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## MEMORANDUM

**To:** BLA File STN 125714/0

**From:** Rabia Ballica, PhD, CMC and Facility Reviewer, OCBQ/DMPQ/BI

**Through:** Lori Peters, MS, Acting Branch Chief, OCBQ/DMPQ/BI  
Carolyn Renshaw, Deputy Division Director, OCBQ/DMPQ

**CC:** Amanda Trayer, RPM, OCBQ/DMPQ/ARB  
Zakaria Ganiyu, RPM, OTAT/DRPM

**Applicant:** Juno Therapeutics, Inc., a Celgene Company

**Product:** lisocabtagene maraleucel (BREYANZI)

**Route of administration:** Intravenous infusion

**Indication(s):** Treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies

**Subject:** DMPQ addendum review memo for final recommendation on Biologics License Application (BLA) STN 125714 (based on the outcome of the pre-license inspections)

**ADD:** November 16, 2020 (missed ADD due to outstanding pre-license inspection stemming from travel limitations due to ongoing COVID-19 public health emergency)

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**Signature Block**

**II. SIGNATURE BLOCK**

| <b>Reviewer/Title/Affiliation</b>                          | <b>Concurrence</b> | <b>Signature and Date</b> |
|--|--------------------|---------------------------|
| Rabia Ballica, Ph.D.<br>CBER/OCBQ/DMPQ/BI                  | Concur             |                           |
| Lori Peters, MS<br>Acting Branch Chief,<br>OCBQ/DMPQ/BI    | Concur             |                           |
| Carolyn Renshaw,<br>Deputy Division Director,<br>OCBQ/DMPQ | Concur             |                           |

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## CONCLUSION AND RECOMMENDATION

This is the DMPQ addendum review memo for the final recommendation on the approval of BLA 125714/0 for lisocabtagene maraleucel (BREYANZI).

The review of the original BLA submission and its amendments was completed prior to the action due date, November 16, 2020. The evaluated information under DMPQ purview (as per CBER SOPP 8404.1) appeared acceptable. The DMPQ review memo was concurred without the final recommendation, because the final recommendation on the BLA approval was not made because the inspection of the (b) (4) facility (contract manufacturer) had not occurred yet and there were outstanding concerns from the JuMP facility inspection prior to the action due date.

Due to the ongoing COVID-19 public health emergency, the pre-license inspection (PLI) of the (b) (4) facility and evaluation of the 483 responses to the observations from the Juno facility inspection could not be completed by the BLA action due date (ADD) and therefore the due date was missed. The PLI of JuMP (Juno) manufacturing facility for lisocabtagene maraleucel drug substance and drug product manufacturing was conducted from October 7-9, 13-16, 2020 with six 483 observations, and the PLI of (b) (4) facility for the (b) (4) lentiviral vector manufacturing was conducted from (b) (4) with four 483 observations. Note the (b) (4) lentiviral vector is a critical component for lisocabtagene maraleucel manufacturing and used to (b) (4). Both PLIs were performed by ORA investigators and both inspections were classified as Voluntary Action Indicated (VAI). For additional information on the inspections, refer to the associated Establishment Inspection Report (EIR) and 483 response assessment memo.

The responses to the 483 observations issued for the JuMP and (b) (4) PLIs and follow-up information requests based on the recommendations of the ORA investigators and unclear and questionable points identified in the 483 responses were provided in the amendments to the BLA file. The CBER inspection support teams and ORA investigators reviewed the response amendments for the JuMP and (b) (4) pre-license inspections and found the responses acceptable (refer to the assessment memos for the 483 responses to the JuMP and (b) (4) observations).

In conclusion, there are no outstanding review and inspectional issues and the issues identified during each inspection do not impact the subject areas covered during the BLA review. Based on the review and evaluation of the information under DMPQ purview that was submitted in the BLA original submission and its amendments and the 483 response amendments, approval of this BLA is recommended with the following inspectional consideration:

Juno and (b) (4) proposed a number of the corrective actions in response to the 483 responses which will be completed by May 2021 and are expected to improve quality systems at both the manufacturing sites. As a verification, a follow up during next inspection of JuMP and (b) (4) facilities (surveillance inspections) is recommended for the implementation and effectiveness of the proposed corrective actions. For the detailed

information on the proposed corrective actions and ORA discussions/recommendations, refer to the 483 response assessment memos and EIRs for both the inspections.

## REVIEW SUMMARY

### Manufacturing Facilities

**Table.** Manufacturing facilities for lisocabtagene maraleucel.

The (b) (4) lentiviral vector is a critical component for lisocabtagene maraleucel manufacturing and used to (b) (4).

| Facility and Address  | FEI and DUNS                              | Manufacturing and Testing Activities   | Inspection/Waiver/ Results   |
|---|---|--|--|
| Juno Therapeutics Inc.<br><br>1522 217th Pl. SE<br>Bothell, WA<br>98021, US | FEI:<br>3011834594;<br>DUNS:<br>079941307 | - CAR-T drug substance (DS) and drug product (DP) manufacturing<br>-Primary and secondary packaging<br>-DP release and stability testing<br>-(b) (4) | ORA Pre-license Inspection<br>10/07-09/2020,<br>10/13-16/2020<br>VAI |
| (b) (4)   | FEI:<br>(b) (4)<br>DUNS:<br>(b) (4)       | (b) (4)  | ORA Pre-license Inspection<br>(b) (4)<br>VAI                         |
| (b) (4)   | FEI:<br>(b) (4)<br>DUNS:<br>(b) (4)       | (b) (4)  | Waived<br>CBER<br>(b) (4)<br>VAI                                     |

CAR: Chimeric Antigen Receptor; DS: Drug Substance; DP: Drug Product

(b) (4); VAI: Voluntary Action Indicated

The information regarding the CMC information provided in the original BLA submission and its amendments were reviewed and evaluated by the product office (PO) and OCBQ reviewers (refer to the final review memos of DMPQ, DBSQC and OTAT). As stated in the DMPQ final review memo, the reviewed and evaluated information under DMPQ purview (as per CBER SOPP 8404.1) appeared acceptable. All the identified deficiencies were addressed with the amendments in response to DMPQ information requests. However, due to the ongoing COVID-19 public health emergency travel restrictions, the inspection of the (b) (4) site was not completed by the BLA action due date, November 16, 2020; thus the Agency did not make a final recommendation regarding this BLA on the date. The pre-license inspection (PLI) of Juno (JuMP) facility for the manufacture of lisocabtagene maraleucel (JCAR017) product was conducted from October 7- October 16, 2020. The (b) (4) inspection was conducted from (b) (4). The pre-license inspections for the JuMP and (b) (4) manufacturing sites were classified as VAI (Voluntary Action Indicated).

The inspection of (b) (4) manufacturing site where the (b) (4) lentiviral vector is manufactured (fill/finish) was waived based on the previous CBER inspection history and the information provided in the original BLA submission and its amendments (refer to the inspection waiver memo).

## **Pre-Inspection Records Reviews**

The pre-inspection records were requested as per FD&C Section 704(a)(4) and reviewed by DMPQ and PO reviewers and information requests (IRs) were submitted as required. A records review was completed for each facility site identified for a pre-license inspection, JuMP and (b) (4) manufacturing facilities.

### Records for JuMP manufacturing facility:

The records provided in the June 19th and October 5th, 2020 amendments to the BLA file were reviewed and appeared acceptable in general. The inspectional items identified based on the review of the records were followed up during the pre-license inspections. For the records review memo, refer to CMS WA# 369518 in CMS.

### Records for (b) (4) manufacturing facility:

The records provided in the June 29th and October 7th, 2020 amendments to the BLA file were reviewed and appeared acceptable in general. The inspectional items identified based on the review of the records were followed up during the pre-license inspections. For the records review memo, refer to CMS (b) (4) in CMS.

## Pre-license Inspections and 483 Responses

### JuMP Pre-License Inspection and 483 Response

#### Summary:

The pre-license inspection of JuMP facility located in Bothell, WA was conducted for the manufacture of lisocabtagene maraleucel product by ORA investigators (October 7-9, 13-16, 2020) and a FDA Form 483 was issued with 6 observations. This inspection covered quality systems, facility and equipment, materials and laboratory controls system, production system, and packaging and labeling. The firm's response was received in an amendment dated November 6, 2020 (Sequence# 84). The responses were initially reviewed by the two ORA inspectors and then by the CBER off-site inspection support team for the final assessment and decision on the acceptability of the 483 responses. Additional information on the 483 responses and the ORA investigators' discussion/recommended was requested and the responses were provided in the December 9<sup>th</sup> (Sequence# 92) and December 18<sup>th</sup> Amendments (Sequence # 95). The CBER inspection support team found all the responses acceptable. However, the CBER inspection support team recommended that the proposed corrective actions (which will be completed by May 2021) be followed up for their implementation and effectiveness during next inspection. Specifically,

1. DMPQ recommended that the effectiveness of the proposed corrective action for SOP-000567 in response to the observation 4 be followed up during next inspection. For additional information on the assessment of the 483 response to the observation 4, refer to the 483 response assessment memo for JuMP PLI.

2. OTAT/DCGT recommended that during the next surveillance inspection the following are evaluated: (b) (5), (b) (7)(E) as described in review of observation 1, the (b) (5), (b) (7)(E) as described in review of observation 2, and (b) (5), (b) (7)(E) as described in review of observation 5.

Note, Juno proposed a number of the corrective actions under DMPQ and PO purview which are expected to improve the quality systems at JuMP and the ones listed above were identified as the most important corrective actions to be given a priority for the follow up. For other corrective actions, refer to the 483 response assessment memo for JuMP PLI.

### (b) (4) Pre-License Inspection and 483 Response

#### Summary:

The pre-license inspection of the (b) (4) manufacturing facility was conducted from (b) (4) by ORA investigators and covered quality systems, facility and equipment, materials and laboratory controls system, production system, and packaging and labeling. A FDA Form 483 was issued with four observations. The firm's response was received in an amendment dated December 18, 2020 (Sequence # 93). The responses were initially

reviewed by the three ORA inspectors and then by the CBER off-site inspection support team for the final assessment and decision on the acceptability of the 483 responses. The Product office (OTAT/DCGT) requested additional information which was provided in the December 23rd Amendment (Sequence # 96). All the responses were found to be acceptable (refer to the 483 response assessment memo). The investigators' discussion items were also evaluated by the off-site inspection support team and found to be minor and would not impact the approval of the BLA. However, the CBER inspection support team recommended that the proposed corrective actions (which will be completed by May 2021) be followed up for their implementation and effectiveness during next inspection. Specifically,

1. (b) (5), (b) (7)(E) in response to the 483 observations.
2. (b) (5), (b) (7)(E) improved in response to the Observation 1.
3. (b) (5), (b) (7)(E) .
4. Revision of the specifics for the (b) (5), (b) (7)(E) in response to the Observation 4, such as for (b) (5), (b) (7)(E)