



Our STN: BLA 125812

**LATE-CYCLE  
MEETING MEMORANDUM**

Humacyte Global, Inc.

Attention: (b) (4)

(b) (4)

Dear Dr. (b) (4)

Attached is a copy of the memorandum summarizing your May 20, 2024 Late-Cycle Meeting with CBER. This memorandum constitutes the official record of the meeting teleconference. If your understanding of the meeting outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact Helen Sansone at (240) 549-2276 or [Helen.Sansone@fda.hhs.gov](mailto:Helen.Sansone@fda.hhs.gov).

Sincerely,

Mara Miller, MA  
Director  
Division of Review Management and Regulatory Review 2  
Office of Review Management and Regulatory Review  
Office of Therapeutic Products  
Center for Biologics Evaluation and Research

### Late-Cycle Meeting Summary

**Meeting Date and Time:** May 20, 2024; 3:00 PM – 4:00 PM ET  
**Meeting Location:** Zoom and In-Person at White Oak, Building 71 – Room 1208/1210  
**Application Number:** BLA 125812  
**Proposed Product Name:** Human Acellular Vessel (under review)  
**Proposed Indications:** Urgent arterial repair following extremity vascular trauma (b) (4) when autologous vein is not feasible (under review)  
**Applicant Name:** Humacyte Global, Inc.  
**Meeting Chair:** Jin Sung Hong, PhD  
**Meeting Recorder:** Helen Sansone

### FDA ATTENDEES

Meghna Alimchandani, MD, CBER/OBPV/DPV  
Tigist Assefa, PharmD, CBER/OTP/ORMRR  
Bethany Baer, MD, CBER/OBPV/DPV  
Michael Brony, PharmD, CBER/OCBQ/DCM/APLB  
Colleen Caldwell, MS, MPH, CBER/OTP/ORMRR  
CDR Leah Crisafi, MD, CBER/OTP/OCE  
Lola Fashoyin-Aje, MD, MPH, CBER/OTP/OCE  
Varsha Garnepudi, MS, RAC, CBER/OCBQ/DBSQC  
Alifiya Ghadiali, PhD, RAC, CBER/OCBQ/DMPQ  
Jin Sung Hong, PhD, CBER/OTP/OCTHT  
Hanh Khuu, MD, CBER/OTP/OCTHT  
Hyesuk Kong, PhD, CBER/OCBQ/DBSQC  
Pratima Labroo, PhD, CBER/OTP/OCTHT  
Carolyn Laurencot, PhD, CBER/OTP/OCTHT  
Robert Lee, MD, CDRH/OPEQ/OHTII/DHTIIB  
Wei Liang, PhD, CBER/OTP  
Heather Lombardi, PhD, CBER/OTP/OCTHT  
Anthony Lorenzo, CBER/OCBQ/DMPQ  
Tiffany Lucas, PhD, CBER/OTP/OGT  
Zainab Mansaray Storms, PhD, CBER/OCBQ/DMPQ  
Adamma Mba-Jonas, MD, MPH CBER/OBPV/DPV/PB  
Mara Miller, MA, CBER/OTP/ORMRR  
Steven Oh, PhD, CBER/OTP/OCTHT  
Lori Peters, CBER/OCBQ/DMPQ  
Vaishali Popat, MD, MPH, CBER/OTP/OCE  
Joseph Quander III, CBER/OCBQ/DMPQ  
Carolyn Renshaw, CBER/OCBQ/DMPQ  
Laura Ricles, PhD, CBER/OTP/OCTHT  
Helen Sansone, CBER/OTP/ORMRR  
Andrey Sarafanov, PhD CBER/OTP/OPPT/DH/HB2

Wen (Aaron) Seeto, PhD, CBER/OTP/OCTHT  
Prateek Shukla, MD, CBER/OTP/OCE  
Ramani Sista, PhD, CBER/OTP/ORMRR  
Wei Tu, CBER/OCBQ/DBSQC/LBVI  
Triet Tran, PharmD, BCSCP, CBER/OCBQ/DIS  
Nicole Verdun, MD, CBER/OTP  
Thomas Zhou, PhD, CBER/OBPV/DB  
Tingting Zhou, PhD, CBER/OBPV/DB

#### **APPLICANT ATTENDEES**

Harold Alterson, SVP, Quality, Humacyte  
Mauricio Berdugo, MD, Sr. Director, Medical Affairs, Humacyte  
Cindy Cao, PhD, Chief Regulatory Officer, Humacyte

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Jeff Jones, MS, Global Head of CMC Regulatory Affairs, Humacyte  
Zak Khondker, PhD, Executive Director and Head of Biometrics, Humacyte  
Rob Kirkton, PhD, Director, New Product Development, Humacyte  
Rubina Mondal, MS, Sr. Director, Regulatory Affairs, Humacyte  
Laura Niklason, MD, PhD, Founder and Chief Executive Officer, Humacyte  
Shamik Parikh, MD, Chief Medical Officer, Humacyte  
Heather Prichard, PhD, Chief Operations Officer, Humacyte  
Warren Prosser, Executive Director, Clinical Operations, Humacyte  
Manira Rayamajhi, PhD, Sr. Director, Regulatory Affairs, Humacyte  
Mark Tulchinsky, MD, Head of Pharmacovigilance and Safety, Humacyte  
Matt Udelhofen, Associate Director, MSAT, Humacyte

#### **BACKGROUND**

BLA 125812 was submitted on December 11, 2023 for SYMVESS

Proposed indication(s): Urgent arterial repair following extremity vascular trauma (b) (4)  
(b) (4) when autologous vein is not feasible (under review)

PDUFA goal date: August 10, 2024

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on May 10, 2024.

## DISCUSSION

### 1. Discussion of Substantive Review Issues

#### **Chemistry, Manufacturing, and Controls (CMC)**

- Extractables and Leachables study related issue: Extractables study data for the final container closure (components) and analysis aligning these data with results of the leachables study is pending from the Applicant. The extractables study performed by the Applicant represents a simulated/accelerated leachables study and did not follow the common practice recommended by (b) (4). Thus, the leachables evaluation may miss detection of some leachable compounds. CMC IR#8 was sent on April 26, 2024 and the Applicant's response is pending, which is due May 10, 2024.

In an amendment received on May 6, 2024, the Applicant has submitted extractable study data from the vendors of the final container closure components and this is currently under review by the FDA. The Applicant stated that they are working with a consultant to perform a material assessment for the (b) (4) bag assembly and associated components that compose the final container closure for the drug product. The Applicant plans to submit a comprehensive report on or before June 7, 2024.

- Excipient sample suitability issue: Excipient sample suitability for sterility and endotoxin needs clarification and further information. A sterility sample suitability study report was submitted to (b) (4) but not to the BLA. For sterility testing, it is unclear whether the study utilized a testing method following (b) (4) with appropriate aerobic and anaerobic bacteria. For endotoxin testing, the testing condition regarding (b) (4) concentration level is unclear. CMC IR#8 was sent on April 26, 2024 and the Applicant's response is pending, which is due May 10, 2024.
- Shipping validation study: The submitted shipping study is limited to information on the temperature control capability of the shipper and does not include any evaluations for drug product quality and safety. CMC IR#8 was sent on April 26, 2024 and the Applicant's response is pending, which is due May 10, 2024.

#### **Clinical**

- We note that the BLA submission includes long-term follow up data for 7 of 54 subjects in the analysis set (that is extremity trauma population) in clinical trial CLN-PRO-V005. Notably, 37 patients (69%) had less than one year follow-up. Our review is ongoing to determine whether the extent of follow up for safety is sufficient to describe the risks of HAV.

- Clinical trial population: FDA’s review of the proposed indication is ongoing and will likely require additional clarity from the applicant regarding the patients in whom use of the autologous vein is not “feasible.”

**Meeting Discussion:**

**Chemistry, Manufacturing, and Controls (CMC):**

Extractables and Leachables: FDA requested that Humacyte provide a list of all the final container closure components and clarify what components have been evaluated for extractables. Humacyte agreed to provide the information and stated they will provide a report to address the gap in the extractables and leachables study. They also stated said they are in the process of assessing the leachables information. FDA commented that this plan is acceptable and noted that the Applicant should consider all container closure materials which contact the media in the assessment. The Applicant confirmed they will conduct the requested analysis.

Excipient sample suitability: Humacyte clarified SYMVESS did not interfere with the endotoxin and sterility test and the methods qualification data have been already submitted. Regarding sterility, FDA stated that the excipient suitability study performed during the IND stage did not include any anaerobic organisms. FDA recommended an anaerobic microorganism be tested in a (b) (4) study per (b) (4) using a sample from the (b) (4) time-point to demonstrate excipient sterility sample suitability. FDA will follow-up with an information request.

Shipping Validation: Humacyte proposed a shipping study plan and stated they will provide a final report. FDA expressed concerns on relying on the shipper validation study for the (b) (4) conditions which are not representative of the real-world situation (b) (4) FDA recommended that Humacyte consider the worst-case scenario (b) (4) (b) (4) in the shipping validation study. FDA will follow up with an information request to ask for Humacyte’s shipping validation plan, including the timeline. In response to Humacyte’s question about allowing the shipping validation study to be completed as a PMC, FDA stated that PMC negotiations will occur no later than July 11, 2024.

(b) (4) Validation: Humacyte indicated that (b) (4) will continue the sterilization validation study with the (b) (4) design and perform additional study with the (b) (4) design to comply with (b) (4) requirements. Humacyte plans to submit the progress and information. FDA requested that the information be submitted earlier than July 24, 2024 since it is close to the PIDUFA due date for the file. FDA suggested that Humacyte could routinely perform aseptic process simulations (APS) to show the bioreactor is maintaining sterility until the sterilization validation study is completed. Regarding this proposal, Humacyte asked if they could test for

sterility using (b) (4) buffer instead of performing APS studies. FDA stated that this approach will need to be discussed internally.

**Clinical:**

Long Term Follow up: Humacyte presented long-term follow-up data indicating that the majority of safety events occurring within the first 6 months after product implantation. The Applicant also referenced 6 years of data from the peripheral artery disease (PAD) study contributing to claims of mechanical stability. Humacyte believes that the data is suitable to show safety. The Applicant agreed to provide this information on long-term follow up and FDA advised that this will be taken into consideration during the ongoing review.

The Applicant clarified that three subjects added during the 120-day safety report were not included in the long term follow up data as they were enrolled after the date of data cutoff for the original BLA submission. Follow up data for these three subjects has been requested in clinical IR and will be provided as requested.

Clinical Trial Population: Humacyte provided explanation to justify the term, “feasible” used in their proposed indication and references to prior FDA communications. FDA acknowledged that this term has been used during the development program and advised that this will be taken into consideration during the ongoing review. Further discussion regarding the appropriate phrasing of the clinical indication will occur during labeling negotiations.

2. Discussion of established Pharmacologic Class

a. Acellular Tissue Engineered Vessel

**Meeting Discussion:**

No discussion during the meeting.

3. Discussion of Minor Review Issues

**Chemistry, Manufacturing, and Controls (CMC)**

Sterility assurance commitment: In response to Observation #1 from the Pre-License Inspection (PLI), received on April 26, 2024, the Applicant indicated that they opened CAPA-2024-03 to assess the addition of a sterile filtration step or re-design of the (b) (4) preparation process to be a (b) (4) (b) (4). However, the Applicant did not provide a commitment to ensure implementation of a sterility assurance strategy.

**Meeting Discussion:**

Sterility Assurance Commitment: FDA elaborated on the 483 Observation #1 and acknowledged the investigation plan that Humacyte has proposed. Humaycte

indicated that they are committed to implement a sterility assurance strategy no later than November 13, 2024. FDA asked Humacyte to share the progress and information collected from their investigation. FDA stated that PMC negotiations will occur no later than July 11, 2024.

#### 4. Additional Applicant Data

**Meeting Discussion:**

Humacyte submitted a revised slide deck on May 17, 2024 with responses to the agenda items. Please refer to item #1 and #3 above.

#### 5. Information Requests

- a. Information Request #23 (pending response by May 22, 2024): Lot Release Protocol Template
- b. Information Request #24 (pending response by May 24, 2024): Questions regarding visual inspection AQL, air/gas qualification, disinfectant efficacy study, and (b) (4) sterilization validation

**Meeting Discussion:**

On May 17, 2024, two additional information requests were sent to Humacyte Global:

- a. Information Request #25 (pending response by May 24, 2024, instead of May 22, 2024): Additional clinical information about select study subjects , imaging compliance, time to event analysis, information to support proposed labeling (Section 2.3).
- b. Information Request #26 (pending response by May 31, 2024): Follow-up identity testing for (b) (4) FMEA study report, DNA testing and specification, (b) (4) analysis for clinical batches, container and carton labeling, LoA, (b) (4) bag assembly and components.

#### 6. Discussion of Upcoming Advisory Committee Meeting

- a. An Advisory Committee meeting is not planned

**Meeting Discussion:**

No discussion during the meeting

#### 7. Risk Management Actions (e.g., REMS, the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk)

- a. There is no anticipation of a REMS at this time.

**Meeting Discussion:**

No discussion during the meeting.

8. Postmarketing Requirements/Postmarketing Commitments

- a. The pharmacovigilance plan is under ongoing review and further comments on any postmarketing study will be provided as needed.

**Meeting Discussion:**

No discussion during the meeting.

9. Major Labeling Issues

- a. Labeling review is ongoing. FDA is considering a boxed warning about rupture risk in the setting of HAV infection which was noted in both extremity and torso/iatrogenic groups.

**Meeting Discussion:**

Labeling review is still ongoing however there are concerns regarding rupture risk noted in both the Applicant's study report and case summaries. The Applicant advised that rupture risks are not unique to their product and that similar failure of grafts has been seen in both the use of autologous veins and synthetic grafts. Humacyte provided further data from subject (b) (6) and subject (b) (6) highlighting non-infectious contributors to loss of graft patency. The applicant proposed to add additional verbiage in section 5 of the USPI warnings and precautions. FDA also highlighted ongoing concerns related to the Applicant's claim of infection resistance. FDA will further communicate any concerns about risks of rupture during labeling negotiations. FDA requested additional long-term data to assess risk of rupture for peripheral arterial disease and dialysis clinical trials. Humacyte agreed that they will collect and submit the data.

10. Review Plans

- a. Review of the BLA is on-going. We will continue sending IRs as necessary to get clarification on any submitted information. FDA plans to start label negotiations no later than July 11, 2024.

**Meeting Discussion:**

No discussion during the meeting.

11. Applicant Questions

**Meeting Discussion:**

Humacyte asked if it is acceptable to submit the Lot Release Protocol (LRP) based on their drug product release testing results which is currently conducted prior to completion of drug product operations (i.e., tray sealing, (b) (4) and cartoning). FDA agreed that this plan is acceptable.



FDA stated Humacyte may establish the upper limit of release specification for (b) (4) based on (b) (4) batches. PMC negotiations will occur no later than July 11, 2024.

Please refer to meeting discussion in agenda 2 regarding the adequate use of the word, “feasible”.

## 12. Wrap-up and Action Items

- a. The Late Cycle Meeting Summary will be sent by June 19, 2024

### **Meeting Discussion:**

No discussion during the meeting.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.