

BER CMC BLA Review Memorandum

BLA STN 125772/0

HEMGENIX (etranacogene dezaparvovec)

**Alifiya H. Ghadiali, Consumer Safety Officer
CBER/OCBQ/DMPQ/MRB3**

1. BLA#: STN 125772/0

2. APPLICANT NAME AND LICENSE NUMBER

CSL Behring LLC, Lic. No. 1767

3. PRODUCT NAME/PRODUCT TYPE

Non-proprietary/Proper/USAN: etranacogene dezaparvovec
 Proprietary name: HEMGENIX

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

- a. Pharmacological category: Adeno-associated virus vector-based gene therapy
- b. Dosage form: Injection, for intravenous infusion
- c. Strength/Potency: 1E13 gc/mL
- d. Route of administration: Intravenous infusion
- e. Indication(s): Treatment of adults with hemophilia B (congenital Factor IX deficiency)

5. MAJOR MILESTONES

Refer to CMC Review Memo

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Alifiya H. Ghadiali, PhD CBER/OCBQ/DMPQ/MRB3	3.2.S Drug Substance 3.2.P Drug Product 3.2.A.1 Facilities and Equipment

Refer to CMC Review Memo for additional reviewers

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations
N/A	N/A	N/A

8. SUBMISSION(S) REVIEWED

Date received	Submission	Comments/ Status
03-24-2022	STN 125772/0.0	Original Application
04-29-2022	STN 125772/0.3	DMPQ IR response
06-07-2022	STN 125772/0.11	CMC IR response (CCS and DP filling bag CoAs)
09-06-2022	STN 125772/0.32	DMPQ IR response
09-16-2022	STN 125772/0.40	CMC IR response (revised 3.2.P.3.4 and 3.2.P.3.5-1)
09-19-2022	STN 125772/0.41	CMC IR response (revised 3.2.S.4.4 and 3.2.P.5.4)

05-05-2022	STN 125772/0.4	PLI associated communication
05-10-2022	STN 125772/0.6	
05-12-2022	STN 125772/0.7	
05-17-2022	STN 125772/0.8	
09-09-2022	STN 125772/0.36	Response to FDA Form 483 Inspectional Observations (reviewed separately)
10-07-2022	STN 125772/0.46	DMPQ IR response
11-08-2022	STN 125772/0.64	DMPQ T-con IR response
11-17-2022	STN 125772/0.74	DMPQ IR responses

CCS = Container Closure System; CoA = Certificate of Analysis; DP = Drug Product; EIR = Establishment Inspection Report; PLI = Pre-License Inspection

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
N/A	N/A	N/A	N/A	N/A

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

CSL Behring LLC submitted an original Biological License Application (BLA, STN 125772/0) for etranacogene dezaparvovec (AMT-061) an adeno-associated virus vector-based gene therapy product for the treatment of adults with Hemophilia B (congenital Factor IX deficiency). The submission has been granted priority review.

The (b) (4) is a recombinant adeno-associated viral (AAV) vector containing a codon-optimized coding DNA sequence for human coagulation factor IX variant R338L (FIX-Padua). The drug product (DP) is a preservative-free, liquid formulation intended for administration after dilution (with 0.9% normal saline solution) for a single-dose intravenous infusion. The DP is presented in a single-use depyrogenated 10 mL (b) (4) glass vial stoppered with a 20 mm rubber stopper and sealed with an aluminum flip-off cap and is provided in kits containing 10 to 48 vials. The total number of vials in each kit corresponds to the dosing requirements for the individual patient depending on the patient's body weight.

The pre-license inspection for the DS manufacturing and the DP fill site (uniQure, Inc., Massachusetts, USA) was conducted by CBER reviewers and ORA investigator on August 15-19, 2022 and an FDA Form 483 with 3 observations was issued. The classification and final outcome for this inspection was Voluntary Action Indicated (refer to the Establishment Inspection Report and review of the responses to the FDA Form 483).

The inspections for the DP labeling, packaging, release, storage site (CSL Behring (b) (4) and the DP release and stability testing (sterility) site (b) (4) were waived based on previous FDA inspection history and the information provided in the original BLA submission and its amendments (refer to the Inspection Waiver memo).

The reviewed and evaluated information under DMPQ purview (as per CBER SOPP 8404.1) appears acceptable. All the identified deficiencies were addressed with the

amendments in response to information requests.

B. RECOMMENDATION

I. APPROVAL

Approval contingent on concurrence by the Office of Tissues and Advanced Therapies.

II. COMPLETE RESPONSE (CR)

N/A

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Alifiya H. Ghadiali, Facility Reviewer CBER/OCBQ/DMPQ/MRB3	Concur	
CDR Donald Ertel, Branch Chief CBER/OCBQ/DMPQ/MRB3	Concur	
Carolyn Renshaw, Division Director CBER/OCBQ/DMPQ	Concur	

Review of CTD

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Module 3

3.2.S DRUG SUBSTANCE

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

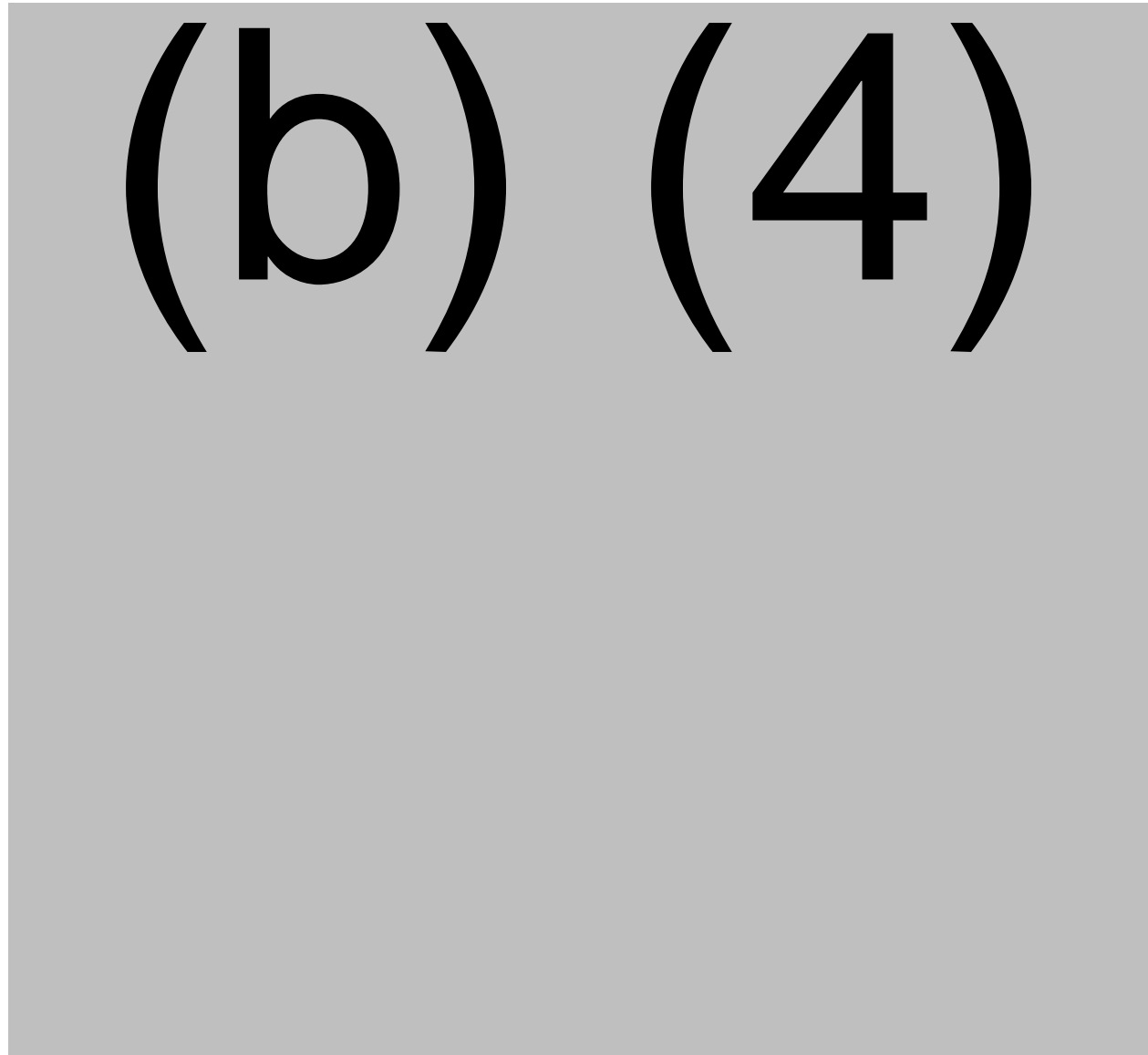
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3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

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3.2.P DRUG PRODUCT

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

The subject drug product (DP) is a preservative-free, liquid formulation intended for administration after dilution (with 0.9% normal saline solution) as a single-dose intravenous infusion. The DP is presented in a single-use depyrogenated 10 mL (b) (4) glass vial stoppered with a 20 mm rubber stopper and sealed with an aluminum flip-off cap and is provided in kits containing 10 to 48 vials. The total number of vials in each kit corresponds to the dosing requirements for the individual patient depending on the patient's body weight.

DP composition

Component	Concentration	Quantity per mL	Quantity per vial	Function	Quality standard
Etranacogene dezaparvovec	1×10^{13} gc/mL	1×10^{13} gc	1×10^{14} gc	Active ingredient	In-house
Polysorbate-20	0.02% v/v	0.22 mg	2.20 mg	(b) (4)	(b) (4)
Potassium chloride	(b) (4)	0.20 mg	2.00 mg	(b) (4)	(b) (4)
Potassium phosphate, monobasic	(b) (4)	0.20 mg	2.00 mg	(b) (4)	(b) (4)
Sodium chloride	(b) (4)	8.00 mg	80.00 mg	(b) (4)	(b) (4)
Sodium (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Component	Concentration	Quantity per mL	Quantity per vial	Function	Quality standard
Sucrose	5% w/v	50.00 mg	500.00 mg	(b) (4)	(b) (4)
(b) (4)					
Water for Injection	(b) (4)				

gc = genome copies; q.s. = *quantum satis*; w/v = weight per volume; v/v = volume per volume

* Fill volume 10.7 mL; extractable volume ≥ 10.0 mL; complies with (b) (4) recommendation

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

(b) (4)

(b) (4)

(b) (4)

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

Deferred to OTAT

3.2.P.2.2.2 Overages

Deferred to OTAT

3.2.P.2.2.3 Physicochemical and Biological Properties

Deferred to OTAT

3.2.P.2.3 Manufacturing Process Development

Deferred to OTAT

3.2.P.2.4 Container Closure System


The container closure system (CCS) was subjected to thermal stress, followed by (b) (4) and (b) (4), to demonstrate that the CCS provides protection against (b) (4).

(b) (4)

(b) (4)

(b) (4)

(b) (4)



Reviewer's Assessment

The (b) (4) CCIT method for the final DP CCS was validated using filled DP vials from (b) (4) PPQ batches. The positive controls with the minimum leak size of (b) (4) were used in the study to demonstrate the sensitivity of the method. The validation data to support the CCS suitability appear acceptable.

Assessment of CCS suitability with respect to materials of construction, protection from moisture, light, oxygen, DP adsorption, and extractables and leachables is deferred to OTAT.

Studies and data to demonstrate integrity of the DP during shipping (i.e., shipping validation) are assessed in 3.2.P.7.

3.2.P.2.5 Microbiological Attributes

The DP is single-dose and does not contain any preservatives.

The DP is manufactured using a (b) (4)



All DP lots are subjected to sterility testing at release.

3.2.P.2.6 Compatibility

Deferred to OTAT

3.2.P.3 Manufacture**3.2.P.3.1 Manufacturer(s)**

Manufacturing/ testing facilities	Responsibilities	Inspection history
uniQure, Inc. 113 Hartwell Avenue, Lexington, MA 02421, USA FEI# 3011357564, DUNS# 052841733	DP manufacture and filling, in-process testing, release and stability testing (except sterility), storage	PLI inspection Aug 15-19, 2022 VAI
CSL Behring (b) (4) [REDACTED]	DP labeling, packaging, release, storage	Team Bio Inspection (b) (4) (Covered labeling) VAI
(b) (4) [REDACTED]	DP release and stability testing (sterility)	ORA Inspection (b) (4) VAI

PLI = Pre-License Inspection; VAI = Voluntary Action Indicated; NAI = No Action Indicated

3.2.P.3.2 Batch Formula

Component	Amount per minimum batch size	Amount per maximum batch size	Quality standard
Etranacogene dezaparvovec	(b) (4)	(4)	
Polysorbate-20			
Potassium chloride			
Potassium phosphate, monobasic			
Sodium chloride			
Sodium phosphate, (b) (4)			
Sucrose (b) (4)			
Water for Injection			

gc = genome copies; q.s. = *quantum satis*

DP batch size example


(b) (4)

Reviewer's Assessment

The overall information provided appears acceptable. Additional assessment is deferred to OTAT.

3.2.P.3.3 Description of Manufacturing Process

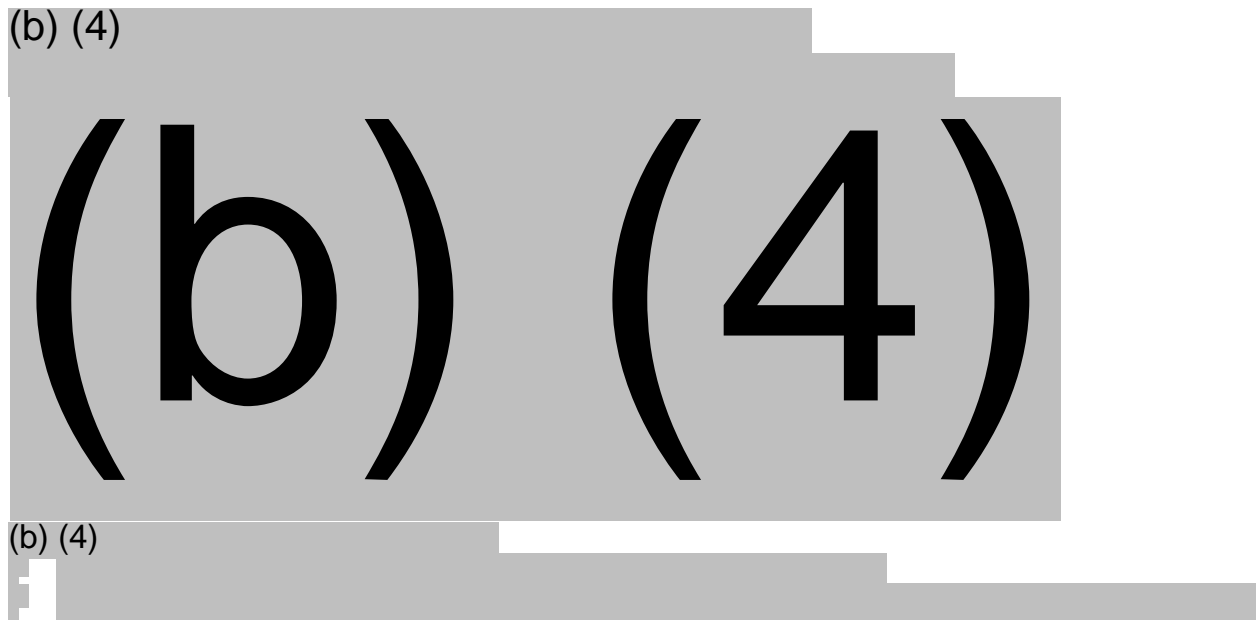
The DP manufacturing process involves (b) (4)



Reviewer's Assessment

The overall information provided appears acceptable. Additional assessment is deferred to OTAT.

(b) (4)



(b) (4)

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Reviewer's Assessment

The in-process controls (under DMPQ purview) and the process intermediate hold times appear acceptable from the microbial quality perspective.

Assessment of other in-process controls and process intermediate hold times from DP quality perspective is deferred to OTAT.

3.2.P.3.5 Process Validation and/or Evaluation

Formulation buffer and DP bulk sterile filtration

(b) (4)

(b) (4)

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- (b) (4)

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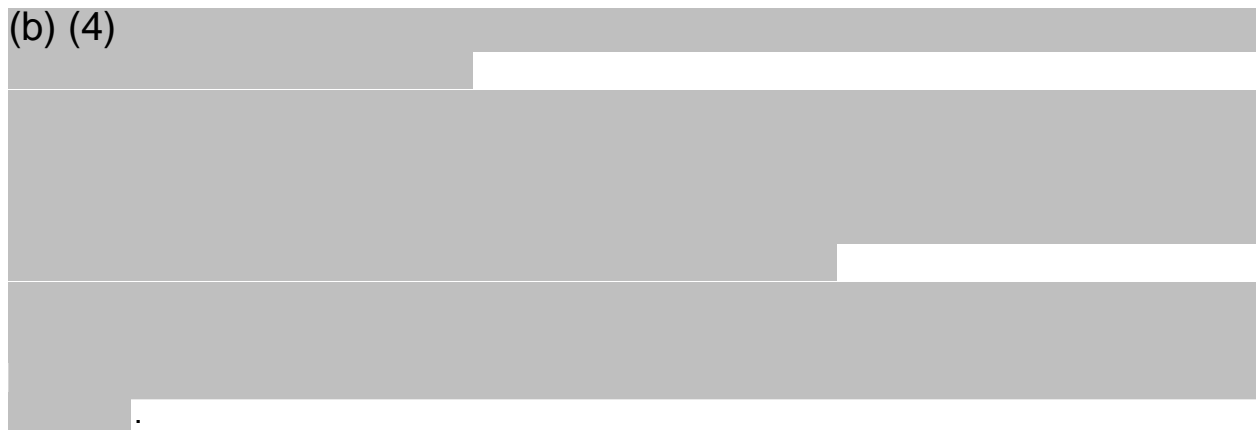
Reviewer's Assessment

The aseptic process simulation data to support the use of the proposed line for aseptic filling of the subject DP appear acceptable.

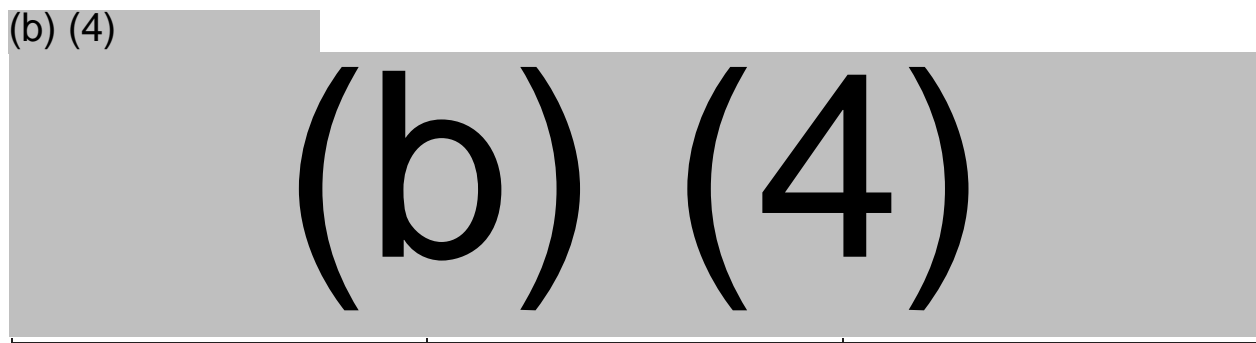
Visual inspection

Visual Inspection of filled DP vials is performed (b) (4)

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(b) (4)

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Reviewer's Assessment

The information regarding the manual visual inspection of the filled DP vials appears acceptable.

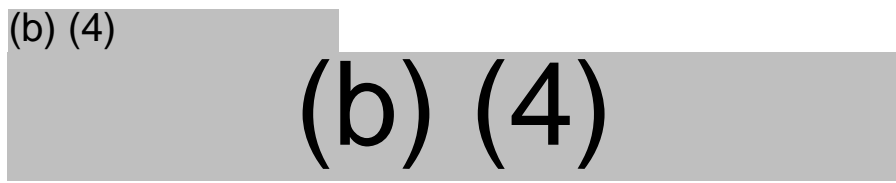
The visual inspection does not have defined Acceptable Quality Limits. However, the DP vials are inspected (b) (4) and have rejection criteria for minor, major and critical defects.

Vial labeling

The variable data of the vial labels are printed via (b) (4)

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(b) (4)

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Reviewer's Assessment

The information regarding the manual vial labeling of the DP vials appears acceptable.

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3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

3.2.P.4.4 Justification of Specifications

3.2.P.4.5 Excipients of Human or Animal Origin

3.2.P.4.6 Novel Excipient

Review of the above six sections are deferred to OTAT

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)

The DP release specifications include the following microbial tests:

Test	Method	Acceptance criteria	Justification of Specification(s)
Bacterial endotoxins	(b) (4)	(b) (4)	(b) (4)
Sterility	(b) (4)	No growth	(b) (4)

Reviewer's Assessment

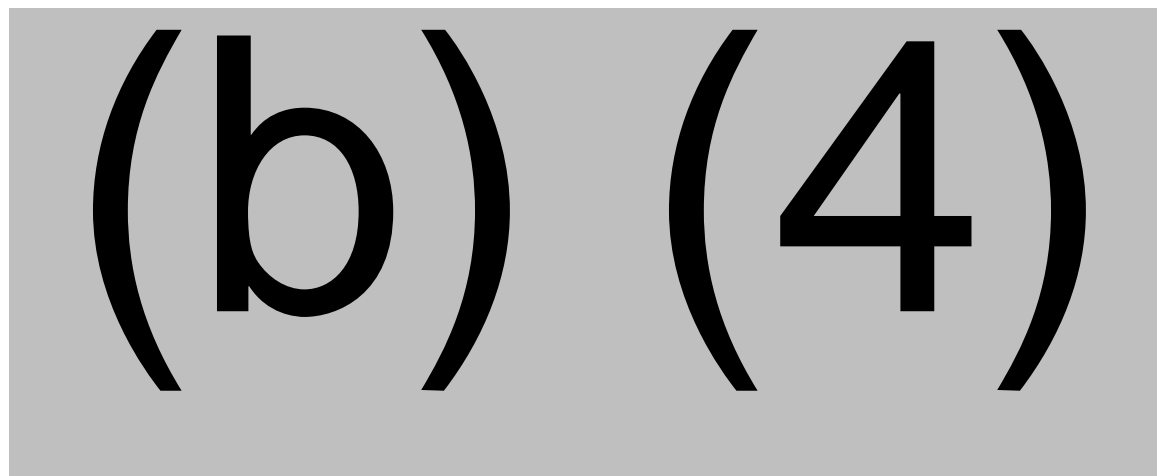
The release testing associated with microbial quality attributes, the acceptance criteria and the justification of specification(s) appear acceptable.

Assessment of the other release tests is deferred to OTAT.

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

Assessment of analytical procedures and validation of the analytical procedures associated with microbial quality attributes is deferred to DBSQC.

Assessment of analytical procedures and validation of the analytical procedures for the other release tests is deferred to OTAT.



Reviewer's Assessment

The PPQ batches met the microbial quality attributes acceptance criteria.

Assessment of the other tests is deferred to OTAT.

3.2.P.5.5 Characterization of Impurities

Deferred to OTAT

3.2.P.6 Reference Standards or Materials

Deferred to OTAT

3.2.P.7 Container Closure System

All of the components of the CCS are obtained ready-to-use (sterile). Incoming glass vials and stoppers are subject to visual inspection and dimensional verification. Samples (n=(b) (4)) from each lot of glass vials and stoppers are (b) (4)

Container closure system

Component	Description	Supplier, part #
Vial	10 mL, ready-to-use, depyrogenated, (b) (4) class glass serum vial with 20 mm opening, 25 mm diameter x 54 mm height, complying with (b) (4)	(b) (4)
Stopper	20 mm ready-to-use serum stopper, gray chlorobutyl rubber base with a copolymer of tetrafluoroethylene and ethylene barrier film coating on wetted surface, complying with (b) (4)	(b) (4)
Seal	20 mm ready-to-use sterile aluminum cap with flip off cap	(b) (4)

(b) (4)

(b) (4)

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(b) (4)

Reviewer's Assessment

The Applicant has provided sufficient information regarding the primary CCS.

The shipment simulation study results indicate that the primary CCS can maintain integrity during the transportation and distribution. The shipping route verification data for DP shipment from manufacturing site to the treatment center (3 trade lanes for US market) appear acceptable.

Assessment of impact of shipping on DP CQAs and shipping simulation stability results is deferred to OTAT.

3.2.P.8 Stability**3.2.A APPENDICES****3.2.A.1 Facilities and Equipment****Manufacturing facilities**

Manufacturing/ testing facilities	Responsibilities	Inspection history
uniQure, Inc. 113 Hartwell Avenue, Lexington, MA 02421, USA FEI# 3011357564, DUNS# 052841733	(b) (4) DP manufacture and filling, in-process testing, release and stability testing (except sterility), storage	PLI inspection Aug 15-19, 2022 VAI
(b) (4)	(b) (4)	Inspection not required
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)


Manufacturing/ testing facilities	Responsibilities	Inspection history
(b) (4)		(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
CSL Behring (b) (4)	DP labeling, packaging, release, storage	Team Bio Inspection (b) (4) VAI
(b) (4)	(b) (4)	(b) (4)
(b) (4)		

Facility design

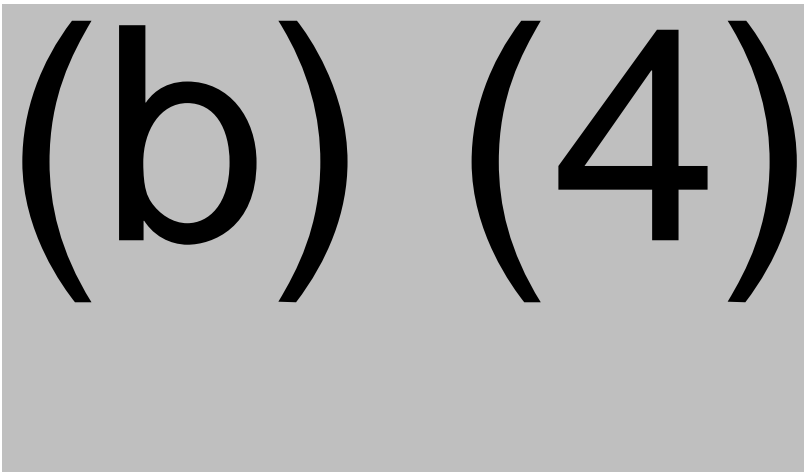
DS and DP manufacturing: uniQure occupies a multi-tenant building in an industrial park in Lexington, MA, USA. Approximately (b) (4) is used for GMP (b) (4) manufacturing and the remainder of the space accommodates manufacturing support, process development laboratories, quality control laboratories, warehousing, and offices. The facility has separate process and building utilities, heating, ventilation, and air conditioning (HVAC), electrical, information technology and communication systems. Both DS and DP are manufactured, tested, and stored within this facility.

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Reviewer's Assessment

The Applicant has provided sufficient information regarding the manufacturing facilities. The facilities appear to be of suitable design to support the manufacturing and labeling of the subject DS and DP.

Equipment

DS and DP manufacturing: (b) (4)

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Reviewer's Assessment


The Applicant has provided sufficient information regarding the equipment used in the manufacturing and labeling of the subject DS and DP.

uniQure: Sterilization validation of (b) (4) product contact equipment used during DP filling is covered in 3.2.P.3.5.

CSL Behring: All equipment is approved for multiproduct use for other CBER licensed products. IOQ/PQ of the labeling equipment is covered in 3.2.P.3.5.

Materials, equipment, personnel flows

DS and DP manufacturing: The floor plans include air handling zoning, room pressure differentials, room air cleanliness classifications, and material, product, waste, equipment and personnel flows. The following areas were evaluated in the floor plans – inoculum/media preparation, (b) (4) manufacturing, DP filling, aseptic corridor, gowning, and material/personnel air locks.

- (b) (4)
- 


Reviewer's Assessment

uniQure: Overall material, equipment and personnel flow appear acceptable. Waste flow, gowning qualification and training records were covered during the PLI and found to be acceptable.


CSL Behring: The material, equipment and personnel flow appear to pose limited risk to the microbial quality/sterility assurance of the stoppered and sealed DP vials. The DP manufacturing areas are already approved for multiproduct use for other CBER approved products.

Cleaning and disinfection

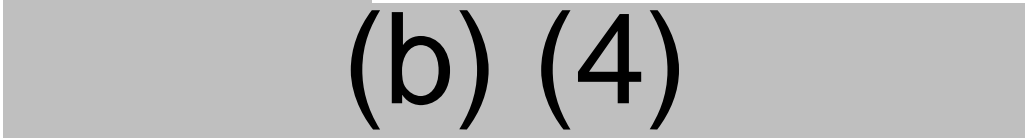
DS and DP manufacturing: The manufacturing facility is cleaned regularly using disinfectants, (b) (4)




(b) (4)



(b) (4)



(b) (4)



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and line clearance of the packaging and labelling area.

Reviewer's Assessment

uniQure: The information provided regarding the facility cleaning, (b) (4) disinfection process and the disinfectant qualification appears acceptable.

The disinfectant efficacy for viral contaminants (e.g., AAV, (b) (4)) was reviewed by OTAT during the PLI and found to be acceptable.

CSL Behring: Not assessed as the labeling equipment pose limited risk to the microbial quality/sterility assurance of the stoppered and sealed DP vials.

Changeover and line clearance

DS and DP manufacturing: uniQure is a (b) (4)



Reviewer's Assessment

The information regarding the changeover and line clearance process appears acceptable.

Other products

(b) (4) DP manufacturing: In addition to the subject DP, other gene therapy products manufactured at uniQure include AMT-060 (Hemophilia B), AMT-130 (Huntington's disease), (b) (4)

(Fabry disease). (b) (4)

Reviewer's Assessment

uniQure: The new product introduction risk assessment/ mitigation strategy appears acceptable.

CSL Behring: Not assessed as the facility is approved for multiproduct use for other CBER licensed products. No changes are reported in the submission.

Heating, Ventilation, and Air Conditioning (HVAC)

The HVAC system is comprised of (b) (4)

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

(b) (4)

(b) (4)

Reviewer's Assessment

uniQure: The Applicant has provided acceptable data regarding the HVAC systems and the initial IOQ and EMPQ. Recent requalification was covered during the PLI and found to be acceptable.

CSL Behring: Not assessed as the facility is approved for multiproduct use for other CBER licensed products. No changes are reported in the submission.

Environmental Monitoring (EM)

An EM program covering all the clean rooms is in place in the facility (QC-SOP-0095 *Environmental Monitoring Program* and QC-SOP-0099 *Environmental Monitoring Procedure*). Sampling methods includes non-viable particle measurements, microbial air sampling (active, passive and surface) and personnel monitoring. Monitoring frequencies, sampling methods and alert/action levels are summarized below. EM results are evaluated on a (b) (4)

(b) (4)

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

(b) (4)

Reviewer's Assessment

uniQure: The Applicant has provided sufficient information regarding the environmental monitoring program. The routine monitoring frequency and alert/action levels appear to be acceptable. Environmental monitoring trends for 2021 and 2022 were assessed during the PLI and found to be acceptable.

CSL Behring: Not assessed as the facility is approved for multiproduct use for other CBER licensed products. No changes are reported in the submission.

Water

The Purified Water (PW) system is comprised of (b) (4)

(b) (4)

(b) (4)

Reviewer's Assessment

uniQure: The Applicant has provided acceptable data regarding the water systems and the initial IOQ and PQ. Recent requalification was covered during the PLI and found to be acceptable.

CSL Behring: Not applicable for labeling and packaging.

Pharmaceutical gases

(b) (4)

(b) (4)

(b) (4)

Reviewer's Assessment

uniQure: The Applicant has provided acceptable data regarding the pharmaceutical gases (process air and oxygen) and the initial IOQ and PQ.

CSL Behring: Not applicable for labeling and packaging.

Computer systems

DS and DP manufacturing: Computerized systems are used to (b) (4)

Reviewer's Assessment

uniQure: The Applicant has provided an acceptable description of the computer systems.

CSL Behring: Not assessed as the facility is approved for multiproduct use for other CBER licensed products. No changes are reported in the submission.

Inspection history

DS and DP manufacturing (uniQure): The DS and DP manufacturing site has no prior FDA inspection history. A PLI was conducted on August 15-19, 2022 in support of this submission and was classified as Voluntary Action Indicated (VAI).

Labeling and packaging (CSL Behring): A GMP surveillance inspection was conducted by Team Bio on (b) (4) and classified as VAI.

DP sterility testing (b) (4): A GMP surveillance inspection was conducted by ORA on (b) (4) and classified as VAI.

Reviewer's Assessment

Refer to the EIR (uniQure) and the DMPQ Facility Waiver Memo (CSL Behring and (b) (4)).

3.2.A.2 Adventitious Agents Safety Evaluation

❑ **Viral Clearance Studies**

Deferred to OTAT

3.2.A.3 Novel Excipients

Not applicable

3.2.R Regional Information (USA)

❑ **Executed Batch Records**

Deferred to OTAT

❑ **Method Validation Package**

Deferred to OTAT

❑ **Combination Products**

Not applicable – not a combination product

❑ **Comparability Protocols**

Deferred to OTAT

Other eCTD Modules

Module 1

1 Administrative Information and Prescribing Information

□ Environmental Assessment or Claim of Categorical Exclusion

Deferred to OTAT

□ Labeling Review

Full Prescribing Information (PI)

Storage temperature: 2-8°C (36-46°F)

Route of administration: Intravenous infusion

Container: Custom kit containing 10-48 10 mL vials

Reconstituted/further diluted DP

The DP is diluted with 0.9% normal saline solution prior to administration. Calculated DP dose (in mL) is withdrawn from the 500 mL infusion bag(s) of 0.9% normal saline solution. The volume of 0.9% normal saline to be removed will vary based on the patient body weight. For patients < 120 kg body weight, DP dose is diluted in one 500 mL infusion bag. For patients ≥ 120 kg body weight, DP dose is divided equally between the two 500 mL infusion bags. Addition of the required volume of the DP dose brings the total volume in each infusion bag back to 500 mL.

The package insert states that “Use the diluted HEMGENIX solution as soon as possible. Do not store the diluted solution beyond 24 hours after the dose preparation. Use an integrated (in-line) 0.2 mcm filter made out of polyethersulfone (PES).”

A hold time study was performed to assess the microbial or endotoxin contamination after DP dilution. The DP vials were diluted in 500 mL 0.9% saline infusion bags (b) (4) (b) (4) vials for high dose and (b) (4) vials for low dose) and sampled at (b) (4) timepoints for microbial testing. The results are summarized below

(b) (4)

Reviewer's Assessment

The microbiological study data to support the post-dilution hold does not accurately represent the in-use conditions as the study was performed in a Biosafety Cabinet using individual syringes for each transfer. The study, therefore, does not simulate potential microbial contamination that may occur during product dilution.

However, patient risk is mitigated by use of an in-line filter prior to administration (also used for the phase III study as per IND 16248 product handling manual).

Based on the above, the proposed post-dilution hold (24 hours at room temperature) is being deemed acceptable.

Carton and Container Label

Deferred to OTAT