

CBER DMPQ CMC/Facility BLA Review Memorandum

BLA STN 125774/0

Product Name: VYJUVEK (beremagene geperpavec)

Wei Wang, Ph. D., Microbiologist, OCBQ/DMPQ/MRB3

Carl Perez, Consumer Safety Officer, OCBQ/DMPQ/MRB3

1. **BLA#:** STN 125774/0

2. **APPLICANT:** Krystal Biotech, Inc., US License Number: 2301

3. **PRODUCT NAME/PRODUCT TYPE**

USAN: beremagene geperpavec, abbreviated as B-VEC

Proprietary Name: VYJUVEK

Other names: KB103

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

- a. **Pharmacological category:** B-VEC is a replication-defective, non-integrating herpes simplex virus type 1(HSV-1)-based gene therapy vector expressing human type VII collagen (COL7).
- b. **Dosage form:** Suspension
- c. **Strength/Potency:** 5×10^9 Plaque Forming Units (PFU) per mL, supplied in a single use vial.
- d. **Route of administration:** B-VEC is mixed with the sterile excipient gel (in a single use vial) prior to topical administration
- e. **Indication(s):** Treatment of wounds in patients 6 months and over of age with dystrophic epidermolysis bullosa (DEB)

5. **MAJOR MILESTONES**

First Committee Meeting	July 11, 2022
Filing Meeting	August 10, 2022
Mid-cycle Meeting	October 14, 2022
Pre-License Inspection	November 11 - 17, 2022
Late-cycle Meeting	December 4, 2022
PDUFA Action Due Date	May 17, 2023

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

Reviewer/Affiliation	Section/Subject Matter
Wei Wang, OCBQ/DMPQ/MRB3	3.2.P (Drug Product Manufacturing) 3.2.A (B-VEC manufacturing facility and Equipment) 3.2.R (Validation reports of shipping, labeling and packaging, and container closure integrity testing methods)
Carl Perez, OCBQ/DMPQ/MRB3	Sections 3.2.S (Manufacturing facilities, equipment and CMC) 3.2.A (HPMC gel manufacturing facility and equipment)

7. INTER-CENTER CONSULTS REQUESTED

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

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/Status
June 20, 2022	STN 125774/0	Module 3 (Manufacturing facilities, equipment and CMC) reviewed
August 15, 2022	STN 125774/0.5 (response to CMC IR dated 08/09/2022)	Module 3 (Manufacturing facilities, equipment and CMC) reviewed
August 17, 2022	STN 125774/0.7 (response to DMPQ IR dated 08/05/2022)	Module 1 reviewed (Tabular summaries of DS and DP manufacturing processes, facility and equipment)
October 18, 2022	STN 125774/0.16 (response to DMPQ IR dated 10/13/2022, HPMC-Gel Production schedule)	Module 1 reviewed
October 21, 2022	STN 125774/0.17 (response to DMPQ IR dated 10/07/2022, simulated placebo DP bulk shipping validation (Thermal, and distribution))	Modules 1 and 3.2.R reviewed
October 31, 2022	STN 125774/0.21 (response to DMPQ IR dated 10/07/2022, Live DP vials shipping validation)	Modules 1 and 3.2.R reviewed
November 14, 2022	STN 125774/0.27 HPMC-Gel Shipping qualification, and labeling adhesion report	Modules 1 and 3.2.R reviewed
December 9, 2022	STN 125774/0.36 (Packaging Validation, protocol, and serialization IOQ)	Modules 1 and 3.2.R reviewed
December 20, 2022	STN 125774/0.37 (Labeling and packaging validation report)	Modules 1 and 3.2.R reviewed
January 4, 2023	STN 125774/0.39 (responses to 483, Krystal PLI, Nov 16, 2022)	Module 1 reviewed
January 13, 2023	STN 125744/0.41 (Responses to CMC IR8)	Module 1 (Sterility testing on shipped DP vials).

Date Received	Submission	Comments/Status
March 31, 2023	STN 125774/0.56 (Response to DMPQ IR dated 03/23/2023, Container closure integrity testing (CCIT) method validation and shipping validation of gel vials)	Modules 1 and 3.2.R

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF (b) (4)	(b) (4)	METHOCEL HG Hydroxypropyl Methylcellulose	Yes	Defer to Office of Therapeutic Product (OTP) reviewer
DMF (b) (4)	(b) (4)	Glass Vials	Yes	No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	(b) (4)	Yes	No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	(b) (4)	Yes	No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	(b) (4)	Yes	No DMF review required, information pertinent to container closure is provided in the BLA

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

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Krystal Biotech Inc. (Krystal) submitted this BLA, STN 125774/0, for its new gene therapy vector product, beremagene geperpavec (B-VEC), for the treatment of wounds in patients 6 months and over of age with dystrophic epidermolysis bullosa (DEB). B-VEC is a replication-defective, non-integrating, engineered HSV-1 based vector expressing two copies of (b) (4) the human type VII (COL7) protein. B-VEC is mixed with an excipient gel prior to topical administration directly on the wound of DEB patients.

The B-VEC drug substance (DS) and drug product (DP) are manufactured at the Krystal Pittsburgh, PA site (FEI: 3013498720). The excipient gel is manufactured by Berkshire Sterile Manufacturing (BSM, a contract manufacturing organization, CMO, located in Lee, MA, FEI: 3012144557). Labeling, packaging and serialization of the final DP are performed by (b) (4)

The manufacture of B-VEC DS and DP was inspected during a pre-license inspection (PLI) of Krystal from November 11, 2022 to November 16, 2022. The manufacture of the excipient gel was inspected in a PLI of BSM facility from January 16, 2023 to January 20, 2023.

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

RECOMMENDATION

I. APPROVAL

- a. Based on information reviewed in this BLA submission, approval is recommended with one inspectional consideration item. Under this license, the applicant is recommended for approval to (i) manufacture the B-VEC DS and DP (bulk filled vials) at the Krystal Pittsburgh, PA facility (FEI: 3013498720), (ii) manufacture the excipient gel (bulk filled vials) at the BSM Lee, MA facility (FEI: 3012144557), and (iii) label, package, and serialize the final DP product at the (b) (4)

Inspectional Consideration Item:

CBER recommends one item may be followed up on the next FDA inspection:

- (i) Verification of the shipment temperature monitoring data of the first three commercial lots of excipient gel which will be used for the manufacturing of the commercial lots of Vyjuvek.

CBER understands that this recommendation may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

II. COMPLETE RESPONSE (CR)

Not applicable.

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Wei Wang, Ph.D./Microbiologist OCBQ/DMPQ/MRB3	Yes	
Carl Perez, CSO OCBQ/DMPQ/MRB3	Yes	
CDR Donald Ertel, Branch Chief OCBQ/DMPQ/MRB3	Yes	
Carolyn Renshaw, Division Director OCBQ/DMPQ	Yes	

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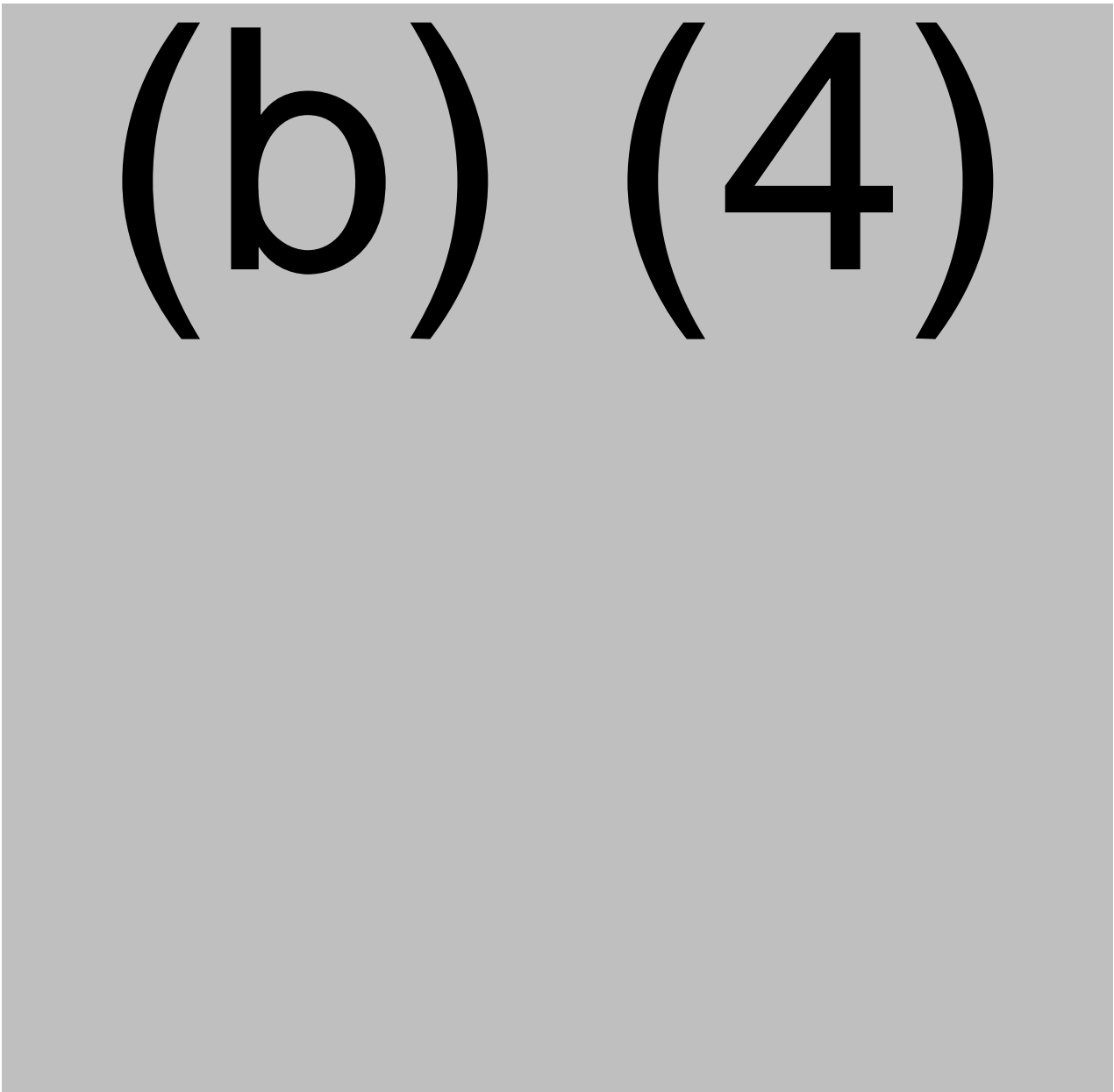


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Module 3

3.2.S DRUG SUBSTANCE

(b) (4)



(b) (4)



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3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

B-VEC DP is a white to off-white, opalescent, sterile suspension, preservative free, supplied in (b) (4) single-dose (b) (4) (~1mL) vials (1mL extractable) at a concentration of 5×10^9 PFU/mL, manufactured by Krystal.

Sterile excipient gel is 4.4% hydroxypropyl methylcellulose (HPMC) formulated in phosphate buffered saline (PBS), supplied in 1.5 mL per vial in 2R (~2 mL) Type (b) (4) borosilicate glass vials, manufactured by Berkshire Sterile Manufacturing (BSM).

Mixing of 1 mL of B-VEC and 1.5 mL of excipient gel is required and performed prior to topical administration at a care site.

3.2.P.2.5 Microbiological Attributes

Sterile B-VEC DP is manufactured by (b) (4), Ready to Use (abbreviated as (b) (4) vials, for more information see Section 3.2.P.7 *Container Closure System*). The aseptic filling of B-VEC was qualified by (b) (4) Media Fill (MF, reviewed below).

The manufacture processing steps of the excipient gel (including (b) (4)) are performed in the BSM facility. Filled gel vials are subjected to (b) (4) using a validated (b) (4) process.

Review Comments: The qualification of (b) (4) sterilization of the (b) (4) filled gel vials was reviewed by CBER inspector during the PLI of BSM and was found acceptable.

3.2.P.3.1 Manufacturer(s)

The manufacturing and testing sites for B-VEC are listed in the table below.

Table 4. Manufacturing Facilities for B-VEC Drug Product and Excipient Gel

Facility Identification Number	Responsibility
Krystal Biotech, Inc. (Krystal) 2100 Wharton Street Suite 701 Pittsburgh, PA 15203 FEI: 3013498720*	B-VEC DP manufacturing DP release testing
(b) (4)	B-VEC DP Stability Studies Intermediate storage for (b) (4)

Facility Identification Number	Responsibility
(b) (4)	B-VEC DP Analytical Testing - Sterility Testing
(b) (4)	B-VEC DP Container Closure Integrity Testing
(b) (4)	Extractables and Leachable Testing
(b) (4)	B-VEC DP Testing of (b) (4)
(b) (4)	B-VEC DP Testing of (b) (4)
Berkshire Sterile Manufacturing (BSM) 480 Pleasant Street Lee, MA 01238 FEI: 3012144557*	Excipient gel manufacture, vial filling and release testing. Excipient gel stability studies
(b) (4)	Excipient gel Testing: Bioburden and Sterility
(b) (4)	Labeling, Finished Packaging and Serialization
(b) (4)	Specialty Distribution Center

* A pre-license inspection (PLI) was performed.

**PLI or Inspection Waiver (IW) is not required for this facility.

***A PLI was waived for this facility and an IW memo was completed

3.2.P.3.3 Description of Manufacturing Process

Drug Product B-VEC

Review Comments: In Section 1.11.1 Quality Information Amendment of STN 125774/0.7 (CBER received on 8/17/2022), Krystal described an (b) (4) filling system (in addition to the (b) (4) filling system that was described in the original BLA submission, STN 125774/0). CBER sent an IR via Email (dated 9/9/2022) to inform Krystal to remove the (b) (4) Filling System from this BLA for the following reasons.

- Please clarify whether you used the (b) (4) filling station in the manufacture of any PPQ lots. If you have not, please remove all information pertaining to the (b) (4) filling station from the BLA.

Krystal responded (in amendment STN 125774/0.9, received by CBER on 9/19/2022) that the (b) (4) Filler was not used during the KB103 PPQ Campaign, and that the applicant proposed to submit the (b) (4) filling system data post the approval of this BLA. Only the (b) (4) Filling System is reviewed in this BLA.

B-VEC DP manufacturing steps, including vial filling, sealing, capping and visual inspection, and information of manufacturing room/areas and major equipment are summarized in the table below. Vial filling (b) (4) of B-VEC is performed in a Grade (b) (4) in a Grade (b) (4) using aseptic manufacturing techniques and pre-sterilized, single-use product contact components. Vial capping of filled vials is performed (b) (4) in a Bioburden Control (b) (4) in a Grade (b) (4) Room.

Table 5. B-VEC Drug Product Manufacturing Steps (at Krystal)

Process Step Process Step Description	Manufacturing Room / Area (Grade: ISO at rest / ISO in operation) Major Equipment (single use / product contact / shared)
Vial Filling: B-VEC DS is filled via a (b) (4), into pre-sterilized pre-closed (b) (4) vials using a (b) (4) pre-closed vial stopper.	(b) (4): (Grade (b) (4) ISO (b) (4) ISO (b) (4)) (b) (4) Filling System: (b) (4) process, non-product contact and (b) (4) filling equipment is reusable. (b) (4) (Grade (b) (4) Reusable, non-product contact
Vial Sealing: (b) (4) trace on the (b) (4) stopper is sealed with a (b) (4)	(b) (4): (Grade (b) (4) ISO (b) (4) ISO (b) (4)) (b) (4) (Grade (b) (4))
Vial Capping: Filled and sealed vials are capped.	(b) (4): Grade (b) (4) ISO (b) (4) ISO (b) (4)

Process Step Process Step Description	Manufacturing Room / Area (Grade: ISO at rest / ISO in operation) Major Equipment (single use / product contact / shared)
	(b) (4) (Bioburden Control)
Vial Inspection: Capped vials are 100% visually inspected, manual process.	(b) (4) Grade (b) (4) ISO (b) (4) ISO (b) (4) Appropriate (b) (4)

Review Comments: The filled DP vials (b) (4) are stored at (b) (4) to shipping to (b) (4) (see Table 4) for the final DP labeling, packaging, and serialization. DMPQ requested the firm to provide information of shipping validation for (b) (4) the final DP packages (see Section 3.2.P.3.5 for IR and shipping validations).

Excipient HPMC-Gel

The HPMC-gel manufacturing process, per batch record section, is summarized below.

Bill of Materials:

Materials required for the process are identified and documented by part number, description, quantities required, lot number and expiry of materials used for the specified batch. All materials have specifications and are released for use through the Quality Unit at BSM.

Review Comments: Water for injection (WFI) is prepared on site at BSM which was reviewed during the PLI of BSM. The WFI system was reviewed during the PLI of BSM and was found acceptable.

Washroom, Component and (b) (4) Preparation:

- Product contact materials, such as connectors, tubing, glassware, utensils, fittings, vessels, mixer parts, are washed with (b) (4)
- Formulation lines and filling assemblies are (b) (4) washing and wrapped for (b) (4) sterilization by (b) (4).
- Glass vials for finished gel product filling are washed using a (b) (4)
- Depyrogenation of washed vials in trays is performed using a (b) (4) (b) (4) Sterilizer, using a load cycle defined for the 2R vial size.
- Wrapped materials and depyrogenated vials are sterilized using a (b) (4) Sterilizer with a defined load map.

- The (b) (4) is prepared by (b) (4) testing and (b) (4) sanitization.
- Ready-to-Use materials (provided pre-sterilized), including filters, stoppers and seals, are inspected prior to transfer into the process without additional sterilization/preparation.

Review Comments: The major equipment and (b) (4) qualifications were reviewed during the PLI of BSM.

Formulation: Formulation consists of the following sequential steps:

- (b) (4)

Aseptic Fill:

The aseptic fill process is performed using a (b) (4)

(b) (4)

Vial Visual Inspection (VI) and Accountability:

Post sterilization, 100% VI is performed using an (b) (4) by qualified operators. Samples are removed for microbiologic testing from (b) (4)

(b) (4)

An Acceptance Quality Limit (AQL) inspection is performed by Quality personnel on the calculated AQL samples size and defined accept/reject limits. If the AQL inspection fails a deviation is initiated and a second 100% inspection may be performed.

Review Comments: During the PLI of BSM, it was noted that a (b) (4) was not used at the point of use (POU) for (b) (4). The BSM agreed to implement a (b) (4) at the POU of (b) (4). The gel manufacturing process steps, including (b) (4) were reviewed during the PLI of BSM.

The sterility (not CCIT) of filled gel vial is tested for release and stability. Krystal indicated that CCIT would be performed to verify the container closure integrity of shipped gel vials in shipping validation studies. However, Krystal changed the shipping temperatures multiple times from (b) (4) to 2°C – 8°C and to -25°C. Krystal also changed the CCIT method from a (b) (4) method to a (b) (4) method (STN 125774/0.56, CBER received on 3/31/2023). Krystal has not provided CCIT data for the shipped gel vials but has provided satisfactory sterility data (“No Growth”) in amendment, STN 125774/0.56 (CBER received on 3/31/2023).

Shipment:

A defined packaging module (b) (4) for Excipient Gel vials (unlabeled) is executed for packaging and shipment of the Excipient Gel to a temperature-controlled storage (b) (4) at (b) (4) (see Table 4). Vial labeling for commercial distribution is performed by (b) (4), a contract packaging organization (see Table 4). Vials are packed in (b) (4) place boxes with foam dunnage. Box lids are sealed with (b) (4) and box labels are applied. (b) (4) boxes are placed into a shipper box with foam dunnage. The shipper boxes are sealed with (b) (4) and labels are applied.

Cases of (b) (4) shipper boxes are packed and cases are palletized. Temperature loggers are placed (b) (4) for temperature monitoring during the shipment. Shipping is performed by (b) (4) from BSM (Lee, MA) to (b) (4).

Review Comments: DMPQ requested Krystal to provide information on gel shipping validation (see Section 3.2.P.3.5 for IR and Shipping Validation information). Noted, Krystal changed the gel storage temperature and shipping temperature multiple times during the review of this BLA. On 11/14/2022, the firm provided a validation study report for (b) (4). However, during the PLI of BSM, the inspectors found that the gel vial shipping conditions had used a (b) (4) from BSM to the storage site without appropriate validation (a FDA Form 483 observation item). In the 483 responses, the firm agreed to and provided shipping validation information (CBER received on 3/31/2023, reviewed below) to support the changed shipping conditions.

B-VEC Drug Product Labeling, Packaging and Serialization

The unlabeled B-VEC vials (DP bulk) and HPMC-Gel vials are shipped to (b) (4) for labeling, packaging and sterilization.

Review Comments: The information on B-VEC DP labeling, packaging and sterilization was not provided in the original BLA submission, but in an amendment, STN 125774/0.37 (CBER received on 12/20/2022) in response to DMPQ IRs.

IR and Responses (Labeling and Packaging)

DMPQ sent the following IR (the item #2 of IR dated 8/5/2022) and the firm's responses (STN 125774/0.7) were received on 8/17/2022.

IR Item #2 (IR dated 8/5/2022): You indicated that labeling, packaging and sterilization processes will be performed by a contract manufacturing organization (CMO), (b) (4). Please confirm (b) (4) is qualified to perform the proposed commercial manufacturing activities related to KB103. Please provide a brief summary of qualification activities and results for this CMO.

The Applicant's Responses: Krystal summarized the manufacturing process steps for the DP labeling, packaging and serialization (reviewed below), and stated that a Validation Project Plan (VPP) was included in Module 3.2.R (noted, this VPP was submitted in amendment, STN 125774/0.5, received by CBER on 8/15/2022), and that Packaging Validation will include 3 KB103 (B-VEC) placebo batches. Because the approved final carton label and Package Insert (PI) will not be available until late in the review cycle, Krystal intends to repeat the real time Packaging Validation Studies with

the approved final carton label on the (b) (4) 3 commercial batches. Data from these studies will be submitted as an amendment to the BLA.

***Review Comments:** The Applicant's responses (without providing a definite date for submitting labeling and packaging validation data) were inadequate.*

DMPQ sent an IR (dated 10/7/2022, Question #2) and the firm's responses (STN 125774/0.16) were received on 10/18/2022.

2. Your response (STN 125774/0.7, CBER received on 8/17/2022) to the CBER Information Request (IR dated 8/5/2022, Item #2) regarding when to provide qualification activities and results for your labeling, packaging, and serialization process was inadequate. You did not provide a definitive date of submission of the requested data.

Please note that the labeling, packaging validation data for the B-VEC DP is required for the review of this BLA.

Krystal Responses: Krystal is working with (b) (4) on completion of qualification, labeling, packaging, and serialization within the review cycle of the BLA. Krystal indicated the following:

- The vial label adhesion report will be submitted in late November 2022.
- The serialization IOQ will be submitted in late November 2022, and that serialization PQ will be performed and submitted on the first three commercial lots post-approval.
- The packaging validation report will be available in late December 2022.

***Review Comments:** The validation of DP labeling and packaging were reviewed below (see Section 3.2.P.3.5.)*

3.2.P.3.4 Controls of Critical Steps and Intermediates

***Review Comments:** DMPQ defers to OTP reviewer to perform comprehensive review of this section, except the following items which were reviewed and covered in this memo, no issues were noted:*

- *Bioburden (specification: (b) (4))*
- *Endotoxin (specification: (b) (4))*
- *Sterility (specification: no growth) is tested per (b) (4)*
- *Aseptic process simulation (APS) of B-VEC (b) (4) DP.*
- *(b) (4) of excipient gel-filled vials.*

3.2.P.3.5 Process Validation and/or Evaluation

Aseptic Process Simulation/Media Fill of B-VEC

In Section 3.2.P.3.5 *Process Validation and/or Evaluation [B-VEC]* Krystal summarized runs of APS (initial qualification runs in 2019, and requalification runs in 2020 and runs in 2021), with (b) (4) vials were tested per run. Krystal indicated that no growth was observed in tested vials.

(b) (4)

Krystal summarized that in all APS runs, no growth was observed in negative controls and tested vials and growth was observed in positive controls.

Review Comments: Noted, the REP-0562 was also reviewed in Section 3.2.S. To evaluate the adequacy of APS results, DMPQ requested additional information (see IR and Responses below).

IR and Responses (APS)

DMPQ sent an IR (dated 10/7/2022, Question #4) and the firm's responses (STN 125774/0.16) were received on 10/18/2022.

In Section 3.2.P.3.5 *Process Validation and/or Evaluation [B-VEC]* of STN 125774/0 you summarized passing results of (b) (4) APS/Media Fill (MF) studies. In reference to your MF studies, please provide the following:

- a. Description of the media used and incubation conditions (time, temperature).
- b. Summary of growth promotion studies including a list of the indicator organisms used

Krystal Responses: APS studies were conducted using (b) (4)

(b) (4)

Review Comments: The firm's responses appear acceptable. The APS results for B-VEC manufacturing process appeared acceptable.

(b) (4) of Gel-filled Vials by (b) (4)

In Sections 3.2.P.3.5 *Process Validation and/or Evaluation [HPMC Gel]* of STN 125774/0.0, Krystal summarized validation studies of (b) (4) by (b) (4). Briefly,

- (b) (4)

Review Comments: The validation results of (b) (4) by (b) (4) appeared acceptable. The (b) (4) of gel vials by (b) (4) was reviewed during the PLI of BSM and no objectionable issues were identified.

Shipping Validation Overview

In Section 3.2.P.3.5 *Process Validation and/or Evaluation [B-VEC]* of STN 125774/0.0, Krystal outlined the shipping qualification plan, including the following (b) (4) segments:

- (b) (4)

- (b) (4)

In Section 3.2.P.3.5 *Process Validation and/or Evaluation [B-VEC]* of STN 125774/0.0, Krystal indicated the following:

- (b) (4)

(b) (4)

(b) (4)

IR and Responses (Shipping Validation)

DMPQ sent an IR (dated 10/7/2022, Question #3) and the firm's responses (STN 125774/0.16) were received on 10/18/2022.

3. Please provide a date to submit the shipping qualification protocol and reports for (i) shipping the (b) (4) vial DP from your Krystal facility to (b) (4) facility, (ii) for shipping packaged DP from (b) (4) facility to the distribution center (i.e., (b) (4) and (iii) for shipping the packaged DP from (b) (4) to health care site.

Please note that the above listed shipping qualification data for the B-VEC DP is required for the review of this BLA.

Krystal Responses: Krystal indicated dates for submitting the following shipping validation reports:

- (1) October 18, 2022 to submit KB-DOCS-01909: *Shipping Qualification:*

(b) (4)

- (2) October 28, 2022 to submit KB-DOCS-01908: *Simulated Live Product Distribution Study* (n= (b) (4) (b) (4)

- (3) November 4, 2022 to submit KB-DOCS-01929: *Representative HPMC-gel Shipments Study* (n= (b) (4) (b) (4)

Review Comments: The above mentioned shipping validation reports were received around the proposed submission dates and were reviewed below.

(b) (4)

[Review Comments: The labeling and packaging validation studies appeared acceptable.]

3.2.P.5.4 Batch Analyses

In Table 1 of Section 3.2.P.5.4 *Batch analyses [B-VEC]* of STN 125774/0 (CBER received 06/20/2022), and Table 1 of Section 3.2.P.5.4 *Batch analyses [HMPC Gel]* of STN 125774/0 (CBER received 06/20/2022). The release testing results for B-VEC under DMPQ purview (e.g., Sterility (b) (4)) met acceptance criteria (e.g., No Growth). The release testing results for HMPC gel under DMPQ purview (e.g., Sterility (b) (4) and Endotoxin (b) (4)) met acceptance criteria (e.g., Sterility: No Growth, and Endotoxin: \leq (b) (4)).

Review Comments: The release testing results for B-VEC and HMPC gel under the DMPQ purview appeared acceptable. DMPQ defers to OTP reviewers to evaluate release results of DP quality attributes. During the PLI of Krystal facility, the firm indicated that there were no deviations related to microbial contamination during the production of B-VEC.

3.2.P.7 Container Closure System

B-VEC CCS: The B-VEC DP primary CCS is 1mL sterile (b) (4) Vial, Ready to Use (abbreviated as (b) (4) vials) for aseptic filling and storage of single dose B-VEC DP. The (b) (4) vials are manufactured by (b) (4) (DMF (b) (4)). The materials of construction of (b) (4) vials are summarized in table below.

Table 10. Overview of Materials of Construction of AT Vials

Component	Materials of Construction
Vial Body	(b) (4)
Stopper	
Top Ring (non-product contact)	
Cap (non-product contact)	

Krystal provided critical dimensions and drawings in the Section 3.2.P.7 *Container Closure System [beremagene geperpavec]*.

Review Comments: The (b) (4) sterile vials were manufactured and provided by (b) (4) with Certificate of Analyses (COA). While the information of (b) (4) vial sterilization qualification was not provided in this BLA, the sterility of (b) (4) vials were verified by media fill studies. The submitted media fill results (review above) appeared to support and demonstrate the sterility of (b) (4) vials.

HPMC-Gel CCS: The primary CCS for excipient gel consists of a 2mL Type (b) (4) glass serum vial (abbreviated as 2R vial) and a 13mm stopper. The primary CCS is sealed with a 13mm flip off-seal (blue). The materials of construction of the excipient gel CCS components are summarized in table below.

Table 11. Materials of Construction of 2R Vials

Component	Materials of Construction
2R Serum Vial	(b) (4) glass serum vial size 2R (2mL), Schott #1563803
13mm Stopper	13mm (b) (4) Bromobutyl (b) (4) Stopper, RTU, (b) (4)
13mm Flip-off Seal	13mm flip off seal (blue) RTU, (b) (4)

The vials, stoppers and seals are sourced by Krystal and provided to BSM. The vials are (b) (4) by BSM. The stoppers and seals are pre-sterilized RTU.

Review Comments: DMPQ defers to the OTP reviewers to evaluate the CCS suitability with respect to materials of construction and chemical comparability. The CCIT was performed for sterility of B-VEC DP and excipient gel vials using a (b) (4) method (reviewed below).

(b) (4) Container Closure Integrity Tests

B-VEC Vials: In Section 3.2.P.2.4 *Container Closure System [B-VEC]* of STN 125774/0.0, Krystal stated that Container closure integrity (CCI) for B-VEC DP is supported by:

- (b) (4)

Review Comments: To verify the adequacy of the B-VEC CCIT method validation and results, DMPQ requested Krystal to provide a description of (b) (4) method, including negative and positive controls, as well as the sensitivity of its CCIT method (see IRs and Responses (CCIT)).

HPMC-Gel Vials: Gel-filled vials are (b) (4). Krystal indicated that excipient gel in the (b) (4) vial with (b) (4) bromobutyl rubber stoppers is stable for at least 12 months.

***Review Comments:** In Section 3.2.P.3.5 Process Validation and/or Evaluation [HPMC Gel], samples of gel filled vials (at (b) (4) of fill of 3 PPQ lots) were tested for sterility, and all sterility results met specification (i.e., No Growth). It was shown that sterility is tested at T0 and T12 (0 and 12 months). During a teleconference (conducted on 2/9/2023), Krystal indicated that CCI of the shipped gel vials will be tested using their validated CCIT method (see IRs and Responses (CCIT)).*

IRs and Responses (CCIT)

DMPQ sent an IR (dated 10/7/2022, Question #5) and the firm's responses (STN 125774/0.16) were received on 10/18/2022.

In Section 3.2.P.2.4 of STN 125774/0 you provide a Container Closure Integrity Test (CCIT) report by using a validated (b) (4) method. Please provide the following:

- The sensitivity of your (b) (4) method, or the smallest/critical leakage size which can be determined by your CCIT method.
- A brief description of your (b) (4) CCIT procedure, including testing conditions, positive controls, negative controls, and the detection method (for example, inspection by (b) (4) in the tested vials).

Krystal Response to (a):


Krystal stated that the validation of CCIT (b) (4) method and the routine CCIT for B-VEC (b) (4) vials is performed by (b) (4)

Krystal summarized the validated CCIT measurements in the table below and describe its (b) (4) CCIT method as the following:

Table 12. Summary of Validation of CCIT (b) (4)

(b) (4)


Krystal Response to (b):

- (b) (4)
- 

Review Comments: The firm's responses for the CCIT method validation and sensitivity were inadequate (see IR dated 03/23/2023 for more information).

DMPQ sent another IR (dated 03/23/2023, Question #1) and the firm's responses (STN 125774/0.56) were received on 03/31/2023.

1. Your responses (Amendment STN 125774/0.16, CBER received on 10/18/2022) regarding the Container Closure Integrity Test (CCIT) (b) (4) method validation were inadequate, including:

- (b) (4)
- 

- (b) (4)

During the PLI of Krystal (conducted from 11/11/2022 to 11/16/2022) and a teleconference (conducted on 2/9/2023), CBER inspector/reviewer informed you of the above deficiencies and you indicated that Krystal would provide the correct information of CCIT method validation and sensitivity. While you indicated that sterility test (not CCIT) is performed for the release and stability of B-VEC and HPMC gel, you indicated (on 2/9/2023 during a teleconference) that CCIT will be performed on the shipped gel vials.

- a) Please address the above listed deficiencies and provide the information of your CCIT method sensitivity and validation summary report by 3/31/2023, or to provide a date when you will be able to provide the requested information.
- b) Please provide a summary of CCIT data of the shipped excipient gel vials by 3/31/2023, or to provide a date when you will be able to provide the requested information.

Krystal Response to a): Krystal validated two container closure integrity methods; (1) (b) (4) used for (b) (4) acceptance of the (b) (4) vials (b) (4) product fill and (2) (b) (4) for stability testing of the vials for both the (b) (4) vials (B-VEC DP) and 2R vials (excipient gel).

(b) (4)

Krystal stated that vials with known defects were not used as positive controls in routine testing but were tested during method validation to confirm the suitability of the method. Krystal indicated the following:

- (b) (4)

- Sensitivity of the (b) (4) CCIT method was determined by (b) (4)

Krystal indicated that the firm validated a new deterministic CCIT method, (b) (4) (reviewed below), for stability of CCI of B-VEC vials and excipient gel vials.

(b) (4)

1 page determined to be not releasable: (b)(4)

- (b) (4)

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

Review Comments: The submitted stability results at the time point T0 under DMPQ purview (e.g., sterility and Endotoxin) were the same as batch release testing results (reviewed above) and met acceptance criteria. DMPQ defers to OTP reviewers to further evaluate DP stability data.

3.2.A.1 Facility and Equipment

Krystal Facility (B-VEC DS and DP bulk) Overview

B-VEC DS and DP bulk are manufactured in the Krystal manufacturing facility. The facility is approximately (b) (4) square feet, including GMP facility on the (b) (4) warehouse/storage and support areas on the (b) (4), and a Quality Control Laboratory (QC lab, CNC) on the (b) (4). The Krystal facility is multi-product facility for investigational new drugs of gene and cell therapy products with control strategies in place to prevent cross-contamination, including facility design, campaign-based manufacturing, change-over procedures, and use of sterile single-use product-contact equipment.

The GMP manufacturing areas consist of a locker room (b) (4) manufacturing cleanroom suites (including (b) (4) which are equipped with (b) (4) (bioburden controlled), except (b) (4) and are equipped with (b) (4) for open operations), controlled-not-classified (CNC) corridors (e.g., (b) (4)).

Each cleanroom suite has separated personnel airlock (PAL) and material airlock (MAL) and is served by a dedicated air handling unit. The access to the locker room (b) (4)

from the building hallway is controlled by electronic key fob, but there are no further access controls from (b) (4) to different cleanroom suites. The flows (personnel, materials, products, and waste) in CNC corridors and in cleanroom airlocks are (b) (4)

The surfaces of GMP manufacturing areas are built with cleanable materials: the ceilings are a (b) (4)

Review Comments: During the PLI of Krystal facility, the sponsor explained that the (b) (4) building limits the design of (b) (4), however, the firm has additional procedural controls (including gowning change in a (b) (4) to prevent or reduce cross contamination. The Gowning SOP was reviewed during the PLI and was found acceptable.

Noted, Krystal has built a new manufacturing facility (for which Krystal gave the CBER inspectors a quick tour during the PLI of Krystal facility although the new facility was out of focus of this BLA review) in the Pittsburgh area. The new facility has (b) (4)

HVAC Systems and Utilities (Krystal)

Each cleanroom suite (including (b) (4)

Each manufacturing suite can be used to manufacture B-VEC or an IND product on a product campaign basis.

Table 14. Overview of Krystal Cleanroom Classifications

Cleanroom Usage	Cleanroom # and Classification	AHU (Area Served)
(b) (4)		

Cleanroom Usage	Cleanroom # and Classification	AHU (Area Served)
(b) (4)		

(b) (4)

Review Comments: During the PLI of Krystal facility, the sponsor stated that requalification of (b) (4) were performed by a contract service provider every (b) (4)

The HVAC systems appeared acceptable.

Krystal does not have a Water for Injection (WFI) generation and distribution system. They use (b) (4) Sterile WFI (sWFI) in (b) (4)

Gases (including (b) (4)

Review Comments: The use and monitoring of sWFI and manufacturing gases were reviewed during the PLI of Krystal facility and were found acceptable.

Facility and Equipment Cleaning (Krystal)

The B-VEC manufacturing process utilizes a closed system, sterile single-use product-contact equipment. Thus, no cleaning of product-contact equipment is needed.

The surfaces of multi-use non-product contact equipment and surfaces of cleanroom areas are cleaned post-use by using validated disinfectant agents per Krystal cleaning procedures.

A (b) (4) decontamination cycle is performed by a contract service provider in (b) (4) as part of changeover procedures.

Environmental Monitoring (EM, Krystal)

During the PLI of Krystal facility, CBER inspectors reviewed EM protocols and a summary report for the 2022 Environmental performance qualification (EMPQ) activities performed in all cleanroom suites (except the (b) (4)). Krystal stated that requalification of (b) (4) were performed by (b) (4) (a contract service provider) (b) (4). No failed (b) (4) requalification tests and no particulates exceeding action limits were noted in the 2022 EMPQ, e.g., for (b) (4).

In addition to the scheduled (b) (4) recertification, Krystal has a routine environmental monitoring program in place to monitor routine (b) (4) particulates per Krystal's Environmental Qualification Master Plan and EM protocols. The EM includes both unscheduled routine monitoring and routine monitoring during critical process steps (in-operation conditions). The EM sampling frequencies, sites and types (b) (4) have been developed through Krystal's Environmental Monitoring and B-VEC Manufacturing Process Contamination Risk Assessment and are implemented by procedure and/or protocol as applicable.

Review Comments: During the PLI of Krystal facility, Krystal's EM SOPs, including KB-DOCS-00042: Environmental Monitoring Sampling, were reviewed. CBER inspectors verified the sampling sites for (b) (4) samples during the observation of the aseptic filling activities in (b) (4). Krystal's EM procedures and EM sampling appear acceptable.

Equipment Qualifications (Krystal)

The qualification of the following major equipment for the manufacture of B-VEC (b) (4) DP were reviewed during the PLI of Krystal facility and were found acceptable:

- (b) (4)
- (b) (4)
- (b) (4) Filling System (b) (4)
- (b) (4)
- Cold Room (2°C – 8°C)
- Freezers (–20°C, (b) (4))
- (b) (4)

Review Comments: During the PLI of Krystal, the firm stated that due to an on-going cleanroom modification the 2022 EMPQ did not include the (b) (4), and that the cleanroom qualification of (b) (4) would be performed after the completion of cleanroom modification. The Krystal facility and procedural controls appeared acceptable for the manufacture of B-VEC DS and DP bulk vials, and for the prevention of contamination and cross-contamination.

BSM Facility (Excipient Gel) Overview

Berkshire Sterile Manufacturing (BSM) is contracted by the applicant to manufacture the excipient gel for this BLA at their manufacturing facility located in Lee, MA. BSM's facility is approximately (b) (4) square feet. The firm occupies approximately (b) (4) square feet of the building, with approximately (b) (4) square feet used for office space; while the remaining (b) (4) square feet is used for laboratory, warehouse and manufacturing purposes. The excipient gel is manufactured and filled at BSM, and shipped to (b) (4) for storage until it is ready for packaging, labeling and serialization with B-VEC at (b) (4).

HVAC Systems and Utilities (BSM)


(b) (4) air is supplied to the BSM cleanroom through (b) (4)

HVAC system (b) (4) consists of the (b) (4)

The most recent HEPA recertification for the BSM cleanroom and (b) (4) was performed on 10/03/2022 with no deviations reported.

(b) (4) systems supply the cleanroom and support areas at BSM. (b) (4) is sampled and tested according to (b) (4) standards at each (b) (4) by the QC lab on a (b) (4) basis. There are (b) (4) points of use at BSM. In addition,

(b) (4)




Prevention of Contamination and Cross-contamination (BSM)

The BSM facility is a multi-product facility with control strategies in place to prevent cross-contamination, including facility design, change-over procedures, dedicated equipment and the use of single-use product contact equipment parts. Other products that are filled in the same fill areas are FDA approved (b) (4)

The firm indicated that there is no toxic, hazardous, or highly sensitizing products/substances (e.g., beta-lactams, cephalosporins, radioactive materials, live bacteria, viruses or prions, spores or spore forming organisms, highly potent hormones) that are manufactured/handled at this facility.

Facility Design (BSM)

BSM utilizes modular cleanrooms installed within the facility. The BSM facility maintains separation of areas to prevent contamination from early to late-stage manufacturing process steps. The facility is divided into the following areas: (b) (4)



area within the building.


Concurrent multi-product manufacturing takes place within the facility. Different products are manufactured within independent filling suites. (b) (4)

. Cross-contamination prevention between these areas is accomplished through gowning, equipment flows, and access control to manufacturing areas. (b) (4)

, with procedures established for the cleaning and changeover of the areas and equipment between different product campaigns.

Flows (BSM)

The cleanroom areas at BSM have dedicated (b) (4) personnel and material airlocks. (b) (4)



BSM facility drawings showing personnel and material flow, room classifications and air flow direction were reviewed, with no objectional issues identified.

Changeover (BSM)

Concurrent multi-product manufacturing takes place within the facility. Different products are manufactured within independent filling suites. (b) (4) and there are procedures established for the cleaning and changeover of the areas and equipment between different product campaigns. (b) (4)

Changeover activities are documented within the batch record and is reviewed by QA.

Disinfectant Qualification (BSM)

A disinfection validation and efficacy study were performed in accordance with the associated protocols. The disinfectants were evaluated by treatment of the following surfaces used in the facility: (b) (4)

The defined challenge organisms consisted of the following (b) (4)

Based on their studies, the following disinfectants were found to be suitable for use at the BSM facility: (b) (4)

Facility Cleaning (BSM)

In order to maintain the classified room environment, a formal room cleaning program is in place governed by a cleaning of the cGMP area SOP. Cleaning is performed from "clean" areas to "less clean" areas. For example, cleaning from (b) (4)

Environmental Monitoring (BSM)

The EM SOPs at BSM identifies sampling sites and defines acceptable counts of surface monitoring (RODAC), (b) (4) and particle levels (b) (4) during the routine environmental monitoring of the cGMP

manufacturing areas. BSM has an EM program in place that measures (b) (4) during routine filling operations and media fill simulations. For (b) (4) monitoring, (b) (4) Surfaces in the (b) (4) involved in the manufacture of excipient gel are monitored using (b) (4) Critical process flow and representative sites are monitored at completion of the filling of the final batch of a campaign. (b) (4) . Organisms detected in the (b) (4) are identified to the species level.

(b) (4)

Continuous (b) (4) monitoring is performed at designated locations during the operation of the (b) (4)

Equipment (BSM)

BSM uses the following major equipment for the manufacture of the excipient gel:

- (b) (4)

The installation, operation and performance qualification (IQ/OQ/PQ) reports for all major manufacturing equipment were reviewed during the PLI, with no objectional issues identified. With the exception of the (b) (4), all product contacting material used in the excipient gel manufacturing process are single use. The (b) (4) is dedicated to the manufacturing of the excipient gel. All production equipment

used in the manufacture of the excipient gel are (b) (4), except for the (b) (4), which is (b) (4) by a contracted laboratory after each use.

Review Comments: The BSM facility and procedure controls appear acceptable to adequately prevent contamination and cross-contamination in the manufacture of the HPMC excipient gel.

3.2.R Regional Information (USA)

Executed Batch Records

DMPQ defers to OTP reviewers to review executed batch records.

Combination Products

N/A. B-VEC is not a combination product.

Comparability Protocols

No comparability protocols under the DMPQ purview were submitted in this BLA, STN 125774/0.