

CBER CMC BLA Review Addendum

BLA STN 125812

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

Jin Sung Hong, PhD, CBER/OTP/OCTHTH/DCT2/TEB2

1. BLA#: STN 125812

2. APPLICANT NAME AND LICENSE NUMBER: Brainstorm Therapeutics

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
Approval Date	December 20, 2024

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Jin Sung Hong (JH), CBER/OTP/OCTHT/DCT2/TEB2	3.2.P.3.2 Batch Formula 3.2.P.5.3. Validation of Analytical Procedures

7. INTER-CENTER CONSULTS REQUESTED

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

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
August 22, 2024	125812/0.69	Communicated PMC Response - Sterilization validation of the bioreactor disposable set (BDS) – DMPQ related PMC item
August 30, 2024	125812/0.70	Communicated PMC Response - Excipient sample suitability study – OTP related PMC item
August 30, 2024	125812/0.71	Communicated PMC Response - In-house environmental isolates related to sterility method qualification – DBSQC related PMC item
November 7, 2024	125812/0.72	Response to CMC IR sent on October 17, 2024 related to batches (b) (4) (b) (4)
November 8, 2024	125812/0.73	Response to CMC IR sent on October 29, 2024 on sterilization validation study for the bioreactor disposable set (BDS)
November 26, 2024	125812/0.74	Communicated PMC Response - Sterility assurance strategy on the (b) (4) OTP related PMC item
December 9, 2024	125812/0.75	Response to CMC IR sent on December 4, 2024 on (b) (4) process
December 13, 2024	125812/0.76	Response to CMC IR sent on December 12, 2024 on PMC updates and lot information for launch

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

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

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

This addendum memo is prepared to incorporate information received and reviewed after the PDUFA action date. There was no decision on the PDUFA action date due to further clarification needed for the clinical benefit/risk assessment. Prior to the PDUFA action date, the Applicant had agreed to seven CMC post-marketing commitment (PMC) items. The Applicant subsequently submitted information to address four of the previously agreed upon CMC PMC items. In this addendum, assessment on those four CMC PMC items is documented. The Applicant sufficiently addressed the concerns related to (b) (4) preparation safety, sterilization of bioreactor disposable set, risk assessment of environmental isolates, and suitability of excipient sample for sterility testing.

There are three remaining PMC items that are related to shipping validation, leachable study data, and establishing upper limits for release tests. The Applicant agreed to these PMC items on December 13, 2024. In BLA 125812/0.76, the Applicant agreed to conduct three remaining PMCs with updated dates. There are no other CMC issues. We recommend approval.

In BLA 125812/0.76, the Applicant indicated that they plan to submit a CBER lot release protocol for batch (b) (4) after the BLA approval and for batch (b) (4) on January 15, 2024. They state these batches will provide sufficient supply for (b) (4) based on their forecast.

Please reference the original submission memo for further information.

B. RECOMMENDATION

C. APPROVAL

a. Approval Letter:

Humacyte, Inc.
2525 E Highway 54
Durham, NC 27713, USA

b. PMC:

PMC #4: 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 #5: Humacyte commits to submit ≥18-month leachable study data targeting (b) (4) specific compounds (b) (4) identified in additional extractables assessment requested by FDA, and additional method validation report (if found required) by January 31, 2025.

Final Report Submission: January 31, 2025

PMC #6: 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. Humacyte 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
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Jin Sung Hong, PhD, CMC Reviewer CBER/OTP/OCTHT/DCT2/TEB2	Concurred	
Zehra Tosun, PhD, Branch Chief, CBER/OTP/OCTHT/DCT2/TEB1	Concurred	
Laura Ricles, PhD Division Director, CBER/OTP/OCTHT/DCT2	Concurred	
Heather Lombardi, PhD Office Director CBER/OTP/OCTHT	Concurred	

Review of CTD

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Module 3

3.2.P.3.2 Batch Formula

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

The Applicant submitted BLA 125812/0.74 on November 26, 2024 in response to the study requested under PMC #9, which was agreed upon previously in BLA 125812/0.61 submitted on July 29, 2024. The agreed PMC #9 was as below:

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

Prior Approval Supplement Submission: November 30, 2024.

In BLA 125812/0.74, the Applicant provided information to support that adding a (b) (4) procedure in (b) (4) process is unacceptable and indicated that they will sample (b) (4) (b) (4) to perform bioburden testing to support (b) (4) sterility assurance. The information provided was insufficient and an information request was sent to the Applicant..

In BLA 125812/0.75, Humacyte provided their response to the information request and agreed to (b) (4) for sterility testing prior use and adjust manufacturing schedule to allow time for the receipt of sterility results before use. For (b) (4) (b) (4) from the (b) (4) (b) (4) of (b) (4) (b) (4) from the (b) (4) (b) (4) (b) (4) and (b) (4) from (b) (4) (b) (4) will be sampled (Figure 1).

Figure 1 Sterility Sample from (b) (4)

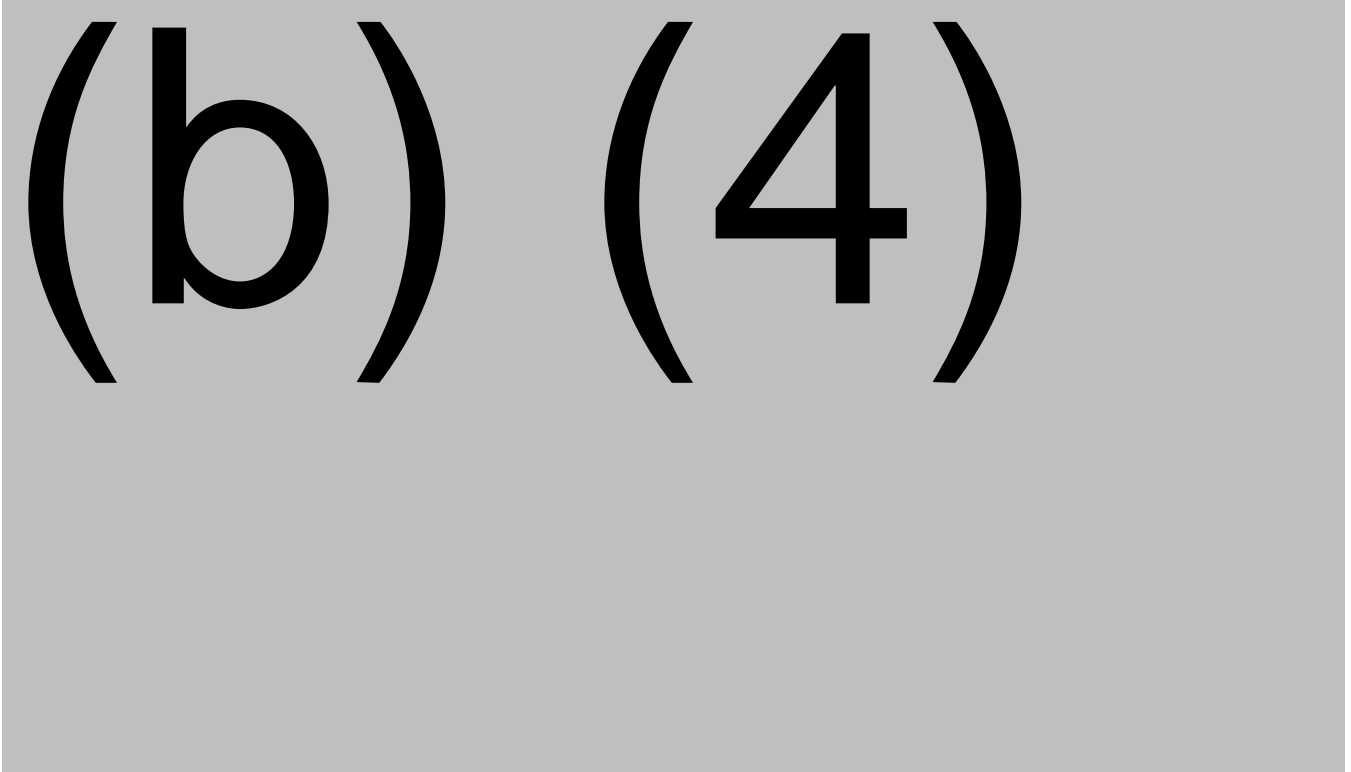
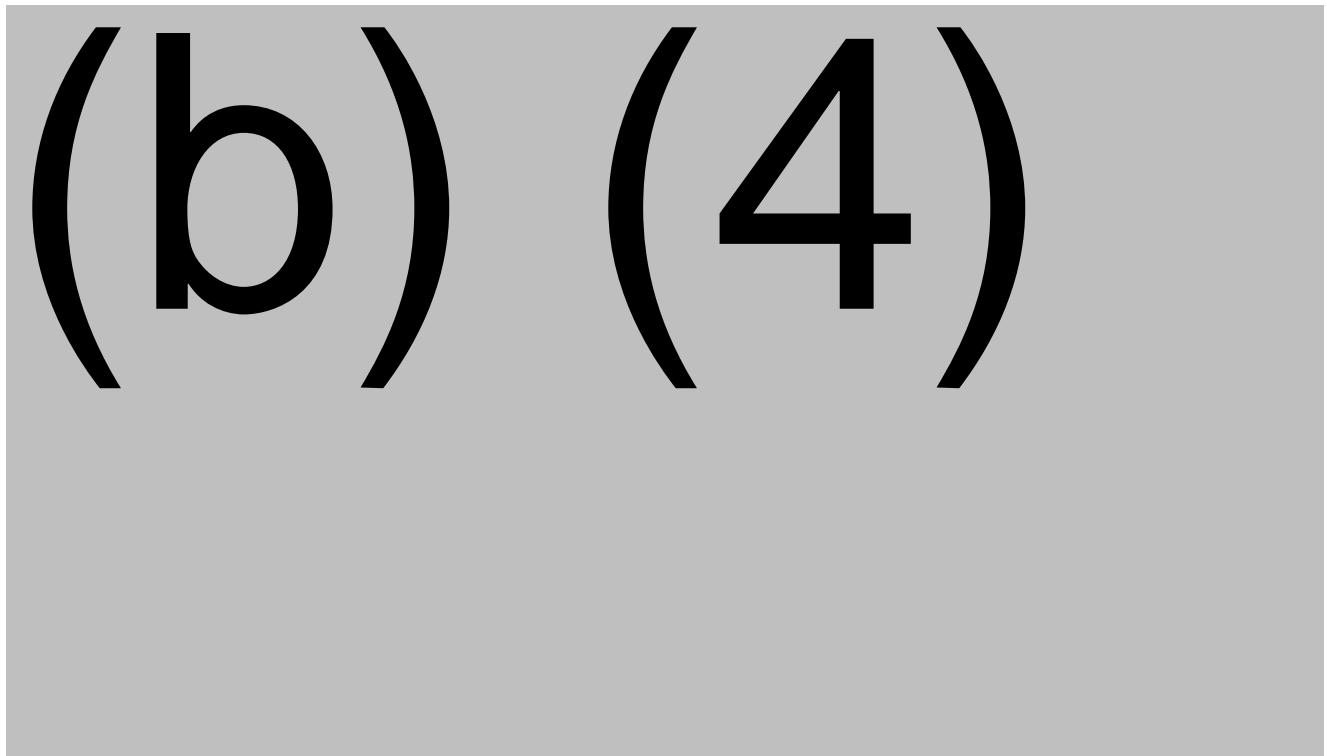


Figure 2 Sterility Sample from (b) (4)



These sterility testing will be performed in addition to the bioburden testing on (b) (4) samples at (b) (4). The Applicant will implement this testing on all batches initiated after November 30, 2024.

Reviewer comment: During the pre-license inspection (PLI), an observation was made related to sterility validation assurance for (b) (4). The Applicant did not perform adequate microbial quality assurance of the (b) (4) used for the (b) (4) (b) (4). Specifically, although the (b) (4) was formulated using (b) (4) (b) (4) was performed. The Applicant indicated that (b) (4) was not feasible due to essential nutrients that are formulated in the (b) (4). However, no sterility testing is performed on the (b) (4). Thus, after our communication of the observation, they opened CAPA-2024-031 to assess the feasibility of (b) (4) (b) (4) procedure which was due on August 31, 2024. Additionally, at the Late-Cycle Communication on May 20, 2024, they indicated that they plan to implement a sterility assurance strategy no later than November 13, 2024. Since the committed due dates were after the PDUFA action date, the issue remaining with the sterility validation assurance for (b) (4) was negotiated as a PMC study to the Applicant in an information request. The agreed upon date for submission of the final study report as a prior approval supplement (PAS) was November 13, 2024.

In BLA 125812/0.74, Humacyte submitted their assessment of adding a (b) (4) step in the (b) (4) preparation process. The Applicant provided information on (b) (4) assessment and feasibility study of using (b) (4) in (b) (4) preparation. However, the assessment concluded that using (b) (4) is unfeasible. Thus, the Applicant proposed to mitigate the risk of contamination in (b) (4) preparation by (b) (4) bioburden testing at (b) (4) 2) and (b) (4) 3) using (b) (4). In BLA 125812/0.75, Humacyte further provided statistical analysis to support their (b) (4) feasibility study and explained the reasons in detail. For example, (b) (4) of (b) (4) resulted in longer cell (b) (4) time at the (b) (4) during the (b) (4) (b) (4) process. The Applicant reasoned that cells with longer (b) (4) time are not applicable to meet (b) (4) of critical in-process controls (CIPC), the (b) (4) and the (b) (4). Due to this conclusion, the Applicant proposed to implement sampling of each of the final containers from (b) (4) and (b) (4) and perform sterility testing on the samples to ensure sterility of the (b) (4) prior to use. Based on the provided information, the Applicant has adequately provided information to ensure safety of (b) (4) preparation and no additional PMC studies are needed.

3.2.P.3.2.3 Bioreactor System Components used in manufacture of SYMVESS Bioreactor disposable set assembly

The Applicant submitted BLA 125812/0.69 on August 22, 2024 in response to the study requested under PMC #5, which was agreed upon previously in BLA 125812/0.61 submitted on July 29, 2024. The agreed PMC #5 was as below:

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) process steps) every (b) (4) until this post-marketing commitment is fulfilled. Humacyte will submit the final study report by September 30, 2024.

Final Report Submission: September 30, 2024

In BLA 125812/0.69, Humacyte submitted BDS (b) (4) Sterilization Validation Report which supports the (b) (4) of the bioreactor disposable set.

Reviewer comment: DMPQ reviewed the information on sterilization of the BDS assembly. In BLA 125812/0.46, the Applicant provided sterility validation information with (b) (4) BDS design. However, since this information (i.e., (b) (4) (b) (4) did not meet the (b) (4) Establishing the Sterilization Dose standards for initial bioburden level, the Applicant indicated that they would perform another validation study using (b) (4) BDS design. The Applicant stated that the study results would be available no later than July 24, 2024. Since the due date was close to the PDUFA action date, this outstanding issue was negotiated as a PMC study to the Applicant in an information request. In BLA 125812/0.69, the Applicant provided the study results using (b) (4) BDS design. The DMPQ reviewer (Dr. Zainab Mansary-Storm) assessed the submitted information to be adequate to resolve this issue. Please refer to DMPQ addendum memo for relevant assessment.

3.2.P.5 Control of Drug Product

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

The Applicant submitted BLA 125812/0.71 on August 30, 2024 in response to the study requested under PMC #4 which was agreed upon previously in BLA 125812/0.61 submitted on July 29, 2024. The agreed PMC #4 was as below:

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

In BLA125812/0.71, the Applicant provided Risk Assessment: Sterility Test Method and the Use of Environmental isolates for System Suitability Testing. They conducted a risk estimation assessment following the principles in SOP-0321, Quality Risk Management

to determine the risk level of not including the 2023 environmental isolates (b) (4)

in an additional system suitability test for Sterility Testing. Based on their risk estimation, the risk not including the environmental isolates was 'Low Risk'.

Review Comment: Dr. Hyesuk Kong (DBSQC) assessed sterility assay. 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 was in the process of preparing their 2023 Annual Environmental Monitoring Trend Report. They stated 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 was after the PDUFA action date, this assessment was negotiated as a PMC to the Applicant in an information request. In BLA 125812/0.71, the Applicant submitted information related to sterility method qualification that is related to in-house environmental isolates. The DBSQC reviewer assessed the submitted information to be adequate to resolve this issue. Please refer to DBSQC addendum memo for relevant assessment.

3.2.P.5.3 Validation of Analytical Procedures

The Applicant submitted BLA 125812/0.70 on August 30, 2024 in response to the study requested under PMC #6 which was agreed upon previously in BLA 125812/0.61 submitted on July 29, 2024. The agreed PMC #6 was as below:

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

Final Report Submission: August 31, 2024

In (b) (4) 125812/0.70, the Applicant provided a study report of sterility testing per (b) (4) (b) (4) for (b) (4) of (b) (4) (b) (4) per (b) (4) in the excipient (b) (4) from (b) (4). The data show that (b) (4) were recovered from the excipient solution following a (b) (4) (b) (4) after (b) (4) culture period as below (Table 1).

Table 1 Sterility Testing Data for (b) (4)

(b) (4)

The study report supports that SYMVESS does not inhibit or interfere with the sterility testing. This completes the excipient suitability for the sterility assay. The Applicant has performed agreed study under the PMC #6.

Review Comment: The Applicant previously submitted a sample suitability study under (b) (4). In (b) (4), received on March 12, 2013, the Applicant submitted a Complete Response to Clinical Hold including issues related to sample suitability regarding sterility and endotoxin testing. However, the information was not sufficient to support the BLA. They performed a (b) (4) study on SYMVESS and tested for microbial recovery after (b) (4) using (b) (4)

(b) (4) specified in (b) (4) and (b) (4) with (b) (4). However, the testing method was not (b) (4) which utilizes (b) (4). (b) (4) (b) (4) (b) (4) (b) (4). Additionally, they did not include (b) (4) organism in the testing. During the Late-Cycle Communication on May 20, 2024, the Agency raised a concern about missing an (b) (4) microorganism testing for sterility sample suitability. Since the bioburden testing performed previously can support excipient suitability for (b) (4) other microorganisms that overlap with (b) (4) recommendation, the Applicant was asked to perform (b) (4) study using an (b) (4) microorganism on (b) (4) sampling timing per (b) (4). In response to IR#29 (CMC IR#12) sent on June 13, 2024, the Applicant indicated that the PRO-119, HAV (b) (4) Microbial Recovery Study was developed in order to perform a (b) (4) study with an (b) (4)

organism, (b) (4) at (b) (4) for (b) (4) incubation in (b) (4). They indicated that the study report would be available no later than July 22, 2024. However, since this due date was close to the PDUFA action date, this item was negotiated as a PMC study to the Applicant in an information request. The Applicant provided their response to PMC #6 in BLA 125812/0.61, submitted on July 29, 2024. Based on the provided information, the Applicant has adequately provided information to support excipient suitability for the sterility assay and no additional PMC studies are needed.