

**CBER CMC BLA Review Memorandum**

**BLA STN 125812**

**Product Name: SYMVESS [acellular tissue engineered vessel- tyod]**

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**1. BLA#: STN 125812****2. APPLICANT NAME AND LICENSE NUMBER**

Humacyte Global Inc. (i.e., Humacyte in the rest of the document)

License Number: 2336 (pending)

**3. PRODUCT NAME/PRODUCT TYPE**

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

Proprietary Name: SYMVESS

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

- a. Pharmacological category: acellular tissue engineered vessel
- b. Dosage form: SYMVESS has an internal diameter of 6 mm and is approximately 42 cm in length (approximately 40 cm of usable length).
- c. Strength/Potency: the length of SYMVESS will vary depending on the clinical need.
- d. Route of administration: surgical implantation.
- e. Indication(s): SYMVESS is a tissue engineered human acellular vessel indicated for urgent arterial repair following extremity vascular trauma when synthetic graft is not indicated and when autologous vein is not feasible.

**5. MAJOR MILESTONES**

Original Submission	December 11, 2023
Application Filed	February 9, 2024
Mid-Cycle Communication	March 28, 2024
Late-Cycle Communication	May 20, 2024
Advisory Committee Meeting	Not Held
Inspections	Pre-License Inspection (PLI): April 1-5, 2024
PDUFA Action Date	August 10, 2024

**6. CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Jin Sung Hong (JH), CBER/OTP/OCTHT/DCT2/TEB1	3.2.S Drug Substance 3.2.P Drug Product 3.2.A Appendix
Wen Seeto (WS), CBER/OTP/OCTHT/DCT2/TEB2	3.2.P.2.4 Container Closure System 3.2.P.3.2 Batch Formula 3.2.P.7 Container Closure System
Pratima Labroo (PL), CBER/OTP/OCTHT/DCT2/TEB1	3.2.P.3.2 Batch Formula 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures 3.2.A.2 Adventitious Agents Safety Evaluation

Andrey Sarafanov (AS), CBER/OTP/OPPT/DH/HB2	3.2.P.2.4 Container Closure System 3.2.P.2.6 Compatibility 3.2.P.7 Container Closure System
Hanh Khuu (HK), CBER/OTP/DHT/HTRS	3.2.P.3.2 Batch Formula 3.2.A.2 Adventitious Agents Safety Evaluation

**7. INTER-CENTER CONSULTS REQUESTED**

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

**8. SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
12/11/2023	125812/0	BLA submission
01/12/2024	125812/0.1 (response to IR#1)	Response to DMPQ IR regarding establishments
01/23/2024	125812/0.2 (response to IR#2)	Response to CMC IR#1 sent on 01/18/2024 on manufacturing process, batch records, (b) (4) assay, and assay validation
1/26/2024	125812/0.3 (response to IR#4)	Response to CMC IR#2 sent on 01/24/2024 on drug substance section and certificate of analysis (CoA) of reagents
01/31/2024	125812/0.7 (response to IR#5)	Response to BIMO IR#1 sent on 01/26/2024 on study manual and IMP handling
01/23/2024	125812/0.8 (response to IR#3)	Response to DMPQ IR#2 sent on 01/23/2024 on manufacturing, facilities, and equipment
02/07/2024	125812/0.9 (response to IR#7)	Response to PT IR#1 sent on 02/02/2024 on manufacturing, facilities, and equipment
02/07/2024	125812/0.10 (response to IR#6)	Response to CMC IR#3 sent on 02/02/2024 on in- process testing methods, batch release, and visual inspection validations
02/22/2024	125812/0.11 (response to IR#8)	Response to DBSQC IR#1 sent on 02/08/2024 on sterility, endotoxin, and (b) (4) testing
02/23/2024	125812/0.12 (response to IR#9)	Response to CMC IR#4 sent on 02/12/2024 on visual inspection, QC testing, manufactured batches, potency testing, and donor testing
03/01/2024	125812/0.13 (response to IR#10)	Response to CMC IR#5 sent on 02/09/2024 on lot release protocol template
03/18/2024	125812/0.14 (response to IR#11)	Response to CMC IR#6 sent on 03/05/2024 on (b) (4) system, supplier testing, stability, PPQ, process validation etc.
03/25/2024	125812/0.15 (response to IR#12)	Response to DBSQC IR#2 sent on 03/11/2024 on (b) (4) content assay
04/03/2024	125812/0.16 (response to IR#16)	Response to Clinical IR#2 sent on 04/01/2024 on humanitarian use
04/08/2024	125812/0.17 (response to IR#18)	Response to DHT IR#1 sent on 04/04/2024 on donor medical history, donor testing etc.

04/15/2024	125812/0.19 (response to IR#15)	Response to DBSQC IR#3 sent on 04/01/2024 on (b) (4)
04/15/2024	125812/0.20 (response to IR#13)	Response to Clinical IR#1 sent on 03/25/2024 on efficacy report, extremity set etc.
04/18/2024	125812/0.21 (response to IR#14)	Response to CMC IR#7 sent on 03/28/2024 on cell bank testing, identity testing, release criteria, bioreactor bag etc.
04/30/2024	125812/0.24 (response to IR#17)	Response to DBSQC IR#4 sent on 04/03/2024 on method validation
04/30/2024	125812/0.25 (response to IR#19)	Response to CMC IR#8 sent on 04/19/2024 on USP labeling section 2.2. and PLR formatting
05/01/2024	125812/0.26	Response to 483 Observations
05/10/2024	125812/0.27	Response to Mid-Cycle Meeting discussion on extractables and leachables
05/07/2024	125812/0.28 (response to IR#17)	Response to DBSQC IR#5 sent on 04/26/2024 on method validation
05/10/2024	125812/0.29 (response to IR#22)	Response to CMC IR#10 sent on 05/03/2024 on biological proper name
05/10/2024	125812/0.30 (response to IR#21)	Response to CMC IR#9 sent on 04/26/2024 on E&L, BDS, excipient suitability etc.
05/22/2024	125812/0.33 (response to IR#23)	Response to DBSQC IR#6 sent on 05/08/2024 on LRP template
05/23/2024	125812/0.34 (response to IR#24)	Response to DMPQ IR#3 sent on 05/09/2024 on AQL inspection, air/gas qualification etc.
05/24/2024	125812/0.36 (response to IR#25)	Response to Clinical IR#3 sent on 05/17/2024 on patient update, imaging compliance etc.
05/31/2024	125812/0.37 (response to IR#26)	Response to CMC IR#11 sent on 05/17/2024 on identity testing, FMEA study, DNA testing etc.
06/07/2024	125812/0.39 (response to IR#21)	Response to CMC IR#9 and CMC IR#11 regarding a full summary report of extractables information
6/20/2024	125812/0.43 (response to IR#29)	Response to CMC IR#12 regarding study plan for excipient suitability and shipping validation, LoA, and post-approval stability study.
6/21/2024	125812/0.44 (response to IR#14)	Response to CMC IR#7 regarding the in-use stability study
6/21/2024	125812/0.45 (response to IR#21)	Response to CMC IR#9 and CMC IR#11 regarding a full summary report of extractables information
6/24/2024	125812/0.46 (response to IR#21)	Follow-up response to bioreactor disposable set sterilization validation
6/25/2024	125812/0.47 (response to IR#28)	Response to revision in lot release protocol template
6/26/2024	125812/0.48	Response to DMPQ question on CCIT
6/27/2024	125812/0.49	Response to DMPQ question on APS
6/27/2024	125812/0.50 (response to IR#21)	Response to CMC IR#9 sent on 04/26/2024 with shipping validation study results
7/2/2024	125812/0.52 (response to IR#33)	Response to DMPQ IR#6 sent on 06/24/2024 on EM process qualification
7/11/2024	125812/0.54	Follow-up on teleconference held on 06/20/2024 and update on PRO-0106-01
7/17/2024	125812/0.55	Response to CMC PMC (CMC IR#13) and Clinical PMR/PMCs (Clinical IR#5) sent on 07/12/2024
7/24/2024	125812/0.57	Response to labeling negotiation
7/26/2024	125812/0.60 (response to IR#39)	Response to CMC IR#14 sent on 07/24/2024 on validation of potency assay

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
(b) (4)				
IND 16746 (Active)	Humacyte	HAV for Vascular Trauma and Peripheral Arterial Disease	N/A	CMC information reviewed and documented in the memo by Zehra Tosun.
(b) (4)				

**10. REVIEWER SUMMARY AND RECOMMENDATION**

**A. EXECUTIVE SUMMARY**

Product Description: SYMVESS is an acellular tissue engineered vessel that is 42 cm in length and 6 mm in diameter. It is composed of extracellular matrix proteins which are mostly collagen that are generated from allogeneic smooth muscle cells

(b) (4) SYMVESS has mechanical properties to withstand the forces associated with the arterial blood flow and suture during the implantation process and can allow cell binding and proliferation. SYMVESS is manufactured using a

tissue engineering process. Human allogeneic vascular smooth muscle cells that are derived from human aortic tissue deemed suitable for transplant are banked, expanded, and seeded onto a tubular mesh scaffold. The cell-seeded scaffold is cultured in a biomimetic bioreactor system to generate an intermediate tubular construct containing vascular smooth muscle cells and the extracellular matrix the cells deposited. A decellularization process during the final stage of manufacturing removes the human cellular and genetic material while maintaining the extracellular matrix structure, mechanical properties, and biological activity. The product has 18 months of shelf-life under 2-8°C. SYMVESS is packaged in a single unit.

Regulatory History: SYMVESS was originally submitted as human acellular vessel (HAV) in Humacyte's Investigational New Drug application (IND) 16746, first submitted to CBER on July 26, 2016. Humacyte was granted a Regenerative Medicine Advanced Therapy (RMAT) designation for the HAV by the FDA to create or establish vascular access for hemodialysis on March 15, 2017. On May 2, 2023, RMAT designation was also granted for HAV for (b) (4) repair following extremity vascular trauma when (b) (4) when autologous vein is not feasible." A Biological License Application (BLA) for HAV was submitted to CBER on December 11, 2023. The BLA was filed on February 8, 2024 with a Priority Review designation and an FDA decision goal date of August 10, 2024.

Manufacturing Assessment Summary: Manufacturing control strategies include testing and characterization of the (b) (4) (b) (4) process performance qualification (PPQ) studies, in-process testing (b) (4) (b) (4) and final drug product testing (sterility, endotoxin, (b) (4) The final product tests and release criteria are acceptable and are sufficient to meet regulatory requirements for identity, purity, and potency. Stability studies (conventional and accelerated conditions) are appropriate and support product expiration date. The process is well controlled and has demonstrated ability to produce drug product of acceptable quality.

Consult Reviews: No inter-center consults were needed but intra-center consults were requested for the primary container closure (assessment on extractables and leachables) and donor eligibility requirement. Both consult assessments support licensure of the drug product.

Review Issues:

The following CMC concerns were raised during the review of this submission and were resolved through information requests:

1. Insufficient justification for sampling strategy of drug product testing.
2. Insufficient justification for rejecting manufacture isolates and cosmetic defects after manual visual inspection.

3. Insufficient justification for changes after process performance qualification run.
4. Insufficient information to support qualification of (b) (4) systems.
5. Insufficient information to support validation of sterilization process.
6. Insufficient information on extractables and leachables on the container closure.
7. Insufficient information on MCB and WCB manufacturing control.

The following CMC concerns were raised during review of this submission that require PMC studies:

1. A shipping validation study to evaluate relevant critical quality attributes of SYMVESS following shipment in (b) (4) shipping conditions.
2. A risk assessment of environmental isolates and perform necessary sterility method qualification using in-house environmental isolates.
3. A sterilization validation study of bioreactor disposable set.
4. An excipient sample suitability study for the sterility assay by conducting a (b) (4) study with an anerobic organism.
5. Leachables study for two specific compounds and additional method validation report (if found required).
6. A feasibility study for sterility assurance of the (b) (4) and implementation of a validated sterility assurance strategy.
7. An establishment of upper limits for the (b) (4) and (b) (4) acceptance criteria for final product release testing based on a total of (b) (4) SYMVESS batches.

7 CMC PMC items were communicated to the Applicant on July 12, 2024 and the Applicant agreed to all on July 17, 2024 (BLA 125812/0.55).

Conclusion: The BLA submission review and pre-license inspection confirmed that the product and manufacturing processes are well controlled and capable of producing a consistent drug product of acceptable quality that satisfies FDA requirements for identity, purity, and potency. The BLA can be approved under the condition that the Applicant commits to perform the PMCs discussed above.

## **B. RECOMMENDATION**

### **I. APPROVAL**

- a. Approval Letter:  
Humacyte, Inc.  
2525 E Highway 54  
Durham, NC 27713, USA

- b. PMC:

PMC #1: Humacyte commits to conduct a shipping validation study to evaluate relevant critical quality attributes of SYMVESS following

shipment in (b) (4) shipping conditions. Humacyte will submit the final study report by February 28, 2025.

Final Report Submission: February 28, 2025

PMC #2: Humacyte commits to conduct a risk assessment of environmental isolates and perform necessary sterility method qualification using in-house environmental isolates. Humacyte will submit the final study report, which includes a risk assessment and results of any method qualification studies, by August 31, 2024.

Final Report Submission: August 31, 2024

PMC #3: Humacyte commits to perform sterilization validation of the commercial bioreactor disposable set and provide the final report, including the 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) s (b) (4) every (b) (4) months until this post-marketing commitment is fulfilled. Humacyte will submit the final study report by September 30, 2024.

Final Report Submission: September 30, 2024

PMC #4:

Humacyte commits to perform an excipient sample suitability study for the sterility assay by conducting a (b) (4) study with an anerobic organism and submit the final study report by August 31, 2024.

Final Report Submission: August 31, 2024

PMC #5: Humacyte commits to submit ≥18-month leachable study data targeting (b) (4) specific compounds (b) (4) - (b) (4) identified in additional extractables assessment requested by FDA, and additional method validation report (if found required) by December 31, 2024.

Final Report Submission: December 31, 2024

PMC #6: Humacyte commits to implement a validated sterility assurance strategy on the (b) (4) based on the proposed feasibility study for a sterile filtration procedure in (b) (4) (b) (4) and submit the study report as a Prior Approval Supplement by November 30, 2024.

Prior Approval Supplement Submission: November 30, 2024.



PMC #7: Humacyte commits to establish upper limits for the (b) (4) acceptance criteria used for final product release testing. The upper limits will be established based on data from a total of (b) (4) SYMVESS batches. Humaycte will provide a justification for the updated acceptance release criteria based on the collected information (i.e., data from (b) (4) SYMVESS batches) and submit a study report as a Prior Approval Supplement by September 30, 2025.

Prior Approval Supplement Submission: September 30, 2025

## II. COMPLETE RESPONSE (CR)

The BLA will not be subject to CR

## III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Jin Sung Hong, PhD, CMC Reviewer CBER/OTP/OCTHT/DCT2/TEB1	Concurred	
Wen Seeto, PhD, CMC Reviewer CBER/OTP/OCTHT/DCT2/TEB2	Concurred	
Pratima Labroo, PhD, CMC Reviewer CBER/OTP/OCTHT/DCT2/TEB1	Concurred	
Andrey Sarafanov, PhD CMC Consult Reviewer CBER/OTP/OPPT/DH/HB2	Concurred	
Hanh Khuu, MD CMC Consult Reviewer CBER/OTP/DHT/HTRS	Concurred	
Laura Ricles, PhD Division Director, CBER/OTP/OCTHT/DCT2	Concurred	
Heather Lombardi, PhD Office Director CBER/OTP/OCTHT	Concurred	

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**INTRODUCTION**

SYMVESS is an acellular tissue engineered vessel intended to treat urgent arterial repair following extremity vascular trauma (b) (4) when autologous vein is not feasible.

The Applicant is Humacyte Global Inc. who has (b) (4) ((b) (4) IND 16746) with the Agency (in CBER/Office of Therapeutic Products) regarding this product for different indications. Clinical studies of the human acellular vessel (HAV; initial name for SYMVESS) began in 2012 with enrollment of the first subject in CLN PROV001, which is a study examining the use of SYMVESS to provide hemodialysis access (b) (4). Two Phase III trials are currently being conducted: CLN-PRO-V006 comparing the SYMVESS with synthetic PTFE grafts, and CLN-PRO-V007 comparing the SYMVESS with autologous arteriovenous fistula. In parallel with the dialysis access indication, Humacyte has been developing the SYMVESS for additional uses including peripheral arterial disease (PAD) (IND 16746 and (b) (4) CLN-PRO-V002 and CLN-PRO-004) and vascular trauma (IND 16746; CLN-PRO-V005). This BLA was submitted for the indication of extremity vascular trauma. The product was granted RMAT designation for vascular trauma indication on May 2, 2023 and the current BLA was reviewed with priority review timeline. Information and previous communications in IND (b) (4) and IND 16746 have been cross-referenced in this BLA submission.

Before the BLA submission, the Applicant and the Agency had several communications including pre-BLA meeting (Type B, CRMTS# 14326; November 23, 2022) and the official response from CBER Director (August 11, 2023) to discuss the content and format of submission for the BLA. In the official response, CBER agreed that clinical efficacy data obtained from CLN-PRO-V005 study combined with the Ukrainian treatment experience in Study CLN-PRO-V017, totaling 50 patients with Day 30 patency data, will be sufficient to support a request for traditional approval of a BLA for the proposed indication along with all the safety data relevant to this indication.

There are two clinical studies in this BLA submission supporting the proposed indication as below:

- 1) CLN-PRO-V005 (under IND 16746): Phase 2/3 study to evaluate the safety and efficacy of the HAV for vascular replacement or reconstruction in patients with life- or limb-threatening vascular trauma.
- 2) CLN-PRO-V017: An Observational Multicenter Study to evaluate the safety and efficacy of HAV in a real world setting for arterial replacement or reconstruction in Ukrainian patients with life or limb-threatening vascular trauma.

**PRODUCT DEVELOPMENT NARRATIVE**

The drug product, SYMVESS, is composed of extracellular matrix (ECM) that possesses material properties to sustain mechanical stress and biological activity such as cell binding and proliferation. The size of SYMVESS is 6 mm in diameter and approximately 42 cm in length. It is supplied on a silicone mandrel immersed in (b) (4) Phosphate Buffered Saline (b) (4) in a sealed and labeled container. At the

surgical site, the length of SYMVESS is customized to the need and is sutured to treat arterial repair.

The development of SYMVESS evolved from (b) (4)

[REDACTED]

PRO-V005 and CLIN-PRO-V017, SYMVESS manufactured from (b) (4) systems were used to support this BLA.

### COMMERCIAL MANUFACTURING SUMMARY

(b) (4)

[REDACTED]

The manufacturing facility is at 2525 E Highway 54 Durham, NC 27713, USA. The pre-license inspection was performed during April 1-5, 2024. Previously, the Agency (OTAT/DCGT and OCBQ/DMPQ) also conducted an RMAT informational site visit during March 25-29, 2019.

### MODULE 3 ORGANIZATION

#### 3.2.S DRUG SUBSTANCE

3.2.S Drug Substance section is not submitted. The Applicant indicated that because SYMVESS is manufactured within its final primary packaging using a proprietary process that contains no product intermediate or Drug Substance, they only submitted information in the Drug Product section but not in Drug Substance section.

(b) (4)

[REDACTED]



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

### 3.2.P DRUG PRODUCT

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

SYMVESS is an acellular tissue engineered vessel composed of organized ECM proteins with approximately 6 mm in inner diameter and 42 cm in length with mean vessel wall thickness (b) (4). The length of SYMVESS to be implanted is dependent on the surgical needs which is determined by the surgeon in the operating room. SYMVESS is manufactured within a custom bioreactor bag which is also its primary packaging. SYMVESS is immersed in (b) (4) within the primary packaging prior to implantation. (b) (4)

(b) (4) In the operating room, SYMVESS is removed from the package after draining the (b) (4) and is slid off from the inner silicone tubing before anastomosis. Only SYMVESS is implanted.

##### 3.2.P.1.1 Nomenclature

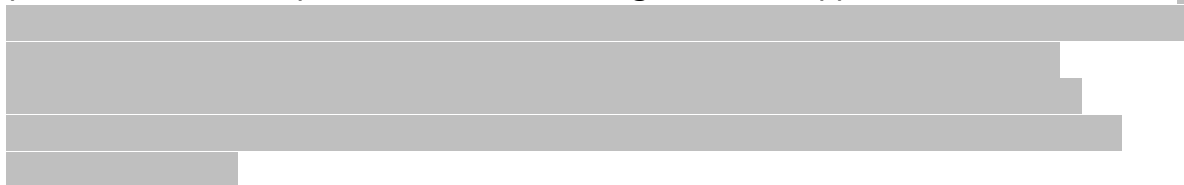
The product is a tissue engineered vessel replacement conduit. As such it does not have a USAN name. The proprietary name is “SYMVESS” and the proper name is “acellular tissue engineered vessel-tyod”.

*Reviewer Comment: The Applicant submitted Section 1.18.1 Proprietary Name Review Request and Section 1.18.2 Biological Proper Name for Agency’s review. Upon review of the proprietary name (Section 1.18.1), SYMVESS was accepted on March 1, 2024. Please refer to APLB’s memo dated February 27, 2024 for further information.*

*Tissue engineered products are excluded from USAN naming schemes for cell-based products. Thus, the Applicant proposed to FDA two options for a proper name, which were “human acellular vessel (HAV)” and “bioengineered human vasculature conduit”. However, Product Office designated a proper name “acellular tissue engineered vessel” based on the nature of the product. In BLA 125812/0.29 received on May 10, 2024, Humacyte agreed on the FDA-designated proper name and proposed options for a suffix for FDA consideration. APBL accepted the suffix, “-tyod”. Please refer to APLB’s memo dated May 21, 2024 for further information.*

##### 3.2.P.1.2 Structure

SYMVESS is an acellular tissue engineered vessel which is used for cell adhesion and proliferation once implanted. As shown in **Figure 1**, the Applicant believes that the (b) (4)



**Figure 1 – SYMVESS Segment Explanted from a Patient After 200 Weeks**

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

(b) (4)

### 3.2.P.1.3 General Properties and Other Characteristics

The general properties of the SYMVESS are characterized via mechanical testing

(b) (4)

(b) (4) content, potency assays (b) (4)

(b) (4)

*Reviewer Comment:* (b) (4) testing, (b) (4)

(b) (4) and potency assays are included in SYMVESS quality control (QC) testing.

### 3.2.P.1.4 Primary Packaging

SYMVESS is manufactured within a bioreactor bag which is aseptically sealed at the end of the manufacturing process which then serves as its primary packaging.

#### **Overall Reviewer's Assessment of Section 3.2.P.1:**

*The information provided for 3.2.P.1 Description and Composition of the Drug Product is adequate. The proper name of SYMVESS is designated as "acellular tissue engineered vessel-tyod" and its composition is mostly collagen proteins.*

### 3.2.P.2 Pharmaceutical Development

#### 3.2.P.2.1 Components of the Drug Product

##### 3.2.P.2.1.1 Drug Substance

Not applicable.

*Reviewer Comment: Due to no Drug Substance designation, no relevant information is provided.*

### **3.2.P.2.1.2 Excipients**

SYMVESS is immersed in (b) (4) within its final primary package. Prior to being implanted, the (b) (4) is drained and then SYMVESS is removed from the primary package.

*Reviewer Comment: Please refer to 3.2.P.4 Control of Excipients for more information on the DPBS excipient solution.*

### **3.2.P.2.2 Drug Product**

#### **3.2.P.2.2.1 Formulation Development**

No formulation is applicable with this product. The SYMVESS is immersed in (b) (4) within its final primary package.

#### **3.2.P.2.2.2 Overages**

Overages is not applicable as the SYMVESS is a solid product and not a liquid formulation.

#### **3.2.P.2.2.3 Physicochemical and Biological Properties**

The Applicant provided information as below (mostly describing the critical quality attributes (CQAs) that are tested using QC analytical methods) to describe physiochemical and biological properties of SYMVESS:

(b) (4)

(b) (4)

### 3.2.P.2.3 Manufacturing Process Development

The Applicant provided manufacturing process development information on the cell bank, (b) (4) mesh, bioreactor, and sterilization process as below:

(b) (4)

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

(b) (4)

#### **3.2.P.2.4 Container Closure System**

*Reviewer Comment: Please refer to 3.2.P.7 Container Closure System.*

#### **3.2.P.2.5 Microbiological Attributes**

SYMVESS and the excipient solution (b) (4) within the primary packaging is sterile. Additionally, the primary packaging undergoes (b) (4) (b) (4) process for sterilization of the outer surface of the primary packaging. Regarding product sterility, (b) (4) sterility testing is performed for drug product release testing and stability. Container closure integrity testing (CCIT) is performed on the primary packaging and a validation report is provided in 3.2.R-9 CCIT Validation Report Rev.00.

*Reviewer Comment: Please refer to DMPQ memo for further information on CCIT.*

#### **3.2.P.2.6 Compatibility**

No dosage or delivery devices are used with SYMVESS. It is not reconstituted. The information regarding the extractables and leachables testing and other aspects of compatibility are located in 3.2.P.2.4 Container Closure System.



*Reviewer Comment: Please refer to consult memo from Andrey Sarafanov (OPPT) for more information.*

**Overall Reviewer's Assessment of Section 3.2.P.2:**

*The information submitted in 3.2.P.2 Pharmaceutical Development adequately provides relevant development information including development history for SYMVESS manufacturing and testing. Comparability between (b) (4) manufacturing systems has been reviewed and assessed to be acceptable.*

**3.2.P.3 Manufacture****3.2.P.3.1 Manufacturer(s)****Table 3 – Summary of Manufacturer(s)**

Company/Organization Name	Manufacturing Role	FEI/DUNS
Humacyte, Inc. 2525 E Highway 54 Durham, NC 27713, USA	<ul style="list-style-type: none"><li>• Drug Product manufacturing, quality control testing, packaging, labeling, and distribution</li><li>• Storage of Working Cell Bank</li><li>• Drug Product stability storage</li></ul>	FEI: 3014294024 DUNS: 557190449

(b) (4)

**3.2.P.3.2 Batch Formula**

*Reviewed by PL and WS.*

(b) (4)

**3.2.P.3.2.1 Master and Working Cell Banks of Smooth Muscle Cells Derived from Human Tissue**

**3.2.P.3.2.1.1 Master Cell bank**

(b) (4)

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

(b) (4)

**3.2.P.3.2.2 Cell Culture Reagents and Components used in manufacture of SYMVESS**

Components used during the MCB and WCB production are listed in **Table 7**, **Table 8**, **Table 9**, and **Table 10**.

**Table 7 – Materials of Biological Origin Used in MCB Production**

(b) (4)

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

(b) (4)

### 3.2.P3.3.5 Secondary Packaging, Tray Sealing, and (b) (4) Sterilization

When the SYMVESS pass visual inspection, the primary package is placed in a (b) (4) tray then sealed with Tyvek lidstock via a heat-sealing process. Next, (b) (4) sterilizes the exterior of the surface of the SYMVESS primary packaging and the interior of the (b) (4) plastic tray and Tyvek lidstock.

*Reviewer Comment: Refer to 3.2.P.3.5 Process Validation and/or Evaluation for (b) (4) sterilization validation assessment.*

### 3.2.P.3.3.6 Quality Control Release Testing

For quality control (QC) release testing, the testing samples are collected as below:

- (b) (4) sample: (b) (4) at the end of (b) (4)
- Sterility and endotoxin samples: excipient (b) (4) fill in the (b) (4) (b) (4) and (b) (4) within the IL fluid path from each (b) (4)
- Destructive QC sample: (b) (4) SYMVESS that passed visual inspection (b) (4) SYMVESS are from the excipient sample position; (b) (4) SYMVESS is from lower drawer of (b) (4) which had excipient sample taken; (b) (4) SYMVESS are sampled from across the remaining (b) (4) by achieving random selection in positions (b) (4)

*Reviewer Comment: Refer to 3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures for further assessment.*

### 3.2.P.3.3.7 Packaging into Container Closure System

The processed SYMVESS are inserted into a custom paperboard carton with instructions for use and a freeze indicator. A label is applied to the exterior of the carton. The SYMVESS unit is then stored in 2-8°C pending release. Once SYMVESS unit is released, the unit is distributed using a validated 2-8°C cold storage shipper, (b) (4) (b) (4) which includes temperature monitoring devices and security seals.

*Reviewer Comment: Refer to 3.2.P.3.5 Process Validation and/or Evaluation for more information.*

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

*Provided information on manufacturing of SYMVESS is acceptable. The description on (b) (4) (including (b) (4) (b) (4) decellularization, visual inspection, packaging and (b) (4) sterilization, and release testing is sufficient to support the BLA.*

*Review concerns related to visual inspection (i.e., increased number of inspection rejections) and release testing sampling strategy (i.e., justification for selecting (b) (4) SYMVESS) were resolved during the IR communications and no further issues are present. Please refer to 3.2.P.5.4 Batch Analyses for further assessment on their strategy for 200% inspection and rejection rate. Also, refer 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s) for further assessment on excipient sample suitability for sterility and endotoxin testing.*

**3.2.P.3.4 Controls of Critical Steps and Intermediates****Table 20 – Summary of Controls in Critical Steps of SYMVESS Manufacturing**

(b) (4)

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



(b) (4)

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

*The information provided in this Section is sufficient to support the BLA. For (b) (4) culture, (b) (4) is measured as in-process control. For (b) (4) (b) (4), (b) (4) is used to control the process with monitoring of DO, DPI, and dry time. QC sampling is adequate.*

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

(b) (4)

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

**Overall Reviewer's Assessment of Section 3.2.P.3:**

*The information on 3.2.P.3 Manufacture is adequate to support this BLA.*

*The information on material and reagents used for the manufacturing of SYMVESS is appropriate to support safety of the product. The description of manufacturing is appropriate to ensure consistency in product quality. The Information on (b) (4)*

*(b) (4) processing from PPQ is sufficient.*

*Information on changes post-PPQ is sufficient. Validation information on different (b) (4) equipment and (b) (4) procedure supports use of different (b) (4) equipment and sterilization procedure.*

*Three PMCs are communicated regarding (b) (4) BDS sterilization validation, and shipping validation as below:*

*First, the Applicant is planning to submit the completion report for feasibility of (b) (4) (b) (4) procedure by August 2024 and implement a validated sterility assurance strategy for (b) (4) by November 2024. This was an observation during the PLI and their approach is acceptable. A PMC is communicated to ask for PAS by November 13, 2024.*

*Second, a PMC is communicated to the Applicant regarding the BDS sterilization validation study. The relevant study is pending results by July 24, 2024 which is close to the ADD. Thus, DMPQ review team recommends a PMC with final study report by September 27, 2024.*

*Third, a PMC is communicated related to shipping validation. The Applicant is planning to perform shipping validation study for (b) (4) conditions in late July 2024 and in January 2025. Since the study results will be available after ADD (i.e., (b) (4) shipping study results available by August 21, 2024, and the (b) (4) shipping study results available by February 12, 2025), a PMC is communicated.*

**3.2.P.4 Control of Excipients**

SYMVESS is stored in the final packaging that is filled with (b) (4) CoA of (b) (4) is provided in Section 3.2.P.3.2 Batch Formula.

**3.2.P.4.1 Specifications****Table 28 – Specifications of Excipients**

Test	Analytical Procedure	Specification	Vendor Testing	Eurofins Lancaster Labs	Testing Site
Endotoxin	(b) (4)				
(b) (4)					

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

(b) (4)

*Reviewer Comment: The Applicant provided material specification template (SPC-0140) of (b) (4) in 3.2.R-109: (b) (4) Specification. The Applicant indicated that a set of side samples for each (b) (4) lot are tested by Humacyte's contract test lab, (b) (4). In response to Question 2 of IR#11 (CMC IR#6) sent on March 5, 2024, the Applicant clarified that "Full Testing" is performed on (b) (4) (b) (4). Once qualified, the material is eligible for (b) (4) which is at least on discriminatory identification test. Additionally, each raw material undergoes an (b) (4) requalification. During the PLI discussion, Humacyte noted that this approach was applied to all reagents. Humacyte indicated that the (b) (4) is now in (b) (4) (b) (4) requalification is performed which adds (b) (4) endotoxin, and sterility. Suppliers are qualified as part of Humacyte's Quality Management System. This is adequate.*

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

Endotoxin (3.2.R-46), (b) (4) and Sterility testing follow (b) (4) methods. (b) (4) Identity testing follow (b) (4) (b) (4) methods. The Applicant provided validation reports to support these methods.

(b) (4)

### 3.2.P.4.4 Justification of Specifications

- Endotoxin: At the upper limit of (b) (4) total endotoxin in the (b) (4) of (b) (4) that the SYMVESS is stored in and potentially be implanted is (b) (4). This is significantly lower than the (b) (4) device.
- (b) (4) The specification of (b) (4) was set based upon the expected value.
- (b) (4) The (b) (4) specification of (b) (4) is based on the physiological (b) (4) of the human body.
- Sterility: The specification of no growth is the (b) (4) requirement.
- (b) (4) identification by (b) (4) the specification is met (b) (4) (b) (4)
- (b) (4) identification by (b) (4) the specification is met when the (b) (4) response of the sample is (b) (4) (b) (4)

*Reviewer Comment: In response to Question 2 of IR#11 (CMC IR#6), they provided justification on (b) (4) identification and cation identification methods. Since (b) (4) is a solution of (b) (4)*

*depending on (b) (4) adjustment), testing a list of components like (b) (4) (b) (4) is adequate.*

### 3.2.P.4.5 Excipients of Human or Animal Origin

No human or animal origin excipient in SYMVESS drug product.

**3.2.P.4.6 Novel Excipient**

No novel excipient in SYMVESS drug product.

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

*The information in Section 3.2.P.4 Control of Excipients is adequate to support the BLA. The excipient, (b) (4) is tested for identity testing by validated methods with reasonable release acceptance criteria. No components of human or animal origin is included in the (b) (4) No issue with the excipient.*

**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)****Table 29 – Drug Product Release Specifications**

Test	Analytical Procedure	Specification	Justification for Specification	Clinical Lots Released Testing Results	PPQ/Validation Lots Released Testing Results
(b) (4)					

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

(b) (4)

Sterility	(b) (4)	Negative (No Growth)	Negative for bioreactor excipient and each IL CFM samples	No Growth	No Growth
Endotoxin	(b) (4)	(b) (4)	Tested for bioreactor excipient and each IL CFM samples based on calculation to ensure endotoxin present in SYMVESS is below (b) (4)	(b) (4) EU/mL	(b) (4)

*Reviewer Comment: The Applicant states that they have established the Target Product Profile early in product and process development which provided the basis for performing a failure mode effects analysis (FMEA) to evaluate the critical quality attributes (CQA) for the SYMVESS. They state that these CQA provide assessment of the biophysical, biochemical, and biological properties that are critical for monitoring and control to control the quality of the SYMVESS. In 3.2.R-63 (b) (4) Comparability*



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

(b) (4)

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

*The information on release specification and its justification is sufficient to support this BLA. The Applicant provided sufficient information and justification to support the release specification and provided manufacturing experience information to support their reasoning.*

*The Applicant committed to establish upper limits in acceptance release criteria of (b) (4) assays by September 5, 2025. Since this due is after the ADD, a PMC is communicated to ask Humacyte to submit a PAS by September 5, 2025.*

*The Applicant committed to complete the excipient sample suitability study by performing (b) (4) study with an (b) (4) organism, (b) (4) (b) (4) at (b) (4) using (b) (4) incubation time in (b) (4) by July 22, 2024. However, since this due date is close to ADD, a PMC is communicated to the Applicant.*

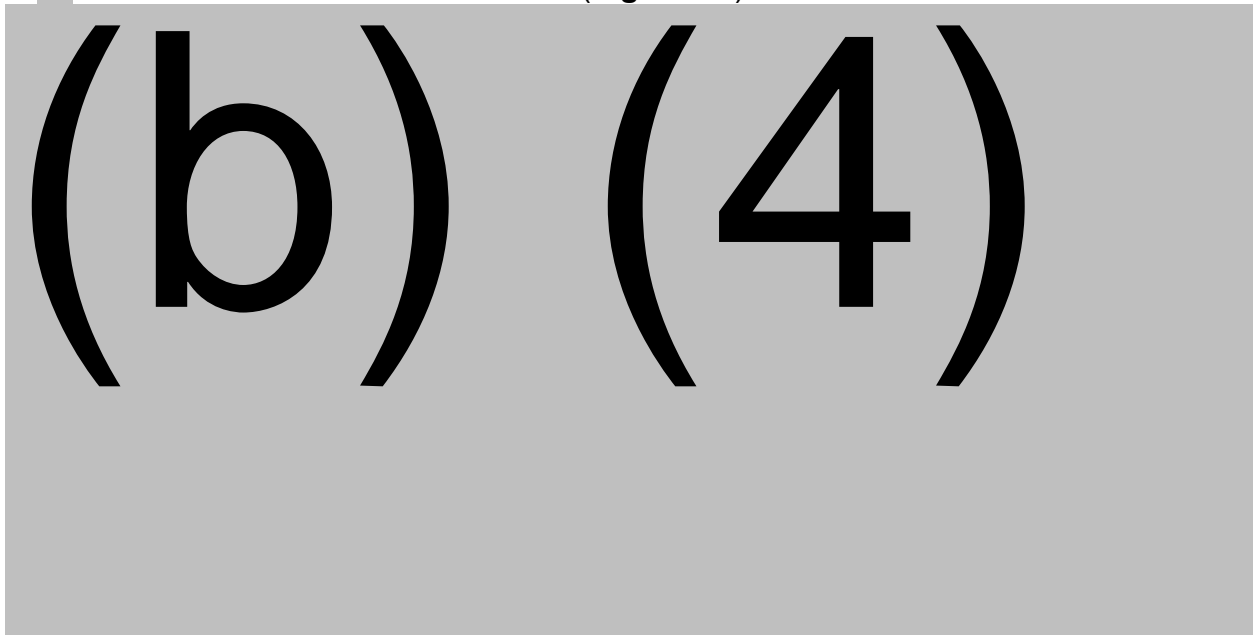
**3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures**

*Reviewed by PL and DBSQC reviewers.*

A summary of the analytical procedures used to test SYMVESS can be found in **Table 30**. At the end of the SYMVESS growth and decellularization process, individual bioreactor bags are aseptically sealed out and tagged. Individual bioreactor bags, each containing a SYMVESS, are then subjected to Manual Visual Inspection (MVI). At the conclusion of MVI, (b) (4) SYMVESS are removed for Quality Control testing to evaluate critical quality attributes. Only SYMVESS that have passed visual inspection are eligible.

**Drug Product sampling Plan**

The <sup>(b) (4)</sup> SYMVESS are selected as follows (**Figure 16**):



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

(b) (4)

**3.2.P.5.2.8 and 3.2.P.5.3.8 Potency – Quantitation of (b) (4)**

(b) (4)

*Method Summary*

(b) (4)

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

(b) (4)

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

*The information provided is acceptable to support the BLA. The validation of methods for (b) (4) assay were adequately performed to assure that methods are suitable for assurance of product identity, and potency. (b) (4) assay follows (b) (4) standard. There are no remaining deficiencies.*

*For assessment of other analytical assays (b) (4)*

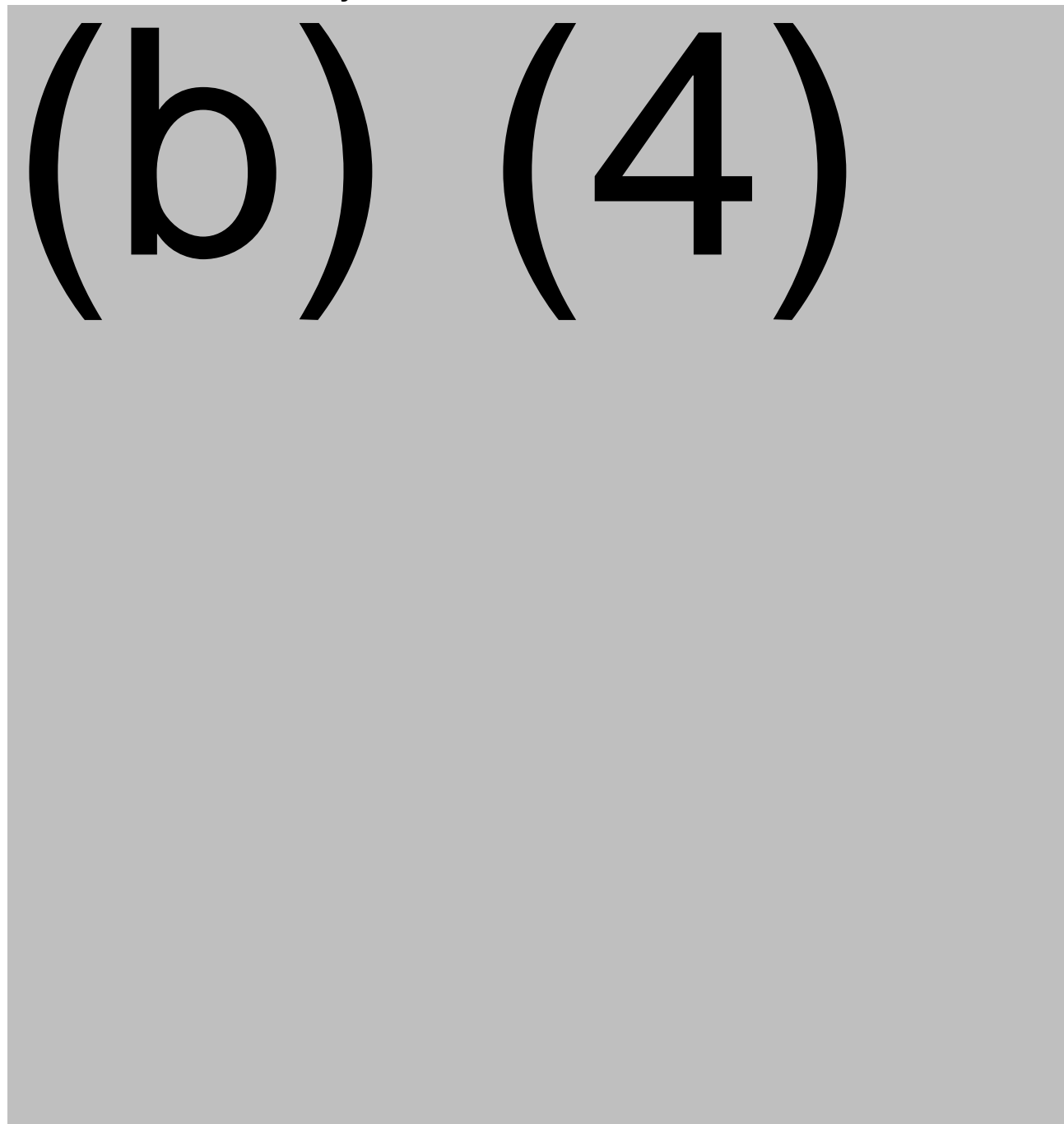
*(b) (4) Sterility, Endotoxin), please refer DBSQC memo. Dr. Hyesuk Kong assessed sterility assay and had one PMC item communicated with the Applicant regarding the sterility qualification related to environmental isolates. In response to IR#8 (DBSQC IR#1) sent on February 8, 2024, Humacyte agreed that environmental isolates from their manufacturing facility will be used in the qualification of their sterility test method (BLA 125812/0.11). Humacyte is in the process of preparing their 2023 Annual Environmental Monitoring Trend Report. A risk assessment will be performed on EM isolates identified in the report to determine the risk associates with using only USP indicator organisms during sterility method qualification. If it is determined that additional sterility method qualification is required using in-house EM isolates, this additional sterility method qualification will be completed. Humacyte opened a corrective and preventive action (i.e., CAPA-2024-011) to capture this commitment with a completion date of August 30, 2024. Since this completion date is after ADD, a PMC is communicated.*

**3.2.P.5.4 Batch Analyses**

Total of (b) (4) GMP batches were manufactured in (b) (4) which were used in CLN-PRO-V005. Additionally, (b) (4) PPQ, (b) (4) PPQ, and (b) (4) PPQ batches were manufactured in (b) (4) which were used in CLN-PRO-V005 and CLN-PRO-V017 (based on the

submission 001). In addition to these batches (b) (4) PPQ and (b) (4) (b) (4) PPQ clinical batches were manufactured in (b) (4) but were terminated due to various reasons. The successful batches are summarized as in **Table 31**.

**Table 31 – Batch Summary**



(b) (4)



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

(b) (4)

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

*The information on batch analysis is sufficient to support this BLA. The Applicant provided sufficient information to support their manufacturing capability and ensure consistent manufacturing of high quality SYMVESS. They have provided sufficient information to explain their rejection rates during the (b) (4) manufacturing process and during the visual inspection. The Applicant provided acceptable plans to reduce the issues with raw material, manpower, and machinery that were suggested as (b) (4) manufacturing rejection causes. Based on variance analysis of release testing results and its correlative analysis to cosmetic rejection number, the final product quality is not affected by rate of rejection in visual inspection. Although there is no correlation between the number of rejected SYMVESS to product quality, the Applicant will continue to monitor the rejected numbers of SYMVESS during the manufacture and will report the number and reasons in their lot release protocol. This is acceptable.*

**3.2.P.5.5 Characterization of Impurities**

The Applicant performed impurity characterization as below in **Table 35**:

(b) (4)

(b) (4)

**Overall Reviewer's Assessment of Sections 3.2.P.5:**

*The information in Section 3.2.P.5 Control of Drug Product is adequate to support the licensure. The Applicant provided sufficient information to support drug product release acceptance criteria with adequate justification. The analytical methods were all validated. They have provided sufficient information to support their manufacturing capability that results in consistent and high quality drug product manufacture.*

*One PMC is communicated related to establishing upper limits in release specifications. The Applicant committed to establish upper limits for (b) (4) (b) (4) release specifications, and submit a PAS by September 5, 2025.*

*Another PMC is communicated on the excipient sample suitability for the sterility assay. The Applicant committed to conduct a (b) (4) study using an anaerobic microorganism and submit the final study report by August 30, 2024.*

**3.2.P.6 Reference Standards or Materials**

No reference standards or material used.

**3.2.P.7 Container Closure System**

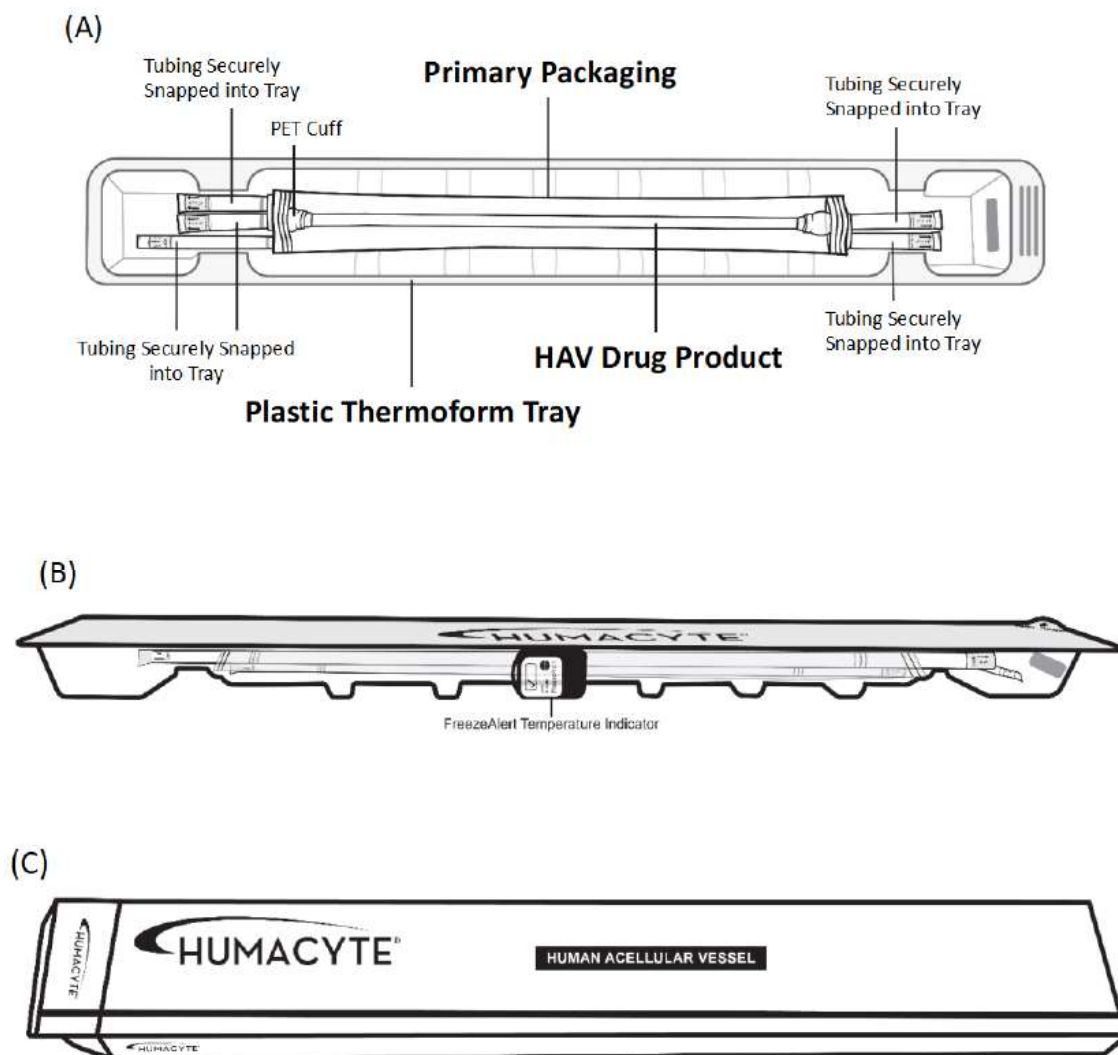
Reviewed by WS.

Description

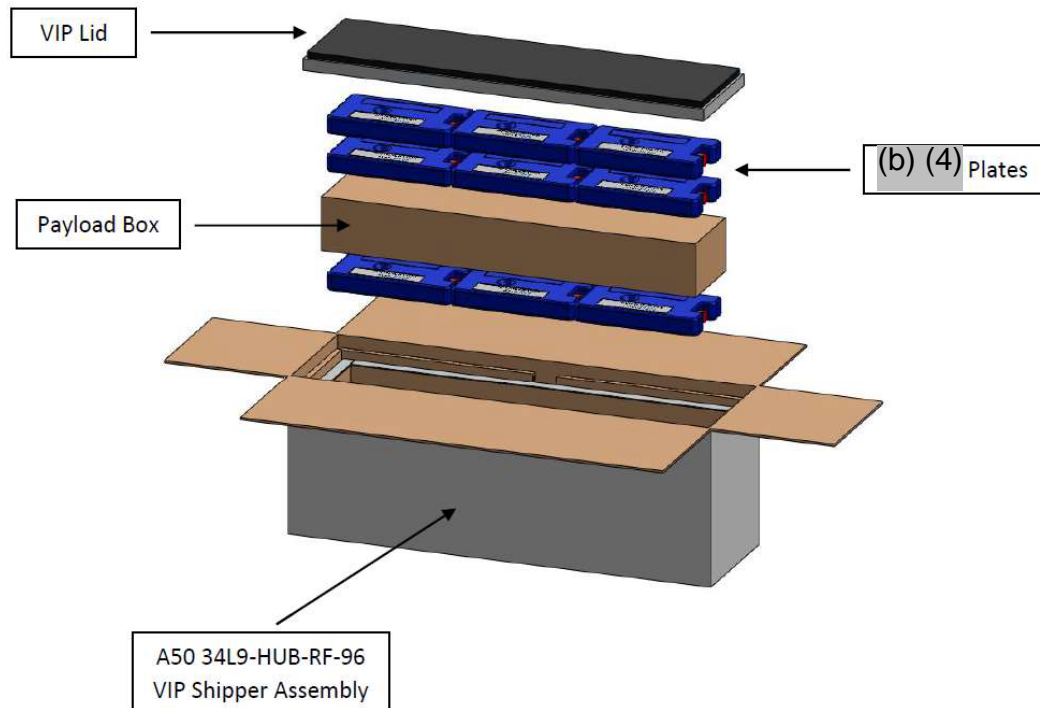
At the end of the manufacturing process, SYMVESS is stored and shipped at 2-8°C. The SYMVESS container closure system (CCS) consists of:

1. Primary packaging (**Figure 21A**) – The bioreactor bag that contains the SYMVESS drug product
2. Secondary packaging (**Figure 21A and B**) – A plastic thermoform tray sealed with a Tyvek lid, which securely holds the primary packaging
3. Market package – A paperboard box (**Figure 21C**) that holds the secondary packaging.
4. Shipper container (**Figure 22 and Figure 23**) – A shipper designed to ship and maintain a shipment of 1–3 SYMVESS units at 2-8°C.

**Figure 21 – CCS of the SYMVESS Drug Product (Reproduced from Figure 3.2.P.2.4-2 of Submission 0001)**



**Figure 22 – Pack-Out Diagram of Shipper Container (Reproduced from Page 2 of A50 34L9-HUB-RF-96 Operational Qualification Report Appendices v1 in Submission 0001)**



**Figure 23 – Payload Box with Max Load (b) (4) units) and Temperature Logger (Reproduced from Page 11 of A50 34L9-HUB-RF-96 Physical Testing Report v1 in Submission 0001)**



**Primary packaging** – The bioreactor bag, which SYMVESS is manufactured within, serves as the primary packaging of the SYMVESS CCS. There are two differences between the bioreactor bag and the primary packaging. One being the polyglycolic acid (PGA) mesh in the bioreactor bag that serves as the initial substrate for cell growth (b) (4)

(b) (4)

Another one is that each bioreactor bag is aseptically sealed and removed from the (b) (4) system using (b) (4) which maintain the sterile boundary of the primary packaging. Among the multiple components of the primary packaging (see Table 19), only the inner silicone tubing, suture and cuff have direct contact with the SYMVESS where the rest of the components (except for the (b) (4) collar) have indirect contact with the SYMVESS (**Figure 24**).

(b) (4)

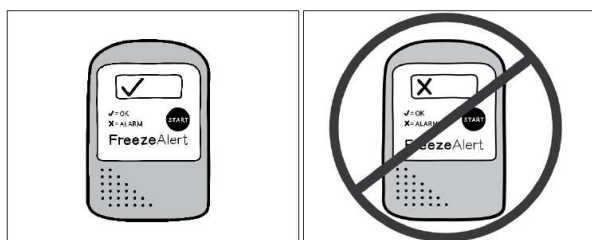
Primary packaging components are listed in **Table 15**. For details of materials of construction of the primary packaging, refer to the description on the BDS in 3.2.P.3.2 Batch Formula of this memo.

**Secondary packaging** – The secondary packaging consists of a Tyvek-sealed (b) (4) plastic thermoform tray that secures the primary packaging. After securing the SYMVESS containing primary packaging, secondary packaging undergoes (b) (4)

sterilization to assure that the outer surface of primary packaging, when prepared for administration in a surgical field, would not contaminate the sterile field in the operating room. The secondary packaging does not contact the SYMVESS during packaging, shipping, or clinical use.

To indicate whether or not the product has encountered freezing temperatures, a digital freeze indicator (b) (4) is secured to the outside of each thermoplastic tray after the (b) (4) sterilization. The indicator is an electronic irreversible freeze indicator with an internal sensor, a factory-programmed alarm, and a visual display for indicating whether a freeze event has occurred during transport or storage. The device indicates with a visual alarm when an exposure to a temperature below (b) (4) has occurred (**Figure 25**). Once an alarm has been triggered, the digital freeze indicator cannot be re-used. Attributes of the freeze indicator are listed in **Table 36**.

**Figure 25 – Digital Freeze Indicator. Reproduced from Figure 3.2.P.7-3 of the 0001 Submission**



**Table 36 – (b) (4) FreezeAlert Temperature Monitor Attributes (Reproduced from Table 3.2.P.2.4-4 of Submission 0001)**

(b) (4)

After the freeze indicator is attached, the secondary packaging is placed in the market package, which is a paperboard carton printed with company-specific information and coated with a polymeric material that protects the packaging from moisture and exposure to the environment.

**Shipper container** – The Applicant employs an (b) (4) (b) (4) shipper to transport the final packaged SYMVESS units to hospitals. The shipper is designed for shipment of (b) (4) SYMVESS units (**Figure 22**). A temperature logger is placed together with the packaged SYMVESS units (**Figure 23**).

#### Suitability

- Seal integrity (container integrity):
  - Primary packaging – Container closure integrity testing (CCIT) for the primary packaging was validated as per the studies described in section 3.2.P.2.5 Microbiological Attributes. Briefly, container closure integrity testing for the primary packaging is assessed using a (b) (4) test method. The method was pursuant to (b) (4) Package Integrity. Evaluation – Sterile Products and modelled after (b) (4) Test Method for Non-destructive Detection of Leaks in Packages by (b) (4) (b) (4).  
*Reviewer comment: DMPQ reviewed the information on CCIT for the primary packaging.*
  - Secondary packaging – Tray seal integrity testing has been evaluated under a stability protocol (3.2.R-8, PRO-0069) using the following methods conducted by (b) (4) (b) (4) Testing. (b) (4) demonstration batches of test articles were utilized. The demonstration batches consisted of a combination of (b) (4) (b) (4) test articles were processed through tray sealing and (b) (4) sterilization in the exact same process used in (b) (4) manufacturing batches. Test results are provided in Tables 3.2.P.2.4-1 through 3.2.P.2.4-3 of submission 0001.  
*Reviewer comment: DMPQ reviewed the information on seal integrity testing of secondary packaging.*  
  
*It was not clear whether the SYMVESS used in stability studies have undergone (b) (4) sterilization. The Applicant was asked to provide clarify in IR#11 (CMC IR #6) sent on March 5, 2024 and they provided their responses in BLA 125812/0.14 on March 18, 2024. The Applicant stated that all SYMVESS used in stability studies have undergone (b) (4) sterilization. This information is acceptable.*
- Temperature – Shipping validation study of the shipper is performed for at least (b) (4) (b) (4) under (b) (4) simulated (b) (4) shipping conditions to demonstrate that the temperature is controlled between 2-8°C. Result summary of shipping studies is provided in Table 3.2.P.3.5-29 of submission 0001. In addition, shipping of packaged SYMVESS was simulated exposing the shipping system to a sequence of (b) (4) tests as outlined in (b) (4) Procedure for Testing “Packaged-Products for Parcel Delivery Systems Shipment



(b) (4) 2018 Revision. Through both the (b) (4) no damage to the packaging system, including the (b) (4) was observed beyond normal fatigue. Following a shipping simulation, seal integrity testing on the Tyvek lid (secondary packaging) was performed using a (b) (4) test. No evidence of (b) (4) was observed following the shipping simulation indicating the tray seal was not impacted by the shipping and remained integral.  
*Reviewer comment: (b) (4) is FDA Recognized Consensus Standards (Recognition number 5-126). CCIT is reviewed by DMPQ.*

- Residual (b) (4) – (b) (4) and its impact on physical and mechanical properties of SYMVESS after (b) (4) exposure were assessed in (b) (4) Testing Summary Report. A batch of SYMVESS, that was previously exposed to (b) (4) of (b) (4) sterilization, was exposed to an additional (b) (4) for (b) (4) (b) (4) (b) (4) The average concentrations for (b) (4) were measured and concluded that extended exposure to (b) (4) has no impact to the SYMVESS (b) (4) (b) (4)
- Biological reactivity – All direct and indirect contacting components used in the manufacture of the primary packaging meet (b) (4) The inner silicone tubing that has direct contact with the entire length of SYMVESS meets (b) (4) (b) (4) and 21 CFR 177.2600 Rubber articles intended for repeated use. The suture used to anchor the meets 21 CFR 878.5010 Nonabsorbable polypropylene surgical suture. (b) (4) and the (b) (4) meet (b) (4).  
*Reviewer comment: (b) (4) are an FDA recognized consensus standards.*
- Extractables and leachables – Extractables and leachables risk assessment reports with toxicological risk assessment of the primary packaging are provided in reports 18-VR-578 and 18-VR-580 of submission 0001.  
*Reviewer comment: Dr. Andrey Sarafanov (CBER/OTP/OPPT/DH/HB2) and Dr. David Cantu reviewed this information. Dr. Sarafanov indicated that the extraction study is a simulated/accelerated leachables study and is not acceptable. This issue was communicated to the Applicant in IR#11 (CMC IR #6) dated March 5, 2024 and the Mid-Cycle Communication dated March 28, 2024. During the Mid-Cycle Communication, the Applicant agreed to provide extractable study data and analysis that aligns with leachable study. In BLA 125812/39 received on June 7, 2024 and in BLA 125812/0.45 received on June 21, 2024, the Applicant provided a full summary report of extractables information which was assessed to be acceptable by Dr. Sarafanov based on the available data. Additionally, Dr. David Cantu (PT reviewer) confirmed that toxicology safety concerns were not identified based on the available extractable and leachable toxicology risk assessment provided by the Applicant since the detected levels of leachables were below the permissible daily exposure (PDE) parental and maximum allowable concentration (MAC). Both Dr. Sarafanov's*

*and Dr. Cantu's assessed that the available analytical extractable and leachables data indicate safety of the drug product and it is sufficient for approval of SYMVESS. Some missing information has been requested to the Applicant during the review period (IR#21 sent on April 26, 2024 and IR#26 sent on May 19, 2024). In BLA 125812/0.45, the Applicant indicated that screening and toxicological assessment for (b) (4) compounds (b) (4) that are missing from the current available data will be completed no later than July 5, 2024 and if the screening and toxicological assessment determines that additional methods validation is required a 12 weeks will be needed. Furthermore, the additional leachables study at an  $\geq 18$ -month time point will also require 12 weeks to be completed. Thus, the Applicant indicated that they can provide the results no later than December 20, 2024. Since this timeline is after ADD, a PMC is communicated to the Applicant.*

#### Quality Control

Description of manufacturing process and all relevant schematic drawings of the BDS, which also serves as the primary packaging after seal out from the (b) (4) manufacturing system, are provided in response to IR#14 (CMC IR#7) in BLA 125812/0.21 received on April 18, 2024. In addition, the Applicant provided quality agreement with (b) (4) (b) (4) BDS manufacturer, to ensure quality control of the BDS.

#### Stability

The primary packaging, i.e., BDS, has a shelf life of (b) (4) based on the (b) (4) study of the (b) (4) mesh scaffold. In addition, CCIT of the primary packaging is currently performed as part of stability program at (b) (4) intervals (b) (4) and at each storage condition. Refer to Section 3.2.P.8 Stability for review.

*Reviewer comment: Dr. Jin Sung Hong (CMC chair) reviewed the information on stability testing of SYMVESS. Although it is unclear whether the BDS used in stability studies Section 3.2.P.8 considered the worst-case scenario (e.g., amount of time the BDS were stored before being used to manufacture the drug products), SYMVESS is generated from ECM deposits during (b) (4)*

*Thus, it is reasonable to consider BDS (b) (4) may have an impact on cell adhesion, but if the cells were able to adhere to (b) (4) mesh and proliferate after (b) (4) post-base treatment (or even (b) (4) post-base treatment which is the worst-case scenario) and generate SYMVESS, the product quality and stability of SYMVESS should be reflected by the established CQAs (i.e., (b) (4) etc.) that met the release specifications and not based on BDS (b) (4) Thus, considering the worst-case scenario for BDS in SYMVESS stability study may not be as critical if the cells were able to bind the (b) (4) mesh, proliferate, and generate SYMVESS.*

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

*The information provided for Section 3.2.P.7 Container Closure System is acceptable. Evaluation of extractables and leachables were performed by Dr. Andrey Saranfanov and Dr. David Cantu, respectively. The Applicant provided additional information on the extractables study by submitting a full summary report of extractables information for all the components used for the container closure. Dr. Saranfanov assessed that the provided information is acceptable. Dr. Cantu confirmed that toxicology safety concerns were not identified based on the extractable and leachable toxicology risk assessment provided by the Applicant.*

*However, a PMC is communicated for the Applicant to complete a toxicology assessment for the (b) (4) compounds (b) (4) (b) (4) and submit its related leachables study at an  $\geq$  18-month time point and method validation data (if found required) by December 20, 2024.*

**3.2.P.8 Stability****3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data**

The Applicant performed stability studies with SYMVESS manufactured with various manufacturing setup as below in **Table 37**:

**Table 37 – Summary of Stability Studies**

Stability Study	System	Tests	Stability Condition
STA-PRO-V001	(b) (4)	(b) (4)	
STA-PRO-V007	(b) (4)		
PRO-0031	(b) (4)		
PRO-0060	(b) (4)		

	(b) (4)
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*Reviewer Comment: In PRO-0031 (PPQ batches), all stability testing results but (b) (4) (b) (4) result met their acceptance criteria through (b) (4) was only acceptable through (b) (4) in (b) (4) For PRO-0060 (clinical batches), the study is still on-going. The batches tested are (b) (4) for visual inspection, sterility, endotoxin, (b) (4)*

*Stability testing results met acceptable criteria through (b) (4) in (b) (4) (b) (4) with (b) (4) (b) (4), and (b) (4) (b) (4) with (b) (4) (b) (4) (b) (4) pressure was also measured for report only purpose and the results were all above (b) (4) which is the approximate (b) (4) pressure of saphenous vein.*

*In response to Question 9 of IR#11 (CMC IR#6) sent on March 5, 2024, the Applicant explained that they have a measure in place to identify QC testing results that are within specification but Out-of-Expectation (OOE). In this case, it will trigger an Out of Expectation Result Investigation per SOP-0302. However, if the release QC testing results are within specification and is in the range of expectation, they assume the batch to be homogenous and they will use single SYMVESS as representative of the batch for stability purpose. They have used a (b) (4) SYMVESS and (b) (4) SYMVESS for the stability study. Their justification is acceptable.*

*Based on this information the expiry of SYMVESS is 18 months in 2-8°C. This is adequate.*

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

The Applicant proposes to conduct post-approval stability study by placing (b) (4) of (b) (4) at (b) (4) storage conditions 2-8°C and (b) (4) as below (Table 38):

**Table 38 – Stability Study Design**

(b) (4)

(b) (4)

*Reviewer Comment: The Applicant indicated that (b) (4) testing will be removed in the post-approval stability study since this is identity testing which is not required for stability. In fact, (b) (4) measurements in the clinical stability study (PRO-0060) showed minimal deviation for (b) (4) in (b) (4) with (b) (4) (b) (4) and (b) (4) months in (b) (4) with (b) (4) that met the release specification of (b) (4). However, since this testing evaluates (b) (4) content, they should continue considering this testing and measure how it is affected by the storage condition. In response to IR#29 (CMC IR#12) sent on June 13, 2024, the Applicant agreed to include (b) (4) testing into the post-approval stability study and updated their study design appropriately. This is adequate.*

*In response to Question 9 of IR#11 (CMC IR#6) sent on March 5, 2024, the Applicant clarified that post-approval stability testing will be conducted on (b) (4) SYMVESS lots that have been (b) (4) sterilized at each time point/condition. This is acceptable.*

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

*The information in Section 3.2.P.8 Stability is sufficient to support the BLA. The applicant has product stability data from (b) (4) stability studies using (b) (4) (b) (4) (PPQ and clinical batches) in recommended and accelerated storage condition to support 18 months of expiry in 2-8°C. Additionally, the Applicant's proposal for post-approval stability study is acceptable.*

### 3.2.A APPENDICES

#### 3.2.A.1 Facilities and Equipment

The location of Humacyte facility is 2525 Highway NC-54, Durham, NC 27713 which is a (b) (4) square foot sized facility. The commercial manufacturing space is located on the (b) (4) (Figure 27) floors and comprises of (b) (4) square feet of the facility. (b) (4)

are performed on the (b) (4) floor.

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

(b) (4)

The cleaning of the controlled areas are performed by following procedures including cleaning frequency, cleaning type, and cleaning agents used as summarized as below in **Table 39**:

**Table 38 – Summary of Controlled Area Cleaning**

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

(b) (4)

Environmental monitoring program is in place for routine static and dynamic monitoring of cleanroom spaces. Environmental monitoring of equipment in the classified areas is performed as the following in **Table 40**:

**Table 39 – Summary of Environmental Monitoring**

Grade	Room/Equipment	Sample Type	Frequency
(b) (4)			



Alert level analysis for the classified areas is performed every (b) (4) (b) (4) for utilities, per the cut-off value approach, using the (b) (4) percentile to assist in determining alert level values. Excursions identified from environmental monitoring samples are investigated in accordance with standard operating procedures. (b) (4) alert-level excursions require a retest, upon completion of any required corrective actions, and are evaluated against trends to determine if elevation to investigation is required. Action limit excursions and defined alert level trends require an investigation, which includes root cause analysis. If root cause is unknown, identification of corrective actions and/or preventative actions, additional (b) (4) to the impacted area, additional monitoring, if applicable, and evaluation of the excursion relative to data trends. The investigation includes a risk-based evaluation of any potential product impact based on the identification of the recovered microorganism or an airborne particle excursion.

(b) (4)

**Assessment of Section 3.2.A.1:**

*The information on Section 3.2.A.1 Facilities and Equipment is appropriate to support the BLA. The manufacturing flow and control for manufacturing area and equipment are appropriate. Currently, SYMVESS is the only drug product manufactured in this facility. Please refer to DMPQ memo and PLI memo for further information.*

**3.2.A.2 Adventitious Agents Safety Evaluation**

Reviewed by PL

Review of Module 3 section 3.2.A.2, Adventitious Agents Safety Evaluation, focused on information covering Control of raw materials of biological origin, Viral and adventitious

agent testing of the MCB and WCB and viral inactivation of the drug product by decellularization. The reviewer confirmed that all of the biological raw materials are adequately tested for microbial safety as per the ICH guidelines and FDA guidance. All of the safety-test assays are performed and validated by contract manufacturing organizations or vendors. Relevant assay validation reports are submitted to the file and reviewed. From a viral and adventitious agents safety perspective, the provided information is complete and supports licensing of the product.

SYMVESS is a biologically active construct which cannot undergo terminal sterilization or virus clearance methods for the final product. The following strategy was used to assess drug product for viral adventitious agents.

#### *Viral Safety Associated with Human Tissue*

Viral safety evaluation includes donor screening required by 21CFR Part 1271. In addition to the viral testing required in 1271, viral testing for the following additional agents were reviewed as part of the Medical Director acceptability determination:

(b) (4)

The viral testing results associated with (b) (4) donor are provided in **Table 41**. All virology testing specified in 21CFR 1271 met acceptance criteria. The (b) (4) donor was non-reactive or negative by the following tests: HIV 1 and 2 antibodies (anti-HIV 1 and anti-HIV 2), Hepatitis B Surface Antigen (HBsAg), Hepatitis B Core Antibody (b) (4) Hepatitis C Antibody (anti-HCV), Hepatitis C Nucleic Acid Test (HCV RNA), HIV Nucleic Acid Test (HIV-1 RNA), Hepatitis B Nucleic Acid Test (HBV DNA), (b) (4). The donor was positive by testing for (b) (4). (b) (4) The positive (b) (4) test results did not impact donor eligibility. Additionally, tests of the WCB for (b) (4) were performed and were negative (**Table 42**).

*Reviewer comment: DHT consult Dr. Hanh Khuu confirmed that the information on the donor eligibility is adequate. Refer to Dr. Hanh Khuu's memo for further information.*

**Table 40 – Viral Testing Associated with (b) (4) Donor**

Test Name	Result
HIV 1/2 Antibodies	Non-Reactive
Hepatitis B Surface Antigen	Non-Reactive
Hepatitis B Core Antibody (b) (4)	Non-Reactive
Hepatitis C Antibody	Non-Reactive
Hepatitis C Nucleic Acid Test	Non-Reactive
HIV Nucleic Acid Test	Non-Reactive
Hepatitis B Nucleic Acid Test	Non-Reactive

(b) (4)

**Table 41 – Viral Adventitious Agents Testing of the (b) (4) WCB**

Test	Result
(b)	(4)

(b) (4)

*Reviewer Comment. The assays mentioned above that were used for evaluation of the adventitious agents and viral safety tests of the cell banks, and reagents are validated according to the ICH guidelines and the regulatory agencies recommendation. Therefore, the tests and their acceptance criteria are acceptable.*

#### *Viral Safety Associated with Fetal Bovine Serum*

Fetal bovine serum (FBS) is required for the cultivation and expansion of the vascular SMCs. Infectious disease risk is minimized since the suppliers source bovine-based components in accordance with 9 CFR 113.53 (Requirements for Ingredients of Animal Origin Used for the Production of Biologics), Guidance on the use of bovine serum in the manufacture of human biological medicinal products (b) (4) and Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (b) (4) as well as other US and international regulatory requirements as summarized in the current (b) (4) Bovine Serum and (b) (4) bovine serum. The fetal bovine serum used in the WCB production and in the manufacture of HAV is (b) (4) by the supplier prior to distribution and tested for presence of virus as per 9 CFR 113.52.

#### *Viral Safety Evaluation Associated with (b) (4)*

The culture medium employed in the bioreactor process is (b) (4)  
(b) (4)  
(b) (4) is collected at FDA licensed donation centers and donations are screened per 21CFR610.40, Testing Requirements for Relevant Transfusion-Transmitted Infections. The (b) (4)  
(b) (4) according to FDA guidelines. The (b) (4)  
(b) (4) product prior to (b) (4) is also tested and found to be negative for (b) (4) by FDA approved methods. In addition, the finished product is tested and found to be negative for (b) (4)  
(b) (4) by FDA approved methods.

#### *Viral Safety Evaluation Associated with (b) (4)*

(b) (4) is a component of the (b) (4) solution used to passage smooth muscle cells during the (b) (4) process. The material is vendor-screened for

(b) (4) In addition, the bulk (b) (4) is (b) (4) prior to compounding.

#### *Non-Viral Safety Evaluation Associated with Human Tissue*

The main non-viral testing requirement specified in 21CFR 1271 is a serological test for Syphilis (rapid plasma reagent test for *T. pallidum*). This test is performed and recorded in the donor relevant medical records.

Non-viral contamination is also assessed for end-of-production steps in the MCB and WCB production process. (b) (4)

#### *Non-Viral Safety Evaluation Associated with Fetal Bovine Serum, (b) (4) and (b) (4)*

Fetal Bovine Serum sterilized by (b) (4) (b) (4) filtration followed by (b) (4) and is tested for sterility by the vendor. The (b) (4) (b) (4) is tested for (b) (4) before compounding. The compounded liquid (b) (4) is vendor tested for sterility. The (b) (4) material is tested for Syphilis at the donor level. In addition, the finished product is tested for (b) (4) and sterility by the vendor.

#### **Viral Clearance Studies**

The decellularization treatments used in SYMVESS manufacturing were evaluated in the inactivation of viral contaminants. The removal or inactivation of viral contaminations was tested according to (b) (4)

At the end of the bioreactor growth phase, the spent medium was aseptically removed from the (b) (4) system and the bioreactor bags, leaving the cell-containing tubular tissue construct within each bioreactor bag. The tubular construct was then treated by sequential exposure to a series of solutions that degrade and remove cellular components, resulting in a cell-free, or “decellularized” tubular construct, or SYMVESS. The solutions act through (b) (4) mechanisms (b) (4) (b) (4) and are circulated through the (b) (4) bioreactor system in sequence to achieve complete removal of cellular components (decellularization).

The decellularization solutions are:

(b) (4)

(b) (4)

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

*The viral clearance studies included a mix of model viruses consisting of RNA and DNA viruses with and without envelopes. Since, SYMVESS does not contain any animal derived materials in the final product and the animal derived reagents utilized during manufacturing are appropriately tested, the viral clearance studies performed by the applicant and the resulting log reduction obtained were considered adequate.*

The information provided in Section 3.2.A.2 Adventitious Agents Safety Evaluation is adequate to support the licensure. Viral risk is minimized through compliance with 21 CFR 1271 regulations, raw material controls and testing, viral inactivation with (b) (4) (b) (4) exposure.

**3.2.R Regional Information (USA)**

**❑ Executed Batch Records**

Master and executed batch records are provided (clinical batch (b) (4))

**❑ Method Validation Package**

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

**❑ Combination Products**

Not applicable.

**□ Comparability Protocols**

*Reviewer Comment: Comparability study has been discussed previously in (b) (4) In (b) (4) (Sequence 55) submitted on November 14, 2017, the Applicant provided high level comparability plan in the Type B meeting package. In IND (b) (4) submitted on October 9, 2018, Humacyte provided a draft of comparability protocol in the Type B meeting package. Previous reviewer reviewed CQA sampling and testing plan. In Meeting Summary (CRMTS 11509) on April 1, 2019, the Applicant clarified the sampling plan (for each CQA) proposed for both the (b) (4) (b) (4) manufacturing systems. The final comparability protocol was submitted in (b) (4) submitted on September 23, 2019. RPT-0130-00 (b) (4) Comparability Report was submitted in (b) (4) submitted on March 8, 2022, and was reviewed by Dr. Wen Seeto. The comparability protocol and study report were assessed to be acceptable. Please refer Dr. Seeto's memo for further information.*

**Other eCTD Modules****Module 1****A. Environmental Assessment or Claim of Categorical Exclusion**

The Applicant claims categorical exclusion per 21CFR 25.31(c) for SYMVESS since the extracellular matrix proteins within the SYMVESS occur naturally in the environment and the proposed action does not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

*Reviewer Comment: The Applicant's categorical exclusion is reasonable, and no significant environmental impact is anticipated. This is adequate.*

**B. Product Designation Request**

Not applicable.

**C. Lot Release Protocol Waiver Request**

In 1.12.5 Request for a Waiver, Humacyte requested a waiver from the requirement of samples and protocols to be submitted for CBER official release described in 21CFR 610.2(a). The primary reasoning for requesting a waiver from CBER official release was based on the lot release testing panel which includes purity (i.e., measurement of

(b) (4) potency (i.e., measurement of (b) (4) (b) (4) sterility, endotoxin, (b) (4)

testing. They stated that the lot release testing panel consists of test methods that characterize the SYMVESS similar to well characterized biologics which are exempt from FDA lot release requirements. However, I disagree with this assessment on the necessity of CBER official release and denied the lot release exemption request.

*Reviewer Comment: The denial decision was based on the characteristics of the drug product and their manufacturing experience. SYMVESS is derived from an allogenic cellular source with a shelf-life of 18 months at 2-8°C which has a potential to treat many patients in the future. Additionally, the manufacturing process is novel and*

*manufacturing experience is limited to the investigational stage. Lastly, based on the provided batch analysis information, several manufactured batches have been rejected due to not meeting its in-process and, in some cases, its final release specifications. Some were even rejected after the PPQ runs. Thus, my overall assessment of the risks involved in the drug product and manufacturing experience deem CBER lot release necessary. Based on internal discussion with Maryna Eichelberger (Director, OCBQ/DBSQC) and Joseph Quander (Chief, DMPQ/Product Release Branch), we agreed that CBER lot release via lot release protocol only, and not with sample submission and testing, is acceptable.*

*In BLA 125812/0.13, Humaycte submitted a lot release protocol (LRP) template in response to IR#10 (CMC IR#5) sent on February 9, 2024. After our further input, Humacyte submitted a revised LRP template in BLA 125812/0.33 received on May 22, 2024. The LRP includes yield information including the rejection number within a batch. This is adequate. In BLA 125812/0.47, the Applicant submitted a final updated LRP that the Agency agreed upon. LRP template is acceptable.*

*During the Mid-Cycle Communication on March 28, 2024, the Applicant inquired whether 15-business day review can be agreed upon by the Agency. However, we disagreed to their proposal indicating that 30-day review is the standard regardless of sample submission. During the Late-Cycle Communication on May 20, 2024, the Agency agreed to the Applicant's proposal to submit the LRP after getting their product release testing data but before completion of their sealing, sterilization, and cartooning procedure.*

#### **D. Labeling Review**

##### **Full Prescribing Information (PI):**

**Table 42 – Summary of CMC Related PI Assessment**

<b>Full PI Section</b>	<b>Assessment</b>
Dosage Forms and Strengths (3),	<p>SYMVESS is an acellular tissue engineered vessel composed of organized extracellular matrix (ECM) proteins. SYMVESS is implanted using standard surgical techniques as a vascular construct to replace a patient's damaged blood vessels after sustaining trauma. SYMVESS has dimensions of 6 mm in inner diameter and 42 cm in length (approximately 40 cm of usable length). Since the length of SYMVESS to be implanted is dependent on the surgical needs, it is cut to length by the surgeon in the operating room.</p> <p><i>Reviewer Comment: The Applicant originally proposed to use the term conduit to describe the product but we changed the description to acellular tissue engineered vessel throughout the labeling. This is acceptable.</i></p>



Description (11)	<p>SYMVESS is a sterile, acellular tissue engineered vessel composed of human extracellular matrix (ECM) proteins typically found in human blood vessels. SYMVESS is 6 mm in internal diameter and 42 cm in length (approximately 40 cm of usable length).</p> <p>SYMVESS is manufactured using a tissue engineering process. Human vascular smooth muscle cells that are derived from human aortic tissue deemed suitable for transplant are banked, expanded, and seeded onto a tubular mesh scaffold. The cell-seeded scaffold is cultured in a biomimetic bioreactor system to generate an intermediate tubular construct containing vascular smooth muscle cells and the extracellular matrix the cells deposited. A final decellularization process removes the human cellular and genetic material while maintaining the extracellular matrix structure, mechanical and biological activity.</p> <p>SYMVESS manufacture includes use of reagents derived from human and animal materials. Human male AB serum and fetal bovine serum (FBS) are used in the manufacturing process for the cultivation and expansion of the vascular smooth muscle cells.</p> <p>SYMVESS is fixed inside the packaging bag between the endcaps with a supporting silicone tube and is immersed in sterile phosphate buffered saline solution.</p> <p><i>Reviewer Comment: The original description on the drug product included collagen compositions and claims for cell repopulation and remodeling of vascular structure. Since this description was based on limited evidence and was promotional, we revised the language to describe how the drug product was manufactured and what reagents were used. The revision is acceptable.</i></p>
Clinical Pharmacology (12)  Mechanism of Action (12.1)	<p>SYMVESS is an acellular tissue engineered vessel composed of human extracellular matrix (ECM) that allows mechanical and biological activity. <i>In vitro</i> studies have shown that SYMVESS can withstand the forces associated with the arterial blood flow and suture during the implantation process, and can allow cell binding and proliferation. However, the exact mechanism of action has not been established.</p> <p><i>Reviewer Comment: The original mechanism of action included description of cell adhesion, remodeling, and promotional claims which was not supported by sufficient evidence. Thus, it was revised as above.</i></p>

How Supplied/Storage and Handling (16)	<i>Reviewer Comment: The original description on how supplied and storage and handling required minimal revision.</i>
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*Reviewer Comment: In response to Question 5 of IR#14 (CMC IR#7) sent on March 28, 2024, the Applicant proposed a 4 hour in-use expiry for the SYMVESS when immersed in a sterile saline filled basin within the operating room. In BLA 125812/0.44 received on June 21, 2024, the Applicant provided in-use stability study data which showed no significant changes in the level of (b) (4)*

*(b) (4) content, and cell proliferation in samples that were stored 4 and 8 hours in saline to that of the release product. The Applicant stated that the study report supports the use of 4 hours of in-use expiry. In BLA 125812/0.57, the Applicant revised the labeling document (USPI) and indicated that they will update the in-use expiry to 8 hours. This is acceptable.*

*In response to Question 6 of IR#14 (CMC IR#7) sent on March 28, 2024, the Applicant provided results from (b) (4) testing which had mean of (b) (4). This is very small (b) (4) and it is likely that the (b) (4) will not occur during the implantation. The Applicant stated that “care should be taken to ensure that the SYMVESS does not (b) (4) (b) (4) within the tunnel and a (b) (4) vessel will result in compromised flow and performance, thereby increasing the risk of thrombosis and failure” was suggested as a general cautionary statement in the PI. Additionally, the Applicant stated that there is no marker on SYMVESS but the surgeon may use surgical marker to place orientation marking as needed. This is acceptable.*

Carton and Container Label:

After (b) (4) decellularization process, (b) (4) are applied to each SYMVESS primary container as below in **Figure 33**:

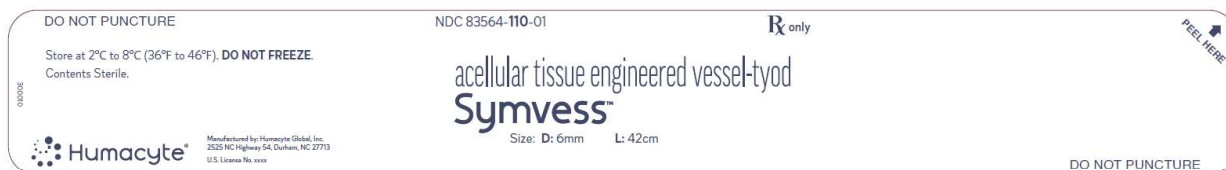
**Figure 33 – Primary Containers with (b) (4)**

(b) (4)

**Figure 34 – SYMVESS Container Label**

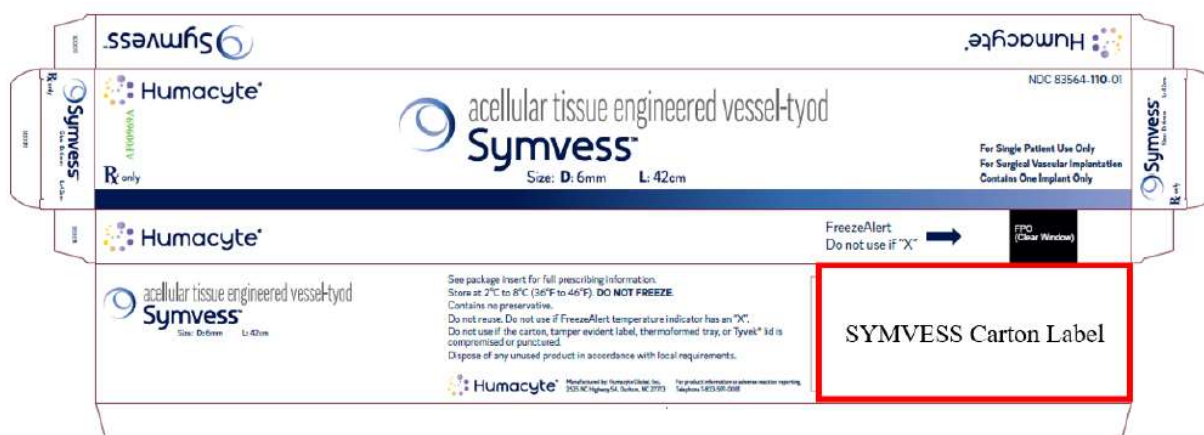


**Figure 35 – Information on the Tyvek Lid**



The Carton is as below in **Figure 36** with Carton Label (**Figure 37**) affixed on the side of the box. The top barcode on the Carton Label encodes the Expiry Date, Parent/Child Lot, and quantity within the carton. The bottom barcode encodes the GTIN and 6-digit SYMVESS Serial Number.

**Figure 36 – Carton**



**Figure 37 – Carton Label**



*Reviewer Comment: In response to IR#26 (CMC IR#11) sent on May 17, 2024, the Applicant clarified the labels as above. This information is appropriate.*

## Module 4 and 5

### Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

In response to Question 2 of IR#2 (CMC IR#1) sent on January 18, 2024, the Applicant clarified that due to the nature of the DP traditional biopharmaceutical studies were not relevant and was not conducted for SYMVESS. The Applicant clarified that panel reactive antibodies (PRA) analysis was performed to assess the eligibility of a patient to receive an organ transplant and the assay is performed by CLIA and AHSI certified laboratories using an FDA cleared diagnostic test. This assay has been used for assessing patients in V005 trauma study. This is not a measure of the efficacy of SYMVESS.

In response to Question 3 of IR#2 (CMC IR#1) sent on January 18, 2024, the Applicant clarified that traditional pharmacology studies are not conducted with SYMVESS. They further clarified that immunohistochemical staining of SYMVESS on explants in Section 2.7.2 were not from pivotal V005 study but from Phase I/II clinical studies for other indications (e.g., AV access and PAD) to support the understanding of the mechanism of action of the product.

*Reviewer Comment: Based on discussion with PT and Clinical reviewers, the Applicant performed limited in vivo analytical analysis on the explant SYMVESS. Additionally, the immunohistology staining images they provided in Module 2 is from different clinical study with different indication. This information may be helpful to understand how SYMVESS may interact with the in vivo surrounding but is insufficient to directly support mechanism of action or efficacy of SYMVESS for the proposed indication.*

#### **Biocompatibility Study (Section 4.2.3.6 Local Tolerance and 4.2.3.7 Other Toxicity Studies)**

<b>Biocompatibility Information</b>			
There is <sup>(b) (4)</sup> tissue contacting products/components/materials			
Material compositions described?: Yes			
Table of Materials and Rationales			
<b>Component</b>	<b>Material</b>	<b>Type of Contact</b>	<b>Identical Material &amp; Rationale</b>
Acellular Tissue Engineered Vessel	ECM	Direct	No, No Rationale
<b>Biocompatibility Material 1:</b>			
Test Component/Material: Acellular Tissue Engineered Vessel/ECM			
Potential for Repeat Exposure?: No			
Type of Tissue Contact: > 30 days (i.e., permanent)			
<b>Cytotoxicity Testing</b>			
Cytotoxicity testing conducted: <sup>(b) (4)</sup>			
Test Article: Tissue engineered vascular graft material			
<b>Extraction Conditions</b>	<b>Methods</b>	<b>Results</b>	<b>Conclusion and Recommendation</b>
<b>(b) (4)</b>			

(b) (4)

(b) (4) <b>Testing</b>			
(b) (4) testing conducted: Yes, (b) (4) Test			
Test Article: Tissue engineered vascular graft material			
Extraction Conditions	Methods	Results	Conclusion and Recommendation

(b) (4)

*Reviewer Comment: The Applicant provided some biocompatibility information in the BLA. Although biocompatibility studies are not required for a biological product, we have reviewed the information to ensure completeness. (b) (4) Test (Study#: 157408; (b) (4) Testing) was submitted in Section 4.2.3.6 Local Tolerance and (b) (4) Assay With (b) (4) (Study#: 157406; Cytotoxicity Testing) was submitted in Section 4.2.3.7 Other Toxicity Studies. Both study reports were from (b) (4) The Applicant indicated that 157408 followed (b) (4)*

*Testing results supported that the extract is acceptable. There were white flake-like particulates observed throughout the (b) (4) test extract and (b) (4) test extract was cloudy and light yellow in color in (b) (4) Testing, but no explanation is provided. This issue is minor and the results of the testing are acceptable.*

*In addition, the Applicant submitted Intramuscular Implant Test One Week Duration (Study#: 157404) and Intramuscular Implant Test Four Week Duration (Study#: 157405) in Section 4.2.3.7 Other Toxicity Studies. I defer assessment of these studies to PT reviewer's memo.*