

**OCBQ SBRA Template as per CBER template T910.07, for STN 125717/0, ZYNTEGLO (betibeglogene autotemcel), bluebird bio Inc.**

**OCBQ review committee members:**

OCBQ/DBSQC reviewer(s) (or LIB Representative) (section 3.b and c): **Claire Wernly, Esmeralda Alvarado Facundo, Varsha Garnepudi, Tao Pan, Most Parvin**

OCBQ/DMPQ reviewer(s) (section 3.d and e): **Wei Wang**

OCBQ/BMB reviewer(s) (section 6.b): **Colonious King**

OCBQ/APLB reviewer(s) (section 8): **Benjamin Cyge, Oluchi Elekwachi**

**Approved by Office Director:** August 4, 2022

**From:** Sarah Lee, RPM, OCBQ/DMPQ

**Forwarded to Product Office:** August 4, 2022

**SBRA Section 3: Chemistry Manufacturing and Controls (CMC)**

**b) Testing specifications**

**DBSQC**

The analytical methods and their validations and/or qualifications reviewed for the ZYNTEGLO drug substance and drug product were found to be adequate for their intended use.

**c) CBER Lot Release**

**DBSQC – CBER Lot Release**

An exemption has been granted from CBER Lot Release testing, including no requirement for submission of product samples to CBER. The basis for this decision is that ZYNTEGLO is an autologous product; as such each lot will treat a single patient. Failure of a single lot will have minimal potential impact on public health.

**d) Facilities review/inspection**

**DMPQ**

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. Inspection histories and activities for facilities involved in the manufacture of beti-cel are summarized in the table below.

**Table: Manufacturing Facilities for beti-cel**

<b>Name/Address</b>	<b>FEI Number</b>	<b>DUNS Number</b>	<b>Waiver or Inspection</b>	<b>Justification and Results</b>
(b) (4)	(b) (4)	(b) (4)	Waived	ORA (b) (4) VAI

Name/Address	FEI Number	DUNS Number	Waiver or Inspection	Justification and Results
<i>drug substance critical intermediates, BB305 LVV, manufacturing and testing</i>				
<b>Lonza Houston, Inc.</b> 14905 Kirby Drive Houston, TX 77047 USA  <i>beti-cel (b) (4)</i> <i>drug product manufacturing and testing</i>	3013629214	832903004	PLI	CBER February 14 - 18, 2022 NAI

CBER conducted a pre-license inspection (PLI) of the Lonza Houston, Inc. facility in February 2022. An FDA Form 483 was not issued, and the inspection was classified as No Action Indicated (NAI).

Office of Regulatory Affairs (ORA) performed a surveillance inspection of (b) (4). All 483 issues were resolved, and the inspection was classified as voluntary action indicated (VAI).

#### e) Container Closure System

##### **DMPQ**

The container closure system (CCS) for beti-cel consists of a primary package container (a 20 mL (b) (4) Cryopreservation bag), a secondary package container (a (b) (4) bag), and a tertiary metal package container (cryocassette). The beti-cel drug product (DP) is filled into (b) (4) bag(s) (e.g., 1 bag for 20 mL DP, or 2 bags for 40 mL DP). The (b) (4) bag is sterile and read-to-use (RTU, manufactured by (b) (4)). Following visual inspection, a product label is applied to the bag, and the product bag is placed inside of a sterile RTU (b) (4) (manufactured by (b) (4)). The (b) (4) bag is (b) (4). The product bag is inserted into a metal cassette that has been labeled with a label containing both product and patient information. The container-closure integrity (CCI) was tested using a (b) (4) method by (b) (4) to determine the primary package container is able to maintain the container integrity under normal use, storage and transportation conditions.

**SBRA Section 6: Clinical /Statistical**

**b) Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance**

**BIMO**

Bioresearch Monitoring inspections were issued for the sponsor and three domestic clinical study sites that participated in the conduct of Study HGB-207, and HGB-212. The inspections did not reveal any issues that impact the data submitted in this original Biologics License Application (BLA).

**SBRA Section 8: Labeling**

**APLB**

The proposed proprietary name, ZYNTEGLO, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on November 5, 2021, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on December 14, 2021.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed Prescribing Information, Patient Package Insert, and package and container labels on August 1, 2022, and found them acceptable from a promotional and comprehension perspective.