

CBER DMPQ CMC/Facility BLA Review Memorandum

BLA STN 125786/0

Name of product: BEQVEZ (fidanacogene elaparvovec, FidaVec)

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

1. **BLA#:** STN 125786/0

2. **APPLICANT:** Pfizer, Inc, US License Number: 2001

3. **PRODUCT NAME/PRODUCT TYPE**

USAN: fidanacogene elaparvovec, abbreviated as FidaVec.

Proprietary Name: BEQVEZ

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

- a. **Pharmacological category:** FidaVec is a non-replicating recombinant adeno-associated viral (AAV)-based gene therapy vector encoding a high activity variant of human Factor IX protein (FIX-R338L).
- b. **Dosage form:** Concentrate suspension.
- c. **Strength/Potency:** 1×10^{13} vector genome (vg)/mL (1E13 vg/mL).
- d. **Route of administration:** Intravenous.
- e. **Indication(s):** Treatment of hemophilia B in patients ≥ 18 years of age. Select patients for therapy based on an FDA-approved companion diagnostic.

5. **MAJOR MILESTONES**

First Committee Meeting	May 19, 2023
Filing Meeting	June 12, 2023
Mid-cycle Meeting	October 19, 2023
Pre-License Inspection	November 6 – 10, 2023
Late-cycle Meeting	January 10, 2024
PDUFA Action Due Date	April 26, 2024

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

Reviewer/Affiliation	Section/Subject Matter
Wei Wang, OCBQ/DMPQ/MRB3	3.2.S: Drug Substance (DS) Manufacturing 3.2.P: Drug Product (DP) Manufacturing 3.2.A.1: Facilities and Equipment 3.2.R: Production Schedule, reprocessing protocol, continued process validation, and risk assessment.

7. **INTER-CENTER CONSULTS REQUESTED**

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

8. SUBMISSION(S) REVIEWED

Date Received	Submission Reviewed	Comments
April 28, 2023	STN 125786/0	Modules 1, 2 and 3
December 19, 2023	STN 125786/0.31	Section 3.2.R. Pfizer Sanford PLI 483 Response
January 31, 2024	STN 125786/0.42	Modules 1 and 3. Additional (b) (4) data to support the use of an (b) (4)
December 19, 2023	STN125786/0.50	Section 1.11. 483 Response

9. Referenced REGULATORY SUBMISSIONS

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF (b) (4)	(b) (4)	(b) (4)	Yes	Defer to OTP reviewers
DMF (b) (4)	(b) (4)	Information on the (b) (4)	Yes	Defer to OTP reviewers
DMF (b) (4)	(b) (4)	Facility and procedures for sterilization of the DP filling kit.	Yes	No DMF review required as information pertinent to sterilization of the drug product filling kit is provided in the BLA

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

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Pfizer submitted this BLA, STN 125786/0, for the manufacture of a new gene therapy vector product, Fidanacogene elaparovect (FidaVec), for the treatment of hemophilia B in patients ≥18 years of age. FidaVec is a non-replicating recombinant adeno-associated viral (AAV) vector carrying the DNA sequence encoding a high activity variant of human Factor IX protein (FIX-R338L). FidaVec is produced by recombinant DNA technology using (b) (4)

The FidaVec (b) (4) drug product (DP, filled vials, unlabeled DP (b) (4)) are manufactured at the Pfizer Sanford, NC site (FEI: 1000110954). CBER conducted a pre-license inspection (PLI) of the Pfizer Sanford, NC facility to support the review of this BLA. The DP vial labeling and packaging are performed by (b) (4)

The PLI of Pfizer Sanford facility covered the Quality, Production, Facility and Equipment, and Laboratory Control systems with focus on the manufacturing of FidaVec. The PLI reviewed documents, including current operating procedures, deviation reports, and facility and major equipment qualification reports. The PLI was classified as voluntary action indicated (VAI). All observations on the Form 483 were resolved. CBER waived the PLIs of (b) (4)

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

B. RECOMMENDATION**I. APPROVAL**

DMPQ recommends approval of this BLA, STN 125786/0 to manufacture FidaVec (b) (4) DP (b) (4) filled vials) at the Pfizer Sanford, NC site (FEI: 1000110954).

II. COMPLETE RESPONSE (CR)

N/A

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Wei Wang, Ph.D., CMC and Facility Reviewer, OCBQ/DMPQ/B3	Concur	
CDR Donald Ertel, OCBQ/DMPQ/B3, Branch Chief	Concur	
Carolyn Renshaw, OCBQ/DMPQ, Division Director	Concur	

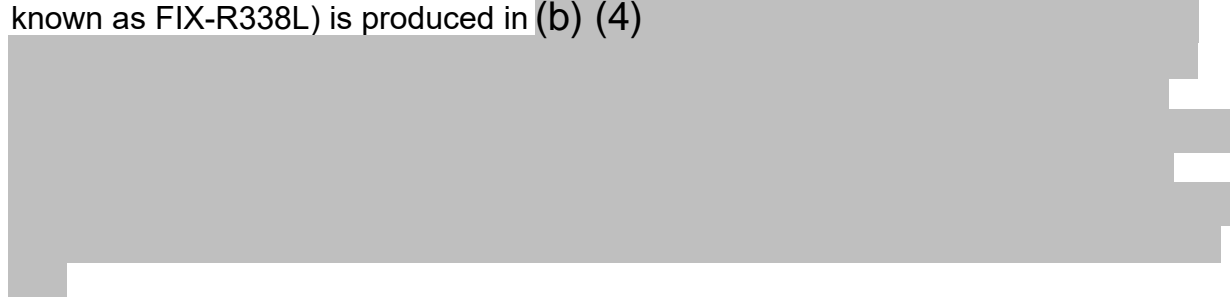
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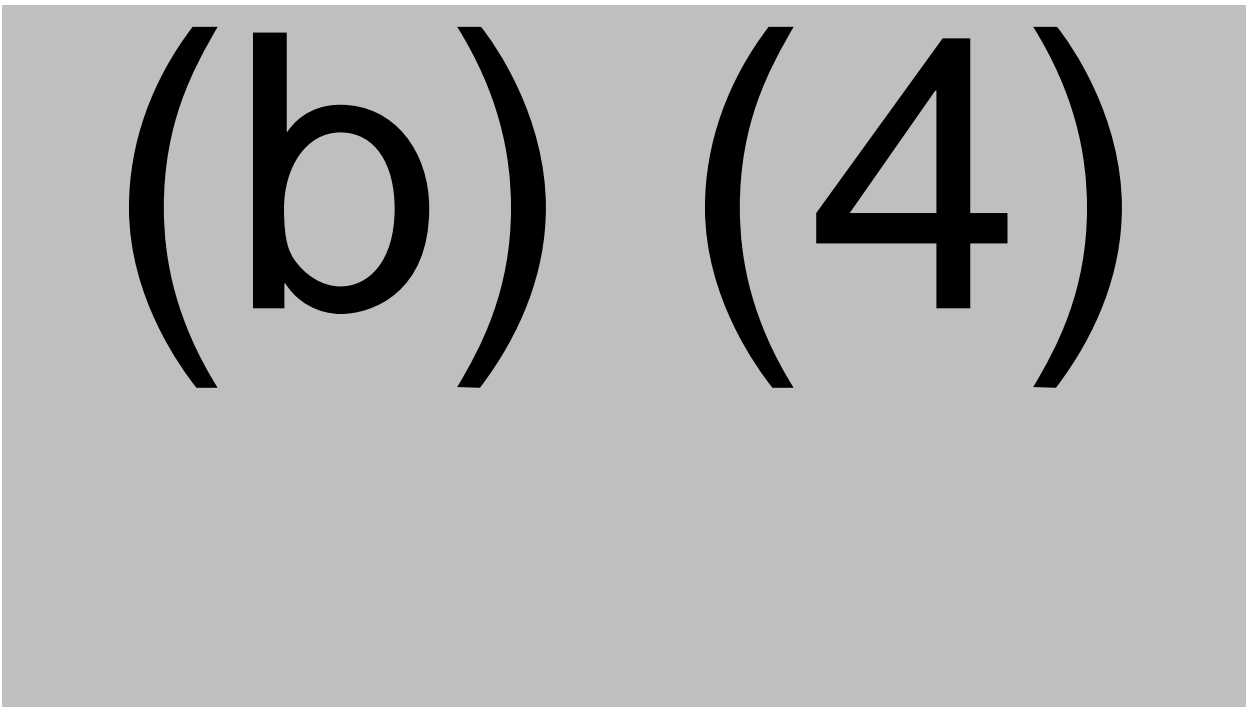
Module 3**3.2.S DRUG SUBSTANCE**

FidaVec is a recombinant adeno-associated viral (AAV) vector carrying the gene that encodes human coagulation Factor IX (FIX) Padua (R338L) variant. FidaVec (also known as FIX-R338L) is produced in (b) (4)

**3.2.S.2 Manufacture****3.2.S.2.1 Manufacturer(s)**

In section 3.2.S.2.1 of the original BLA submission, STN 125786/0, the applicant provided a complete list of FidaVec (b) (4) manufacturing and testing sites (Table 1). The applicant indicated in Form 356h that all (b) (4) manufacturing and testing sites are ready for inspection.

(b) (4)



(b) (4)

3.2.P DRUG PRODUCT

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

The composition of fidanacogene elaparvovec drug product was summarized in Table 3.2.P.1-1, of STN 125786/0. The sterile FidaVec DP solution is filled in a clear, sterile 2 mL cyclic olefin copolymer vial which is pre-assembled with elastomeric stopper and plastic, snap-fit cap. Each vial is designed to deliver 1 mL of FidaVec DP for single use with a nominal concentration of 1.00E13 vg/mL. The 1-mL DP solution contains no preservative.

3.2.P.2.5 Microbiological Attributes

For FidaVec DP release, sterility testing is performed per (b) (4) and bacterial endotoxins testing is performed per (b) (4)

In Section 3.2.P.2.5 Microbiological Attributes of STN 125786/0, the applicant described two different methods to assess the container closure integrity (CCI) methods:

- A (b) (4) CCI testing (CCIT) method is used to test and demonstrate that the integrity of the DP container closure system (CCS) can be maintained. The (b) (4) method was shown to detect (b) (4)
- A (b) (4) analysis CCIT method is used to test and demonstrate that the integrity of the DP CCS can be maintained under manufacturing conditions (e.g., during the manufacturing of process validation lots), and the long term storage and DP shipping conditions. The (b) (4) method was shown to (b) (4).

Review Comments: Noted, a (b) (4) analysis was used for 100% CCIT during the manufacturing of DP PPQ lots.

3.2.P.2.5.2.1 CCIT by (b) (4) Method

(b) (4)

- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
- | [REDACTED]

CCIT Method: In each test, (b) (4)

Validity of Test: (b) (4) .

CCIT Acceptance Criteria: All test vials must (b) (4)
to be considered to pass the test.



CCIT Results: All test vials (after storage) passed the (b) (4)

Review Comments: By using the above described validated (b) (4) CCIT method, the applicant has demonstrated that the integrity of DP CCS is maintained under routine manufacturing conditions. No objectionable issues were noted.

3.2.P.2.5.2.2 CCIT by (b) (4) Analysis

(b) (4)

(b) (4)



Review Comments: Noted, the CCI data (b) (4)

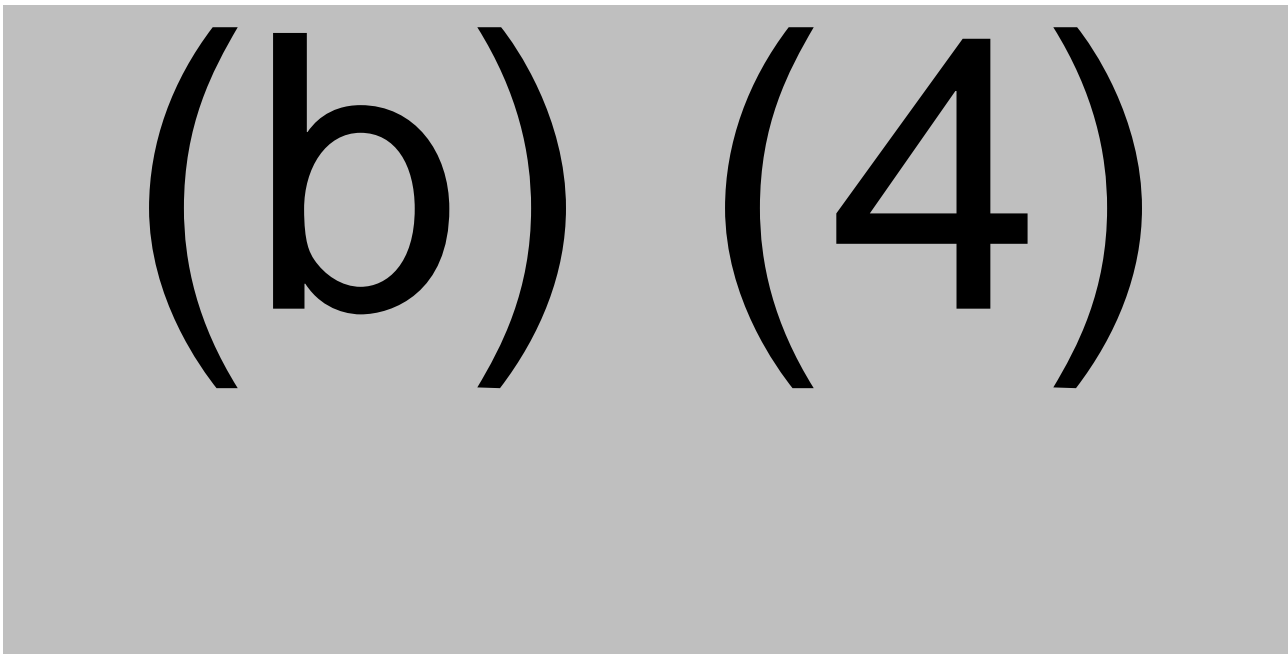
The applicant has demonstrated that the integrity of DP CCS is maintained under long term storage conditions and routine DP shipping conditions. (b) (4) is performed as part of DP release for each PPQ batch. The applicant stated that in addition to the above described CCIT, the sterility testing is performed for the DP release to assess microbial control and the integrity of filled DP vials. No issues were identified in the review of Section 3.2.P.2.5 Microbial Attributes.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

In section 3.2.P.3.1 of the original BLA submission, STN 125786/0, the applicant provided a complete list of FidaVec PD manufacturing and testing sites (Table 8). The applicant indicated in the Form 356h that all DP manufacturing and testing sites are ready for inspection.

(b) (4)



(b) (4)

3.2.P.3.3 Description of Manufacturing Process

DP ^{(b) (4)} Lots

The manufacturing processing steps of DP ^{(b) (4)} lots and IPTs under the DMPQ purview are summarized in Table 9. The DP manufacturing activities (Table 9) are conducted at the Pfizer Sanford, NC site.

(b) (4)


(b) (4)

Review Comments: The information of DP manufacturing steps provided appears acceptable.

(b) (4)


(b) (4)

(b) (4)




DP Vial Labeling and Packaging

(b) (4)



The packaging FidaVec DP vials for commercial distribution includes the following steps:

- (b) (4)
- 

Pfizer provided RPT-172215, *Process Validation Report of the labeling and packaging Process for US of Gene Therapy Product* (in 2.0 mL and 10 mL formats), to show that the maximum number of complete freeze/thaw cycles is not more than (NMT) (b) (4) and that the cumulative time for DP at room temperature is NMT (b) (4).

Review Comments: The DP vial labeling and packaging validation information provided in RPT-172215 appears acceptable.

DP Repackaging Criteria

In the event that a patient treatment order is cancelled, labelled DP vials are removed from a patient specific kit (the tertiary packaging) and stored in a freezer at –90 °C to –60 °C. The DP vials from the cancelled order may be repackaged (re-kitted) for a new patient order. A repackaging event can occur only once to not exceed the maximum number of complete freeze/thaw cycles.

Review Comments: The OTP has agreed with the described repackaging criteria.

3.2.P.3.4 Controls of Critical Steps and Intermediates

DMPQ defers to OTP to review this section.

3.2.P.3.5 Process Validation and/or Evaluation

DP Manufacturing on (b) (4) in Building (b) (4)

The FidaVec DP process can be performed by (b) (4)

Per RPT-128123, *Summary Report of the PPQ for FidaVec DP Process at Sanford, NC Facility*, (b) (4) DP PPQ lots were manufactured between (b) (4) (Table 10).

(b) (4)

In RPT-128123, it was shown that all IPT results for the (b) (4) PPQ DP lots under the DMPQ purview met acceptance criteria, including:

(b) (4)

(b) (4)

DP Labeling and Packaging

Filled DP vial (b) (4) are shipped to (b) (4) of the (b) (4) facilities (Table 8, (b) (4) (b) (4) for DP vial labeling (pre-labeling) and packaging per the manufacturing process described in Section 3.2.P.3.3. The product is packaged (kitted) as a patient-specific pack with different number of labelled DP vials based on patient weight.

(b) (4)

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


- (b) (4)

Review Comments: It appears that manual pre-labeling and packaging processes at the (b) (4) site have been adequately validated for US market of 2 mL (b) (4) vials for gene therapy products, including FidaVec.

(b) (4)

(b) (4)

(b) (4)

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

- ☐ The process validation information under the DMPQ purview in this section appears acceptable.
- ☐ No objectionable issues were noted.

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)**

See section 3.2.P.2.5 for testing (sterility, endotoxin and CCIT) under the DMPQ purview.

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

See section 3.2.P.2.5 for testing (CCIT methods) under the DMPQ purview.

3.2.P.5.4 Batch Analyses


The submitted batch analyses information under the DMPQ purview (e.g., testing results of sterility and bacterial endotoxin) appeared acceptable. DMPQ defers to OTP to evaluate other DP quality testing results.

Overall Reviewer's Assessment of Sections 3.2.P.5.4

- ☐ The information provided under the DMPQ purview appears acceptable.

3.2.P.7 Container Closure System

The FidaVec DP is filled into pre-assembled (b) (4)-closed vials consisting of a 2 mL cyclic olefin copolymer (COC) vial body (product contact component), a thermoplastic elastomeric (TPE) stopper (product contact component) and a top ring (non-product contact component). A snap-fit flip away plastic cap and a bottom ring (non-product contact components) are associated with the container closure system. The (b) (4)



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

Review Comments: CCIT methods were reviewed in Section 3.2.P.2.5. CCIT was performed using a (b) (4) analysis on all (100%) DP filled vials of PPQ lots (reviewed in Section 3.2.P.3.5).

Overall Reviewer's Assessment of Section 3.2.P.7:

- ☐ The information provided appears acceptable.

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

Pfizer provided some stability information for FidaVec DP stored under the following conditions:

- The long-term condition: at -60°C to -90°C for 36 months (study ongoing).
- The accelerated condition: at (b) (4) months (completed).
- (b) (4)

Pfizer indicated that for DP stored under the long-term condition, container closure integrity (CCI) will be tested using (b) (4) analysis method at time-points of 12, 24, 36 (b) (4) months, and endotoxin will be tested at time-points of 0 and (b) (4) months.

Stability results under the DMPQ purview all met acceptance criteria, including:

- (b) (4)

Review Comments: Endotoxin testing results at time-point 0 month were the same as the DP release testing results. Noted, CCIT is (but sterility is not) tested for stability under the long-term storage condition, which appears acceptable per the FDA Guidance for Industry (2008): Container and Closure System Integrity Testing in lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products.

Overall Reviewer's Assessment of Sections 3.2.P.8.1 and 3.2.P.8.3:

- ☐ The information provided under the DMPQ purview appears acceptable.

3.2.A APPENDICES**Manufacturing Facility Overview**

Facilities involved in FidaVec Manufacture are listed in Table 13.

Pfizer Sanford site is a multi-product facility to manufacture licensed vaccine (b) (4) in dedicated production areas. No penicillin, antibiotics or hazardous products (e.g., steroid hormones, cytostatics, or immune-suppressive drugs) are manufactured at the Pfizer Sanford site. Pfizer Sanford site has been inspected regularly by FDA for the manufacture of its licensed vaccine (b) (4)

Table 13. FidaVec Manufacturing Facilities

Facility FEI# Responsibilities	Inspection? Waiver? Not Required?	Compliance Check Required?	RMS-BLA Entry Required ?	Comments
Wyeth Pharmaceutical Division of Wyeth Holdings LLC ^a 4300 Oak Park Rd. Sanford, NC 27330 USA FEI#: 1000110954 (b) (4)/DP manufacturing and testing, (b) (4)	Inspection	Yes	Yes	CBER PLI 11/06/2023 to 11/10/2023 Voluntary Action Indicated (VAI) ORA Last inspection 11/09/2022 to 11/18/2022 VAI
(b) (4)	Waiver	Yes	Yes	ORA Last inspection (b) (4) VAI
(b) (4)	Waiver	Yes	Yes	ORA Last inspection (b) (4) No Action Indicated (NAI)

Facility FEI# Responsibilities	Inspection? Waiver? Not Required?	Compliance Check Required?	RMS-BLA Entry Required ?	Comments
(b) (4)	Waiver	Yes	Yes	ORA Last inspection (b) (4) VAI
(b) (4)	Waiver	Yes	Yes	ORA Last inspection (b) (4) VAI
(b) (4)	Not required	No	Yes	
(b) (4)	Not required	No	Yes	

Facility FEI# Responsibilities	Inspection? Waiver? Not Required?	Compliance Check Required?	RMS-BLA Entry Required ?	Comments
(b) (4)	Not required	No	Yes	
(b) (4)	Not required	No	Yes	
(b) (4)	Not required	No	Yes	
(b) (4)	Not required	No	Yes	

Facility FEI# Responsibilities	Inspection? Waiver? Not Required?	Compliance Check Required?	RMS-BLA Entry Required ?	Comments
(b) (4)	Not required	No	Yes	

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

^b (b) (4)

Pfizer Gene Therapy Manufacturing Facility

The Pfizer Gene Therapy (GTx) manufacturing facility (also referred to as (b) (4)) is located in a portion of Building (b) (4) and Building (b) (4), as an expansion of (b) (4). The GTx facility was designed as a flexible manufacturing space with multiple independent suites for different GTx products and processes.

Review Comments: The manufacture of the FidaVec (b) (4) DP PPQ lots was conducted in (b) (4). Review of the Pfizer facility and equipment was focused on the (b) (4) for this BLA submission.

Cross-Contamination Control

The Pfizer (b) (4) is a multi-product manufacturing area with individual processing areas for the production of (b) (4) drug product. The GTx facility uses several control strategies to prevent cross-contamination, including facility design features (e.g., segregation of different manufacturing areas and pressures differentials), a campaign-based manufacturing operations in each of suites in (b) (4) the use of single-use product contact equipment parts (except (b) (4) see section 3.2.S), and procedural controls (e.g., labeling and change-over procedures).

Pfizer performed risk assessments to evaluate the controls in place to mitigate product cross-contamination events during multiproduct operations in the Building (b) (4). Pfizer stated that the risk assessment did not identify any major risks.

Heating, Ventilation and Air Conditioning (HVAC) Systems

(b) (4) suites and the existing support areas (e.g., warehouse, raw material sampling suite, central dispensing area (CDA) in (b) (4), QC laboratories and (b) (4) in Building (b) (4) were designed and constructed for concurrent multi-product manufacture of clinical and commercial (b) (4).

(b) (4) HVAC system uses dedicated air handling units (AHU, Table 14) to provide HEPA-filtered clean air for each defined area/suite, and to maintain appropriate pressure differentials (PD).

PD specifications include:

- (b) (4)

HVAC (b) (4) :

- (b) (4)

(b) (4)

Review Comments: The HVAC action levels appeared acceptable. The HVAC Pressurization Plan (Drawing Number T4-101-HP3-1001) showed cleanroom pressures

and air flows and indicated that the PDs between cleanroom areas of the same or different classifications appear acceptable, and that all airlocks (AL) in the table below including separated and dedicated material airlocks (MAL) and personnel airlock (PAL) are (b) (4) with air pressure positive to the adjacent areas.

Table 14. Summary of HVAC and AHU in (b) (4)

(b) (4)


Utilities

The clean utilities (including WFI, clean steam, and compressed gases) for the (b) (4) GTx manufacturing suites are supplied by the validated existing utility infrastructure within Building (b) (4)

WFI

(b) (4)


(b) (4)

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Review Comments: The GTX (b) (4) WFI system and WFI monitoring program appeared acceptable. No objectionable issues were noted.

Clean Steam System

(b) (4)

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Review Comments: The existing clean steam generation and distribution systems appeared acceptable to provide dry, saturated, clean steam at the POU's within the (b) (4) suites. No objectionable issues were noted.

Gases

The existing qualified gas systems in Pfizer Sanford site provide services to (b) (4) suites, including:

- (b) (4)

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[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

(b) (4)

Review Comments: The compressed gas systems, (b) (4), appeared to be operated in a validated state and are maintained and monitored to verify compliance with the abovementioned quality parameters. During the PLI, Pfizer stated that that (b) (4) were used in all process (b) (4), and that controls (e.g., (b) (4) are in place to ensure (b) (4) operate as intended per SOP-124045: "Sanford Site Microbiological contamination control strategy Procedure". No objectional issues were noted.

Flows

Pfizer provided diagrams for personnel flow, (b) (4), materials flow, products flow, and waste flow.

(b) (4)

(b) (4)

Review Comments: *The ~~flow diagrams depicted~~ Separated and dedicated production areas, flows, cleanroom classifications, and air pressures appear appropriate in terms of providing physical and/or temporal segregation for preventing cross-contamination and containment control. No objectionable issues were noted.*

Facility Product Changeover

After a product manufacturing campaign, product changeover (PCO) process is executed by performing various cleaning activities and procedural controls per the Pfizer Sanford site current procedures (or current Standard Operating Procedures, SOP), including:

- (b) (4)

Review Comments: *The changeover procedure appears acceptable. The following procedures were reviewed during the PLI of the Pfizer Sanford GTx facility and no objectionable issues were noted:*

- SOP-31504: Manufacturing Changeover and Shutdown Procedure
- SOP-104640: GTx Cleaning and Sanitization of GMP Areas
- SOP-104959: EM Program for (b) (4) Gene Therapy in Sanford, NC.

Environmental Qualification (EQ) and Monitoring (EM)

All areas within (b) (4) Building (b) (4) used for manufacturing are classified based on the activities that occur within the area and the required level of containment and environmental control. The environmental qualifications involved sampling over extended periods of time under conditions of at rest and in operation. Pfizer has a facility EQ and EM programs in place to sample (b) (4)

per Pfizer Sanford site SOP.

The following routine monitoring frequencies were selected: (b) (4) areas are monitored not less than (b) (4) and (b) (4) areas are monitored not less than (b) (4).

The following non-viable and viable monitoring types are performed:

- (b) (4)

The routine EM program detects any changes in microbiological conditions and provides documented evidence to evaluate the effectiveness of the cleaning and sanitization program.

Personnel performing open operations and critical task operations in biosafety cabinet areas are monitored.

The EM sampling plan, testing and specifications are defined in SOP-104959, *Environmental Monitoring Program for (b) (4) Building (b) (4) and Building (b) (4) Gene Therapy in Sanford, NC.*

Review Comments: The EM sampling and specifications summarized in SOP-104959 appeared acceptable. No objectionable issues were noted.

Equipment Cleaning and Cleaning Validation

During the FidaVec (b) (4) manufacturing process (see Table 2), the product-contact equipment are (b) (4), except the following product-dedicated equipment can be cleaned for the manufacture of the next (b) (4):


- (b) (4)

The reusable product contact equipment and systems are (b) (4) using (b) (4) cleaning processes, including the following cleaning steps:

- (b) (4)

Review Comments: No reusable equipment is used during the DP manufacturing process.





(b) (4)



Equipment Sterilization and Decontamination

(b) (4) Decontamination

In Section 3.2.A.1 *Facilities and Equipment – Pfizer [Sanford, NC], Sterilization and Decontamination of Containers, Closures, and Equipment* (b) (4) Building (b) (4), Pfizer stated the following:

- (b) (4)
- 
- 
- 
- 

(b) (4)

Process Equipment and Computer Systems

Process Equipment

In Table 3.2.A.1-1 of Section 3.2.A.1. *Facilities and Equipment – Pfizer [Sanford, NC], Process Equipment* of STN 125786/0, Pfizer listed process equipment which are used for the manufacture of FidaVec (b) (4), including:

- (b) (4)

The major process equipment for the manufacture of FidaVec DP include:

- (b) (4)

Review Comments: During the DP manufacturing process, all product contact equipment is (b) (4). The satisfactory testing results of both PPQ lots and (b) (4) lots (reviewed above) appeared to indicate that process equipment were in valid status. The installation and operational qualification (IOQ) documents were reviewed for major manufacturing equipment during the PLI of Pfizer Sanford facility. No objectional issues were noted.

Computer System

Review Comments: The computerized systems (b) (4)

were reviewed during the PLI of Pfizer Sanford facility. The CBER inspectors noted no objectionable findings.

Overall Reviewer's Assessment of Section 3.2.A.1:

- ☐ Information provided in this section appeared acceptable.

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

DMPQ defers to OTP reviewers to review this section.

Combination Products

This is not a combination product.

Comparability Protocols

There is no comparability protocol under the DMPQ purview.