences between the bioreactor system components that are used during the growth stage of acellular tissue engineered vessel manufacturing, and the final DP as supplied in the primary packaging:



- (b) (4)  
(b) (4) (b) (4) (b) (4)  
(b) (4)
- (b) (4)  
(b) (4) (b) (4) (b) (4)  
(b) (4)

The primary packaging components and material construction of the acellular tissue engineered vessel container closure system are summarized below.

Component	Material Construction	Specification
(b) (4)	(b) (4)	(b) (4)
End caps	(b) (4)	(b) (4)
Inner Silicone Tubing	Silicone	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Zip Ties	Plastic	Not Applicable; no product contact

### Secondary Packaging

The secondary package for the acellular tissue engineered vessel drug product consists of a thermoformed plastic tray in which the primary packaging is placed and sealed with a Tyvek lid. The secondary packaging is subject to (b) (4). Prior to tertiary packaging, a digital freeze indicator is attached to the plastic tray.

The components of the secondary package are summarized below.

Component	Description and Function
(b) (4) Tray	The thermoplastic tray is specifically designed to secure and protect the primary packaging
Tyvek	The Tyvek seal protects the primary package from contamination. It is (b) (4) permeable and allows for sterilization of the surfaces inside the secondary package including outer surfaces of the primary package and also provides a barrier against microbial ingress.
Freeze Indicator	The digital freeze indicator is secured to the outside of the thermoplastic tray and indicates whether or not the product has encountered freezing temperatures.

#### Outer Box

The secondary packaging is then placed within an (b) (4), (b) (4) (b) (4) carton box. The box protects the primary packaging and the thermoform tray and Tyvek lid from damage.

#### **Container Closure Integrity (CCI) Testing**

##### Primary Packaging

Container closure integrity testing for the primary packaging uses a (b) (4) test method to assess the container closure integrity of the primary packaging in accordance with (b) (4) and modelled after (b) (4). The package consisted of a (b) (4) Bioreactor package system fully occluded with a packaged silicone mandrel and surrounded by a 42cm predominantly collagen based acellular tissue engineered vessel in (b) (4).

To validate the CCI testing method, (b) (4)

(b) (4)

(b) (4)

(b) (4)

Two deviations were observed during the (b) (4) test period, one regarding the LOD and the other a bypassed testing of a master sample after the gross defect positive control. For both, the investigation by the firm determined there was no impact to the validation.

During the PAI inspection of Humacyte, the firm indicated a second CCIT method, (b) (4) method, was validated for the primary packaging and plans to implement this method for future CCIT testing.

In response to an IR (BLA 125812/0/48, received 26 June 2024), Humacyte confirms it plans to use the (b) (4) method as the validation demonstrated that the method is able to detect (b) (4) (b) (4) (b) (4) A summary of the method validation is provided below.

A new container integrity test, (b) (4) method, was developed, validated and implemented in December 2023. The method is in pursuant to (b) (4) The (b) (4) method for flexible bag systems works on the principle of (b) (4) that is detectable by visual inspection. The BDS is placed into a (b) (4)

(b) (4) (b) (4)

Method validation consisted of a total of (b) (4) test series: (b) (4)

(b) (4)

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(b) (4)

**Reviewer's Comment:** The applicant performed CCIT of the primary packing using (b) (4) test method. The results of all negative controls passed and all positive controls samples (b) (4) (b) (4) were able to be detected. The firm determined sensitivity of the CCIT method to be (b) (4) defect size. In addition, CCIT of the secondary packaging was performed using the (b) (4) (b) (4) test methods. All results met the established acceptance criteria for the respective test methods. The container closure system and tests appear acceptable.

CCIT was also reviewed during the PLI of Humacyte. The method validation of the CCIT method (b) (4) Method) for the primary packaging was reviewed. No objectionable findings were noted.

### 3.2.P.8 Stability

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

The stability tests under DMPQ purview include CCIT (b) (4) of the primary packaging, bacterial endotoxins (b) (4) and sterility (b) (4). The acceptance criteria for commercial stability are as follows:

- Endotoxin: (b) (4)
- Sterility: No growth
- CCIT (b) (4) method): Pass (integral)

The applicant committed to submit CCIT, sterility and endotoxin long-term stability data annually through the end of shelf life for (b) (4) batch at (b) (4) storage conditions 2-8°C (b) (4)

(b) (4) Data provided (up to (b) (4) months) for stability for the quality attributes under DMPQ purview meet the established commercial stability specification, described above.

### 3.2.A APPENDICES

The following table includes a full listing of all facilities associated with the manufacturing and testing of acellular tissue engineered vessels.

Facility & Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	CMO	Comments
<b>Facility:</b> HUMACYTE INC 2525 E. Highway Nc 54 Durham NC 27713-2201 <b>FEI:</b> 3014294024 <b>DUNS:</b> 557190449 Drug Product (DP) manufacturing, quality control testing, packaging, labeling, and distribution, DP stability storage, WCB storage	Inspection	Yes	Yes	No	CBER/DMPQ PLI April 2024 VAI
(b) (4)	Waiver	Yes	Yes	Yes	ORA/OBPO Surveillance (b) (4) NAI
	Waiver	Yes	Yes	Yes	ORA/OPQO Surveillance (b) (4) NAI
	Not required	No	Yes	Yes	N/A
	Not required	No	Yes	Yes	N/A

(b) (4)

### 3.2.A.1 Facilities and Equipment: Humacyte Global, Inc. (Humacyte), Durham, North Carolina - Acellular tissue engineered vessel Manufacturing

#### Overview

Humacyte's manufacturing facility in Durham, NC is a (b) (4) facility that contains commercial and clinical manufacturing, quality control, research and development, and administrative functions. The manufacturing space is approximately (b) (4) and is located on the (b) (4). The facility has controlled badge access system to restrict access.

The acellular tissue engineered vessel manufacturing process is operated as (b) (4) (b) (4) (b) (4) acellular tissue engineered vessels from a WCB. All manufacturing operations are performed in controlled classified processing areas. A summary of the room classifications for each operation is provided below:

(b) (4)

The (b) (4) area located on the (b) (4) is utilized for (b) (4) (b) (4) Equipment in the (b) (4) area includes (b) (4)

The (b) (4) area located on the (b) (4) contains the (b) (4) (b) (4)

The (b) (4) areas are located on the (b) (4) and are utilized for MVI, secondary packaging, (b) (4) Equipment in this area includes inspection stations, tray sealer for secondary packaging, and (b) (4) equipment. There are no product contact materials utilized in this area.

Finally, the packaging area located on the (b) (4) is used for final packaging into the outer paperboard box and shipping pack out. The area only contains a refrigerator unit and there are no product contact materials.

#### Other Products Manufactured in Facility

Per Humacyte, no other products are currently or previously manufactured in this facility.

### **Manufacturing Flows**

#### *Personnel Flow and Gowning*

Personnel access to production areas is regulated by electronic access. Only trained personnel have unaccompanied access. All personnel airlocks (PAL) are (b) (4) Gowning requirements are in place for all production rooms. Additional gowning and training in aseptic gowning is required for all (b) (4) areas. Additionally, work within the biosafety cabinets requires additional gowning and training, including aseptic operator qualification. Personnel flow through production areas on the (b) (4) is (b) (4) and (b) (4) on the (b) (4)

#### *Material Flow*

Materials used include chemicals, media, master and working cell banks and single-use consumables. Entry and exit is via (b) (4) There is (b) (4) movement of material within all major production areas.

#### *Product Flow*

Product flow through production areas on the (b) (4) (b) (4)

#### *Waste Flow*

Waste flow is (b) (4) in all areas of facility.

(b) (4)

(b) (4)



(b) (4)

**Reviewer Comment:** The facility flows described and illustrated for movement of waste, product, personnel, and materials appear to be appropriate. All manufacturing areas are access controlled and gowning is progressive. Waste and incoming materials appear to take separate paths. (b) (4) is implemented for all paths in production areas. The information appears acceptable.

The manufacturing flows and waste decontamination stations were reviewed during the PLI of Humacyte and found to be acceptable.

### Contamination/ Cross-Contamination Controls

In the original submission, the firm did not describe measures in place to prevent contamination and cross-contamination. An IR was sent to Humacyte on 23 January 2024, and in their response to the IR (STN 125812/0/8), the firm provided a description of cross-contamination procedures.

Per the firm, acellular tissue engineered vessel is the only product manufactured in the Humacyte facility in Durham, NC. No other products utilize the same cGMP manufacturing areas or equipment, and therefore cross-contamination between products is not a concern. However, there are a mix of facility design and procedural controls in place to prevent cross-contamination between acellular tissue engineered vessel batches.

Humacyte facility has a maximum capacity of (b) (4) acellular tissue engineered vessel manufacturing batches. Prior to operations in the manufacturing area, area clearance is performed per internal procedures. This includes cleaning of equipment and work areas/stations. Quality Assurance sign-off and approval before operations can be performed in the area.

Manufacturing areas are designed to support concurrent manufacturing of acellular tissue engineered vessels batches. The (b) (4) bioprocessing areas have designated workstations and equipment in each area to provide batch segregation.

For closed processes in (b) (4) (b) (4) All operations in the (b) (4) and (b) (4) areas utilize (b) (4) (b) (4) materials for all product contact materials. Additionally, all operations performed in these areas are (b) (4) processes utilizing (b) (4) (b) (4) for all connections. For (b) (4) aseptic operations in (b) (4) BSCs, only (b) (4) batch can be processed at a time. Prior to operations with another batch in the cell culture room, cleaning of the BSC is required. All materials used in the (b) (4) Room are (b) (4) use materials.

The manufacturing areas are served by (b) (4)  
(b) (4)

**Reviewer Comment:** Cross-contamination controls are designed to minimize contamination from multiple sources including people, product, equipment, waste, and environment. EM is performed in all classified areas, and action limits appear acceptable (see EM section). The information provided appears acceptable.

### Heating, Ventilation, and Air Conditioning (HVAC) Systems

The Humacyte facility has (b) (4) The supply air for (b) (4) and (b) (4) is combined into a single supply header that supplies the manufacturing areas. (b) (4) supplies air to the warehouse spaces, labs, mechanical spaces, and offices. (b) (4) supplies air to general office space. (b) (4) rooms are independently contained and do not receive supply air from (b) (4) (b) (4) Performance of the air handling systems is controlled by the building automation system (BAS) with local monitoring and alarming.

The classified areas within the manufacturing areas are served by (b) (4) and (b) (4)  
(b) (4)

Air change rates for manufacturing areas are dependent on the classification of the room. Air change rates must be (b) (4)

### HVAC Qualification

The HVAC system performance has been established to maintain controlled environmental conditions through qualification of classified manufacturing areas. As part of the operational qualification (OQ), (b) (4)

were performed. All OQs were successfully completed.

(b) (4)

**Reviewer's Comment:** *The HVAC system has been validated and maintains (b) (4) and (b) (4) manufacturing areas. Manufacturing areas in (b) (4) floors have dedicated air handling units. The HVAC controls and segregation for each suite appears acceptable. EMPQ met acceptance criteria and support the action limits for routine monitoring and found to be acceptable. The deviations observed during the qualification tests were reviewed and found to be acceptable.*

*HVAC and EMPQ were also reviewed during the PLI of Humacyte, and no objectionable findings were noted.*

*A recommendation was sent to the firm to use (b) (4) designations for area classifications in the future as their current use of Grade (b) (4) and Grade (b) (4) does not align with the (b) (4) guidance.*

### **Environmental Monitoring**

Humacyte states that the EM program encompasses routine static and dynamic monitoring of cleanroom spaces performed by QC personnel and additional dynamic monitoring performed by Bioprocessing personnel during open aseptic processing within Grade (b) (4) BSCs and monitoring of the compressed gas systems. Per the firm, the EM requirements for sample location, sample frequency, test methods and specifications for the classification of clean rooms and critical areas were determined using a risk-based approach consistent with (b) (4) and guidance in accordance with (b) (4) FDA Guidance for Aseptic Processing, (b) (4) and (b) (4)

The EM room/system classifications, sample locations, sampling procedures, frequencies, test methods and specifications for viable and nonviable air, surface and personnel monitoring are based on the EMPQ and are defined in EM procedures.

(b) (4)

(b) (4)

**Reviewer's Comment:** EM is performed in all classified areas, and action levels appear acceptable. Humacyte refers to classified areas as Grade <sup>(b) (4)</sup> and Grade <sup>(b) (4)</sup> but the particulate monitoring for these areas is performed to meet <sup>(b) (4)</sup> and <sup>(b) (4)</sup> under dynamic conditions, respectively. This is in consistent with <sup>(b) (4)</sup> <sup>(b) (4)</sup> Classification. A recommendation was sent to Humacyte to use <sup>(b) (4)</sup>

*designations for area classifications to avoid confusion for future inspections and submissions.*

*The routine EM for the facility was reviewed during the PLI at Humacyte and found to be acceptable.*

*The (b) (4) CCR acceptance criteria established by Humacyte is higher than that recommended in (b) (4). Considering that the (b) (4) areas are used for closed processes and the trending of EM data reviewed during the PLI indicate that the (b) (4) CCR in the facility are well below the acceptance criteria, the (b) (4) CCR is being deemed acceptable. Additionally, it was noted during the PLI that a Change Control is being implemented to reclassify the Grade (b) (4) (CNC) areas to (b) (4). An inspectional follow up is recommended for the assessment of EM trending data and the CCR of the (existing and new) (b) (4) areas at Humacyte.*

### **Equipment**

A list of the major equipment used in acellular tissue engineered vessel manufacturing process is summarized below.

Process Area	Equipment Type	Manufacturer	Equipment Number
(b) (4)	(b) (4)	(b) (4)	(b) (4)

(b) (4)	(b) (4)
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### **Equipment Qualification**

Humacyte states that all equipment is qualified before use. Equipment requalification is performed as required per internal site procedures. All major process equipment/ process systems were qualified by their respective performance qualifications.

Validation maintenance is defined in SOPs for each equipment. Humacyte provided the Installation and Operational Qualification (IOQ) reports for all major equipment listed above. The qualification of all major equipment used in acellular tissue engineered vessel manufacturing were reviewed during the PLI of Humacyte and were found to be acceptable. A brief description of the (b) (4) qualification is provided below.

(b) (4)

#### Biosafety Cabinets

Biosafety cabinets are used to maintain aseptic conditions during (b) (4) processing. BSCs are certified every (b) (4) months; testing includes (b) (4) (b) (4)

**Reviewer's Comments:** All equipment in manufacturing suites were qualified and supported by the PPQ. Equipment qualification reports were provided. All predefined acceptance criteria were met for the qualification of each equipment. The performance qualification of equipment is representative of the acellular tissue engineered vessel manufacturing process. The information appears acceptable.

Additionally, during the PLI of Humacyte, initial qualification and most recent requalification of all major equipment, including the (b) (4) and BSCs were reviewed. Major deviations were reviewed and found to be handled appropriately. There were no objectionable findings noted.

#### Equipment Cleaning

All steps in the acellular tissue engineered vessel manufacturing process utilize (b) (4) (b) (4) consumables for product contact. There is no product-contact fixed equipment used in the manufacturing process. Therefore, per the firm, equipment cleaning validation and sterilization validation is not required.

Exterior equipment surfaces are routinely cleaned with disinfectant on a periodic basis per approved procedures. Systems with large internal surface area including the BSCs, incubators, and (b) (4) are cleaned regularly with a (b) (4) (b) (4) per approved procedures. Additionally, all equipment utilized in the manufacturing process are cleaned with (b) (4) (b) (4)

**Reviewer's Comments:** *There is no cleaning validation as all product contact equipment are (b) (4) (b) (4) consumables. Routine cleaning of exterior of fixed equipment is performed. This cleaning process was reviewed during PLI for all major equipment and appear to be appropriate. Additional information regarding the equipment cleaning can be referenced in the EIR.*

### Facility Cleaning

The firm states that the cleaning of the controlled areas is governed by approved procedures which specifies cleaning frequency, type, agents, contact times and order of room cleaning. The table below provides a summary of the frequency, cleaning type, and agent used in the facility.

Area Classification	Frequency	Cleaning Description	Cleaning Agent
(b) (4)			

The cleaning agents and microbial disinfectants are provided in a ready to use format. In addition, EM trends are used to evaluate cleaning effectiveness and disinfectant efficacy studies continue in response to findings in EM trends.

#### *Disinfectant effectiveness studies*

In IR STN 125812/0/34 (received 23 May 2024), Humacyte indicated that disinfectant efficacy studies were performed on the disinfectant agents by a qualified supplier using



(b) (4) microbial strains recommended by (b) (4) The efficacy of chemical agents was determined at the dilution for use and the selected contact times that have been implemented for the routine cleaning and disinfection of the facility.

The following (b) (4) microbial strains, types of surfaces and disinfectants were used in the disinfectant efficacy studies:

Disinfectant	Surface	Contact Time	Organisms
(b) (4)			

(b) (4)			
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(b) (4)

**Reviewer Comments:** *The firm performed disinfectant efficacy studies for all disinfectants used in the facility. The surfaces tested are representative of surfaces in the facility and identified disinfectant effectiveness for each surface. For each disinfectant, the predefined acceptance criteria were met. The validation of disinfectants appears acceptable. The frequency of cleaning appears appropriate.*

*Disinfectant efficacy studies were reviewed during the PLI of Humacyte. No objectionable findings were noted.*

#### Utilities

The utilities used at the Humacyte facility includes liquid and (b) (4)  
(b) (4) The only clean product  
contact utilities used during manufacturing (b) (4)  
All buffers, reagents, and media used in the process are purchased (b) (4) in  
(b) (4) system used to support manufacturing.

(b) (4)

(b) (4)

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(b) (4)

**Reviewer's Comment:** (b) (4)

systems were provided. The information provided appears acceptable.

*All site utilities were reviewed during the PLI of Humacyte. No objectionable findings were noted.*

## **Computer Systems**

### *Automation and Control Systems*

Humacyte facility is equipped with several automation and control systems.

- Building Automation System (BAS) – (b) (4)
- Process Automation System (PAS) – (b) (4)
- (b) (4)
- Data Historian System – (b) (4)
- Data Reporting System – (b) (4)

The BAS is a control and monitoring system for the facility systems and equipment. This includes building HVAC (airflow, valve positions, temperature, humidity, and pressure), site security (door status and interlocks), life safety monitoring (fire alarms, O<sub>2</sub>/H<sub>2</sub>O<sub>2</sub> levels), and controlled temperature unit monitoring (b) (4)

(b) (4) A (b) (4) is utilized to interface with the monitoring and control of all these systems and controllers.

The PAS is comprised of several individual manufacturing equipment and facility utilities, that are more directly involved in the manufacturing process. These systems include (b) (4)

These equipment and utilities are connected, monitored, and controlled through the distributed control system (b) (4) and a Process Control System that allows access and data flow in the controlled network.

A (b) (4) provides logging for the data generated from the BAS and PAS systems. Additionally, a Data Reporting System, (b) (4), is utilized that pulls from (b) (4) as well as the BAS and PAS.

The firm stated that an Automation Master Plan is in effect that outlines the requirements for establishment and validation of automation systems for the facility and manufacturing systems.

### *Computerized Systems*

The main computerized systems used to support manufacturing operations at Humacyte facility include:

- (b) (4) - QC sample tracking and associated data management
- (b) (4) Quality Management Software system - quality record management, including document management, training, and change control.
- (b) (4) Process data management
- (b) (4) Warehouse management system
- (b) (4) Calibration Management Software – calibration management, including periodic maintenance and workorders.

All computerized systems are qualified and maintained in a validated state.

**Reviewer's Comment:** *Computer systems are qualified and maintained in a validated state. The information provided appears acceptable.*

*Computer systems were reviewed during the PLI of Humacyte. No objectionable findings were noted.*