

CBER CMC BLA Review Memorandum

BLA STN 125786

**fidanacogene elaparvovec - dzkt
BEQVEZ**

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FRONT MATTER

BLA#: STN 125786

APPLICANT NAME AND LICENSE NUMBER

Pfizer Inc , License No. 2001

PRODUCT NAME/PRODUCT TYPE

- a. Non-Proprietary/Proper/USAN: Fidanacogene elaparvovec -dzkt
- b. Proprietary Name: FIDANACOGENE ELAPARVOVEC
- c. Company codename: PF-06838435
- d. UNII Code: 413EU9081Y
- e. NDC Code (vial): 0069-0422-01
- f. Chemical Abstract Service Name (registry number): 1954659-47-2

GENERAL DESCRIPTION OF THE FINAL PRODUCT

- g. Pharmacological category Adeno associated virus vector-based gene therapy
- h. Dosage form Suspension for injection
- i. Strength/Potency - 1E13 Viral genome (vg)/mL
- j. Route of administration - Intravenous infusion
- k. Indication(s) treatment of adults with moderate to severe hemophilia B (congenital factor IX deficiency) who are receiving routine prophylaxis and without pre-existing neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid detected by an FDA-approved test.

MAJOR MILESTONES

- Received: April 28, 2023
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- Mid-cycle communication: October 19, 2023
- Late-cycle meeting: January 10, 2024
- PDUFA action due: Apr 26, 2024

CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Ronit Jolles-Mazor, PhD, OTP/OGT/DGT2/GTIB	Elucidation of structure, shedding, environmental assessment, stability, comparability, labeling, Clinical and Nonclinical bioanalytical assays
Jianyang Wang, PhD, OTP/OGT/DGT1/GTB2	Manufacturing Process and Process Controls, Process Validation, Batch Analysis, Control of materials
Bo Liang, PhD, OTP/OGT/DGT1/GTB2	Analytical procedures, Validation of analytical procedures, Justification of Specification
Anurag Sharma, PhD, OTP/OGT/DGT1/GTB2	Control of materials, Container Closure System, Adventitious Agents Safety Evaluation
Andrey Sarafanov, PhD, OTP/OPPT/DH/HB2	Extractable and leachables, Container Closure System
Leonid Parunov, PhD, OTP/OPPT/DH/HB2	Validation and design of Potency Assay Clinical activity assay

INTER-CENTER CONSULTS REQUESTED: N/A

SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
04/28/2023	125786/0	Original submission
7/6/2023	125786/10	Response to CMC IR#7 (part 1) dated 06/26/2023
7/17/2023	125786/12	Response to CMC IR#7 (part 2) dated 06/26/2023
9/6/2023	125786/16	Response to CMC IR#11 dated 08/21/2023, IR#12 dated 08/29/2023 and IR#12 dated 08/29/2023
10/18/2023	125786/20	Response to CMC IR#15 dated 10/04/2023
10/31/2024	125786/22	Response to CMC IR#7 (part 3) dated 06/26/2023
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11/17/2023	125786/24	Response to CMC IR#18 (part 1) dated 11/03/2023
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12/8/2023	125786/27	Response to CMC IR#20 (part 1) dated 11/30/2023
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12/13/2023	125786/30	Response to CMC IR#20 (part 2) dated 11/30/2023
12/18/2023	125786/31	Response to CMC IR#24 (part 1) dated 12/07/2023
12/26/2023	125786/35	Response to CMC IR#26 dated 12/14/2023
12/27/2023	125786/36	Response to CMC IR#28 (part 1) dated 12/21/2023
1/9/2024	125786/38	Response to CMC IR#28 (part 2) dated 12/21/2023
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3/22/2024	125786/55	Response to CMC IR#42 dated 03/12/2024
03/22/2024	125786/56	Response to CMC IR#39

REFERENCED REGULATORY SUBMISSIONS

Submission Type & #	Holder	Referenced Item	LOA	Comments/Status
IND 016437	Pfizer	Entire IND	N/A*	No outstanding issues
PMA (b) (4)	(b) (4)	(b) (4)	Yes	(b) (4)
DMF Type III (b) (4)	(b) (4)	(b) (4)	Yes	No outstanding issues identified. Pertinent information reviewed and assessed by AS and AGS.
DMF Type III (b) (4)	(b) (4)	(b) (4)	Yes	No outstanding issues identified. Pertinent information reviewed and assessed by AS and AGS.
DMF Type V (b) (4)	(b) (4)	(b) (4)	Yes	No outstanding issues identified. Pertinent information reviewed and assessed by AS and AGS.
DMF Type III (b) (4)	(b) (4)	(b) (4)	Yes	No outstanding issues identified. Pertinent information reviewed and assessed by AS and AGS.

*N/A applicant is the holder of the IND

REVIEWER SUMMARY AND RECOMMENDATION

EXECUTIVE SUMMARY

Based on the review of the collective information submitted by the Applicant and subsequent information requests received throughout the review period, the CMC review team concludes that the manufacturing and controls for fidanacogene elaparovec- dzkt (BEQVEZ) are capable of yielding a drug product with consistent quality attributes deemed acceptable for commercial manufacturing under the BLA.

Description of the product

BEQVEZ is a recombinant adeno-associated viral (AAV) vector carrying a genome that encodes the human coagulation factor IX (FIX) R338L variant. BEQVEZ drug product is supplied as a sterile, frozen suspension for infusion containing fidanacogene elaparovec- dzkt in a phosphate buffer containing (b) (4) excipients (described below) in a 2 mL cryogenic vial. Each vial has a nominal fill of 1 mL. The drug product should be stored at -60°C to -90°C.

Manufacturing and quality

Fidanacogene elaparovec- dzkt is produced using (b) (4)

Fidanacogene elaparovec is (b) (4)

followed by final filtration and fill of the DP.

Each vial of the DP is designed to deliver 1 mL of BEQVEZ at (b) (4) with a nominal concentration of 1E13 vector genomes (vg) per mL. Each vial also includes 0.3 mg Sodium Phosphate (monobasic), 2.2 mg Sodium Phosphate (dibasic), 10.5 mg Sodium Chloride, 0.01 Poloxamer 188 and water for injection. The drug product is supplied in a clear 2 mL cyclic olefin copolymer vial with pre-assembled elastomeric stopper and plastic, snap-fit cap. The drug product contains no preservative and is for single use only. The secondary packaging is a carton that contains 4-7 vials (depending on the weight and/or the BMI of the patient).

Manufacturing process consistency is controlled by (1) raw material and reagent qualification programs, (2) in-process monitoring and in-process control testing, (3) validation of the manufacturing process, and (4) lot release tests. The manufacturer accepts raw materials based on specified quality attributes, including identity, concentration, and purity and routinely performs tests upon receipt. Each raw material has a corresponding raw material specification and unique tracking identification number. Raw materials derived from animals and humans are used in the establishment of the (b) (4)

fidanacogene elaparovec drug substance manufacturing. All raw materials derived from animals are appropriately controlled to ensure the absence of microbial contaminants. The control strategy includes testing of the (b) (4), DP, (b) (4)

materials for microbial contaminants, identity, purity, strength, and potency. (b) (4) DP quality are controlled and characterized by acceptable release tests. These tests include a (b) (4) . These test also include (b) (4) potency assays that (b) (4) using an (b) (4) and a (b) (4) . In addition, the (b) (4) DP are controlled by several assays measuring the purity of the product. The applicant committed to improve the control of the (b) (4) potency assays by adding negative and positive controls. The post-change revalidation will be provided as a post-marketing commitment and submitted as a supplement.

The validation of the fidanacogene elaparvovec (b) (4) manufacturing process included (b) (4) successful process performance qualification (PPQ) batches. All (b) (4) batches met all pre-defined PPQ acceptance criteria. Sanitary processing capability was successfully demonstrated at manufacturing scale by consistently meeting in-process (b) (4) acceptance criteria.

Process validation for the DP manufacturing process was conducted by manufacturing (b) (4) PPQ DP lots that are derived from (b) (4) . In-process (b) (4) were validated at full scale to demonstrate biochemical or physicochemical stability and microbiological integrity of fidanacogene elaparvovec over a set period of time under controlled conditions and in containers representative of those used in manufacturing. Additional validation studies were also performed, including aseptic filling, sterilizing (b) (4) and shipping.

Stability

The DP is stable for 36 months when stored at the recommended temperature of -60° to -90°C. The DS is stable for (b) (4) when stored at the same temperature of (b) (4) . Prior to administration, the DP is diluted in 0.9% sodium chloride and 0.25% w/v human serum albumin (HSA). Once diluted, the DP in the infusion bag protected from light is stable for up to 24 hours at ambient temperatures up to 30°C.

Testing Specifications

The analytical methods and their validations and/or verifications for the DS and DP, as well as their acceptance criteria, were found to be adequate for their intended purpose.

Comparability

Throughout clinical trials the manufacturing process was optimized and scaled up. The current manufacturing process produces the DP with critical quality attributes that are comparable to those of clinical lots used in clinical studies.

RECOMMENDATION:

APPROVAL

This biologics license application (BLA) provides an adequate description of the manufacturing process and quality of the new drug product fidanacogene elaparvovec-dzkt. The CMC review team has concluded that the manufacturing process, along with associated test methods and control measures, can yield a product with consistent quality

characteristics. This information, along with one post-marketing commitment (PMC) from the applicant, satisfies 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.

Post-Marketing Commitments (PMCs):

Pfizer Commits submitting the following Post-Marketing Commitments:

PMC#1

For method (b) (4), Pfizer commits to introduce system suitability control materials, including:

- a. A (b) (4) product-specific control material starting from the stage of (b) (4),
- b. A negative control sample starting from the stage of (b) (4),
- c. A FIX suitability control material for the chromogenic assay, and
- d. A FIX suitability control material for the (b) (4)

Pfizer commits to perform post-change revalidation and a statistically powered equivalence study for the updated method (b) (4). The results will be submitted as a Prior Approval Supplement (PAS) specifying the submission in fulfillment of a "Postmarketing Study Commitment – Final Study Report".

Final Study Report Submission: September 30, 2025

SIGNATURE BLOCK

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Andrey Sarafanov, PhD, Chemist; OTP/OPPT/DH/HB2	Concur	
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Andrew Byrnes Division Director; OTP/OGT/DGT1	Concur	
Denise Gavin Office Director: OTP/OGT	Concur	

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3.2.S DRUG SUBSTANCE

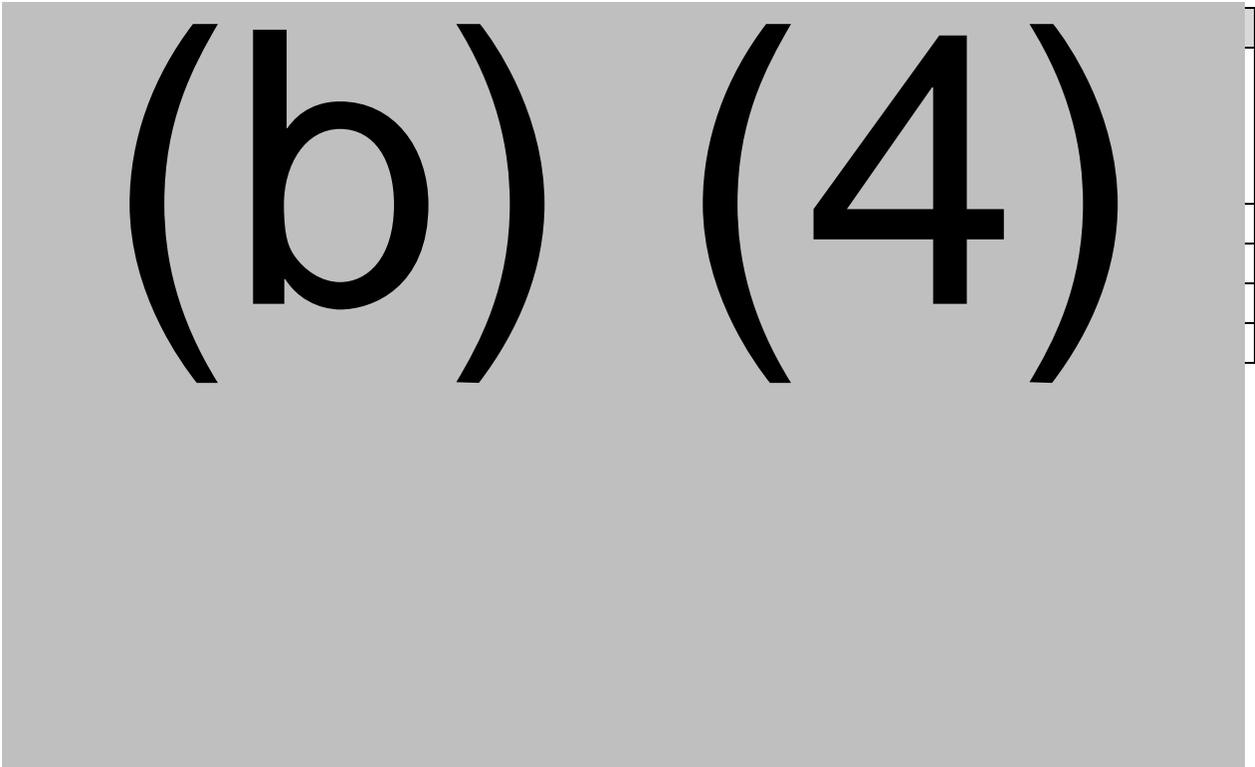
3.2.S.1 DS Nomenclature, Properties, and Mechanism of Action

(Reviewed by RM)

3.2.S.1.1 Nomenclature (Table 1 and Table 2)

- Proper (non-proprietary) name: fidanacogene elaparvovec - dzkt
- Proprietary name: BEQVEZ

Table 1. Nomenclature of fidanacogene elaparvovec Drug Substance



(b) (4)

(b) (4)



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

(b) (4)

(b) (4)

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of DP

(Reviewed by JW)

DP is formulated at 1.00E13 vector genomes (vg)/mL in sodium phosphate monobasic monohydrate and sodium phosphate dibasic heptahydrate (to achieve a (b) (4) mM sodium phosphate buffer at target (b) (4) sodium chloride, and 0.001% w/v poloxamer 188. The composition of DP is provided in [Table 42](#), along with the function and quality standard applicable to each component.

Each vial is designed to deliver 1 mL DP at (b) (4) with a nominal concentration of 1.00E13 vector genomes (vg) per mL. There are no excipients of human or animal origin, and no novel excipients utilized in the formulation. DP is supplied in a clear 2 mL cyclic olefin copolymer vial with pre-assembled elastomeric stopper and plastic, snap-fit cap. DP contains no preservative and is for single use only.

Table 42. Composition of Fidanacogene elaparvovec, Solution for Infusion, 1mL/vial

Name of Ingredients	Reference to Standard	Function	Amount per Vial (per 1 mL)
fidanacogene elaparvovec	In-house specification	Active Ingredient	1.00E13 vg
Sodium Phosphate, monobasic, monohydrate ^c (NaH ₂ PO ₄ H ₂ O)	(b) (4)	(b) (4)	0.3 mg
Sodium Phosphate, dibasic, heptahydrate ^d (Na ₂ HPO ₄ 7H ₂ O)	(b) (4)	(b) (4)	2.2 mg
Sodium Chloride (NaCl)	(b) (4)	(b) (4)	10.5 mg

Poloxamer 188 ^a (HO[C ₂ H ₄ O] ₈₀ [C ₃ H ₆ O] ₂₇ [C ₂ H ₄ O] ₈₀ H)	(b) (4)	(b) (4)	0.01 mg
Water for injection	(b) (4)	Solvent	q.s. ^b to 1 mL

a. Poloxamer 188 is (b) (4)

b. q.s. is an abbreviation for *quantum satis*, meaning as much as is sufficient

c. Sodium Phosphate, monobasic, monohydrate (b) (4)

d. Sodium Phosphate, dibasic, heptahydrate (b) (4)

vg – vector genome

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

(Reviewed by AS)

3.2.P.2.1.1 Drug Substance and 3.2.P.2.1.2 Excipients

Please refer to the sections [3.2.P.1 Description and Composition of DP](#) and [3.2.P.4 Control of Excipients](#) for details.

3.2.P.2.2 Drug Product

(Reviewed by JW)

3.2.P.2.2.1 Formulation Development

The formulation composition has been maintained from early clinical development to commercial manufacturing and is the intended commercial formulation: a target concentration of 1.00E13 vg/mL as a frozen liquid in (b) (4) sodium phosphate buffer, (b) (4) sodium chloride, and 0.001% w/v poloxamer 188 at (b) (4). This formulation was developed and used by Spark Therapeutics for Phase 1/2 clinical studies and was adopted by Pfizer based on support from scientific knowledge:

- The (b) (4) capacity of **sodium phosphate** at (b) (4) established suitability of sodium phosphate as a (b) (4) for Fidanacogene elaparovec.
 - **Sodium chloride** was (b) (4)
 - **Poloxamer 188** was included to (b) (4)
- In addition, poloxamer 188 has been used in approved gene therapy products (e.g. Luxturna®).
- Human serum albumin is added to the intravenous (IV) diluent prior to DP dilution, to (b) (4)

During manufacture of pivotal (Phase 3) clinical supplies, (b) (4)

adjustment and streamline the manufacturing process. Additionally, (b) (4) Process 2 and Process 3 (commercial manufacturing) from the (b) (4). These adjustments do not alter the final (b) (4) or other physicochemical characteristics of the formulation; and based on product stability data from pivotal clinical supply lots, the adjustment does not affect product quality. The target concentration, expressed as vector genomes (vg) per milliliter (mL), and the drug product dosage form (frozen liquid) have remained the same throughout development.

Formulation robustness studies were performed to evaluate (b) (4) DP, (b) (4) of which have the (b) (4) formulation. These studies assessed the impact of intentional variation of (b) (4)

Empirical observations from formulation development and robustness studies have confirmed that:

- Current formulation excipients provide adequate stability, safety, and compatibility for dosing;
- Variations in the formulations within the currently specified (b) (4) ranges do not adversely impact product quality when subjected to up to (b) (4)
- Formulation (b) (4) (Table 43 below) observed from Process (b) (4) manufacturing maintain product quality throughout processing steps and during the shelf life.

Table 43. Comparison of Process (b) (4) Manufacturing Ranges

(b)	(4)
-----	-----

3.2.P.2.2.2 Overages

To ensure that 1 mL nominal volume can be withdrawn from the vial, there is a target overfill of approximately (b) (4). There are manufacturing overages within the (b) (4) phase of the manufacturing process. To ensure that the target Poloxamer 188 concentration of 0.0010% is met, a manufacturing (b) (4) has been added to account for any potential adsorption during the remainder of the manufacturing process. Additionally, there is a target of (b) (4) for fidanacogene elaparvovec to control for incidental (b) (4) due to (b) (4) experienced during the DP fill operations. These overages achieve final target Poloxamer 188 and fidanacogene elaparvovec

concentrations, as demonstrated by historical batches (Please refer to [3.2.P.5.4 Batch Analyses](#) in this memo).

3.2.P.2.2.3 Physicochemical and Biological Properties

Key physicochemical characteristics of the fidanacogene elaparvovec active ingredient are described in [Table 44](#) below and Section [3.2.S.3.1 Elucidation of Structure and Other Characteristics](#) in this memo.

Table 44. Fidanacogene elaparvovec Physicochemical and Biological Properties

Capsid Serotype	Fidanacogene elaparvovec uses an engineered AAV capsid derived from the naturally occurring Rh74 AAV serotype with (b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Biological Activity	Fidanacogene elaparvovec encodes the human coagulation Factor IX (FIX) R338L variant for the sustained treatment of hemophilia B (HB) through constitutive endogenous persistent production of replacement FIX.
(b) (4)	(b) (4)

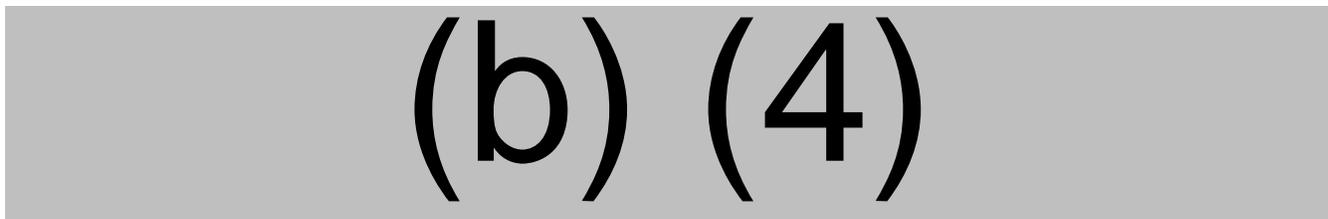
3.2.P.2.3 Manufacturing Process Development

[Reviewed by JW, RM (for comparability), and AGS (for leachable assessment)]

3.2.P.2.3.1. DP Process Development Changes

Throughout product development, the DP manufacturing process has been updated to enhance control and consistency. [Table 45](#) summarized (b) (4) DP manufacturing process comparison and development history. Please refer to [Table 20](#) in Module [3.2.S.2.6.1. DS Process Development Changes](#) for the summary of three DS manufacturing processes. **Commercial manufacturing process is referred as (b) (4)**

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



3.2.P.2.3.2. Identification of CQAs, CPPs, and CMAs

Using risk assessments described in Module 3.2.S.2.6.3 *Process Characterization* in this memo, DP quality attributes were identified and assessed as critical (CQAs) (Table 46 below) and non-critical (non-CQA) and parameters or material attributes from the DP manufacturing process that impact CQAs have been identified as critical process parameters (CPPs) or critical material attributes (CMAs) all of which are listed in Table 61 in Module 3.2.P.3.4 *Controls of Critical Steps and Intermediates*. in this memo. For CQA criticality justifications, please refer to Module 3.2.P.2.3. in BLA submission.

Table 46. DP Critical Quality Attributes (CQA)

Characteristics	Purity and Product-Related Impurities
Appearance (Clarity)	(b) (4)
Appearance (Color)	
Appearance (Visible Particulates)	
(b) (4)	
Extractable Volume	
(b) (4)	Biological Activity (Relative Potency)
Container Closure Integrity	(b) (4)
Vector Genome (b) (4)	
(b) (4)	Safety
Identity and Integrity	Sterility
(b) (4)	Endotoxin

Pfizer stated that Poloxamer 188 (P188) is considered as a non-CQA because the formulation robustness and developmental stability samples with low P188 content demonstrate no impact to product quality.

3.2.P.2.3.3. Process Risk Assessment Strategy

Please refer to [3.2.S.2.6.3.1. Risk Assessment Tools: C&E Assessment and FEMA Scoring](#) in this memo.

3.2.P.2.3.4. DP Manufacturing Process Characterization

Prior to process characterization, impact of DP manufacturing process parameters on CQA(s) was assessed using risk assessment described in [3.2.S.2.6.3.1. Risk Assessment Tools: C&E Assessment and FEMA Scoring](#) and parameters required further characterization were identified. Characterization study criteria were established based on manufacturing experience, developmental stability studies, and analytical variability at the time when a study was performed. Both (b) (4) engineering experiments and (b) (4) models to be relevant to and representative of parameters and stresses anticipated during commercial production were used in the process development and characterization studies, which are summarized below in the order of unit operations.

(b) (4)



(b) (4)

(b) (4)

3.2.P.2.3.4.3. Bioburden Reduction (BBR) and Sterile Filtrations

Data collected at both laboratory and commercial manufacturing scale demonstrate that the physical stresses of filtration that exceed those anticipated in routine manufacturing are not detrimental to the product quality. Product quality is preserved after up to (b) (4)

Because filtration is the main process step that ensures DP sterility, (b) (4) is monitored to ensure filter integrity during the process. These results and supporting information support the commercial DP process filtration parameters described in [Table 61](#) in Module [3.2.P.3.4. Controls of Critical Steps and Intermediates](#) in this memo.

3.2.P.2.3.4.4. Vial Filling, Sealing, and Capping

The decontamination of the (b) (4) in the DP manufacturing suite is carried out using (b) (4). The ability of DP vials to **prevent** (b) (4) was assessed by (b) (4) vials to (b) (4) scenarios of (b) (4), representing worse-case (b) (4). All results met criteria indicating DP vials are suitable to withstand (b) (4).

The impact of anticipated (b) (4) on DP vector genome (b) (4) was assessed using a lab-scale (b) (4) study using syringes, which demonstrated that product quality is maintained after exposure to worst-case (b) (4) that result from (b) (4). Therefore, the

anticipated (b) (4) from the manufacturing process (including (b) (4)) is suitable to maintain product quality.

The **need for a (b) (4) of the DP filling kit** prior to filling was assessed at commercial scale by testing the (b) (4) DP vials from (b) (4) batches (relative potency). Results do not indicate a functional relationship between product quality location of filled vial within a DP batch (beginning, middle, or end) which was further assessed and confirmed during DP process homogeneity validation described in [3.2.P.3.5 Process Validation and/or Evaluation](#) in this memo. Therefore, a (b) (4) prior to filling is not necessary to ensure product quality in the (b) (4) filled vials.

The **filling volume accuracy** performance was assessed by a filling capability study using the (b) (4) than that of commercial process (b) (4) which indicates low process variability and being well-centered around the target fill weight and suggests that the filling system intended for use in commercial DP manufacturing is well-suited to fill vials reliably and reproducibly within the commercial fill volume tolerance range. Of notice, Pfizer stated that while fill volume accuracy was well-controlled throughout manufacturing clinical batches ((b) (4)) experienced out of range of previous manufacturing experience, which resulted in the (b) (4) to reflect the capability of the system and the (b) (4) verifications as described and commented in Module [3.2.P.3.5. Process Validation and/or Evaluation](#) in this memo. Therefore, (b) (4) are maintained throughout the process to achieve (b) (4) (volumes) that meet the label claim. The (b) (4) range (input) has been classified as a CPP for the DP filling process step directly affects extractable volume.

DP container closure integrity (CCI) was assessed using (b) (4) challenge and (b) (4) analysis method to determine if the mechanical stopper (b) (4) of stopper impart CCI after vials are filled with DP. Results indicates that the DP vials can be integral in the absence of (b) (4) or the vial cap, which represents worst-case scenarios but the DP process will continue to include the (b) (4) and capping steps to reduce any potential risk. Additionally an in-process CCI test is performed to ensure that released DP vials are integral and maintain DP sterility. Of notice, the (b) (4) parameters used in DP manufacturing process were developed and qualified by the vendor and have been further confirmed by manufacturing experience at Pfizer to generate integral DP container and validated by qualification of

(b) (4) parameters such as (b) (4)

The results of the validation indicate that the filling equipment can (b) (4) stoppers that have been punctured by the filling needle to produce integral containers when the (b) (4) is in the validated range. The (b) (4) has been classified as a CPP for the DP filling process step.

3.2.P.2.3.4.5. Storage and Shipping

3.2.P.2.3.4.5.1 DP storage

DP vials are stored at -60 °C to -90 °C in validated freezers that are connected to validated temperature monitoring systems at manufacturing site prior to shipment. To ensure vials are always completely frozen before removing from frozen storage, a study was performed to determine the minimum time required to completely freeze vials and data indicate that a **minimum freeze time of (b) (4) is required** based on the inflection point observed.

3.2.P.2.3.4.5.2 DP Shipping

Shipping validation for DP has been performed and reviewed by Wei Wang and Jie He (CBER/OCBQ/DMPQ) and documented in DMPQ review memo. No issues were found with the shipping validation. This section provides ancillary information and data that are not considered part of the validation package but instead provide qualification data to support the commercial shipping process.

Manufacturing experience and lab-scale studies representing worse-case conditions anticipated during normal processing, shipping, and handling of DP prior to patient administration, including exposure to (b) (4)

occurred in unplanned temperature excursions, indicate that these steps and parameters do not affect any tested CQAs [appearance, (b) (4)

. DP product quality attributes are maintained after exposure to worse-case conditions summarized in [Table 47](#) with corresponding assessment data shown in [Table 48](#) to [Table 54](#), and [Figure 39](#).

(b) (4)

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

(b) (4)

In conclusion, the results of developmental experiments that pertain to DP vial freezing, storage, and shipping indicate that the commercial process and supply chain controls and acceptable ranges are suitable to maintain product quality between DP manufacturing and patient dosing.

(b) (4)

(b) (4)

(b) (4)

3.2.P.2.3.5 Manufacturing Process Comparability

[Reviewed by RM]

3.2.P.2.3.5.1. Comparability Strategy

(b) (4) processes have been implemented in the manufacturing of fidanacogene elaparvovec clinical material. A given process is associated with both a unique drug substance process and unique drug product process (meaning Process (b) (4) is the ingoing material for Process (b) (4) DP, Process (b) (4) is the ingoing material for Process (b) (4) drug product, and so forth).

Process (b) (4) materials were used for part of the clinical Phase 1/2a trials. The (b) (4) manufactured Process (b) (4) DP. The remaining clinical Phase 1/2a trial material came from Process (b) (4) which also supplied the initial material for the pivotal Phase 3 trial from a subsequent campaign. Process (b) (4) was manufactured at Spark Therapeutics (Spark) and the DP was manufactured at (b) (4). Additional Phase 3 trial material utilized Process (b) (4) the proposed commercial process, where the (b) (4) drug product are manufactured by Pfizer in Sanford, NC (Wyeth Pharmaceutical Division of Wyeth Holdings LLC in Sanford, NC).

The comparability strategy includes four components:

1. (b) (4)

4. (b) (4)

Reviewer's comment: This strategy was negotiated with the FDA in several meetings prior to BLA submission and feedback requests. The separation of the (b) (4) was requested by the FDA to replace the initial comparison where the (b) (4)

This is acceptable. Similarly, the request for comparability criteria that are based on statistical equivalency criteria and additional statistical analysis when necessary was requested by the FDA and the sponsor agreed to all our recommendations. Therefore, the approach is acceptable.

The selection of assays (and if they were compared in a (b) (4) manner, or by comparison of release results) is acceptable. CQA that may have impact on safety and efficacy such as potency and purity assays were compared in a (b) (4) manner. The other CQA such as (b) (4) were compared by comparison of release results.

Reviewer's comment: The sponsor selected appropriate assays to compare in a (b) (4) manner, and acceptable assays to compare by comparison of release results.

In order to show consistency in meeting the Phase 3 clinical specifications, all applicable results from the comparability assessment for all materials from Process (b) (4) were evaluated against the Phase 3 release acceptance criteria for most assays. (b) (4)

that were tighter than the phase 3 AC. The refined AC for (b) (4)

The refined Acceptance Criteria of the (b) (4)

that would have been obtained by the Process (b) (4) DP (b) (4) to achieve (b) (4) which was used in phase 1.

For statistically amenable attributes, a (b) (4) was performed to compare Process (b) (4). Process (b) (4) and Process (b) (4). Process (b) (4) with (b) (4)

Reviewer's comment: This approach is acceptable. Of note, some of the ACs used in this stage of comparability are wide (for example, (b) (4)). This would not be acceptable on its own. However, the sponsor also included (b) (4) testing for these CQA. Together, the two approaches complement one another and are acceptable.

3.2.P.2.3.5.2. Comparability results

Comparability results from the historical release testing for DP lots and (b) (4) showed that all lots in the (b) (4) manufacturing processes passed phase 3 specifications, with a few exceptions:

- (b) (4)

Reviewer's comment: Some results in the historical release did not have values because the sponsor used qualitative AC earlier during the development. This would not be acceptable on its own. However, as stated above, the sponsor also included (b) (4) testing for these CQA, and that comparison (detailed below) is acceptable.

The results of the (b) (4) comparison showed comparable results for most CQA despite the small sample size. There were (b) (4) assays that were not comparable but either represented improvement of a more pure product such as (b) (4) assay and (b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

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

- (b) (4)

3.2.P.2.4 Container Closure System (AS and AGS E/L)

(Reviewed by AS)

Please refer to [3.2.P.7 Container Closure System](#)

3.2.P.2.4.3. Extractables and Leachables studies

(Reviewed by AGS)

(b) (4)

(b) (4)



Reviewer's comment: Initially, the submission had multiple deficiencies such as no inclusion of elemental leachables testing in the ongoing leachables study, insufficient information about validation of the methods for (b) (4), and absence of the study reports for the ongoing study.

Upon FDA request for the missing data, Pfizer included the analyses of elemental leachables in the ongoing study and submitted all requested data along with the results of the testing at (b) (4) ' time point.

o (b) (4)



(b) (4)

Pfizer concluded that the data indicate negligible risk to humans and confirmed that the testing is to proceed until the (b) (4) months' time point.

Reviewer's comment: Analytical assessment of leachables in DP is acceptable. The available data from the ongoing leachables study indicate no significant trends in concentrations of leachables in DP through the time course up to (b) (4) months, in particular in the (b) (4) identified (b) (4) and in (b) (4) found at relatively low levels. However, if the shelf life is requested to be extended, the respective time point(s) should be supported by leachables analysis at respective storage period. Pfizer stated that they would submit the data for the remaining time points post-approval in annual reports(s). Based on review of available toxicological data, the identified leachables appear unlikely to pose a significant safety risk to subjects.

3.2.P.2.5 Microbiological Attributes

(Reviewed by AS)

The DP is sterile filtered and aseptically filled. The DP is tested for sterility at the time of release. The stability study shows that the sterility is maintained on long-term storage. The acceptance criteria for endotoxin the drug product is (b) (4). At this level, endotoxin exposure from DP will not exceed (b) (4). The formulation does not contain a preservative, and the DP is supplied as a single-use formulation.

The (b) (4) are tested for integrity as part of the manufacturing process. The container closure integrity testing (CCIT) was performed to determine risk for microbial

contamination after vials are filled. Please refer to the DMPQ review memo for further information on container closure integrity testing and (b) (4) integrity testing.

3.2.P.2.6 Compatibility

(Reviewed by AS)

For dose preparation and administration, fidanacogene elaparovec DP is diluted based on the concentration and patient weight in 0.9% sodium chloride and 0.25% w/v human serum albumin (HSA) prior to administration as an intravenous (IV) infusion. The proposed in-use period should not be longer than 24 hours at up to 2 – 30 °C for prepared dosing solutions.

Studies were performed to evaluate the compatibility of diluted fidanacogene elaparovec commercially available administration components that are commonly used during preparation and storage of the dosing solution (Table 56) with results shown in Table 57. The components evaluated were manufactured with different materials of construction and procured from different vendors. The conditions evaluated (i.e., hold time and temperature) represent typical or worst-case conditions during dose preparation and administration at the dosing sites.

(b) (4)



(b) (4)

(b) (4)

(b) (4)

(b) (4)

Overall Reviewer’s Assessment of Section 3.2.P.2:

Overall, the results from the presented studies support the compatibility of the diluted DP of the dosing solutions in the most common globally available administration components after dilution in 0.9% sodium chloride with HSA for up to 24 hours at ambient temperatures up to 30°C. The dosage and administration simulation studies support the preparation and administration of fidanacogene elaparvovec as anticipated and as directed in the proposed product label.

3.2.P.3 Manufacture

(Reviewed by JW)

3.2.P.3.1 Manufacturer(s)

Table 58 lists the sites that have responsibilities in the production of fidanacogene elaparvovec DP and their specified functions.

Table 58. Sites and Responsibilities for DP Manufacture and Testing

Name and Address	FEI Number/ DUNS Number	Responsibility
Wyeth Pharmaceutical Division of Wyeth Holdings LLC^a 4300 Oak Park Rd Sanford, North Carolina (NC) 27330 United States (USA)	1000110954/ 883534067	Manufacturing and primary packaging Drug product testing: Appearance: clarity, color, visible particulates; (b) (4) ; Extractable Volume; (b) (4) ; Endotoxin; Sterility; Poloxamer 188 (b) (4) (b) (4)
(b) (4)	(b) (4)	Secondary packaging
(b) (4)	(b) (4)	Drug product testing: Endotoxin; Sterility Drug product storage, secondary packaging
(b) (4)	(b) (4)	Drug product testing: Poloxamer 188 (b) (4) (b) (4)
(b) (4)	(b) (4)	Drug product testing: Appearance: clarity, color, visible; Particulates (b) (4) ; Extractable Volume; (b) (4)
(b) (4)	(b) (4)	Drug product testing: Container Closure Integrity (b) (4)

^a. Wyeth is a wholly owned subsidiary of Pfizer Inc. Site may be referred to elsewhere in this dossier as Pfizer Sanford, NC, or similar.

3.2.P.3.2 Batch Formula

(Reviewed by JW)

The DP batch scale/size is defined as the (b) (4) available to initiate the DP manufacturing process. Based on (b) (4), the DP batch scale/size may vary between approximately (b) (4). Table 59 presents the batch formula for (b) (4) (b) (4) DP solution as well as the batch formula for minimum and maximum batch sizes. The target amount for each ingredient present in (b) (4) is listed. There is no additional formulation step during DP manufacturing process.

Table 59. Batch Formula for fidanacogene elaparvovec Drug Product

Name of Ingredients	Reference to Standard	Unit Formula per (b) (4)	Quantity per (b) (4) Batch	Quantity per (b) (4) Batch
Fidanacogene elaparvovec	(b)	(4)	(b)	(4)
Sodium Phosphate, monobasic, monohydrate				
Sodium Phosphate, dibasic, heptahydrate				
Sodium Chloride				
Poloxamer 188 ^b				
Water for injection				

- a. (b) (4)
- b. Poloxamer 188 is named as (b) (4)
- c. For poloxamer 188, (b) (4)
- d. q.s. is an abbreviation for *quantum satis*, meaning as much as is sufficient
- e. (b) (4)
- f. (b) (4)

Overall Reviewer’s Assessment of Section 3.2.P.3.1. and 3.2.P.3.2:
The information provided on DP manufacturers, their corresponding responsibilities, and DP formula, is acceptable.

3.2.P.3.3 Description of Manufacturing Process

(Reviewed by JW)

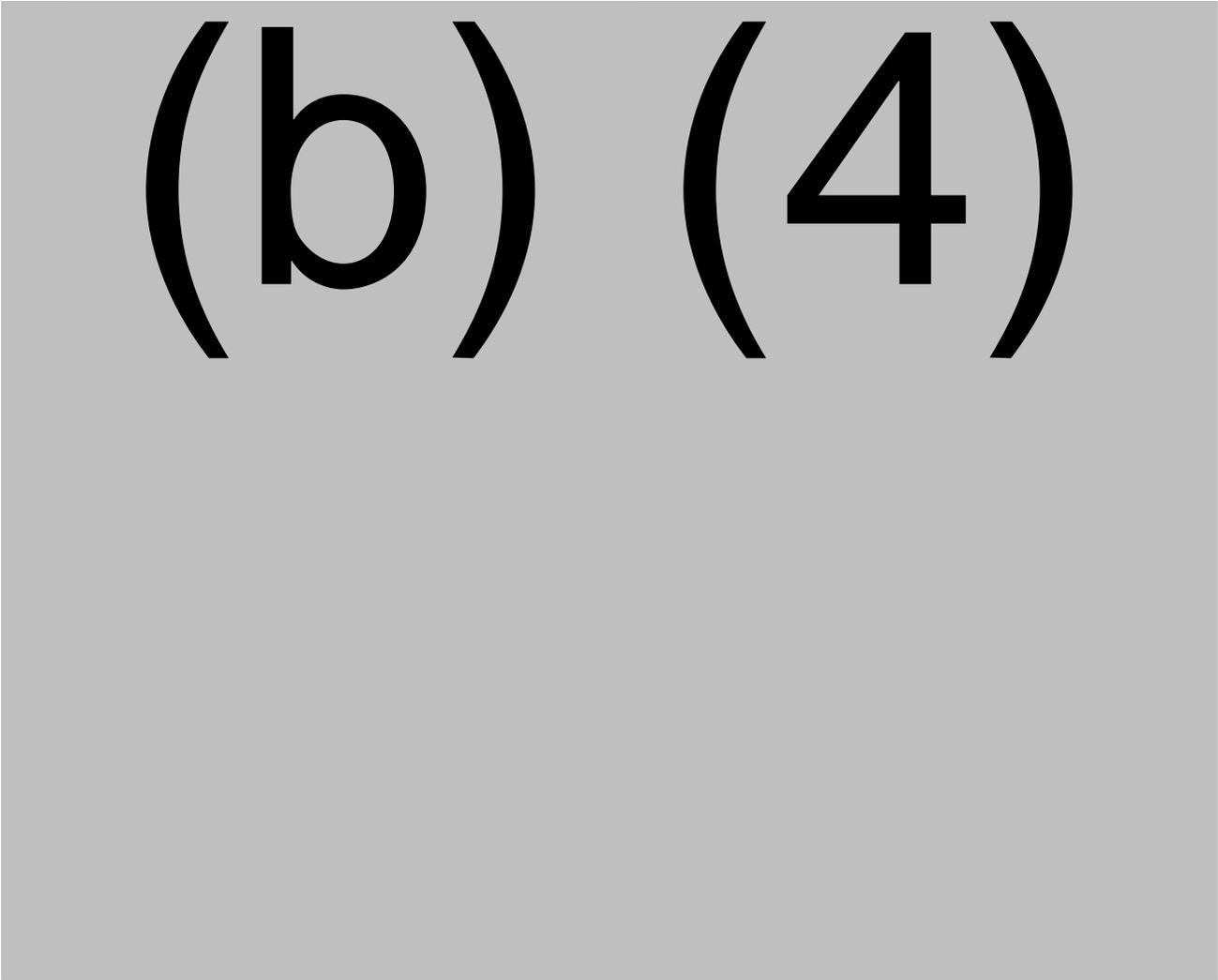
During DP Manufacturing, (b) (4) is progressed to DP operations without additional formulation. The frozen (b) (4)

- o (b) (4)

(b) (4)

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(b) (4)

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Overall Reviewer's Assessment of Section 3.2.P.3.3:

The information provided in the DP manufacturing process description and flowchart in the BLA is acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates

(Reviewed by JW)

3.2.P.3.4.1. Overall Control Strategy

Please refer to Module 3.2.S.2.4.1. *Overall Control Strategy* in this memo for a complete description of combined overall control strategy for both DS and DP using a holistic approach.

3.2.P.3.4.2. DP Critical Quality Attributes (CQAs), Critical Process Parameters (CPP), operating ranges, and in-process tests (IPT)

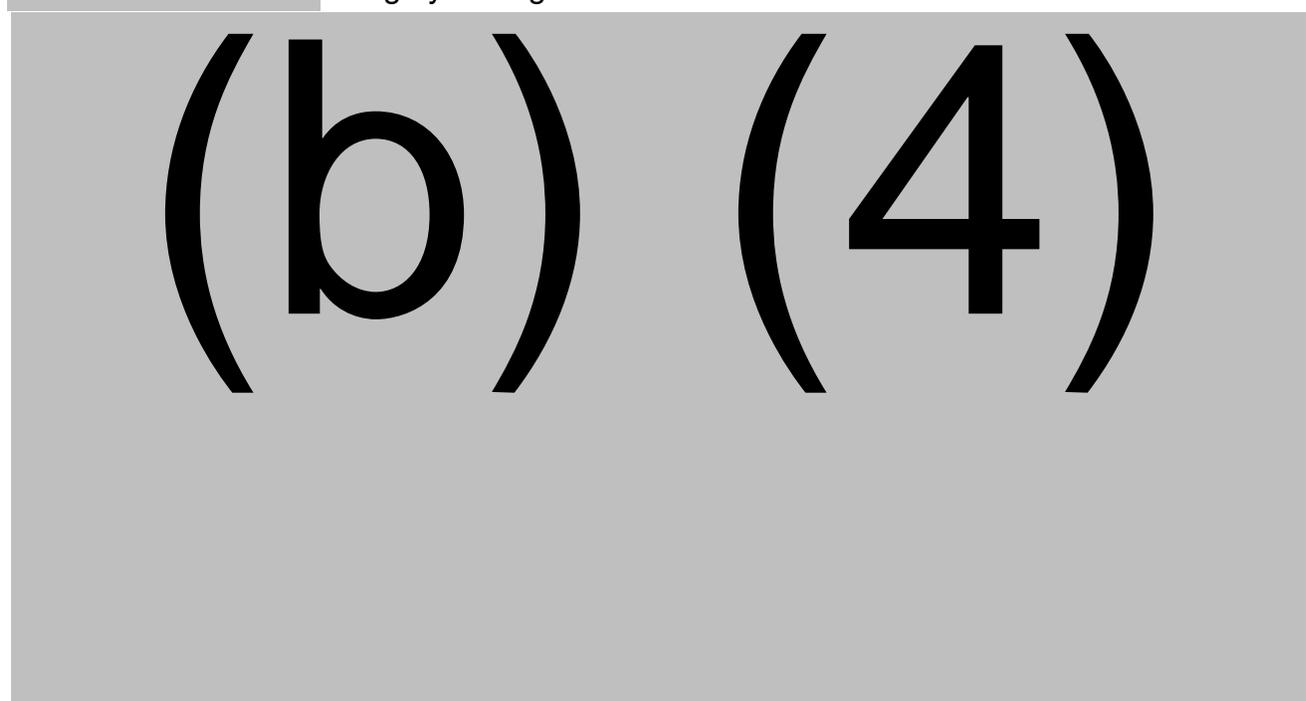
CQAs: Due to the high uncertainty and emerging knowledge in the field, all DP quality attributes were elevated to CQAs, with the exception of poloxamer 188. The control strategy of all CQAs is summarized in Table 60. Please refer to Table 3.2.P.2.3.-1 in the submission for corresponding justifications of these proposed control strategy.

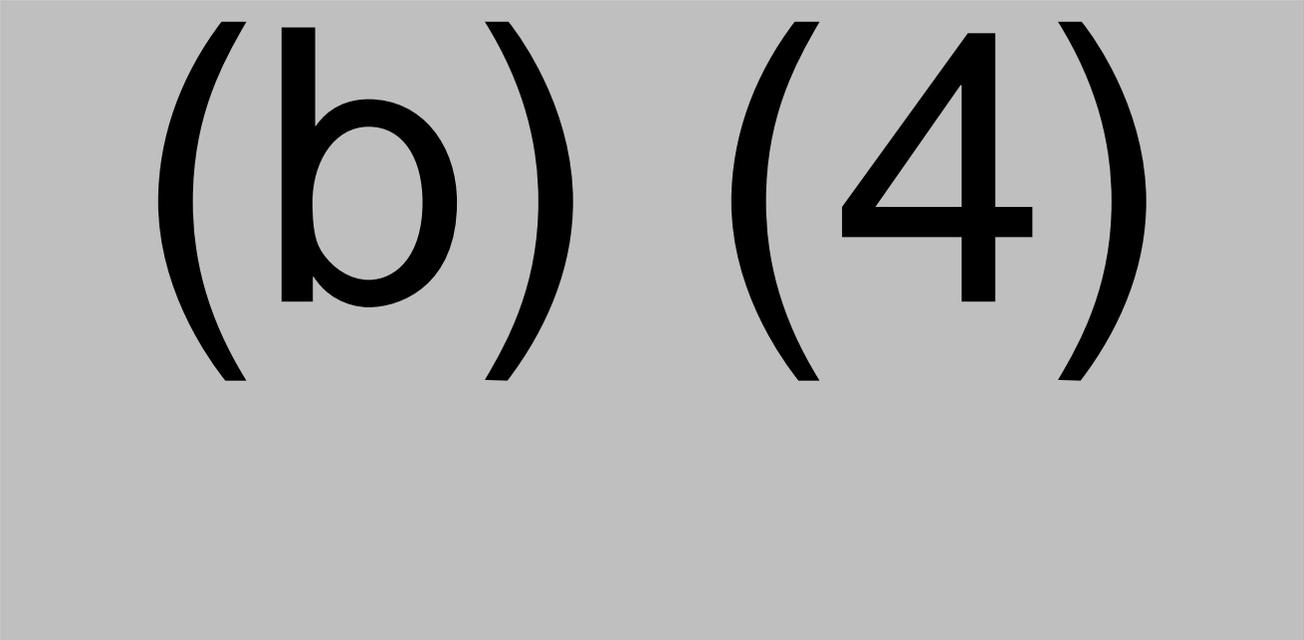
Table 60. DP CQAs and Control Strategy

CQA	Analytical Technique	Control Strategy
Characteristics		
Appearance (Clarity, Color)	Appearance (Clarity, Color)	Release and Stability Testing
Appearance (Visible Particulates)	Visible Particulates	Process design and controls: (Sterile Filtration and 100% Visual Inspection); Control of Materials; Release and Stability Testing
(b) (4)	(b) (4)	Release and Stability Testing
(b) (4)	(b) (4)	Release Testing
Extractable Volume	(b) (4) Extractable Volume	Process Design and Controls (b) (4) Control of Materials; Release Testing
(b) (4)	(b) (4)	Release and Stability Testing
Container Closure Integrity		Process Design and Controls (b) (4) Control of Materials; Stability Testing
Vector Genome (b) (4)	(b) (4)	Process Design and Controls
(b) (4)	(b) (4)	Control of materials Release and Stability Testing
Identity and Integrity		
(b) (4)	(b) (4)	Release Testing
(b) (4)	(b) (4)	Release Testing
(b) (4)	(b) (4)	Release Testing
Purity and Product-Related Impurities		
(b) (4)	(b) (4)	Release and Stability Testing

(b) (4)	(b) (4)	Release and Stability Testing
(b) (4)	(b) (4)	Release and Stability Testing
(b) (4)	(b) (4)	Product Characterization
(b) (4)	(b) (4)	Release and Stability Testing
(b) (4)	(b) (4)	Process Design and Controls Product Characterization
Biological Activity (Relative Potency)		
Factor IX Activity	(b) (4)	Process Design and Controls Release and Stability Testing
Factor IX Expression		
(b) (4)		
Safety		
Sterility	(b) (4) Sterility	Process design and controls
Endotoxin	Endotoxin testing (b) (4)	Release and Stability Testing

Process Controls / CPPs/ CMAs: The output process controls employed during manufacture of DP are monitored or controlled to ensure that product quality and integrity are maintained. During (b) (4) verifications, vials outside of the control limit are rejected. Operations or results outside of other control or action limits are investigated, and the disposition decision will be determined based on the outcome of the investigation. Bioburden (b) (4), sterile filtration, and aseptic filling, sealing, and capping are identified as critical steps within the manufacturing process of DP. The (b) (4) integrity testing is performed by means of a (b) (4). [Table 61](#) lists process controls with their control limits ranges and CPPs/CMAs with their acceptable ranges for DP manufacturing process. Control limits for (b) (4) integrity testing are applied for (b) (4) integrity testing.





Overall Reviewer’s Assessment of Section 3.2.P.3.4:

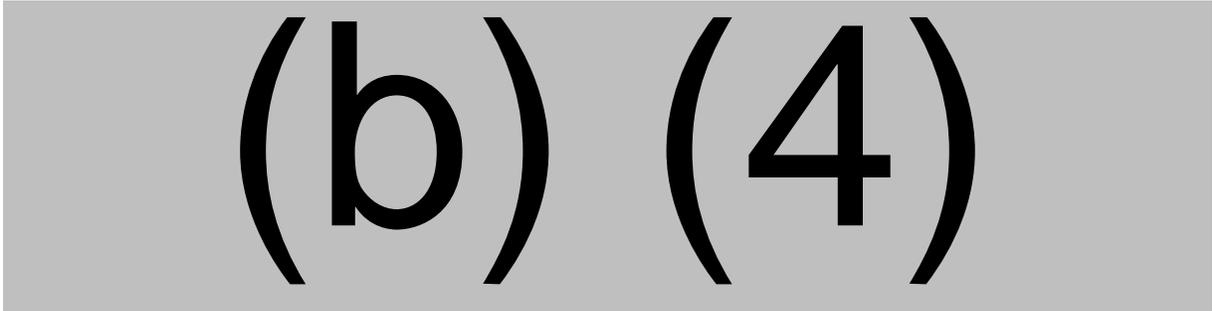
The information provided on controls of critical steps and intermediates during DP manufacturing in the BLA is acceptable.

3.2.P.3.5 Process Validation and/or Evaluation

[Reviewed by JW and AGS (for E/L in (b) (4)]

3.2.P.3.5.1 Process Validation Studies

Pfizer executed (b) (4) DP PPQ batches (Table 62) to validate the performance of the commercial DP manufacturing process (b) (4)



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

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Overall Reviewer's Assessment of Section 3.2.P.3.5.:

The effectiveness of the process is demonstrated by meeting the AC for CPPs, select non-CPPs, select quality attributes (QAs/CQAs), select CMAs, and relevant PPAs. PPQ results demonstrate process control, consistency, and filling homogeneity of DP process. Results obtained for the evaluated process parameters, in-process tests, in-process controls, and release tests met PPQ acceptance criteria and QA release criteria for three or (b) (4) PPQ batches (b) (4) homogeneity was demonstrated through (b) (4) batches, i.e., (b) (4); Please refer

to Table 66, Module 3.2.P.3.5 Process Validation and/or Evaluation in this memo and its comments).

3.2.P.4 Control of Excipients

(Reviewed by BL)

3.2.P.4.1 Specifications

The (b) (4) excipients used in manufacture of fidanacogene elaparvovec DP are shown in Table 72. specifications will comply with the current version of (b) (4).

Table 72. Specification for (b) (4) Excipients

Excipient	Reference to Standard
Sodium Phosphate, monobasic, monohydrate (NaH ₂ PO ₄ H ₂ O)	(b) (4)
Sodium Phosphate, dibasic, heptahydrate (Na ₂ HPO ₄ 7H ₂ O)	(b) (4)
Sodium Chloride (NaCl)	(b) (4)
Poloxamer 188a	(b) (4)
Water for Injection	(b) (4)

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

The excipients used in manufacture of DP are tested in accordance with current (b) (4) analytical procedures.

3.2.P.4.4 Justification of Specifications

All excipients are tested in accordance with (b) (4) standards and methods.

3.2.P.4.5 Excipients of Human or Animal Origin

No excipients of human or animal excipients are used in manufacture of DP.

3.2.P.4.6 Novel Excipient

No novel excipients are used in manufactured of DP.

Overall Reviewer's Assessment of Section 3.2.P.4:

Information on the excipients used in drug product manufacturing is acceptable.

3.2.P.5 Control of Drug Product

(Reviewed by BL)

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

(BL and LP- potency)

The DP lot release specifications are shown in [Table 73](#).

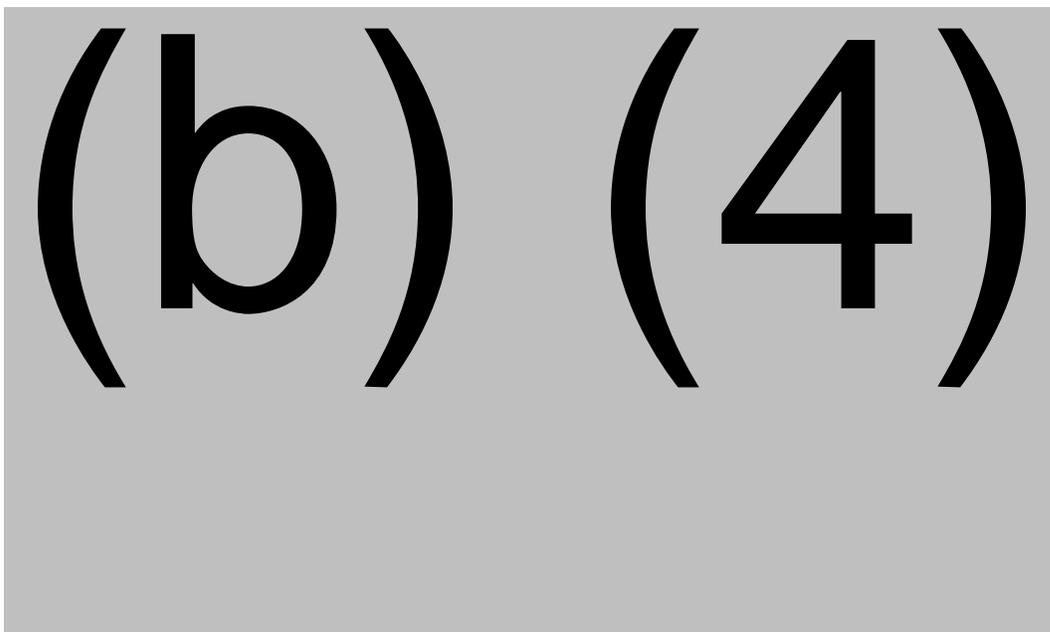
Table 73. Fidanacogene elaparvovec Drug Product Specification

Quality Attribute	Analytical Procedure	Acceptance Criteria	
Appearance (Clarity)	(b) (4)	(b) (4)	
Appearance (Color)		(b) (4)	
Appearance (Visible Particulates)		Essentially free from visible particulates	
(b) (4)		(b) (4)	
Extractable Volume		Not less than labeled volume	
(b) (4)		(b) (4)	(b) (4)
Poloxamer 188			
(b) (4)			
(b) (4)			
Vector Genome (b) (4)			
(b) (4)			
(b) (4)			
Vector Capsid (b) (4)			
(b) (4)			
(b) (4)			
(b) (4)			
(b) (4)			
(b) (4)			
(b) (4)			
(b) (4)			
Factor IX (b) (4)			
(b) (4)			
(b) (4)			
Endotoxin			
Sterility	No Growth Detected		

^a Action limit of (b) (4)

3.2.P.5.6.4. Appearance (Clarity)

The Applicant’s calculated stability (b) (4) using Process (b) (4) and Process (b) (4) lots. FDA’s calculated (b) (4) based only on Process (b) (4) lot release data is (b) (4) (Figure 45). Per FDA’s recommendation, the Applicant agreed to set the AC as (b) (4) as documented in Amendment 19 dated 10/18/2023.



3.2.P.5.6.5. Appearance (Color)

All DP lot release and stability test results are (b) (4). Because there is no discernable change of color from (b) (4) DP, the AC for DP are set the same as AC for (b) (4).

3.2.P.5.6.6. Appearance (Visible Particulates)

The test is conducted only on DP, not on (b) (4), to conform to the (b) (4) requirements (b) (4). The AC is set as "Essentially free from visible particulates".

Reviewer's comments: This test is performed on DP that has been subjected to 100% visual inspection as part of the DP manufacturing process. (b) (4) indicates that "essentially free" means that when injectable products are inspected, no more than the specified number of units may be observed to contain visible particulates. The specific number of units shall be defined in the assay SOP. According to the SOP-73930 Table 12, (b) (4) is examined for visible particulate. Based on communication with DBSQC reviewer (Kouassi Ayikoe), this approach is acceptable with the (b) (4) assay. Also, considering that the DP vials are 100% visually inspected. This AC is acceptable.

3.2.P.5.6.7. (b) (4)

[Redacted content]

(b) (4)

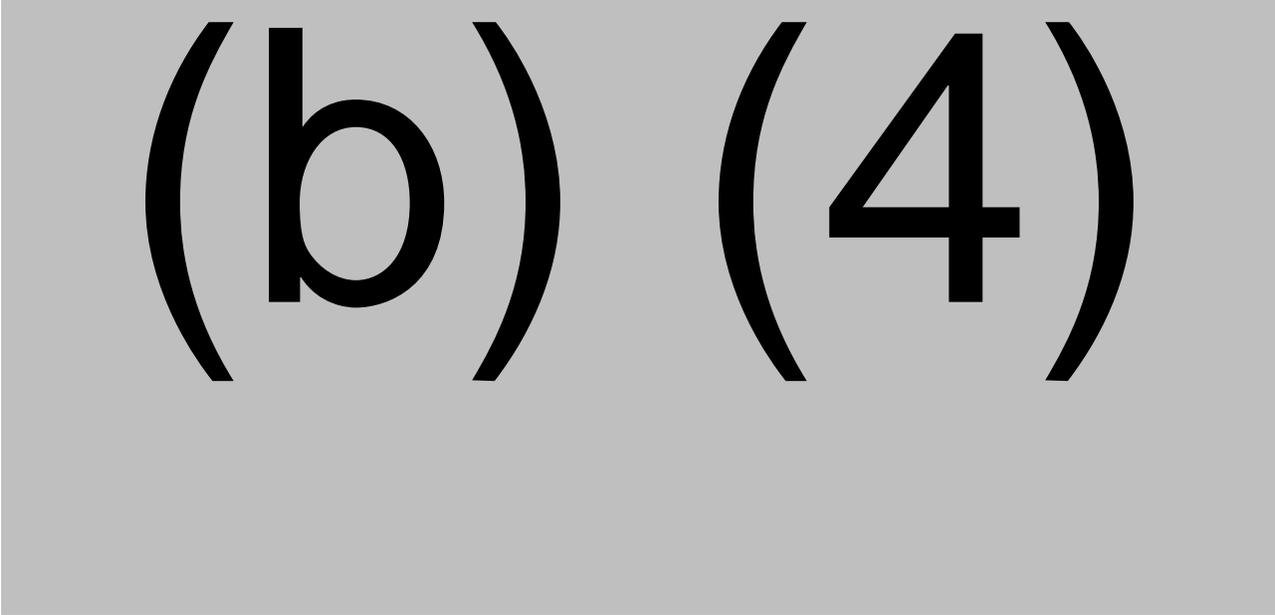
3.2.P.5.6.8. Extractable Volume

The analytical procedure to test the extractable volume is performed according to (b) (4). The commercial specification for Extractable Volume is “No Less than Labeled Volume”.

Reviewer’s comments: DP vial fill volume (b) (4) has been validated. The (b) (4) range is a CPP that is monitored during commercial DP manufacturing process. The AC is acceptable.

3.2.P.5.6.9. (b) (4)

(b) (4)



3.2.P.5.6.10. Poloxamer 188

Poloxamer 188 (b) (4)

(b) (4) Poloxamer (b) (4) in the DP is tested using (b) (4)



In Amendment 19 dated 10/19/2023, the Applicant agreed to set the lower limit as (b) (4) per FDA's suggestion but insisted on proposing an upper limit of (b) (4). The Applicant justified the upper limit (b) (4) with the safety of a much (b) (4) of Poloxamer 188 in Roctavian and the Applicant's formulation studies demonstrating no impact to product potency or purity with Poloxamer concentration of (b) (4). In a follow-up IR #28, FDA ask that the Applicant set an action limit at (b) (4), and if the

test result is over the action limit, an investigation will be conducted. In Amendment 36, the Applicant agreed.

Figure 48. Justification of DP AC for Poloxamer 188

<p>(b) (4)</p>	<p><i>Reviewer's comments: The applicant's justifications for the upper limit of (b) (4) are reasonable. The risk to product safety and quality is low with the proposed upper limit. The action limit of (b) (4) based on statistical tolerance interval of historical data is acceptable.</i></p>
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3.2.P.5.6.11. Subvisible Particles

The commercial AC for (b) (4) is set to meet the (b) (4) standards defined in (b) (4)

3.2.P.5.6.12. Vector Genome (b) (4)

The vector genome (b) (4) test is a (b) (4)

(b) (4)

(b) (4)

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

(b) (4)

3.2.P.5.6.19. Endotoxin

Endotoxin testing is performed on DP. The endotoxin AC is set based on the (b) (4) limit of no more than (b) (4)

The upper limit in DP is no more than (b) (4). The AC is set as (b) (4) with an (b) (4) safety margin. All Phase 3 lot release test results for endotoxin are (b) (4). The AC was subsequently converted to (b) (4) based on the target DP vg (b) (4) of 1E13 vg/mL.

Reviewer's comment: The proposed AC for endotoxin is acceptable.

3.2.P.5.6.20. Sterility

The sterility test is conducted according to (b) (4) AC is set as "No growth detected".

3.2.P.5.6.21. Container Closure Integrity

The container closure integrity test is conducted as a surrogate for sterility test to monitor the integrity of the primary container during stability studies. The AC is set as "Pass".

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:

In response to FDA's IR, the Applicant revised the DP lot release AC for Appearance (b) (4)

The Applicant also added an action limit for the poloxamer 188. The finalized DP lot release specification is acceptable.

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

[Reviewed by BL and LP (for Potency)]

The analytical methods used for (b) (4) DP release testing are described in Sections 3.2.S.4.2 *Analytical Procedures* and 3.2.S.4.3 *Validation of Analytical Procedures*. All analytical methods used only for DP lot release testing, including tests for poloxamer 188, (b) (4), and sterility, are reviewed by DBSQC and are deemed acceptable. Please refer to DBSQC review memo for those methods used only for DP lot release testing.

*Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:
DP lot release testing methods reviewed by OTP are acceptable.*

3.2.P.5.4 Batch Analyses

(Reviewed by BL)

DP lots used in clinical studies, stability, and process validation are summarized in [Table 83](#). Lot release test results for these (b) (4) batches are submitted in the BLA. The information provided represent the analytical methods, acceptance criteria, and data reporting used at the time of lot release.

(b) (4)

3.2.P.5.5 Characterization of Impurities

(Reviewed by BL and AGS)

No additional impurities are introduced by DP manufacturing process. There are no process-related impurities associated with DP formulation and filling.

Regarding leachables characterization, this section refers to the ongoing leachables study described in Module [3.2.P.2.4 Container Closure System](#) (AS and AGS E/L)

Overall Reviewer’s Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:

The information provided is acceptable as submitted and impurities in DP are adequately controlled.

3.2.P.6 Reference Standards or Materials

(Reviewed by AS)

Please refer to Module [3.2.S.5 Reference Standards or Materials](#)

3.2.P.7 Container Closure System

[Reviewed by AS and AGS (for E/L)]

The container closure system for the DP consists of a 2 mL cyclic olefin copolymer (COC) vial body that is pre-assembled with a thermoplastic elastomeric (TPE) stopper and a top ring. A snap-fit flip away plastic cap and a bottom ring are associated with the container closure system. The assembled components are sterilized by (b) (4) to produce a ready-to-fill container closure system. A description of the components is summarized in the table below ([Table 84](#)).

(b) (4)

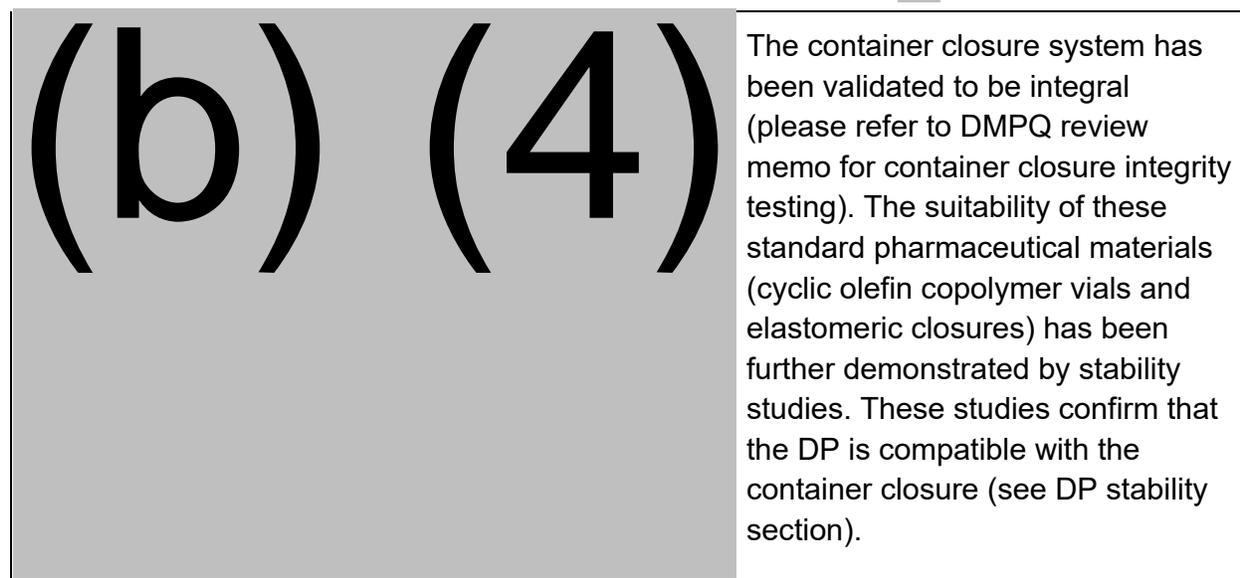
(b) (4)

- (b) (4)

The incoming vials are inspected per the receiving site’s procedures and the supplier’s certificate may be accepted for tests where applicable.

Representative drawings of the container closure system components es are illustrated in [Figure 59](#).

Figure 59. Diagram of the Components of the 2mL (b) (4)-Closed Vial



Labeled drug product vials are packaged inside cartons. A development study was conducted to determine if the secondary packaging for the DP is suitable to protect DP from visible and UV light exposure. The results indicate that the secondary package provides a high level of protection from both visible (b) (4) reduction) and UV light (b) (4) reduction) exposure.

Regarding leachables characterization from CCS, this section refers to the ongoing leachables study described in Module [3.2.P.2.4 Container Closure System](#).

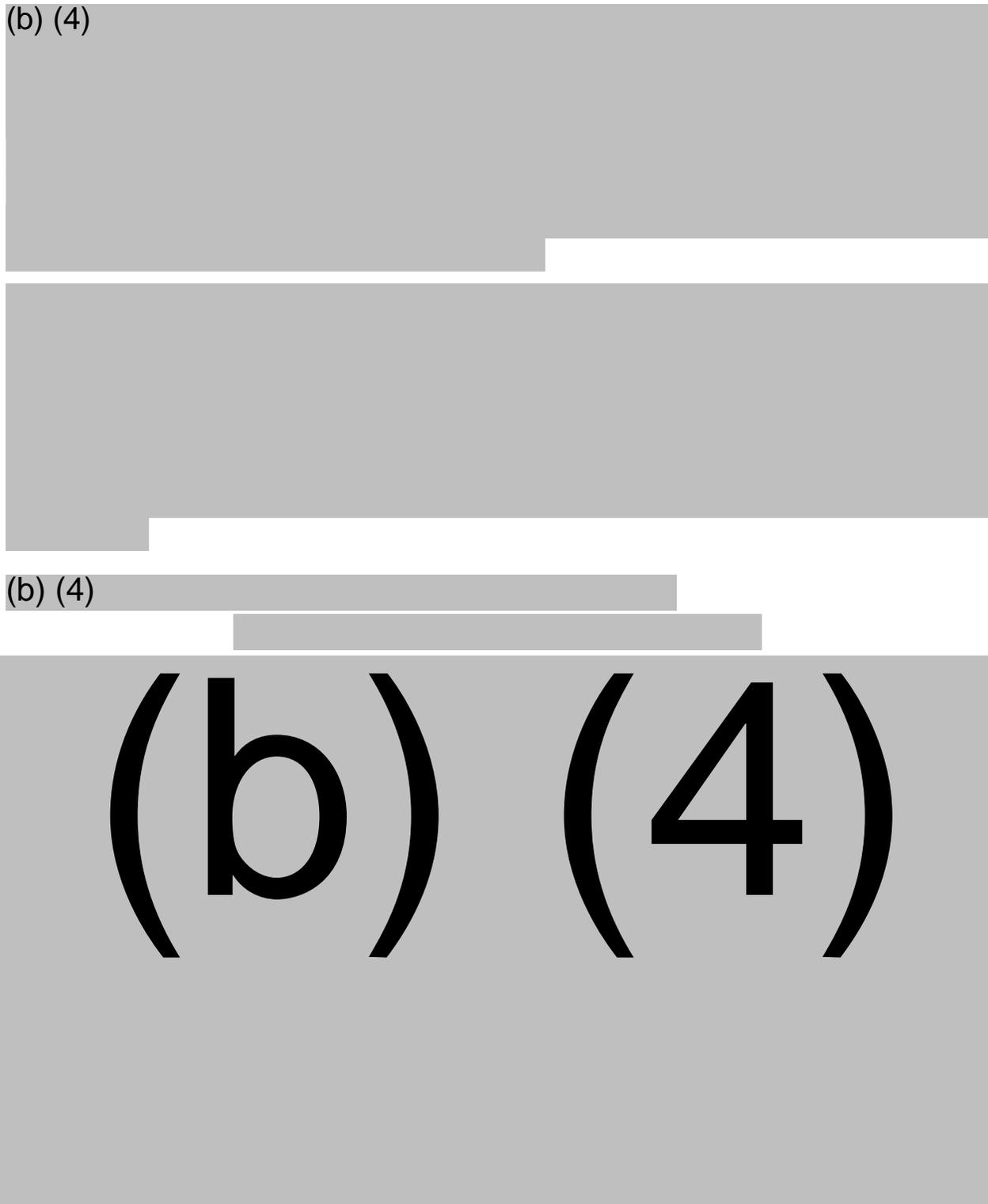
Overall Reviewer’s Assessment of Section 3.2.P.7:
The information provided for the drug product container closure system is acceptable.

3.2.P.8 Stability

(Reviewed by RM)

3.2.P.8.1 Stability Summary and Conclusion

(b) (4)



(b) (4)

(b) (4)

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

(b) (4)

3.2.P.8.2 Stability Data

3.2.P.8.2.1. Results of Long-Term Stability

The initial submission did not include any statistical analysis of the stability data. Two IR requests were sent requesting statistical and poolability analysis of the data (IR #17 dated 19 Oct 2023 and IR20 dated 29 Nov 2023) in agreement with Guidance to industry “Q1A(R2) stability testing of new drug substances and products” and in Guidance to industry “Q1E Evaluation of stability data”. The provided statistical analysis to evaluate the poolability was received in amendment 23 dated 2 Nov 2023 and amendment 27 dated 08 Dec 2023 and is shown in [Table 88](#) below. Based on this analysis, data from almost all can be pooled to calculate slope (but not intercepts) for most assays, including Factor IX (b) (4) and Vector Genome (b) (4). Data from three assays can not be pooled. These assays are (b) (4)

(b) (4)

(b) (4)

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

3.2.P.8.3. Post-Approval Stability Protocol and Stability Commitment

(Reviewed by RM)

Post-approval, a minimum of (b) (4) drug product (b) (4) will be enrolled in the commercial stability program at the long-term storage condition of -60 to -90 °C (b) (4). Time proposed points of 0, 6, 12, 24, 36 (b) (4) are acceptable. The CQA to be assayed include all the CQA that were tested in the long-term stability study with the addition of (b) (4). This is acceptable.

The applicant added one sentence at the end of 3.2.P.8.1 stability summary and conclusions that in accordance with Guidance for Industry: Chemistry Manufacturing and Controls Change to an Approved Application: Certain Biological Products (June 2021), future shelf-life updates will be submitted as an annual report. This approach was not acceptable due to the concern of loss of stability at later time points with no appropriate review. Per FDA communication in IR#38 from 26 Feb 2024, the applicant revised this statement in amendment 125786/051 from 11 Mar 2024. Any future post approval shelf life extensions will be submitted as prior approval supplement (PAS).

Overall Reviewer's Assessment of Section 3.2.P.8:

- *Primary stability studies for DP included the following studies: (1) long term stability in conditions of -60° to -90° C, (2) accelerated condition of (b) (4) over the course of (b) (4), as well as (3) (b) (4) and (4) stability after (b) (4). The drug product shelf life is 36 months when stored at the recommended temperature of -60° to -90°C. The shelf-life claim is based on available data for (b) (4) months (b) (4) 36 months (b) (4)) and (b) (4) supportive lots with date for (b) (4) months. Overall, the applicant demonstrated acceptable stability for up to 36 months with no major concerns. There are no remaining deficiencies.*
- *The applicant plans to enroll (b) (4) drug product (b) (4) in the commercial stability program (b) (4). Any future post approval shelf life extensions will be submitted as a prior approval supplement (PAS).*

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Reviewed by DMPQ

3.2.A.2 Adventitious Agents Safety Evaluation

(Reviewed by AS)

3.2.A.2.1. Adventitious Agents Control Strategy

The strategy to control adventitious agents comprises of:

- (b) (4) [Redacted]

Reviewer's comment: Materials of Biological Origin including the production (b) (4) [Redacted] were reviewed in 3.2.S.2.3 Control of Materials. The materials are of satisfactorily controlled.

3.2.A.2.2. Viral Clearance Studies

The ability of the purification process to remove virus was evaluated using (b) (4) model viruses (Table 89):

- (b) (4) [Redacted]

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

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(b) (4)

3.2.A.3 Novel Excipients

No novel excipients are used in manufacture of fidanacogene elaparvovec DP.

3.2.R Regional Information (USA)

(Reviewed by JW)

3.2.R.1. Executed Batch Records

(b) (4)

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3.2.R.2. 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*).

3.2.R.3. Combination Products

Not applicable, as fidanacogene elaparvovec is not a combination product.

3.2.R.4. Comparability Protocols

The applicant did not propose any future manufacturing changes that will be evaluated under a comparability protocol.

Other eCTD Modules

Module 1

(Reviewed by RM)

A. Environmental Assessment

The environmental assessment is provided in 1.12.14 in accordance with 21 CFR 25. This application is not eligible for categorical exclusion because fidanacogene elaparvovec is not a substance that occurs naturally in the environment, and the applicant does not make a claim of categorical exclusion. The applicant does not propose any alternative action other than approval.

Reviewer's comment: An EA is required and adequate for the purposes of filing and approving this application [21 CFR 25.15(a)]. No significant impact on the environment was noted. I concur with the sponsor risk evaluation primarily due to the low likelihood of any of the postulated events. For more information, please see review memo for environmental assessment Finding of No Significant Impact (FONSI).

B. Reference Product Designation Request

The applicant has requested reference product designation in section 1.3.5.3 of the CTD.

Reviewer's comment: Reference Product Exclusivity Determination form submitted. Board meeting on 19 Mar 2024.

C. Labeling Review

(Reviewed by RM)

C.1. Full Prescribing Information (PI):

The product is supplied at a nominal titer of 1×10^{13} vector genomes vg/mL and each vial contains extractable volume of 1 mL. The product is supplied in kits containing 4 to 7 single-use vials, each kit constituting a dosage unit based on the patient's body weight. The individual product vial and each of the possible kits has a separate NDC number.

The recommended dose of the product is 5×10^{11} vector genomes per kg (vg/kg) of body weight with an adjustment of height and BMI for patients with BMI >30 kg/m² (see PI for more information), administered as a single intravenous infusion after dilution with 0.9% sodium chloride and 0.25% human serum albumin (HSA) for a total infusion volume of 200 mL.

Dose preparation involves significant manipulation. Preparation of the product diluent includes dilution of (b) (4) 25% HSA in (b) (4) 0.9% sodium chloride. This is followed by calculating the required dose of the DP, thawing and dilution of the DP in the 0.9% sodium chloride and 0.25% human serum albumin (HSA). The solution for infusion should be administered to the patient over approximately 60 minutes and an in-line 0.2 µm IV filter may be used for administration.

Reviewer's comment: In original submission, the overall instructions in the PI to prepare and administer the product lacked detail and were not organized properly. Comments on the PI were sent to the applicant on 21 Mar 2024 and on 09 Apr 2024 and revised to provide the acceptable details.

The product is supplied in a kit of 4 to 7 vials, packaged into a carton. The number of vials depend on the weight of the patient, and there is a kit for every 20-kg of weight between 75 and 135 kg. Body mass index (BMI) in kg/m² of patients is also calculated and patients that are >30 kg/m² shall be dosed will receive an adjusted dose which is adjusted to 30 kg/m². For example, a patient that weighs 120kg with height of 1.84 m will receive 5.08 ml of the DP and not 6 ml. The calculations are described properly in the PI.

The customized kit is accompanied with patient's specific identifier number on the outer carton. Each FIDANACOGENE ELAPARVOVEC kit may contain different drug product lots. The product kit is shipped frozen (-100 °C to -60 °C [-148 °F to -76 °F]) in plastic vials with an elastomeric stopper and plastic snap fit cap with an extractable volume of 1 mL. Upon receipt, the kit should be placed immediately in a freezer between -90 °C to -60 °C and stored upright.

Reviewer's comment: The information provided in the PI is consistent with the information in the BLA. This product is provided in a kit format based on the weight of the patient. The PI contains adequate instructions for dose preparation and administration and the storage of the kit in a -100 °C to -60 °C freezer, with appropriate instructions to use the diluted product in the infusion bags.

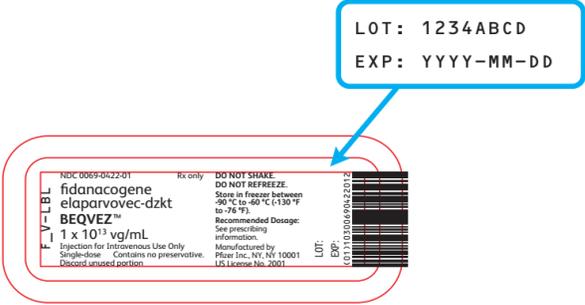
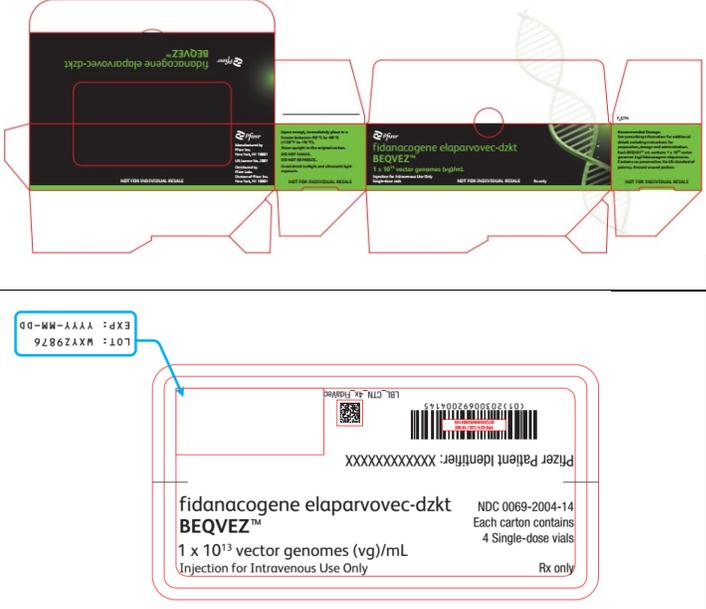
C.2. Carton and Container Labels

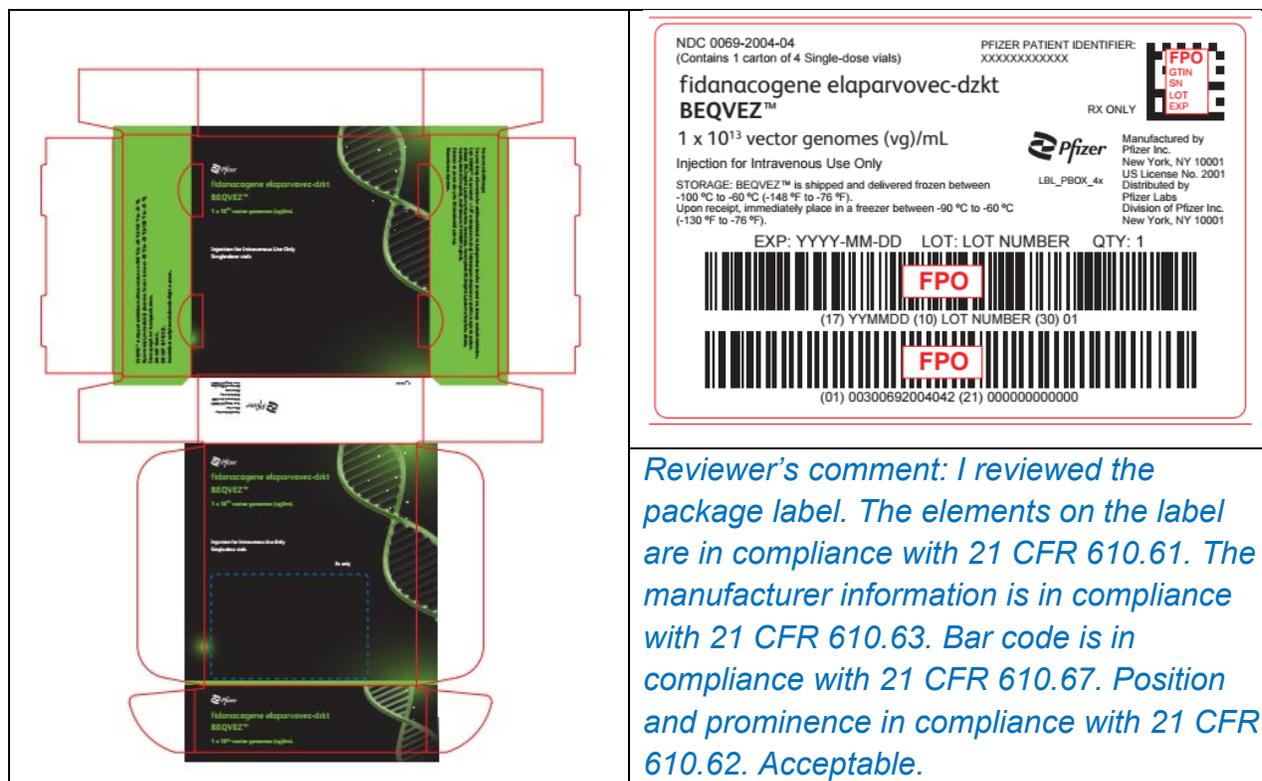
The product is supplied frozen at a nominal concentration of 1.0×10^{13} vg/mL and each vial contain an extractable volume of 1 mL [Figure 63a](#). The product is provided as a customized treatment pack containing the number of vials required to meet dosing requirements for each patient. The outer carton includes patient specific identifier number

(Pfizer Patient Identifier) [Figure 63c](#). The inner carton fits inside the outer carton and is used to place the vials in the holes in the inner carton. The inner carton has a label, shown in [Figure 63b](#).

Please refer to regulatory project manager (RPM)'s review memo for additional details.

Figure 63. Carton and Container Labels

<p>Figure 63a. Vial Sample Label</p>  <p>1mL: 47mm x 17mm</p>	<p><i>Reviewer's comment: I reviewed the vial label and communicated to the sponsor deficiencies in the label in IR#28, IR#30 and IR#38 from 21st Dec 2023, 09 Jan 2024 and 26 Feb 2024. All deficiencies were corrected. The details on the label are in compliance with the required elements of a full labels per 21 CFR 610.60. The manufacturer information is in compliance with 21 CFR 610.63. Bar code is in compliance with 21 CFR 610.67. Position and prominence in compliance with 21 CFR 610.62. Acceptable.</i></p>
<p>Figure 63b. Intermediate Carton Sample and Label</p> 	<p><i>Reviewer's comment: I reviewed the intermediate package label. Even though this is an intermediate package and not the external package, the elements on the label are in compliance with 21 CFR 610.61. The manufacturer information is in compliance with 21 CFR 610.63. Bar code is in compliance with 21 CFR 610.67. Position and prominence in compliance with 21 CFR 610.62. Acceptable.</i></p>
<p>Figure 63c. Outer Carton Sample and Label</p>	



Reviewer’s comment: I reviewed the package label. The elements on the label are in compliance with 21 CFR 610.61. The manufacturer information is in compliance with 21 CFR 610.63. Bar code is in compliance with 21 CFR 610.67. Position and prominence in compliance with 21 CFR 610.62. Acceptable.

*Versions of cartons and labels were provided in amendment 125786/53 from 11 Mar 2024.

The initial submission had incorrect NDC and the tradename BEQVEZ was disproportionately prominent. These deficiencies were communicated to the applicant in IR#28, IR#30 and IR#38 from 21st Dec 2023, 09 Jan 2024 and 26 Feb 2024. The final version of the vial and carton labels were updated in Amendment 125786/0053 from 11 Mar 2024.

There are four labels for intermediate carton that correspond to four kits that will have 4, 5, 6 or 7 vials. The number of vials is properly described. In the original submission, the NDC on the label of the intermediate carton was not assigned correctly and had a single NDC regardless of whether the kit had 4,5,6 or 7 vials. Per FDA IR#28 from 12 Dec 2023, the applicant revised the NDC in the inner carton to four different NDCs in amendment 125786/38 from 10 Jan 2024. In this amendment the applicant reviewed and revised their NDC assignments and voluntarily included separate NDCs for the intermediate carton and the outer carton. Final NDCs associated with this product are summarized in [Table 91](#).

Table 91. NDC Numbers for BEQVEZ Kit Formats

Total Number of Vials per Kit	Vial	Inner carton	Payload box
4	NDC 0069-0422-01	NDC 0069-2004-14	NDC 0069-2004-04

5		NDC 0069-2004-15	NDC 0069-2004-05
6		NDC 0069-2004-16	NDC 0069-2004-06
7		NDC 0069-2004-17	NDC 0069-2004-07

Modules 4 and 5

[Reviewed by RM and LP (for FIX activity and neutralization)]

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

(b) (4) 



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

(b) (4)

The text "(b) (4)" is followed by three large rectangular grey redaction boxes covering the majority of the page's content.

Overall Reviewer's Assessment of Relevant Sections of Module 4 and 5:

- ❑ *There are three activity assays to assess FIX activity. All three assays are validated with acceptable performance. However, the One-Stage Assay (SynthASil Reagent) Reagent) provides different results than the results obtained by the One-Stage Assay (Actin-FSL) or the Chromogenic Assay. therefore, the PI recommends where possible to use the same laboratory for monitoring clotting activity. This is acceptable.*
- ❑ *Shedding assay is qualified but not validated. The assay and qualification are acceptable and were demonstrated as appropriate for its intended purpose.*
- ❑ *Other assays used in the clinical studies include detection of binding and neutralizing antibodies to the capsid, presence of FIX in the plasma, antibodies to FIX, inhibition of FIX and two assays for presence of T cells in the peripheral blood that activate against AAVrH74var or FIX derived peptides.*
- ❑ *No deficiencies identified.*