

CBER Facility/CMC BLA Review Memorandum

BLA STN 125717/0

Product Name: Zynteglo (betibeglogene autotemcel, beti-cel)

Wei Wang, Ph.D./Microbiologist/OCBQ/DMPQ/B3

1. **BLA#:** STN 125717/0

2. **APPLICANT NAME AND LICENSE NUMBER**

bluebird bio, Inc. (abbreviated as bluebird) US License # 2160

3. **PRODUCT NAME/PRODUCT TYPE**

USAN: Betibeglogene autotemcel, beti-cel

Proprietary Name: Zynteglo

Other names: LentiGlobin BB305 Drug Product, (b) (4)

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

- a. **Pharmacologic Class:** Betibeglogene autotemcel is a gene therapy consisting of autologous CD34+ cells containing hematopoietic stem cells (HSC) transduced with lentiviral vector (LVV) encoding β^{A-T87Q} -globin.
- b. **Dosage form:** Suspension for intravenous infusion
- c. **Strength/Potency:** (b) (4) -20×10^6 cells/mL
- d. **Route of administration:** Intravenous
- e. **Indication(s):** treatment of patients with β -thalassemia who require regular red blood cell (RBC) transfusions

5. **MAJOR MILESTONES**

First Committee Meeting	Friday, October 15, 2021, 12-1 PM
Filing Meeting	Friday, November 5, 2021, 3-4 PM
Mid-cycle Meeting	January 18, 2022
Pre-License Inspection	February 14-18, 2022
Late-cycle Meeting	May 23, 2022
Advisory Committee Meeting	June 9 – 10, 2022
PDUFA Action Date	August 19, 2022

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

Reviewer/Affiliation	Section/Subject Matter
Wei Wang/OCBQ/DMPQ/B3	Manufacturing facilities, equipment and CMC (Sections 3.2.S, 3.2.P, and 3.2.A.1)

7. **INTER-CENTER CONSULTS REQUESTED**

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
None		N/A

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
9/20/2021	STN 125717/0.1 (part 2 of 2)	Module 3, Reviewed
11/30/2021	STN 125717/0.8 (response to CBER IR dated 11/19/2021)	Update 3.2.S.2.1 LVV, Reviewed
11/30/2021	STN 125717/0.9 (response to DMPQ IR dated 11/16/2021)	Comparisons of facility and equipment between BLAs 125717/0 and 125755, Reviewed
4/22/2022	STN 125717/0.55 (response to DMPQ IR dated 4/6/2022)	Container closure integrity test (CCIT) method sensitivity

9. Referenced REGULATORY SUBMISSIONS (including IND and Master File)

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	Defer to OTAT reviewers
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	Defer to OTAT reviewers
MF (b) (4)	Lonza Houston Inc.	Lonza Houston Cell and Gene Therapy Manufacturing Facility	Yes	No DMF review required, information pertinent to manufacturing facility is provided in the BLA
BB-MF (b) (4)	(b) (4)	Type V Master File, Manufacturing and Laboratory Facilities and Quality Systems	Yes	No DMF review required, information pertinent to manufacturing facility is provided in the BLA

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

bluebird submits this BLA, STN 125717/0, for its new gene therapy product beti-cel for the treatment of patients with β -thalassemia who require regular red blood cell (RBC) transfusions. Beti-cel consists of autologous CD34+ cells containing hematopoietic stem cells (HSC) which are transduced with a BB305 lentiviral vector (LVV) encoding β^{A-T87Q} -globin.

The drug substance (DS) critical component (i.e., BB305 LVV) is manufactured at the (b) (4) site (abbreviated as (b) (4) and beti-cel (b) (4) drug product (DP) are manufactured at the Lonza Houston Inc., TX site (abbreviated as LHI, FEI #3013629214). The manufacturing of BB305 LVV was covered during a surveillance inspection of (b) (4) by the Office of Regulatory Affairs (ORA) in (b) (4) per DMPQ request. This inspection of (b) (4) was classified as Voluntary Action Indicated (VAI) and all observations listed in the Form 483 have been resolved.

CBER performed the pre-license inspection (PLI) of the LHI facility in February 2022 for the manufacture of beti-cel (and eli-cel under the other BLA 125755/0 from the applicant) (b) (4) DP. No Form 483 was issued at the end of this PLI, and the inspection was classified as No Action Indicated (NAI).

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

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

B. RECOMMENDATION

I. APPROVAL

Based on information reviewed in this submission, approval is recommended with one post-approval commitment from DMPQ. The applicant commits to provide the sensitivity of a (b) (4) container closure integrity test (CCIT) method by February 28, 2023. Under this license, the applicant is recommended for approval to manufacture the DS component, BB305 LVV, at (b) (4) the beti-cel DS, the final formulated beti-cel DP, filling, labelling, and packaging at Lonza Houston, Inc., Houston, TX, US.

II. COMPLETE RESPONSE (CR)

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Wei Wang, Ph.D./Microbiologist OCBQ/DMPQ/B3	Concur	
Jie He, Team Lead OCBQ/DMPQ/B3	Concur	
Carolyn Renshaw, Division Director OCBQ/DMPQ	Concur	

Review of CTD

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Module 3

3.2.S DRUG SUBSTANCE

beti-cel DS is autologous CD34+ cell-enriched population that contains hematopoietic stem cells (HSCs) transduced with BB305 LVV encoding the β^{A-T87Q} -globin gene.

Review Comments: DMPQ defers to the Office of Tissues and Advanced Therapies (OTAT) reviewers to review sections 3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties.



3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Table 1 lists the sites (updated in the amendment, STN 125717/0.8, received on 11/30/2021) for manufacture, testing, and storage of BB305 lentiviral vector which is used to manufacture betibeglogene autotemcel (beti-cel) under this BLA, STN 125717/0.

(b) (4)

(b) (4)



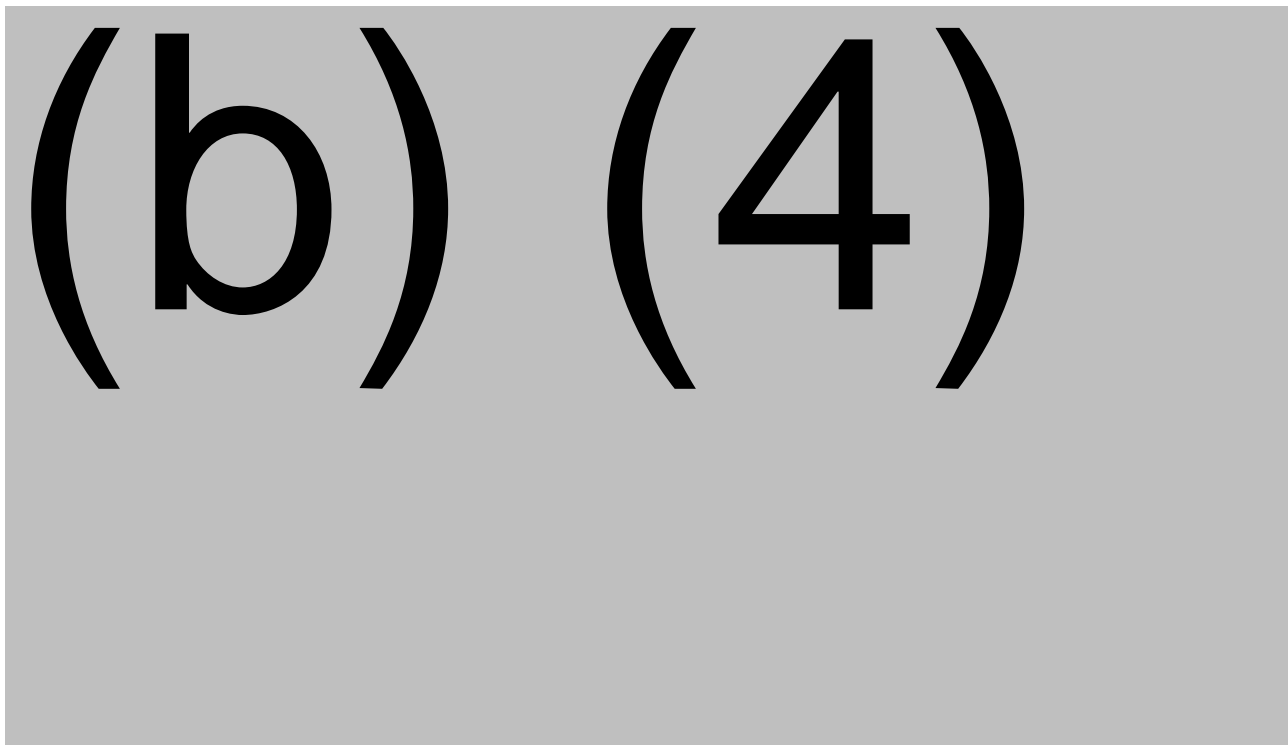
3.2.S.2.2 Description of Manufacturing Process

Manufacturing Process Steps

Table 3 summarizes the BB305 LVV manufacturing process steps and information on manufacturing equipment and manufacturing rooms. Table 4 summarizes the beti-cel DS and DP manufacturing process steps and information on manufacturing equipment and manufacturing rooms.

Review Comments: The Tables 3 and 4 are composed based on information provided in Section 3.2.S.2.2 Description of Manufacturing Process and Controls of the original BLA, STN 125717/0 (CBER received on 9/20/2021) and the amendment, STN 125717/0.9 (CBER received on 11/30/2021).

(b) (4)



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

Beti-cell Process Step (Room)	Equipment
(b) (4)	(b) (4)
(b) (4)	(b) (4)
<u>Formulation*, Filling* (including Initial Product and Cassette Labeling)</u> (b) (4), Room (b) (4) or (b) (4), Room (b) (4))	(b) (4) (Grade (b) (4) (b) (4)
<u>Visual Inspection, Final Product Labeling*</u> (Room (b) (4)	Visual Inspection Station
<u>Cryopreservation*</u> (Room (b) (4)	(b) (4) freezer Liquid nitrogen (b) (4)
<u>beti-cel Storage*</u> (Long-Term Storage Area (b) (4)	Liquid Nitrogen Storage Freezer
<u>beti-cel Shipment</u> (Staging Dock Area (b) (4)	Cryoshipper - (b) (4)

*These are beti-cel drug product manufacturing steps. There is no hold-step between drug substance and drug product manufacturing processes.

Review Comments: DMPQ defers to OTAT to review all IPCs for the manufacture of BB305 LVV and beti-cel.

BB305 LVV Batch Numbering, (b) (4) and Scale Definition

Review Comments: DMPQ defers to the OTAT reviewers to review this section. DS, beti-cel, is patient specific batch.

BB305 LVV Storage and Shipping

The applicant stated that “BB305 LVV vials are stored at $\leq -65^{\circ}\text{C}$. After release, the vials may be shipped to a (b) (4) beti-cel manufacturing site (see Table 2). Vials are packed in shipping containers containing

(b) (4) to maintain temperatures $\leq -65^{\circ}\text{C}$. Temperature monitoring is performed during transit of all BB305 LVV shipments”.

Review Comments: The primary container closure system (CCS) for BB305 LVV is reviewed in 3.2.S.6 LVV. The LVV shipping validation is reviewed in 3.2.S.2.5 LVV.

DMPQ defers to OTAT reviewers to review the following sections for the adequacy of IPC limits or acceptance criteria:

- *3.2.S.2.3 Control of Materials*
- *3.2.S.2.4 Controls of Critical Steps and Intermediates*

3.2.S.2.5 Process Validation and/or Evaluation

(b) (4)

(b) (4)

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

(b) (4)

[REDACTED]

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

(b) (4)

- (b) (4)

3.2.P DRUG PRODUCT

beti-cel DS is autologous CD34+ cell-enriched population that contains hematopoietic stem cells (HSCs) transduced with BB305 LVV encoding the β A-T87Q-globin gene. The sole excipient in beti-cel is (b) (4) which is a commercially available, protein-free cryopreservation solution.

Review Comments: DMPQ defers to OTAT reviewers to evaluate the following Sections, except that study of the container closure integrity test (CCIT) is reviewed by both OTAT and DMPQ:

- 3.2.P.1 *Description and Composition of the Drug Product*
- 3.2.P.2 *Pharmaceutical Development*
 - 3.2.P.2.1 *Components of the Drug Product*
 - 3.2.P.2.2 *Drug Product – Formulation, Overages, Physicochemical and Biological Properties*
 - 3.2.P.2.3 *Manufacturing Process Development*
 - 3.2.P.2.4 *Container Closure System (CCS) – DMPQ defers to OTAT to review (i) CCS suitability with respect to materials of construction, protection from moisture, light, oxygen, and adsorption of the Drug*

Product to the container, (ii) E&L studies and data as it pertains to safety and product quality.

- 3.2.P.2.5 *Microbiological Attributes - beti-cel is comprised of living cells and is manufactured under aseptic conditions. All container-closure components and excipients are verified to be sterile before use. DP lot release testing includes compendial methods for safety; sterility and endotoxin samples are aseptically obtained from the final container immediately prior to freezing of the DP bag. The drug product is stored frozen and does not contain preservatives. The final beti-cel container is a fluorinated ethylene propylene (FEP) film bag. Each bag is (b) (4) by the manufacturer. Bags are (b) (4) sterilized by the vendor. Each lot is evaluated for sterility and endotoxin.*
- 3.2.P.2.6 *Compatibility*

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The manufacturing and testing sites for beti-cel are listed in Table 8.

Table 8. Manufacturing and Testing Facilities for the drug Product beti-cel

Facility	Identification Numbers	Responsibility
Lonza Houston, Inc 14905 Kirby Dr. Houston, TX 77047 USA	FEI: 3013629214* DUNS: 832903004	Drug product manufacturing, packaging, labeling; and in-process, release testing
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Drug product release testing and stability testing
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Drug product release testing and stability testing
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Drug product release and stability testing
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Drug product release and stability testing

*PLI of this site was performed 2/14/2022 to 2/18/2022, and the PLI was classified as No Action Indicated (NAI).

**PLI of this site was waived. The Inspection Waiver memo was uploaded to CBER Connect on (b) (4)

Review Comments: DMPQ defers to OTAT to review the following sections:





- 3.2.P.3.2 Batch Formula
- 3.2.P.3.3 Description of Manufacturing Process – also see Table 4 of this review memo.
- 3.2.P.3.4 Controls of Critical Steps and Intermediates

3.2.P.3.5 Process Validation and/or Evaluation

Aseptic Process Simulation

Review comments: DMPQ defers to OTAT to perform comprehensive review of Process Validation and/or Evaluation and the manufacture of beti-cel PPQ lots. The following APS documents were submitted in Module 3.2.P.3.5 and were reviewed:

(b) (4)



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

(b) (4)

(b) (4)

3.2.P.4 Control of Excipients to 3.2.P.6 Reference Standards or Materials

Review Comments: DMPQ defers to OTAT to review the following sections, except release testing results of sterility and endotoxin:

- 3.2.P.4 Control of Excipients
 - 3.2.P.4.1 Specifications
 - 3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures
 - 3.2.P.4.4 Justification of Specifications
 - 3.2.P.4.5 Excipients of Human or Animal Origin
 - 3.2.P.4.6 Novel 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).
 - 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures. *Noted, the applicant used a validated (b) (4) method to evaluate the final drug product container closure integrity (CCI) of the (b) (4) bag under normal use and DP transportation and storage conditions (see Section 3.2.P.7 for review of CCIT under the DMPQ purview). DMPQ defers to OTAT device review team to further evaluate additional tests required for the (b) (4) bag.*
- 3.2.P.5.4 Batch Analyses – *The release testing results (e.g., Sterility and Endotoxin) under the DMPQ purview all met pre-defined acceptance criteria of Sterility (No Growth) and Endotoxin (b) (4) per kg patient weight, or (b) (4)*
- 3.2.P.5.5 Characterization of Impurities
- 3.2.P.6 Reference Standards or Materials

3.2.P.7 Container Closure System

The container closure system for beti-cel consists of a primary package container (i.e., (b) (4) Cryopreservation bag), a secondary package container (b) (4) and a tertiary package container (a metal cryo-cassette).

Primary Packaging

The primary container closure for beti-cel is the (b) (4), a 20-mL fluorinated ethylene propylene (FEP) cryopreservation bag, manufactured by (b) (4). In Section 3.2.P.7 of STN 125717/0.1, the applicant provided specifications and technical information as well as representative drawing of the (b) (4) bag.

The applicant stated the following:

- The (b) (4) bag has been demonstrated to meet (b) (4) requirements.

- (b) (4) bags are manufactured under cGMP in an ISO (b) (4) clean room and are (b) (4) tested with (b) (4)
- The bags are (b) (4) by the manufacturer using a (b) (4) that is validated to achieve a (b) (4) (b) (4)
- (b) (4) bags are accepted for use at the beti-cel manufacturing site based on visual inspection and review of vendor certificates for (b) (4)
- Sterility (Acceptance criteria: no growth) and endotoxin (acceptance criteria: (b) (4) testing are performed on (b) (4) bag from each lot received.

Review Comments: DMPQ reviewed the CCIT method validation for the DP (b) (4) bag. DMPQ defers to the OTAT device review to evaluate the suitability and additional physical characteristics of the DP primary package container.

Container Closure Integrity Test

The applicant stated that the container closure integrity (CCI) of the (b) (4) bags was tested and confirmed and provided the following documents in Section 3.2.P.2 of STN 125717/0.1:

- (b) (4) [REDACTED]

(b) (4)

Review Comments: While the results of both positive controls and the bacteriostasis controls demonstrated the suitability to the described CCIT method, the applicant did not provide any information of the sensitivity of its CCIT-(b) (4) method to indicate if the method is able to detect critical leakage sizes that are much smaller than the positive control (i.e., (b) (4)). DMPQ requested the applicant to provide this missing information.

Information Request and Responses

The following information request (IR) items were sent to the applicant on 4/6/2022 and the responses were received on 4/22/2022 (STN 125717/0.55).

In your BLAs, STNs 125717/0 and 125755/0, you submitted a qualification summary for the container closure integrity testing (CCIT, (b) (4)) method used for the cryopreservation bag (cryo-bag) for the autologous drug products beti-cel (125717/0) and eli-cel (BLA 125755/0). You stated that a (b) (4) is used as a positive control during the CCIT method validation and the routine CCIT tests. You stated that each test article was examined for growth after the (b) (4) periods.

1. To justify the use of a larger leakage size (i.e., (b) (4)) as a positive control in your routine CCIT, please provide the information of the sensitivity (e.g., (b) (4)) of your CCIT method.

The applicant response: The (b) (4) testing was conducted as supportive testing for the drug product cryopreservation bag container closure integrity evaluation to establish the ability of the bag to maintain the sterile barrier under challenge conditions (including (b) (4)). Bluebird bio wishes to clarify that this method has not been and is not intended for routine testing for commercial release or on stability program in lieu of sterility testing for drug product. Currently, a (b) (4) method is being developed for CCIT, and following successful validation this method could be considered as an alternative for sterility testing in stability programs.

The (b) (4) size used as the positive control for the (b) (4) test represents the lowest defect size that was tested by (b) (4) for this container. However, the (b) (4) control demonstrated that when (b) (4), contamination (b) (4) can be detected using this method.

Review Comments: The applicant did not provide the requested information of the sensitivity of its CCIT method, even though the applicant stated that the (b) (4) represents the lowest defect size that was tested by (b) (4). Noted, the (b) (4) represents a leakage size of approximately (b) (4).

Given that the (b) (4) method is considered more sensitive, DMPQ will follow-up with the applicant on the time-line of implementing the (b) (4) CCIT method.

2. Please clarify whether your methods of examination of test articles for (b) (4) are based on visual inspection (human eyes) and/or (b) (4) and if you have information regarding what (smaller than (b) (4)) leakage sizes your examination method(s) are able to detect 100% positive controls for (b) (4)

The applicant response: The test articles, positive control and negative control were inspected via a visual qualitative measure while the (b) (4) control was inspected via both a visual qualitative measure and by (b) (4). All positive controls showed (b) (4) in the (b) (4) bags using the lowest method sensitivity for defect size (b) (4). The (b) (4) controls showed (b) (4) following (b) (4) (average (b) (4) however those samples were prepared by (b) (4) therefore it is not possible to provide information on the limit of detection for defects smaller than the (b) (4).

Review Comments: Because the applicant has not conducted study to determine the sensitivity for its CCIT method (see IR Item 1), the applicant was unable to provide information requested.

3. Please clarify if the container closure system has been verified to be able to maintain integrity after storage and transportation conditions.

The applicant response: The container closure system was verified to maintain integrity after storage and transportation conditions in the (b) (4) study VAL-VEN-RPT-0126.

Review Comments: Given that the test samples were prepared by the applicant and shipped (frozen) to (b) (4), the primary container system could be considered to have been verified to maintain integrity after storage and transportation based on the VAL-VEN-RPT-0126. As mentioned above, the applicant did not provide the information of the sensitivity of the (b) (4) CCIT method, it remains questionable what the critical leakage size can be detected by this CCIT method.

4. It is recommended to perform CCIT in lieu of sterility test when sterility assurance is assessed in your stability program.

The applicant response: Due to the flexible cryopreservation bag used for the drug product final container and the sizing of this container, there is not a well-established method available yet other than sterility. A (b) (4) CCIT method is being developed. The feasibility study for the (b) (4) (stability) and (b) (4) (drug product) containers has been completed and the initial method parameters consistently distinguish between positive controls sized (b) (4) and negative controls. The method parameters were optimized to improve sensitivity and robustness, and the ability to incorporate the method into the stability program testing will be assessed following completion of the method development and validation.

Review Comments: The applicant's responses (i.e., test the sterility for stability) appeared acceptable. The ongoing development of the (b) (4) CCIT method appeared appropriate using a positive control with a defect size of (b) (4). Noted, during the late-cycle meeting (5/23/2022), DMPQ asked the applicant about a timeline for change from the (b) (4) CCIT method to a more sensitive (b) (4) method. Bluebird stated that the new method is still under development and did not provide a timeline for implementation.

Post-Approval Commitment

Review Comments: In the applicant's response (received by CBER on 6/30/2022, STN 125717/0.78) to an OTAT request to test CCI under worst scenario conditions, specifically including multiple freeze/thaw cycles (Item #2 of IR dated 6/6/2022), the applicant indicated that a new "study design considers the feedback from FDA regarding the need for smaller defect sizes in positive controls, provided in DMPQ IR02 dated 06APR2022, and will utilize positive controls with defects below the range of visual inspection".

It is unclear, in the new study design if the applicant "will utilize positive controls with defects below the range of visual inspection" to determine the sensitivity of its (b) (4) CCIT method, or to replace the current positive control (i.e., (b) (4) which was to demonstrate the suitability of (b) (4) CCIT method.

DMPQ sent the following IR to the applicant on 7/18/2022 and the applicant's response was received on 7/22/2022.

The DMPQ has the following post-approval commitment (PMC) items:

You have utilized a (b) (4) container closure integrity test (CCIT) method to verify the integrity of (b) (4) bag under conditions of normal use, storage and transportation by using (b) (4) (which represents a defect size of approximate (b) (4) as positive controls without demonstrating the sensitivity of this method.

- a) Please commit to provide a definite timeline for implementing a (b) (4) CCIT method, as you stated in your response (received by CBER on 4/22/2022) to the DMPQ IR dated 4/6/2022, to replace the current (b) (4) CCIT method. And please provide new CCIT data from a study using the (b) (4) for the (b) (4) bag by 28Feb2023.
- b) If you are not able to fulfill the commitment described immediately above, please commit to provide the information of the sensitivity of the current the (b) (4) CCIT method by 28Feb2023.

The Applicant's Response:

- a) bluebird bio commits to providing sensitivity of the current (b) (4) container closure integrity (CCI) method by 28 Feb 2023.

A revised (b) (4) testing plan (b) (4) uses (b) (4) controls with defect size of (b) (4). Additional (b) (4) controls ranging from (b) (4) will be evaluated to establish the sensitivity of the (b) (4) method for the (b) (4) bag.

- b) bluebird bio is continuing to develop the (b) (4) method with the intent of validating this method for use with (b) (4) cryopreservation solution filled bags.

Review Comments: The applicant responses were acceptable.

3.2.P.8 Stability

Review Comments: The submitted stability data submitted in Section 3.2.P.8.3 Stability Data under the DMPQ purview all met acceptance criteria, including Sterility (acceptance criteria: No Growth) and Endotoxin (Acceptance criteria: (b) (4))

DMPQ defers to OTAT to evaluate the adequacy of the following stability protocols submitted in Section 3.2.P.8.1 Stability Summary and Conclusion:

- Long-term stability ($\leq -140^{\circ}\text{C}$ for 12-months)
- Accelerated stability (b) (4)
- Stress stability (b) (4)

DMPQ defers to OTAT to evaluate the adequacy of additional stability data and any impact of storage on the DP safety, quality, identity, and potency. DMPQ defers to

OTAT to review the Section 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment.

3.2.A.1 Facilities and Equipment

Facility and Equipment (b) (4)

Overview

(b) (4)

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

(b) (4)

Facility and Equipment (LHI)

Major Equipment Overview

LHI is contracted by the applicant to manufacture beti-cel (and eli-cel, under BLA 125755/0) (b) (4) DP. The LHI facility consists of (b) (4)

(b) (4)

HVAC System and Utilities

The HVAC system performance has been established to maintain controlled environmental conditions through IQ/OQ of both manufacturing suites, (b) (4) The HVAC system was covered during the PLI, including review the recent HVAC and High Efficiency Particulate (Air HEPA) filter re certification reports. Briefly,

- (b) (4)

- (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Prevention of Contamination and Cross-Contamination

Prevention of contamination and cross-contamination is achieved through the facility design features and the application of LHI's control and operational measures used in the facility.

Facility Design: The following facility features are designed to prevent contamination and cross-contamination:

- (b) (4)

Procedural Controls: Following procedures are in place to prevent contamination and cross-contaminations:

- (b) (4)

Environmental Monitoring

EM is performed to ensure the facility is operating within a state of microbial control. All manufacturing activities at LHI take place in the appropriate class of environment following the established guidelines and requirements

Lonza SOP USWV-30403: *Central Environment Monitoring Procedure* governs the EM program in LHI. Each cleanroom suite (e.g., (b) (4)) has its own EM program to specify sampling locations, frequencies, and alert and action limits. Action levels are driven by ISO (b) (4)

and FDA Aseptic Processing of Biological Products Guidance.

Review Comments: The submitted facility floor maps, flow diagrams, HVAC zoning maps, and cleanroom classification appeared acceptable. Furthermore, CBER (DMPQ and OTAT) conducted a PLI of the LHI (FEI: 3013629214) from 2/14/2022 to 2/18/2022 in support of two BLAs, STNs 125717/0 (beti-cel) and 125755/0 (eli-cel).

The PLI of Lonza Houston facility was conducted per Compliance Program Guidance Manual-45 Biological Drug Products 7345.848. The equivalent of a Level I inspection covered the following systems (see EIR for details):

- Quality, including review of Quality Manual, Deviation and CAPA procedures, change control procedure.
- Facility and Equipment, including review of qualification HVAC systems, EMPQ of (b) (4) management systems, EM programs, facility and equipment cleaning procedures, major equipment qualifications, flows of personnel, materials, DP samples, and waist. Noted, personnel and material (b) (4)
- Production, including review of APS study report, batch record of the process validation lots, (b) (4), and observation of DP manufacturing steps (e.g., formulation, filling, labeling and visual inspection). Noted, only one product is manufactured in a cleanroom suite (b) (4) and associated production areas (e.g., visual inspection and packaging areas) at a given time.
- Packaging and Labelling
- Laboratory Control.

The PLI included walkthrough inspection of the facility, observation of portions of manufacturing operations, and review of various documents, records and reports including those related to facility and equipment qualification, validation, batch records, training, laboratory, change control, deviation reports, and Corrective and Preventive Action (CAPA). No FDA Form 483 was issued at the end of this PLI. However, discussion items were conveyed to the Lonza Houston management in daily wrap-up meetings and in the final close out meeting (see General Discussions with Management section of EIR).

3.2.R Regional Information (USA)

Review Comments: DMPQ defers to OTAT to review following documents:

- Executed Batch Records
- Method Validation Package
- Combination Products: N/A
- Comparability Protocols: N/A