

CBER CMC BLA Review Memorandum

BLA STN 125774

**Vyjuvek
beremagene geperpavec-svdt**

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1. BLA#: 125774**2. APPLICANT NAME AND LICENSE NUMBER**

Krystal Biotech Inc. License #: 2301

3. PRODUCT NAME/PRODUCT TYPE

Non-Proprietary/Proper Name/USAN:	beremagene geperpavec-svdt
Proprietary Name:	Vyjuvek
Company codename:	KB103, B-VEC
UNII Code:	AQN7K24KQU
NDC Code:	82194-510-02 (carton); 82194-510-01 (Vyjuvek); 82194-001-01 (Excipient gel)

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

Pharmacological category:	Herpes-simplex virus type 1 (HSV-1) vector-based gene therapy
Dosage form:	Suspension for topical application
Strength/Potency:	5×10^9 plaque forming units (PFU)/mL
Route of administration:	Topical application
Indication:	Treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene

5. MAJOR MILESTONES

Initial IND Submission (BB-IND 18100)	March 26, 2018
IND allowed to proceed	April 25, 2018
Fast Track Designation granted	May 23, 2018
Orphan Drug Designation granted	November 2, 2017
Rare Pediatric Disease designation granted	December 29, 2016
Regenerative Medicine Advanced Therapy Designation (RPD-2018-193) granted	June 21, 2019
Pre-BLA Meeting	March 25, 2022 (cancelled by Applicant)
BLA Submission	June 20, 2022
First Committee Meeting	July 11, 2022
Filing Meeting	August 10, 2022
Mid-Cycle Meeting	October 14, 2022
External Late-Cycle Meeting	December 15, 2022
PDUFA action due date (original)	February 18, 2022
Major Amendment Acknowledgement	January 5, 2023
PDUFA action due date:	May 19, 2023

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Anna Kwilas, Ph.D., OTP/OGT/DGT2/GTB5	DP comparability, stability, labeling/packaging/distribution
Bo Liang, Ph.D., OTP/OGT/DGT1/GTB2	DS/DP process characterization/validation, specifications
Jianyang Wang, Ph.D., OTP/OGT/DGT1/GTB2	DS/DP raw material qualification, analytical method validation
Massoud Motamed, Ph.D., Previously CBER/OTAT/DCGT/GTB2	Control of Materials, Excipient gel

7. INTER-CENTER CONSULTS REQUESTED

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

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
6/20/2022	125774/0	Original submission
8/15/2022	125774/5	Response to CMC IR #1 dated 8/9/2022
9/19/2022	125774/9	Response to CMC IR #2 dated 9/9/2022
9/26/2022	125774/10	Response to CMC IR #3 dated 9/16/2022
10/31/2022	125774/21	Packaging/labeling/shipping validation data
11/4/2022	125774/23	Ancoris facility 704 request information
11/7/2022	125774/24	Response to CMC IR #4 dated 10/21/2022
11/14/2022	125774/27	Packaging/labeling/shipping validation data
11/28/2022	125774/32	Response to CMC IR #5 dated 11/18/2022
11/30/2022	125774/33	Stability data
12/1/2022	125774/34	Updated prescribing information (PI)
12/2/2022	125774/35	Updated lot release protocol (LRP)
12/9/2022	125774/36	Packaging/labeling/shipping validation data
12/20/2022	125774/37	Response to CMC IR #6 dated 12/5/2022
1/4/2023	125774/39	Ancoris 483 responses
1/4/2023	125774/40	Response to CMC IR #7 dated 12/20/2022
1/13/2023	125774/41	Response to CMC IR #8 dated 1/6/2023
2/7/2023	125774/43	Response to CMC IR #9 dated 1/30/2023
2/7/2023	125774/44	Updated LRP
2/21/2023	125774/47	Krystal 483 responses
2/24/2023	125774/48	Response to CMC IR #10 dated 2/21/2023
3/3/2023	125774/50	Updated prescribing information (PI)
3/10/2023	125774/51	Response to CMC IR #11 dated 3/3/2023
3/17/2023	125774/53	Updated LRP

3/28/2023	125774/55	Updated LRP
3/31/2023	125774/56	Packaging/labeling/shipping validation data
4/3/2023	125774/57	Updated PI; bandage study data
4/5/2023	125774/58	Updated vial/carton labels
4/18/2023	125774/60	Updated PI
4/20/2023	125774/62	Agreed upon CMC PMCs 1-8
4/27/2023	125774/64	Updated PI
4/27/2023	125774/65	Agreed upon CMC PMC 9
4/28/2023	125774/66	Updated PI
4/28/2023	125774/67	Response to CMC IR #12 dated 4/27/2023
4/28/2023	125774/69	Updated PI
5/1/2023	125774/70	Updated vial/carton labels
5/3/2023	125774/71	Updated vial/carton labels
5/4/2023	125774/72	Updated PI
	125774/73	Updated PI
5/9/2023	125774/74	Response to CMC IR #13 dated 5/5/2023
5/9/2023	125774/75	Updated vial/carton labels
5/9/2023	125774/76	Response to CMC IR #15 dated 5/8/2023
5/9/2023	125774/77	Response to CMC IR #14 dated 5/8/2023
5/10/2023	125774/78	Response to CMC IR #14 dated 5/8/2023 Update of Module 3 based on IR responses
5/16/2023	125774/79	Updated PI
5/16/2023	125774/80	Response to CMC IR #16 dated 5/15/2023

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 (Hydroxypropyl Methylcellulose)	✓	(b) (4)
DMF (b) (4)	(b) (4)	(b) (4)	✓	(b) (4)
DMF (b) (4)		(b) (4)	✓	

DMF (b) (4)	(b) (4)	(b) (4)	✓	(b) (4)
DMF (b) (4)	(b) (4)	(b) (4)	✓	(b) (4)
DMF (b) (4)	(b) (4)	(b) (4)	✓	(b) (4)
DMF (b) (4)	(b) (4)	(b) (4)	✓	(b) (4)
DMF (b) (4)	(b) (4)	(b) (4)	✓	(b) (4)

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

The CMC review team concludes that the manufacturing process, test methods and control measures for beremagene geperpavec-svdt (B-VEC; Vyjuvek; KB103) are capable of yielding products with consistent quality attributes deemed acceptable for commercial manufacturing under this BLA.

KB103 is intended to treat wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene. KB103 is a recombinant, replication-incompetent, non-integrating herpes simplex virus type 1 (HSV-1)-based gene therapy vector engineered to express full-length, functional human type VII collagen (COL7). KB103 was generated by (b) (4)

The proposed KB103 mechanism of action is that upon topical application to cutaneous wounds, KB103 transduces both keratinocytes and fibroblasts and expresses procollagen 7. Procollagen 7 is secreted by the cell and proteolytically processed. Processed procollagen 7 arranges into long, thin bundles of mature COL7 that form anchoring fibrils (AF). The AFs hold the epidermis and dermis

together and are essential for maintaining skin integrity. KB103 is applied to wounds once weekly until closure. Following wound closure, KB103 can be applied to additional wounds up to a weekly dose of 1.6×10^9 plaque forming units (PFU)/mL (patients 6 months to <3 years old) or 3.2×10^9 PFU/mL (patients ≥ 3 years old). If the originally treated wounds reopen, KB103 can be reapplied to the original wounds as well.

KB103 is manufactured at the Krystal Biotech Inc. Ancoris facility (Pittsburgh, PA)

(b) (4)

KB103 stability at (b) (4) (and -20°C) was supported up to 12 months.

To facilitate topical administration, KB103 is mixed with hydroxypropyl methylcellulose (HPMC) Excipient Gel. HPMC Gel is manufactured for Krystal Biotech, Inc. by Berkshire Sterile Manufacturing (BSM). HPMC Gel is manufactured by (b) (4) 7.5mM Tris PBS buffer to a target concentration of 4.4% HPMC. Following (b) (4)

The HPMC Gel is then filled into 2.0 mL (b) (4) glass vials before being (b) (4). HPMC Gel stability at -20°C was supported up to 12 months.

Following manufacture and release, the KB103 and HPMC Gel are shipped to (b) (4) for labeling and final packaging. One vial of KB103 and one vial of HPMC Gel are co-packaged into a single product carton to be stored at -20°C . The cartons are then shipped to the third-party logistics warehouse (b) (4). The cartons are stored at -20°C at (b) (4) until a request for the product is received. After receiving a request, the cartons are shipped to a healthcare facility (Site of Care) either directly using a Specialty Distributor or through a Specialty Pharmacy. Requests are received through a controlled distribution channel managed by the Applicant's internal Patient Services portal (Krystal Connect). Once at the Site of Care, the KB103 cartons are stored at -20°C or at $2^\circ - 8^\circ\text{C}$ for up to 1 month. Prior to administration, the KB103 and HPMC Gel are thawed and mixed at a 1:1.5 ratio and loaded into administration syringes at the Site of Care. Following preparation, the capped administration syringes are placed in a sealable plastic bag in an appropriate insulated secondary container at 2° to 8°C for transport from the preparation site to the administration site. Topical administration takes place at either the Site of Care or at the patient's home by a healthcare professional. KB103 Gel is administered within 8 hours of preparation.

Manufacturing process consistency is assured through (b) (4)

Raw materials derived from animals and humans are appropriately controlled to ensure the absence of microbial contaminants and adventitious agents. Lot release test methods are suitably validated or verified and product specifications are adequate to ensure product quality and consistency with drug product used in the clinical study. The manufacturing process has been adequately validated and continuous process verification is in place.

B. RECOMMENDATION

I. APPROVAL

This biological license application (BLA) provides an adequate description of the manufacturing process and characterization of the new drug product beremagene geperpavec- svdt (B-VEC; Vyjuvek). Based on the information submitted in the initial submission, the CMC review team has concluded that the manufacturing process, along with associated test methods and control measures, is capable of yielding a product with consistent quality characteristics. This information along with the post-marketing commitments listed below satisfy the CMC requirements for biological product licensure per the provisions of section 351(a) of the Public Health Service (PHS) Act controlling the manufacture and sale of biological products. This information combined with the information gathered during the pre-license inspections of the Krystal, Inc. Ancoris facility and the Berkshire Sterile Manufacturing (BSM) facility, the CMC review team recommends approval of this BLA.

CBER Lot release:

B-VEC will be subjected to CBER lot release protocol review. Please see final Lot Release Protocol in the DBSQC Memo.

Post-Marketing Commitments (PMCs):

1. Krystal Biotech commits to reassessing the commercial B-VEC (b) (4) lot release acceptance criteria after data have been collected on (b) (4) commercial lots and submit as a Postmarketing Study Commitment – Final Study Report.

Final Report Submission: January 31, 2025

2. Krystal Biotech commits to reassessing the commercial B-VEC COL-7A1 (b) (4) lot release acceptance criterion after data have been collected on (b) (4) commercial lots and submit as a Postmarketing Study Commitment – Final Study Report.

Final Report Submission: January 31, 2025

3. Krystal Biotech commits to assessing the consistency of the percentage of the COL7A1 transgene variant (b) (4) in the Phase 3 clinical and Process Performance Qualification (PPQ) B-VEC lots and submit as a Postmarketing Study Commitment – Final Study Report.

Final Report Submission: November 30, 2023

4. Krystal Biotech commits to re-validating the (b) (4) COL7A1 (b) (4) Assay in support of its use for commercial B-VEC lot release. The re-validation will include validating the (b) (4) using appropriate test material and providing the validation results in copies (b) (4) and submit as a Postmarketing Study Commitment – Final Study Report.

Final Report Submission: November 30, 2023

5. Krystal Biotech commits to performing additional robustness assessments of (b) (4) Quantification of HSV Genome Copy Number by (b) (4) and submit as a Postmarketing Study Commitment – Final Study Report.

Final Report Submission: November 30, 2023

6. Krystal Biotech commits to validating the HPMC concentration assay and implementing this assay, along with an appropriate acceptance criterion, as part of the commercial HPMC gel lot release specification and submit as a Postmarketing Study Commitment – Final Study Report.

Final Report Submission: November 30, 2023

7. Krystal Biotech commits to providing HPMC concentration stability data in support of the current HPMC gel expiry date and submit as a Postmarketing Study Commitment – Final Study Report.

Final Report Submission: May 31, 2024

8. Krystal Biotech commits to providing HPMC gel (b) (4) data in support of the current HPMC gel storage, shipping, and labeling conditions and submit as a Postmarketing Study Commitment – Final Study Report.

Final Report Submission: November 30, 2023

9. Krystal Biotech commits to optimize the HSV-1 Plaque Assay to (b) (4) if necessary, and submit as a Postmarketing Study Commitment – Final Study Report.

Final Report Submission: May 31, 2024

II. COMPLETE RESPONSE (CR)

Not applicable

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Anna Kwilas Review Committee Chair Lead Biologist OTP/OGT/DGT2/GTB5	Concur	
Bo Liang Staff Fellow OTP/OGT/DGT1/GTB2	Concur	
Jianyang Wang Biologist OTP/OGT/DGT1/GTB2	Concur	
Kimberly Schultz Branch Chief OTP/OGT/DGT2/GTB5	Concur	
Denise Gavin Office/Division Director OTP/OGT/DGT2	Concur	

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Module 3**3.2.S DRUG SUBSTANCE****3.2.S.1 General Information***(Reviewed by AK)***3.2.S.1.1 Nomenclature**

United States Adopted Name (USA):

beremagene geperpavec-svdt

International Nonproprietary Name (INN):

beremagene geperpavec

Company or laboratory code:

B-VEC, KB103

Proposed propriety name:

Vyjuvek

(b) (4)

(b) (4)

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

(b) (4)

3.2.P DRUG PRODUCT

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

KB103 is a white to off-white, opalescent preservative free, sterile suspension in 10% glycerol DPBS (Dulbecco's phosphate buffer saline). KB103 is supplied as 1.15 mL (1mL extractable) in (b) (4) vials (b) (4) vials) at a nominal concentration of 5×10^9 PFU per mL. Mixing with 4.4% hydroxypropyl methylcellulose (HPMC) Excipient Gel at a ratio of 1:1.5mL is required prior to administering KB103. HPMC is formulated in 7.5mM Tris 1× PBS to produce the HPMC Gel.

HPMC Gel is supplied as 1.5 mL in 2R (~2 mL) (b) (4) borosilicate glass vials.

The DS is filled aseptically into ready to use, (b) (4) vials to form the DP. (b) (4) is generated; the vial (b) (4) the DP.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

(Reviewed by BL)

3.2.P.2.1.1 Drug Substance

KB103 active ingredient is a replication-defective, non-integrating, genetically modified HSV-1 vector encoding COL7. The (b) (4) is formulated in DPBS containing 10% glycerol. Compatibility of KB103 with the formulation buffer (i.e., DPBS with 10% glycerol) was evaluated as part of the preclinical proof-of-concept study conducted using the homozygous Col7a1^{flNeo} mouse model that closely resembles the characteristics of severe human DEB. Transgene expression and biological activity of KB103 in the formulation buffer was demonstrated in proof-of-concept preclinical studies.

Reviewer Comments: The preclinical POC study demonstrated that KB103 is biologically active in the formulation buffer.

3.2.P.2.1.2 Excipients

Because KB103 DP is the (b) (4) filled into vials (b) (4), there are no additional excipients other than DPBS and 10% glycerol in the DP.

Prior to topical administration, KB103 DP is mixed with an HPMC Gel to increase the viscosity for ease of drug application. Physiochemical properties of KB103 DP, the formulation buffer (10% glycerol in DPBS), and the HPMC Gel are shown in Table 34.

Table 34. Physiochemical Properties of KB103 DP

Property	Value
(b) (4) KB103 in DPBS/10% glycerol formulation buffer	(b) (4)
(b) (4) HPMC gel excipient	
(b) (4) , formulation buffer	
(b) (4) , HPMC gel excipient	
Viscosity, HPMC gel excipient	

Please refer to Section 3.2.P.4 Control of Excipients for additional information on the 4.4% HPMC Gel.

3.2.P.2.2 Drug Product

(Reviewed by BL)

3.2.P.2.2.1 Formulation Development

The DP formulation, DP/excipient gel formulation processes, and container-closure systems used throughout DP development are summarized in Table 35. The excipient gel formulation has been modified during product development. The product compatibility with various excipient gel formulations is assessed in compatibility studies described in Section 3.2.P.2.6 Compatibility. Details about the container closure selection are provided in Section 3.2.P.2.4 Container Closure System.

(b) (4)

(b) (4)

10% glycerol in DPBS is purchased from (b) (4) It is formulated using (b) (4)

A summary of the information provided in the BLA on the 10% glycerol in DPBS formulation buffer is provided in Table 36.

Table 36. Summary of Information Provided on the 10% glycerol in DPBS Formulation Buffer

(b) (4)

(b) (4)

3.2.P.2.2.2 Overages

There are no overages for KB103 DP.

3.2.P.2.2.3 Physicochemical and Biological Properties

(b) (4) State

The KB103 DP is characterized by (b) (4) according to (b) (4). Analysis of B-VEC by the (b) (4). The (b) (4) was tested during process validation studies. The mean (b) (4) PPQ lots was (b) (4) with % CV of (b) (4), which is close to the anticipated (b) (4). The test for (b) (4) is also included as part of the CPV plan not only for DP but also for process intermediates.

Infectious Particles

The concentration of infectious viral particle is quantified with the plaque formation unit (PFU). Concentration of viral particles is measured by quantification of HSV-1 genome copy titer. The (b) (4) is calculated for lot release.

3.2.P.2.3 Manufacturing Process Development

(Reviewed by BL)

The DP manufacturing process is comprised of aseptic filling of the DS into vials. Throughout the product development history (Table 37), there are (b) (4) notable changes to the DP manufacturing process: 1(b) (4)

Table 37. DP Manufacturing Process Development History

(b) (4)

3.2.P.2.4 Container Closure System

(Reviewed by JW)

The container closure systems for KB103 DP and HPMC Gel are (b) (4) vial respectively.

3.2.P.2.4.1 Container Closure System for KB103 DP

The commercial KB103 DP container closure system is the (b) (4) closed-system filling vials (b) (4) DMF (b) (4). This container closure system was used for DP in the Phase 3 clinical trials. The 1mL nominal fill volume vial will be covered with a green cap.

- (b) (4)

3.2.P.2.4.2 Container Closure System for Excipient (HPMC) Gel

The container closure system for HPMC Gel is the (b) (4) vial (DMF (b) (4) with a (b) (4) bromobutyl rubber stopper (DMF (b) (4)).

- (b) (4)

KB103 DP is stored at (b) (4) and shipped at -20°C. The HPMC Gel is stored at -20°C and shipped at (b) (4). The (b) (4) shippers are tested and used for the shipping of KB103 DP and HPMC Gel. The shipping qualification studies showed that all shippers maintained -20°C for the (b) (4) of shipping, no critical damage was incurred for any of the (b) (4) shipper configurations upon return to Krystal, and all KB103 samples tested for titer and potency met acceptance criteria. Label adhesion

study report demonstrated the ability of KB-103 vial label to adhere to (b) (4) and HPMC Gel vial label to adhere to HPMC Gel vials.

Reviewer Comments:

- All 3 LOAs from DMF holders and CCS drawings were provided. This is adequate.
- No leachables of concern were identified.
- The testing and specifications of CCS are reviewed in further detail in Section 3.2.P.7 Container Closure System (CCS).
- Extractables and Leachables study is reviewed in detail in Section 3.2.P.2.4.3. Leachables/extractables (L/E).
- Stability of DP and HPMC Gel is reviewed in Section 3.2.P.8 Stability.

3.2.P.2.4.3. Leachables/extractables (L/E)

(Reviewed by BL)

L/E risk assessment for single-use components

All single-use components used in the KB103 manufacturing process should meet the biocompatibility (b) (4) sterility, and (b) (4) risk requirements. A leachable/extractable (L/E) risk assessment for product contact materials other than the (b) (4) DP container closure system was conducted. This L/E risk assessment was performed using the methodology described in an industry recommended approach (b) (4)

In the L/E risk assessment, all (b) (4)

(b) (4)

- (b) (4)

(b) (4)

3.2.P.2.5 Microbiological Attributes

(Reviewed by JW)

B-VEC is manufactured under aseptic conditions. All container-closure components (b) (4) and excipients are verified to be sterile before use. DP lot release testing includes (b) (4) sterility and endotoxin testing with samples that are aseptically obtained from the final container. The (b) (4) is tested for (b) (4)

The integrity of (b) (4) has been demonstrated by both the manufacturer using a (b) (4) test and the supplier by (b) (4). The supplier also conducted (b) (4)

The DP filling operation was qualified at Krystal. Passing results (no growth observed) demonstrated the suitability of the (b) (4) and associated filling process for sterile product manufacturing. (b) (4) aseptic performance re-qualification is planned.

3.2.P.2.6 Compatibility

Compatibility of KB103 DP with 10% glycerol in was evaluated preclinically by measuring viral functionality. This formulation buffer has not been changed throughout development.

To facilitate topical administration, HPMC Gel is mixed with KB103 at the site of care. The purpose of the HPMC Gel is to provide sufficient viscosity to retain KB103 in open wounds to be treated. Studies were conducted to ensure that the gel did not hinder or assist the action of KB103. As development progressed, a range of viscosities were also tested. 3% HPMC Gel (b) (4) was evaluated in the preclinical setting to evaluate COL7 expression and functionality following topical administration. This HPMC Gel was manufactured at (b) (4) and was used in the Phase 1 and Phase 2 clinical studies. However, the viscosity was increased to make topical administration easier for the Phase 3 clinical study. For Phase 3 clinical studies, KB103 was mixed with a 4% HPMC Gel manufactured by (b) (4) (early in the Phase 3 trial) or a 4.4% HPMC Gel manufactured by BSM (majority of the Phase 3 trial) prior to topical administration. The 4 and 4.4% versions of the HPMC Gel were also formulated in a Tris PBS buffer solution instead of (b) (4). The 4.4% HPMC Gel provides the mixture with increased viscosity over the 3 and 4% gels which facilitates retention of the applied material in the area to be treated.

As an analytical comparability study could not be conducted to establish comparability of the KB103/HPMC Gel formulation, a nonclinical study was performed (REP-0564.00) to confirm that the gels used throughout clinical development had no effect on KB103 titer or potency. To demonstrate that gel viscosity did not affect KB103 delivery, KB103 mixed with 3, 4 and (b) (4) HPMC Gel were compared in a short-term pharmacology study in mice. The results in study report KB103-IVV-FD009 show similar activity of KB103 mixed with 3, 4 or (b) (4) HPMC Gels.

Reviewer Comment: As per the P/T reviewer, an insufficient number of mice were used in this study to establish equivalency. However, the data appeared similar regardless of HPMC Gel concentration. For additional information on this study, please refer to the P/T review memo.

Overall Reviewer's Assessment:

Information provided in this section is acceptable. Concerns on the leachables/extractables studies on product contact components used in manufacture, container closure system, and administration device were adequately addressed through IRs.

3.2.P.3 Manufacture**3.2.P.3.1 Manufacturer(s)***(Reviewed by BL)*

KB103 (b) (4) DP is manufactured from vial thaw through filling at Krystal Biotech located in Pittsburgh, PA. Finished packaging will be performed at (b) (4) and shipped to (b) (4) for distribution throughout the U.S. Manufacturing, packaging, distribution, and testing sites are listed below (Table 38).

Table 38. KB103 DP Manufacturer and Testing Site Information

Site Name	Site Address	FEI	Responsibility	Contact Person
Krystal Biotech, Inc.	2100 Wharton Street Suite 701 Pittsburgh PA 15203	3013498720	Drug Product Manufacturing Testing and Release Site	Rebekah Byrne rbyrne@krystalbio.com

(b) (4)

3.2.P.3.2 Batch Formula

Each vial of KB103 DP contains (b) (4) of 5×10^9 PFU per mL in 10% Glycerol in DPBS. The KB103 batch formula is provided in Table 39.

Table 39. KB103 Batch Formula

Component	Unit Quantity / Concentration	Amount per Batch (b) (4) / Final Concentration
KB103 (b) (4) (HSV 1- COL7)	(b) (4)	5×10^9 PFU/mL
10% Glycerol in DPBS	(b) (4)	Quantity Sufficient to meet (b) (4) volume

The commercial batch target range is (b) (4) which results in a target yield of (b) (4) vials (range: (b) (4) vials).


3.2.P.3.3 Description of Manufacturing Process

(Reviewed by BL)

(b) (4)



(b) (4)







Overall Reviewer's Assessment:

Information provided on KB103 DP commercial manufacturing process is acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates

(Reviewed by BL)

(b) (4)



(b) (4)

3.2.P.4 Control of Excipients

HMPC Gel is mixed with KB103 immediately prior to KB103 administration. The following information on the HMPC Gel was provided in the indicated drug product sections of the BLA. For the purposes of this review, all information pertaining to HMPC Gel is presented in this section.

3.2.P.1 Description and Composition of the Drug Product [HPMC Gel]

HPMC Gel is manufactured for Krystal Biotech, Inc. by Berkshire Sterile Manufacturing (BSM). The gel is defined as 4.4% HPMC formulated in a Tris buffer solution. The gel is mixed with KB103 DP prior to application to thicken the DP to keep it in place on the site of administration until the wound can be covered. The physiochemical properties of the gel include (b) (4) viscosity, (b) (4)

The components of the HPMC Gel are presented in Table 41.

Table 41. Components for the HPMC Gel

Component	Materials	Quality	Final Formulation concentration
Tromethamine Solution (b) (4)	(b) (4)	(b) (4)	0.91g/L (7.5mM final)
1X Phosphate Buffered Saline Solution (b) (4)	(b) (4)	(b) (4)	0.21 g/L 9 g/L 0.726 g/L
Hydroxypropyl Methylcellulose	(b) (4)	(b) (4)	4.4% w/w

Reviewer Comment: Lyophilized HPMC is reconstituted and tested per the respective compendium upon receipt from the vendor.

3.2.P.2.2 Drug Product [HPMC Gel]

Over the course of the KB103 preclinical and clinical product lifecycle, the HPMC Gel was comprised of 3 - 4.4% HPMC in a diluent of (b) (4) except for the clinical Phase 2b study, which used (b) (4). Accordingly, a summary of the gel utilized throughout KB103 development is provided in Table 42.

Table 42. HPMC Gel Throughout Development

(b) (4)

***Reviewer Comment:** The Applicant specifies that the (b) (4) HPMC Gel was tested in a nonclinical study (KB103-IVV-013) to provide a comparison to 4% HPMC Gel. From this study, the Applicant concluded that mixing the KB103 DP into different percent HPMC Gel formulations did not result in a difference in the infectivity of the virus or the expression of the COL7 protein in vivo.*

3.2.P.2.3 Manufacturing Process Development [HPMC Gel]

As summarized in Table 42, the HPMC Gel manufacturing process evolved during KB103 clinical development. The process of dissolving lyophilized HPMC in a buffer was relatively constant but the percentage of HPMC and the composition of the buffer changed. Of note, the manufacturing process was revised from Phase 3 to the proposed commercial process. The differences between the Phase 3 and commercial processes are captured in Table 43.

Table 43. Changes to the Manufacture of HPMC Gel

(b) (4)

(b) (4)

Reviewer Comment: As it was difficult to establish analytical comparability between the different HPMC Gel iterations, shown in Table 42, non-clinical studies were performed to establish comparability and support similar effects (or lack thereof) on KB103. Please see Section 3.2.P.2.6 Compatibility for additional details.

3.2.P.2.4 Container Closure System [HPMC Gel]

The HPMC Gel container closure is detailed in Table 61. An extractables/leachables study was performed by (b) (4). For this study, materials listed in Table 44 were evaluated. For the extractables portion of the study, the (b) (4). The simulated leachables studies was conducted as presented in Table 45. For the extraction study, component materials were stored in sample solutions at (b) (4).

(b) (4)

This study utilized several analytical technologies intended to capture different categories of extractables and leachables, including: (b) (4)

The leachables study found no significant interactions between the HPMC Gel and the container closure (b) (4)

Reviewer Comments: These studies utilized the proposed HPMC Gel commercial container closure. The extractables study identified a number of compounds as capable of being extracted from the intended commercial stopper (especially with the application of (b) (4)). There was not a corresponding toxicological evaluation. However, these extractables did not appear in the respective leachable study. Therefore, they are not a risk for this product.

During evaluation of the leachables samples, there was not clear negative control gating in relation to the test sample. In response to CMC IR#4, dated 10/21/2022, an updated report (Report STUQL21AA1197-2 Revision 3) with better negative control (b) (4) was provided in Amendment 24. In the updated report, all compounds detected in the test samples were confirmed to also be present in the control samples. An investigation was also opened to determine the root cause of the use of the inappropriate negative control (b) (4) scheme. In totality, this leachable study supports the use of this container closure for the HPMC Gel.

3.2.P.2.5 Microbiological Attributes [HPMC Gel]

The Applicant specifies that sterility is ensured through terminal sterilization and sterility testing. Sterility testing is included in the stability study as a means of ensuring container closure integrity (CCIT).

Reviewer Comment: A container closure integrity assessment was also performed. Please see DMPQ memo for additional details on this study.

3.2.P.3.1 Manufacturer(s) [HPMC Gel]

Table 46 summarizes the facilities utilized for the manufacturing and testing of the HPMC Gel.

Table 46. Facilities for the Manufacture and Testing of HPMC Gel

Facility Name	Address	FEI	Responsibility
Berkshire Sterile Manufacturing (BSM)	480 Pleasant Street, Lee, MA 01238	3012144557	Excipient gel manufacture, vial filling, release testing, and stability studies
(b) (4)			

(b) (4)

Reviewer Comment: All manufacturers retain a suitable registration status.

3.2.P.3.2 Batch Formula [HPMC Gel]

4.4% HPMC is formulated in 7.5 mM Tris in PBS. The Batch formula for (b) (4), which is used to manufacture the 7.5 mM Tris in PBS is captured in Table 47. The batch formula for 7.5mM Tris 1× PBS is captured in Table 48 and the batch formula for 4.4% HPMC Gel is captured in Table 49.

(b) (4)

(b) (4)

(b) (4)

Reviewer Comments: All materials are compendial and suitable.

3.2.P.3.3 Description of Manufacturing Process and Process Controls [HPMC Gel]

The HPMC Gel manufacturing process begins with (b) (4)

(b) (4)

(b) (4)

3.2.P.3.4 Controls of Critical Steps and Intermediates [HPMC Gel]

Controls for the manufacture of HPMC Gel are presented in Table 50.


Table 50. Controls (CPPs) for the Manufacture of HPMC Gel

(b) (4)

3.2.P.3.5 Process Validation and/or Evaluation [HPMC Gel]


HPMC Gel process validation is outlined in the report PR-132-012-R01 titled “PPQ Report Client 132 KB1203 Excipient Gel”. To validate the process, three (b) (4) batches of HPMC Gel were manufactured. (b) (4)

(b) (4)

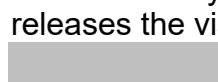
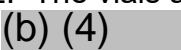


(b) (4)

(b) (4)



3.2.P.7 Container Closure System [HPMC Gel]

The HPMC Gel container closure is detailed in Table 61. The vials, stoppers and seals are sourced by Krystal Biotech and then provided to BSM. BSM receives, tests, and releases the vial components as specified in Table 62. The vials are (b) (4)  by BSM. The stoppers and seals are (b) (4)  ready to use.

(b) (4)

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

3.2.P.8.1 Stability Summary and Conclusions [HPMC Gel] and 3.2.P.8.3 Stability Data [HPMC Gel]

The Applicant evaluated the impact of (b) (4) on the HPMC Gel. An outline of the stability protocols is provided in Table 63. A summary of the available stability data is provided in Table 64.

Table 63. HPMC Gel Stability Protocol

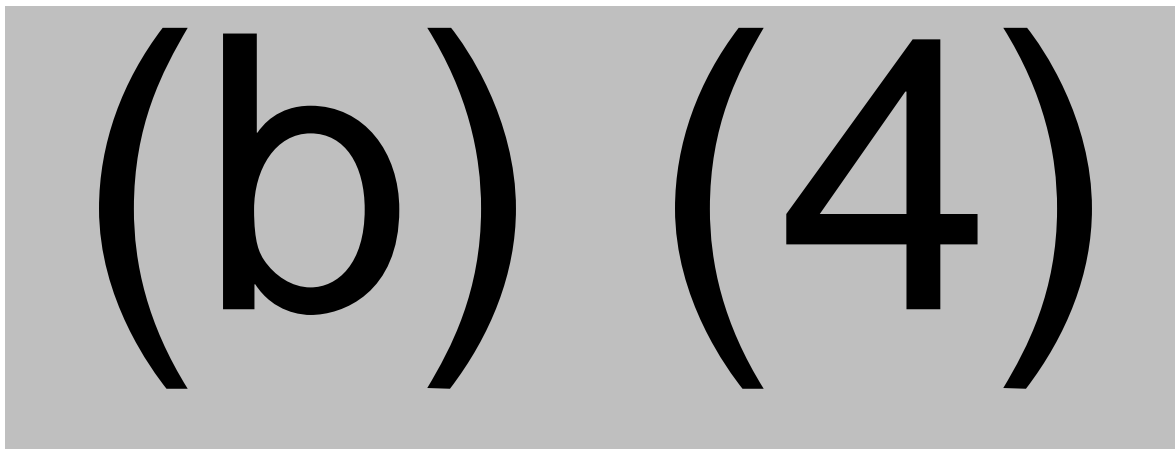
Test	Method	Specifications for Phase 3 lots	Specifications for PPQ lots 132-005-	Frequency
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Visual appearance	(b) (4)	Clear to opaque, colorless, slightly viscous gel	Clear, colorless viscous gel, visibly free from particulates	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Viscosity	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sterility	(b) (4)	No Growth	No Growth	(b) (4)
				(b) (4)

Table 64. HPMC Gel Batches Stability Summary

HPMC Gel Lot Number	Storage Condition	Duration (months)
(b) (4)	-20°C±5°C	(b) (4)
	(b) (4)	(b) (4)
	(b) (4)	(b) (4)
	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	-20°C±5°C	12
	(b) (4)	(b) (4)
	(b) (4)	(b) (4)
	(b) (4)	(b) (4)
(b) (4)	-20°C±5°C	12
	(b) (4)	(b) (4)
	(b) (4)	(b) (4)
	(b) (4)	(b) (4)
(b) (4)	-20°C±5°C	9
	(b) (4)	(b) (4)
	(b) (4)	(b) (4)
	(b) (4)	(b) (4)

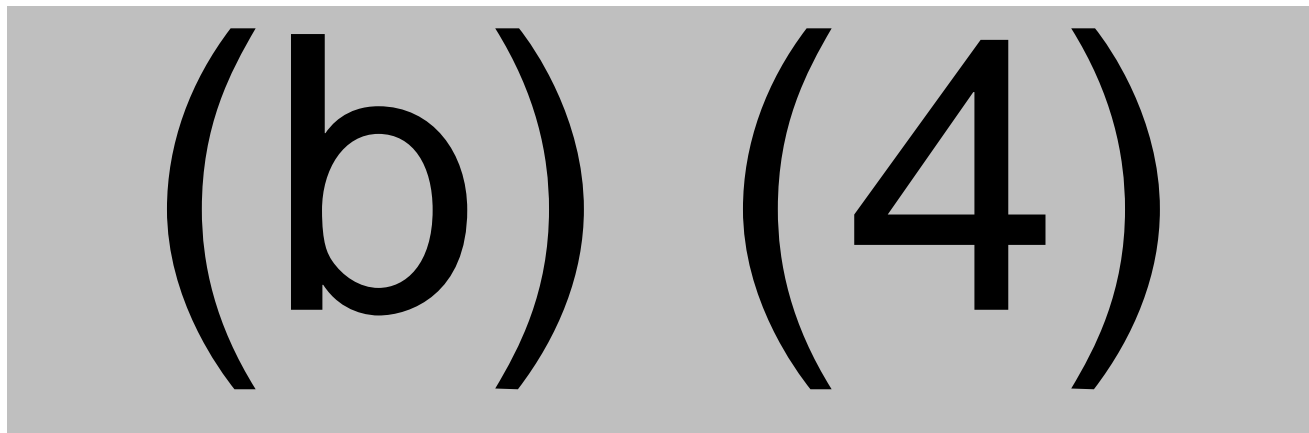
Reviewer Comments: There was concern that, in the absence of a HPMC concentration assessment, the stability protocol lacked assessments that may be considered as indicative of stability. In response to CMC IRs #3 and #4, dated 9/16/2022 and 10/21/2022, respectively, the Applicant provided an analysis of the accelerated stability data at elevated temperatures supporting the stability indicating

nature of the (b) (4) viscosity measurements in Amendment 24. Representative data from HPMC Gel Lot (b) (4) is depicted in Figure 23.



Reviewer Comments: *While it is not completely clear why a (b) (4) in (b) (4) is being observed with this (b) (4) solution, it is understandable that the viscosity measurement may be stability indicating. However, note that it is unclear whether the (b) (4) in viscosity at (b) (4) is due to HPMC (b) (4) or lower HPMC (b) (4). Nonetheless, the viscosity stability data will be further discussed below.*

The HPMC Gel viscosity stability data at the intended storage conditions (-20°C and (b) (4)) are summarized in Figure 24.



Reviewer Comments: *Though the HPMC Gel was originally stored at (b) (4), the Applicant noted improved stability at -20°C and thus chose to implement long-term storage of the gel at -20°C for commercial manufacture. We were originally willing to agree to an expiry of 9 months for the HPMC gel based on the originally submitted data. However, 12 month stability data were provided for HPMC Gel Lots (b) (4) in Amendment 43 to support a 12 month expiry.*

Note, the stability studies did not include an assessment of HPMC concentration. The currently available data can support a shelf life of 12 months however, a determination

of HPMC contraction should be considered in the assignment of shelf life. Thus, PMC #7 was implemented to obtain adequate HPMC contraction stability data following implementation of the HPMC contraction lot release specification.

3.2.P.8.2 Postapproval Stability Protocol and Stability Commitment [HPMC Gel]

One HPMC Gel commercial batch will be placed on stability per year according to Table 65. Initial batches will be tested out to (b) (4) (at -20°C), though additional lots may be extended to (b) (4).

Table 65. Stability Protocol for HPMC Gel Commercial Lots

Test	Method	Specifications for Future Commercial lots	Frequency
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Visual appearance	(b) (4)	Clear, colorless viscous gel, visibly free from particulates	
(b) (4)	(b) (4)	(b) (4)	
Viscosity	(b) (4)	(b) (4)	(b) (4)
Sterility	(b) (4)	No Growth	
CCIT	(b) (4)	(b) (4)	

***Reviewer Comments:** The Applicant updated the post approval stability acceptance criteria to match that of the lot release acceptance criteria in Amendment 80. This is acceptable.*

3.2.P.4.5 Excipients of Human or Animal Origin

There are no excipients of human or animal origin.

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)

(Reviewed by BL)

DP lot release specifications

In-process tests for (b) (4) are part of the DP lot release specification (Table 66).

(b) (4)

(b) (4)

The commercial DP lot release specifications for tests performed on the vial DP are shown (Table 69). There were multiple rounds of negotiation and revision of the quantitative DP lot release AC during the original BLA review. The AC shown in the Table 67. are agreed upon by the FDA and the Applicant after negotiation. The Applicant updated the DP lot release specification accordingly in the BLA in Amendment 51.

Table 67. B103 DP Lot Release Specifications

Method Number	Analytical Method	Acceptance Criteria	Action limit
(b) (4)	Sterility (b) (4)	No growth	NA
(b) (4)	Drug Product and Raw Material Appearance	Opalescent yellow to colorless liquid, free from extrinsic visible particulates	NA
(b) (4)	KB103 Identity (b) (4)	(b) (4)	NA
(b) (4)	KB103 (b) (4)	(b) (4)	NA
(b) (4)	Detection of Replication Competent HSV on (b) (4) Cells	Not Detected	NA
(b) (4)	B-VEC (HSV-1) Virus (b) (4) Assay	Sensitive	NA
(b) (4)	Herpes Simplex Virus-1 (HSV- 1) Plaque Assay	(b) (4)	NA
(b) (4)	Quantification of HSV Genome Copy number by (b) (4)	(b) (4)	NA
(b) (4)	(b) (4)	(b) (4)	NA
(b) (4)	B-VEC Potency (b) (4)	(b) (4)	NA
(b) (4)	B-VEC COL7A1 (b) (4) Assay	(b) (4)	NA
(b) (4)	Quantitation of (b) (4)	(b) (4)	(b) (4)
(b) (4)	Residual (b) (4) Quantification in HSV-1 Samples by (b) (4)	(b) (4)	NA
(b) (4)	Quantification of (b) (4) HSV-1 Samples by (b) (4)	(b) (4)	(b) (4)
(b) (4)	Quantification of (b) (4) in HSV-1 Samples by (b) (4)	(b) (4)	(b) (4)

(b) (4)	(b) (4)	Quantification of	(b) (4)	NA
		Bacterial Endotoxins		
(b) (4)	(b) (4)	Measurement	(b) (4)	NA

Reviewer Comments: *Of note, initially Krystal was performing all lot release testing on final filled, but unlabeled, vials of KB103. In response to CMC IR#4, dated 10/21/2022, Krystal agreed to confirm identity on labeled vials of KB103 using the (b) (4) in Amendment 24 (submitted 11/7/22). (b) (4) labeled packaged samples will be transported from (b) (4) to Krystal at the completion of each batch. One packaged sample will be tested for identity and (b) (4) samples will be stored as retain samples. This is acceptable.*

Justification of DP lot release specifications

DP release specifications were established based on historical data from (b) (4)

(b) (4)

(b) (4)

(b) (4)

HSV-1 Plaque Assay (b) (4)

(b) (4)

Reviewer Comments:

- *There were several rounds of negotiation for the HSV1 virus titer AC. During the late-cycle meeting, the Applicant intended to justify their original AC of (b) (4) based on assay variability and stability data. FDA pointed out that*


the Applicant's approaches to justify the AC based on stability data is not appropriate. And FDA's requested commercial AC of (b) (4) PFU/mL already takes into consideration the assay variability of (b) (4) with the nominal titer of 5×10^9 PFU/mL for dosing. The AC of (b) (4) PFU/mL requested by the FDA takes into consideration of the Phase 3 clinical experience, the target DP concentration, and inclusion of an extra margin. In Amendment 37 in response to Comment 5a of IR#6 dated 12/5/2022, the Applicant agrees to set the AC as (b) (4) PFU/mL.

- Most subjects in the Phase 3 pivotal trial were treated with multiple lots of different HSV1 virus titers. To confirm that the lowest titer in all pivotal lots, i.e., (b) (4) PFU/mL, is clinically effective, the clinical reviewer Ning Hu (CBER/OTP/OCE/DCEGM/GMB2) was consulted to identify all lots received by each subject in the pivotal trial. It was found that subject (b) (6) was treated with Lot (b) (4) only and showed clinical benefit. This lot has titer of (b) (4) PFU/mL, the lowest among all Phase 3 pivotal lots. Therefore, the lower limit of AC is adequately supported by clinical data from the pivotal trial. No notable adverse events were reported to be associated with any of the Phase 3 clinical lots. Therefore, the upper limit of (b) (4) PFU/mL is also supported by the clinical data from the pivotal trial.*
- It should be noted that because the AC for PPQ lot release was set as (b) (4) PFU/mL, PPQ lots (b) (4) PFU/mL and (b) (4) PFU/mL are considered successful PPQ runs, although they did not pass the commercial release AC of (b) (4) PFU/mL.*


HSV Genome Copy by (b) (4))
(b) (4)

(b) (4)

Potency (b) (4)
(b) (4)




Col7A1 (b) (4)
(b) (4)




Reviewer Comments: FDA asked the Applicant to reassess and tighten this AC as appropriate after collecting more data from commercial manufacturing of KB103. This commitment is described in PMC #2.

(b) (4)



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

(b) (4)




(b) (4) Endotoxin (b) (4)

A theoretical maximum limit of endotoxin was calculated based the limit of (b) (4)



(b) (4)



(b) (4) Sterility

Sterility testing is performed using the (b) (4) method according to (b) (4)
Specification is “no growth”.

Appearance (b) (4)

Physical appearance is tested to ensure the DP conforms to the specification of “opalescent yellow to colorless liquid, free from extrinsic visible particulates”. This specification is based on (b) (4) confirmation that no foreign matter or particulates are present in the vial DP, and no unexpected change of color or clarity occurred due to an error in process to affect batch uniformity.

Identity by (b) (4)


This method is used to confirm identity of KB103 DP by testing (b) (4)



Identity by (b) (4)



(b) (4)



Replication-competent HSV (b) (4)

This method is to screen for replication-competent HSV-1 in KB103 DP by (b) (4)

The specification is “not detected” to ensure that patients are not exposed to replicating HSV-1 from KB103 DP.

Overall Reviewer’s Assessment:

FDA disagreed with the Applicant’s initially proposed KB103 DP lot release AC. Those have been revised through multiple rounds of negotiation. The final agreed lot release AC listed are deemed acceptable for KB103 commercial lot release. In response to FDA’s request, the Applicant includes two PMCs to reassess lot release AC for Col7A1 (b) (4), when more data are collected from commercial manufacturing. These PMCs are acceptable.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

(Reviewed by JW)

Each method listed in Table 69 has been validated or verified by Krystal or a CRO. provides a summary of parameters validated for individual assay. Table 69 provides a summary of parameters validated for individual assay.


Reviewer Comment: *The validation or verification of Appearance, (b) (4) Sterility, Endotoxin, (b) (4)*

assays is reviewed by DBSQC and found acceptable. Please refer to the DBSQC review memo.

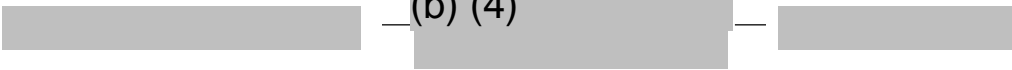
(b) (4)

Herpes Simplex Virus-1 (HSV-1) Plaque Assay


Assay Procedure: The HSV-1 plaque assay is used to quantitate infectious virus or titer of KB-103. (b) (4)



(b) (4)



(b) (4)



(b) (4)

(b) (4)

Reviewer Comments:




- Please note the intermediate precision (%CV) is as high as (b) (4). In response to IR#12 dated 04/27/2023, in Amendment 67 dated 04/28/2023, the Applicant agreed to reduce the variability (%CV) observed in intermediate precision during assay validation, re-validate the optimized assay. This commitment is described in PMC #9.
- The initially proposed range of (b) (4) is not based on the cumulative results from the linearity, accuracy, and precision and is incorrect. This issue was discussed in IR#4, dated 10/21/2022, IR#6 dated 12/05/2022, an informal

teleconference on 17JAN2023, IR#8 dated 01/06/2023, IR#9 dated 01/30/2023, and IR#10 dated 02/21/2023.

- *In Amendment 24 dated 11/07/2022, Amendment 37 dated 12/20/2022, and Amendment 43 dated 02/07/2023, the Applicant stated that the assay results should be based on plaque counts, which we agreed. However, the Applicant insisted that the AC for this assay, i.e., plaque count of (b) (4), should be used to calculate the assay range (b) (4) PFU/mL. Based on the totality of data in the assay validation report, FDA agrees the range of plaque count (b) (4) which was communicated to the Applicant in the 2nd informal teleconference on 09Feb2023.*
 - *In Amendment 48 dated 02/21/2023, the Applicant agreed that a plaque count range of (b) (4) will be used to calculate the validated assay range.*
- *There are almost (b) (4) plaque count differences during assessment of different parameters (accuracy, intermediate precision, and robustness) even using the (b) (4) of B-VEC (b) (4) lot. For example, the average plaque counts for High Titer-(b) (4) range from (b) (4) plaques.*
 - *In response to IR#4 dated 10/21/2023, in Amendment 24 dated 11/07/2023, the Applicant attributed the plaque count differences among the (b) (4) B-VEC samples to the assay variability and stated that the variability of the counts is in alignment with the variability of the method of (b) (4). This is acceptable.*

B-VEC Potency (b) (4)

(b) (4)



(b) (4)

B-VEC Col7A1 (b) (4) Assay

Assay Procedure: This method describes the procedure for (b) (4) analysis from (b) (4)



(b) (4)

(b) (4)

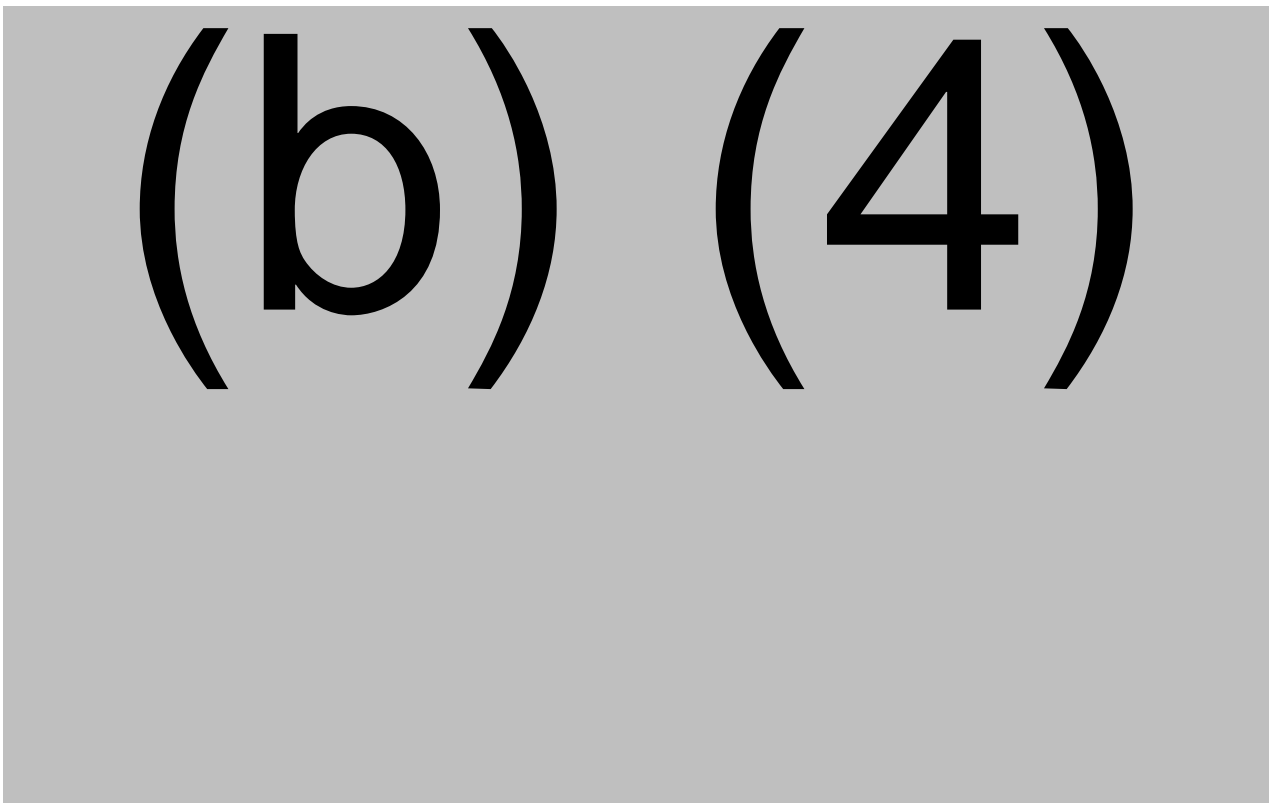
B-VEC Identity (b) (4)



(b) (4)



(b) (4)



(b) (4)

(b) (4)

Quantification of HSV Genome Copy Number by (b) (4) Assay

Assay Procedure: HSV-1 genome copy number in KB103 test article is quantified using

(b) (4)

(b) (4)

(b) (4)

3.2.P.5.4 Batch Analyses

(Reviewed by BL)

The toxicology batch (Lot (b) (4)) was manufactured using a process similar to the Phase 1 clinical product manufacturing process on a smaller scale in Krystal's R&D laboratory and had the same formulation (1xDPBS, 10% glycerol). Tests for titer (b) (4), HSV genome copy number, and process (b) (4) were performed at (b) (4) or Krystal's R&D laboratory.

The Phase 1 batch (Lot (b) (4)) and Phase 2 batch (Lot (b) (4)) were manufactured using (b) (4) respectively, at (b) (4)

(b) (4) Phase 3 clinical lots ((b) (4)) and (b) (4) additional Phase 3 lots used in Open Label Extension study (b) (4)

(b) (4)) were manufactured using (b) (4) was also manufactured using (b) (4) is used as the current RS.

Lot (b) (4) and three PPQ lots (b) (4) were manufactured using (b) (4) Their batch analysis data are provided in Module 3.2.S.2.6. The COAs for PPQ lots and three post-PPQ launch lots (b) (4) are provided. The lot release test results of three PPQ lots and three post-PPQ launch lots passed the pre-established PPQ lot release AC.

Reviewer Comments: Overall, the test results for residuals (b) (4) are consistent among (b) (4) lots. The lot-to-lot consistency for residuals were improved in (b) (4) compared to (b) (4) lots. (b) (4) lot release data were used to justify the commercial lot release specifications. As noted above, there is still a concern of the consistency of the HSV1 virus titer as (b) (4) PPQ lots and (b) (4) recently manufactured post-PPQ launch lot did not meet the lower limit of the agreed commercial AC of (b) (4) PFU/mL, although they all met the PPQ lot release AC. The Applicant has included (b) (4) tests for HSV1 titer for (b) (4) as part of the continued process validation plan to gain further understanding of the process from future commercial manufacturing. This is acceptable.

3.2.P.5.5 Characterization of Impurities

(Reviewed by JW)

Impurities in B-VEC are divided into (b) (4)

The Applicant stated that KB103 impurities are controlled within specification limits by proper selection and preparation of incoming materials and using a validated manufacturing process. Impurities were monitored and evaluated in each DP lot. Table 78 and Table 79 summarize results for process-related impurities and product-related impurities respectively from samples in (b) (4) B-VEC DP lots including the 3 PPQ lots.

(b) (4)

(b) (4)

(b) (4)

Reviewer Comments:

- The comparisons (refer to the column Maximum Observed) of impurity profiles from (b) (4) DP lots with DP lot release AC showed that levels of both the process-related impurities and the product-related impurities met clinical DP lot release AC and DP impurities are adequately controlled.
- It was noteworthy that among (b) (4) lots compared, Lot (b) (4) has the highest level of (b) (4) and (b) (4). The Applicant stated that Lot (b) (4) was manufactured by (b) (4) but was not used in the clinic and is currently being qualified as reference material.
- The Applicant stated: (b) (4)

3.2.P.6 Reference Standards or Materials

(Reviewed by JW)

3.2.P.6.1 Overview of Reference Standard Program

KB103 engineering Lot (b) (4) is the current RS. KB103 Lot (b) (4) is currently being qualified as a new RS. The RS serve as an assay control to assess system suitability for the plaque titer, potency, identity by (b) (4), quantification of HSV-1 genomes, replication competent HSV-1, (b) (4) in release and stability testing, method qualification, and validation.

Reviewer Comment: Both RS lots were manufactured using the (b) (4) thus neither RS lot is representative of commercial lots manufactured using the (b) (4)

3.2.P.6.2 Establishment and Qualification of RS KB103 (b) (4)

The RS KB103 (b) (4) was retrospectively established. It was manufactured at Krystal using (b) (4)

(b) (4)

Table 80. Reference Standard KB103 Lot (b) (4) Qualification Test Results

Test	Results			
	Range	Mean	SD	%CV
Plaque Titer (PFU/mL)	(b) (4)			
HSV Genome by (b) (4)				
Potency (b) (4)				
COL7 expression by (b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
² Identity-(b) (4)				
(b) (4)				
(b) (4)				
² Sterility	No Growth			
² Bacteriostasis and Fungistasis Final Product (b) (4) Method)	No Inhibition			

¹ (b) (4)

(b) (4)

(b) (4)

3.2.P.6.3 Stability of KB103 Lot (b) (4)

The KB103 Lot (b) (4) has been placed on a stability study at (b) (4) and a subset of CQAs are tested according to protocol. Stability is monitored to confirm that KB103 Lot (b) (4) remains suitable for the intended use. The stability study design and results are shown in Table 81.

(b) (4)

(b) (4)

3.2.P.6.4 Strategy for Establishing KB103 (b) (4) as a New RS

A new primary RS, KB103 (b) (4), was selected prior to depletion of the current RS. It was manufactured at Krystal using (b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.P.7 Container Closure System (CCS)

(Reviewed by JW)

3.2.P.7.1. Container Closure System for Drug Product (Primary CCS, Secondary CCS, and Shelf Carton)

Primary CCS for DP: (b) (4). The (b) (4) vials (Table 85) are sourced from (b) (4), and then release tested by the Applicant as specified in Table 86.

Table 85. Materials of Construction of Primary Container Closure System for DP

Component	Materials of Construction	Source	DMF Reference
Vial Body	(b) (4)	(b) (4)	(b) (4)
Vial Stopper	(b) (4)		
Top Ring	(b) (4)		
Vial Cap	(b) (4)		

DMF=Drug Master File.

Table 86. Specifications for (b) (4) Vial

Test Attribute	Acceptance Criteria	Analytical Procedure
Specifications for (b) (4) Vial		
Plastic Materials of Construction Sterility Tests	Pass/Fail Pass/Fail	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

(b) (4)

Reviewer Comment:

- *The Applicant stated that the (b) (4) has been selected because it reduces microbial contamination risk relative to open vial filling, is less prone to breakage than conventional glass vials, and is easier to use in vial filling operations.*
- *For detailed justifications for its use in KB103 DP packaging, please refer to the Section 3.2.P.2.4 Container Closure System.*

Secondary CCS for DP: Tray + Bag + Cardboard Box (Table 87)

- 1) The packing of the assembled (b) (4) vial in a tray is performed in an (b) (4) background.
- 2) Sterilization is performed via (b) (4)
- 3) The sterilization dose range has been assessed according to (b) (4) .

Table 87. Materials of Construction of Secondary Container Closure System

(b) (4)

Shelf Carton

The product shelf carton is procured, received, received and released for packaging by (b) (4) located in (b) (4). The KB103 shelf carton is made of (b) (4).

The shelf carton will hold the KB103 vial and HPMC Gel vial in place, provide a compartment for a package insert and protect the contents from light.

(b) (4)

3.2.P.8 Stability**3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data**

Following manufacture, KB103 is initially frozen and stored at (b) (4) at the manufacturing facility. However, shipping from the manufacturing facility (and all future shipping procedures) labeling, packaging, and storage of the final product cartons (containing both KB103 and HPMC Gel) is under -20°C conditions. Additionally, the final product cartons are able to be stored at 2-8°C at clinical sites for up to 1 month. Table 88 summarizes all the KB103 DP stability data provided for establishing shelf life at these temperatures.

Table 88. Summary of Available KB103 Stability Data

Batch Number	(b) (4)	(b) (4)	(b) (4)	(b) (4)9	(b) (4)	(b) (4)	(b) (4)
Use	Process Performance Qualification			RS	Phase 3 Clinical		RS
Fill volume	(b) (4)			(b) (4)	(b) (4)	(b) (4)	(b) (4)
Storage Temperature(s)	2-8°C, -20°C, and (b) (4)			(b) (4)	-20°C and (b) (4)	-20°C and (b) (4)	(b) (4)
Available Data/Planned Duration (months)	9/(b) (4)	9/(b) (4)	9/(b) (4)	12/(b) (4)	18/(b) (4)	12/12	(b) (4)
(b) (4)	√	√	√	√	√	√	√
	√	√	√	√	√	√	√
	√	√	√	√	√	√	√

(b) (4)	(b) (4)	√	√	√	√	NT	NT	NT
(b) (4)	(b) (4)	√	√	√	√	NT	NT	NT
MET-5023: Product Appearance	Opalescent yellow to colorless liquid, free from visible extrinsic particulates	√	√	√	√	NT	NT	NT
(b) (4) Sterility (b) (4) method)	No Growth	√	√	√	√	√	√	√

All batches were tested using qualified or validated analytical methods at Krystal except Lot (b) (4). This batch was tested for plaque titer and (b) (4) through 9 months. The 12-month timepoint was tested by Krystal using the validated assays. There was not a formal transfer of the assays from (b) (4) Krystal. Both methods were developed at Krystal and provided to (b) (4) for release of the Phase 1 (Lot (b) (4) and Phase 2 (Lot (b) (4) clinical lots.

(b) (4)

The KB103 Plaque Titer Assay and Potency (b) (4) stability data are summarized in Figure 25 and Figure 26, respectively.

(b) (4)

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

(b) (4)

Reviewer Comments: In response to CMC IR#6, dated 12/5/2022, the Applicant provided all the potency data in (b) (4) in Amendment 37. While in some lots there does appear to be a decrease in titer and/or potency with time (particularly at (b) (4)), all the data met the stability acceptance criteria. The variability observed is most likely due to assay variability rather than the stability of the product itself.

Based on the stability data provided in the original submission and the additional stability data provided in Amendments 33 and 41, the Applicant proposed a KB103 shelf-life of (b) (4) months. At least (b) (4) of the supporting lots completed 12 months of stability testing, thus, 12 months was agreed to as the KB103 expiration date.

Stability following mixing with HPMC Gel

KB103 DP is mixed with HPMC Gel at a ratio of 1mL to 1.5mL, respectively, prior to topical administration. A formal stability study was conducted to assess the allowable time the mixture can remain at ambient temperature in the administration syringes without impacting strength and potency of the DP. The study tested stability over (b) (4) hours post-syringe fill. For this study, KB103 (b) (4) (PPQ) was combined with HPMC Gel and (b) (4) of this mixture was pulled into a 1mL syringe. For each timepoint, (b) (4) syringes were tested for titer and potency. The average value of the results from the syringes was reported. The stability data are provided in Table 89.

Table 89. KB103 Syringe Hold Time Study, Ambient Temperature

Test Attribute	0 hrs	2 hrs	4 hrs	8 hrs	(b) (4)
(b) (4) Herpes Simplex Virus-1 (HSV-1) Plaque Assay	(b) (4)				
(b) (4) B-VEC Potency (b) (4)					

An additional study was performed on mixed KB103 + HPMC Gel in syringes stored at (b) (4) for up to (b) (4). For this study, KB103 B20025 was combined with HPMC Gel and (b) (4) was pulled into a 1mL syringe. The volume of (b) (4) was chosen based on clinical administration procedures at the time the study was initiated. The commercial presentation will be (b) (4) in a 1 mL syringe. For each timepoint, (b) (4) syringes were tested for titer. The average value of the results from the syringes was reported. The stability data are provided in Table 90.

(b) (4)

Reviewer Comments: For the ambient temperature study, the titer and potency remained within acceptance limits at all timepoints. However, there appeared to be a decrease at the (b) (4)-hour timepoint in the potency sample. Thus, the Applicant proposed a limit of 8 hours at ambient temperature for the filled syringes. This is acceptable and is clearly stated in the product insert (PI).

For the (b) (4) study, the titer remained within acceptance limits at all timepoints. Thus, the study concluded that mixed KB103 + HPMC Gel is stable for (b) (4) if stored at (b) (4). Of note, the Applicant is not proposing to store the syringes at (b) (4) at this time. If they choose to implement syringe (b) (4) in the future, they will need to perform a formal stability study at the correct volume and include potency testing.

Following a request to add additional handling details in the PI, the Applicant added that the capped administration syringes are to be placed in a sealable plastic bag in an appropriate insulated secondary container at 2° to 8°C for transport from the preparation site to the administration site. To support this, in Amendment 79, the applicant provided stability data for mixed KB103 + HPMC Gel in syringes stored at 2 - 8°C. KB103 Lot (b) (4) (commercial batch) was combined with HPMC Gel Lot (b) (4) and 0.4mL of this mixture was pulled into a 1mL syringe. For each timepoint, titer and potency were evaluated (Table 91).

Table 91. KB103 Syringe Hold Time Study, 2° to 8°C

Test Attribute		0 hrs	24 hrs	48 hrs	(b) (4)
(b) (4)	Herpes Simplex Virus-1 (HSV-1) Plaque Assay	(b) (4)			
(b) (4)	B-VEC Potency (b) (4)				

These study data do support that the KB103 + HPMC Gel remains stable in the filled syringe for up to (b) (4) hours when stored at 2 - 8°C and thus support the PI transport instructions.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

One KB103 commercial batch, filled at (b) (4) in (b) (4) closed vials, will be placed on stability per (b) (4) at -20°C±5°C as outlined in Table 92. The primary registration batches will continue to be evaluated for stability at both (b) (4) and -20°C, as indicated by the previous stability protocol. If during this evaluation there is a significant discrepancy between the (b) (4) temperatures, the post-approval stability protocol will be revised for the next commercial lot to include (b) (4) stability. If the post-approval stability study indicates that any lot is confirmed to be outside of the approved specifications included in the stability protocol, the Applicant commits to report this to FDA.

Table 92. Post-Approval Stability Study for Commercial KB103 DP Stored at -20°C±5°C

Method	Acceptance Criteria	Upright Test Intervals (Months)							
		0	3	6	9	12	(b) (4)	(b) (4)	(b) (4)
(b) (4) Plaque Assay Titer	(b) (4) of Release Titer	X	X	X	X	X	X	X	X
(b) (4) Potency (b) (4)	(b) (4)	X	X	X	X	X	X	X	X
(b) (4) Identity (b) (4)	(b) (4)	X	X	X	X	X	X	X	X
(b) (4)	(b) (4)	X	X	X	X	X	X	X	X
(b) (4) Product Appearance	Opalescent yellow to colorless liquid, free from extrinsic visible particulates	X	X	X	X	X	X	X	X
Container Closure Integrity Testing (b) (4)	Conforms	NT	NT	NT	NT	X	NT	X	X
Sterility	No Growth	X	NT	NT	NT	NT	NT	NT	NT

Reviewer Comments: *In Amendment 41, the Applicant provided updated post-approval stability acceptance criteria based on the agreed upon lot release acceptance criterion for Potency. Since the majority of KB103 DP storage takes place under -20°C conditions, the post-approval stability study is acceptable.*

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Reviewed by DMPQ. Please see DMPQ review memo for details.

A pre-license inspection of the Krystal Biotech, Inc. Ancoris facility located 2100 Wharton St Suite 701, Pittsburgh, PA 15203 in support of BLA 125774 approval was conducted between 11/11/2022 to 11/16/2022. Five FDA Form 483 items were identified. A number of discussion items were also conveyed. Please note that it was during this inspection that the change in (b) (4) was identified. Krystal Biotech adequately addressed all Form 483 items.

A pre-license inspection of the BSM manufacturing facility located at 480 Pleasant St., Lee, MA 01238 in support of BLA 125774 approval was also conducted between 1/16/2023 and 1/20/2023. Six FDA Form 483 items were identified. A number of discussion items were also conveyed. Krystal Biotech adequately addressed all Form 483 items.

Please see Establishment Inspection Reports (EIR) for additional details.

3.2.A.2 Adventitious Agents Safety Evaluation

Raw materials, Material of Biological Origin, and Starting materials

(Review by JW)

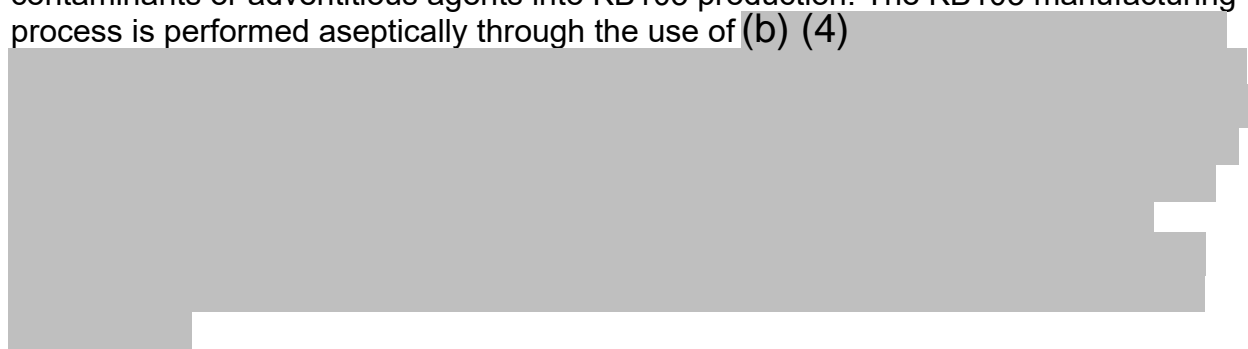
(b) (4)



Manufacturing Controls for KB103 Production and Product Testing


(Review by JW)

Controls have been put in place to minimize the potential for introduction of contaminants or adventitious agents into KB103 production. The KB103 manufacturing process is performed aseptically through the use of (b) (4)



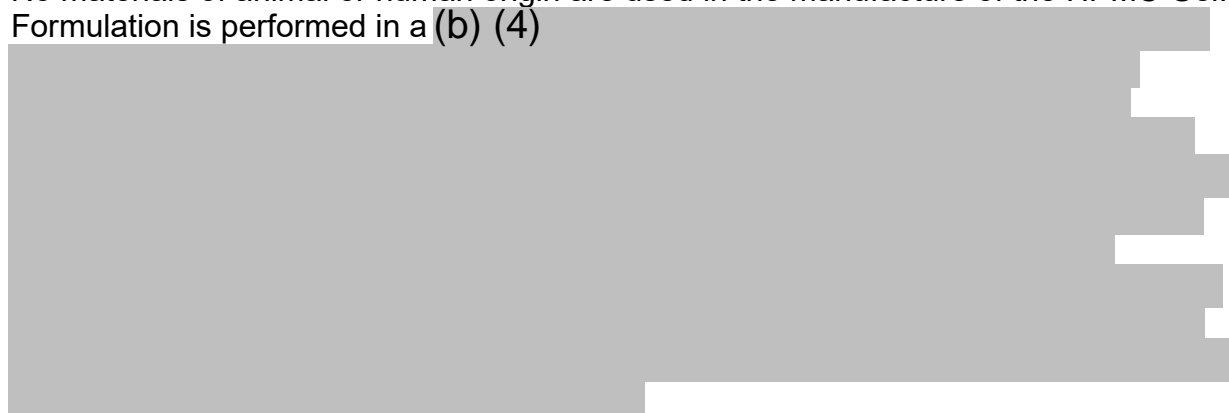
Each lot of KB103 also undergoes testing for sterility, (b) (4) endotoxin, replication competent virus, and (b) (4)

. The samples for each test are taken at the stage of production at which contamination is most likely to be detected. Samples for (b) (4)

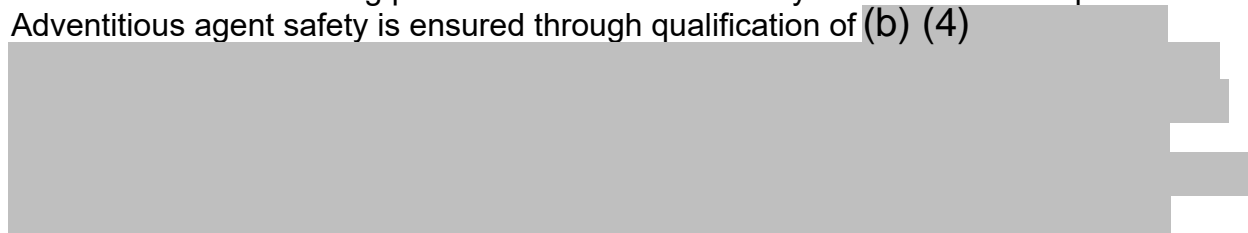


Excipient Gel*(Review by JW)*

No materials of animal or human origin are used in the manufacture of the HPMC Gel. Formulation is performed in a (b) (4)

**Viral Clearance Studies**

The KB103 manufacturing process does not contain any viral clearance steps. Adventitious agent safety is ensured through qualification of (b) (4)

**3.2.A.3 Novel Excipients**

Please see information on HPPMC Gel provided in Section 3.2.P.4 Control of Excipients.

3.2.R Regional Information (USA)**Executed Batch Records***(Reviewed by BL)*

A master batch record for the commercial manufacturing process (with the replacement (b) (4) system) and executed batch records for a PPQ lot (b) (4) and a post-PPQ launch lot (b) (4) were submitted and reviewed. During the PLI, executed batch records for (b) (4) PPQ lots (b) (4)) were also reviewed. Please refer to the Krystal facility EIR for additional details on the executed batch record review conducted during PLI.

The master batch record for HPMC Gel Lot (b) (4) was submitted and reviewed.
(Reviewed by MM)

Reviewer Comment: *Notes regarding aseptic filling and minor deviations from the batch record were conveyed to DMPQ. None of these deviations impact the process or product quality. Please refer to the BSM facility EIR for details on how these deviations are handled.*

Method Validation Package

Full method validation reports were provided. Validations are described in method validation sections (3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures).

Combination Products

Not applicable as KB103 is not a combination product.


Comparability Protocols

No prospective comparability protocols were provided in the BLA submission.


Distribution Plan


(Reviewed by AK)

The distribution plan for KB103, the HPMC Gel and the final product carton is outlined in Figure 27. Briefly, KB103 is stored at (b) (4) until it is shipped to the labeling/packaging facility, (b) (4). During shipping to (b) (4), and from that point forward, KB103 is stored at -20°C. At (b) (4), KB103 vials are labeled and packaged into cartons with HPMC Gel. The HPMC Gel is stored at -20°C at the manufacturing site (BSM) and at the storage facility, (b) (4)



(b) (4)



- (b) (4)
- 

Reviewer Comment: Based on the genetic modifications included in KB103 and the extra containment precautions taken, I concur that there is no significant environmental impact of approving KB103 and a finding of no significant impact (FONSI) was prepared. This conclusion is also based on the vector shedding and infectivity data observed during the KB103 clinical trials. Please see Shedding Analysis for additional details.

Reference Product Designation Request

(Reviewed by AK)

Krystal claims a reference product exclusivity period of 12 years from the date of approval of this BLA. According to Krystal, approval of this BLA will constitute “first licensure” for KB103 and there are no licensed biological products that are structurally related to KB103 for which Krystal or one of its affiliates, licensors, predecessors in interest, or related entities are the current or previous license holders.

Reviewer Comment: The proposed reference product exclusivity period of 12 years is acceptable.

Labeling Review

(Reviewed by AK)

Full Prescribing Information (PI):

The following sections of the PI were reviewed: Section 2 (Dose and Administration), Section 3 (Dosage Forms and Strengths), Section 11 (Description), Section 12 (Clinical Pharmacology – Mechanism of Action) and Section 16 (How supplied / storage and handling). The PI provides a detailed and correct description of KB103 and its mechanism of action. The PI also carefully and correctly describes the receipt and preparation procedures for KB103 as well as appropriate disposal procedures of product contact materials.

Reviewer Comment: There were multiple interactions with the Applicant during review of the PI where the Applicant was asked to clarify multiple details on product handling, preparation, administration and disposal procedures of KB103 and KB103 contact materials (i.e., bandaging). The Applicant agreed to make the requested changes and the changes were found to be adequate.

Carton and Container Label:

Examples of the KB103 vial (Figure 29), Excipient gel vial (Figure 30), and carton (Figure 31) labels are provided below.

Figure 29. B-VEC Vial Label



Figure 30. Excipient Gel Vial Label

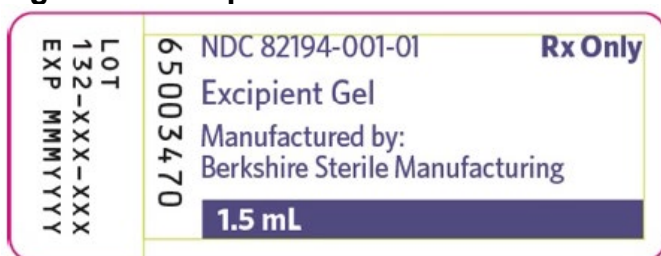
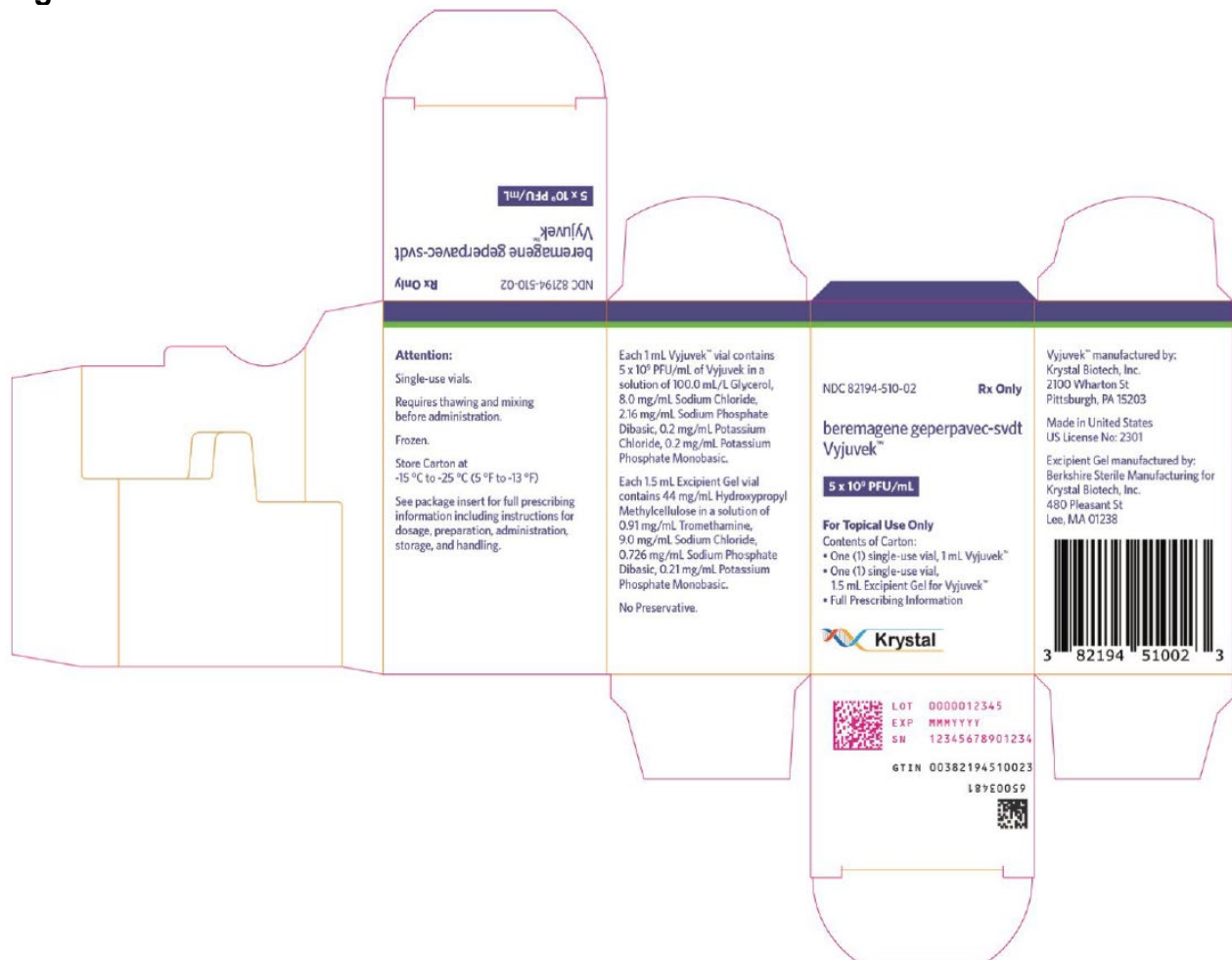


Figure 31. B-VEC Carton Label



***Reviewer Comments:** There were multiple interactions with the Applicant during review of the PI where the Applicant was asked to modify the container and carton labels (e.g., add NDCs, update name font and size, modify compositions, etc.). The Applicant agreed to make the requested changes and the changes were found to be adequate. The agreed upon labels included in the figures above were submitted in Amendment 75. Please see Rommel Maglalang's labeling memo for additional details.*

Module 5

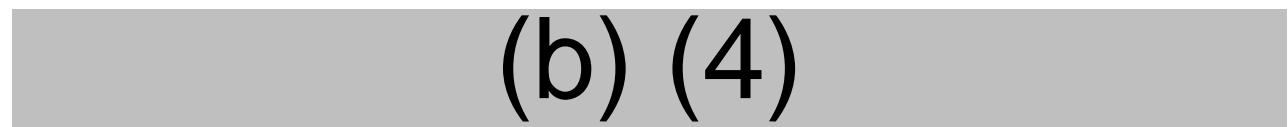





Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

5.3.1.4. Reports of Bioanalytical and Analytical Methods for Human Studies

(Reviewed by JW)

CTM-001 B-VEC Plaque Reduction Neutralization Test (PRNT) (REP-CQA-20-002)

(b) (4)



(b) (4)

