CBER DMPQ CMC/Facility BLA Review Memorandum

BLA STN 125769/0

ABRYSVO [Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine (RSVpreF)]

Hector Carrero, Consumer Safety Officer, OCBQ/DMPQ/MRBII
Zainab Mansaray-Storms, Consumer Safety Officer, OCBQ/DMPQ/MRBII

1. BLA#: STN 125769/0

2. APPLICANT NAME AND LICENSE NUMBER
Pfizer, Inc., Lic #2001

3. PRODUCT NAME/PRODUCT TYPE
ABRYSVO, Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine (RSVpreF)

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

a. Pharmacological category
Vaccine

b. Dosage form
Lyophilized powder

c. Strength/Potency
120 µg/vial

d. Route of Administration
Intramuscular

e. Indication (s)
Prevention of (b) (4) lower respiratory tract disease caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older

5. MAJOR MILESTONES
Submission Received: 9/30/2022
First Committee Meeting: 10/21/2022
Filing Meeting: 11/14/2022
Mid-cycle meeting: 01/13/2023
Late-cycle meeting 03/23/2023
Action due date: 03/31/2023

6. DMPQ CMC/FACILITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Hector Carrero, CSO, OCBQ/DMPQ/MRBII	Drug Product and Diluent, Facilities and Equipment (b) (4) (Sections 3.2.P, 3.2.R and 3.2.A.1)
Zainab Mansaray-Storms, CSO, OCBQ/DMPQ/MRBII	Drug Substance, Facilities and Equipment (b) (4) (Sections 3.2.S, 3.2.R and 3.2.A.1)

7. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
09/30/2022	STN 125769/0	Original submission

Date Received	Submission	Comments/ Status
11/23/2022 02/27/2023	STN 125769/0/2; STN 125769/0/39 (Response to 11/18/2022 information request (IR)	(b) (4) facilities inspectional readiness
01/31/2023	STN 125769/0/22	An update with additional DS storage facility
02/10/2023	STN 125769/0/25 (Response to 1/27/2023 IR)	Regarding (b) (4) QSRs for the formulation/holding vessels, and QS for the vial washer
04/26/2023	STN 125769/0/56 (Response to 4/19/2023 IR)	Regarding cleaning validation, terminal sterilization mapping, shipping validation, qualification summary reports

8. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

CBER received this electronic submission on September 30, 2022. Pfizer Inc. submitted this BLA to provide information to support US market authorization of lyophilized Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine ([ABRYSVO], (also referred to as RSVpreF Vaccine) supplied with sterile water diluent. ABRYSVO is presented in single-dose vials containing 120 µg of lyophilized product per vial, and the sterile water diluent is supplied in a pre-filled syringe. The manufacturing of RSVpreF vaccine drug substance (b) (4) (b) (4) is performed at (b) (4) manufacturing of drug product (formulation, filling, lyophilization and inspection) and manufacturing of diluent (filling and terminal sterilization) is performed at Pfizer Manufacturing in (b) (4) The drug substance is shipped to Pfizer (b) (4) (b) (4) from (b) (4) Vial labeling and secondary packaging can also be performed at Pfizer (b) (4) in addition to Pfizer (b) (4)

To support this BLA, the firm provided manufacturing process description and process validation information including descriptions of aseptic process simulations, facility information, equipment qualifications, cleaning validation, sterilization validations, lyophilization studies, computer systems, container closure systems and container closure integrity, stability studies, and shipping validations. An inspection waiver recommendation for this BLA submission's drug substance, drug product and diluent manufacturing sites was dated January 05, 2023.

This review memo covers the facility and equipment, and manufacturing process of RSVpreF Vaccine drug substance (b) (4) performed

at (b) (4) in (b) (4) manufacturing process of drug product (formulation, filling, lyophilization and inspection) performed at Pfizer (b) (4) in (b) (4) and manufacturing of diluent performed at Pfizer (b) (4) in (b) (4) . We reviewed applicable information provided under STN 125769/0 and amendments 125769/0/2, 125769/0/22, 125769/0/25, 125769/0/39, 125769/0/56.

B. RECOMMENDATION

I. APPROVAL

Approval is recommended with the following inspectional recommendation. CBER understands that the recommendation may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

- (b) (5)

Below is a listing of the drug substance (DS) and drug product (DP) facilities to be named in the approval letter:

(b) (4)

Pfizer (b) (4)

Pfizer (b) (4)

(b) (4)

Below is a list of approvable comparability protocols (CP):

- COMPARABILITY PROTOCOL FOR REPROCESSING OF (b) (4) (b) (4)
- COMPARABILITY PROTOCOL FOR (b) (4) USE VALIDATION
- INTRODUCTION OF ALTERNATE FILTERS AT PFIZER (b) (4)

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Hector Carrero, Consumer Safety Officer, OCBQ/DMPQ/MRBII	Concur	
Zainab Mansaray-Storms, Consumer Safety Officer, OCBQ/DMPQ/MRBII	Concur	
Anthony Lorenzo, Branch Chief, OCBQ/DMPQ/MRBII	Concur	
N. Trudel for Carolyn Renshaw, Division Director, OCBQ/DMPQ	Concur	

Table of Contents

Module 3

3.2.S DRUG SUBSTANCE

(b) (4)

15 pages have been determined to be not releasable: (b)(4)

(b) (4)

3.2.P DRUG PRODUCT (RSVPreF)

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

The drug product (DP) is a sterile lyophilized powder that consists of equal amounts of two stabilized drug substance antigens, (b) (4) The lyophilized drug product is presented in a 2 mL clear glass vial sealed with a stopper and an aluminum overseal with flip-off plastic cap.

The drug product presentation has a target strength of 120 µg/vial; it is designed to deliver a 60-µg dose of each prefusion protein, equivalent to a 120-µg dose of total protein in a 0.5 mL injection.

The lyophilized DP is reconstituted prior to use, in the vial with a prefilled syringe containing sterile water diluent (reviewed in 3.2.P Drug Product Diluent in this memo) using a vial adapter, and the entire content is withdrawn to enable a dose of 0.5 mL for intramuscular administration.

3.2.P.2.5 Microbiological Attributes

Microbiological attributes are provided in Section 3.2.P.7 Container Closure System of this review memo.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The following facilities are associated with the manufacture of drug product:

Site	FEI/DUNS Number	Responsibility
Pfizer (b) (4)	(b) (4)	Bulk drug product formulation Fill and finish PFS Diluent terminal sterilization Primary packaging Secondary packaging Testing (sterility, endotoxin, moisture)
Pfizer (b) (4)	(b) (4)	DP release and stability testing

Site	FEI/DUNS Number	Responsibility
(b) (4)	(b) (4)	Primary packaging Secondary packaging

3.2.P.3.3 Description of Manufacturing Process

Manufacturing of RSVpreF drug product performed at Pfizer (b) (4) is described briefly as follows:

The manufacturing of RSVpreF Vaccine drug product includes the following steps:

(b) (4)

(b) (4)

3.2.P.3.4 Controls of Critical Steps and Intermediates

See following section 3.2.P.3.5 Process Validation and/or Evaluation for in-process controls.

3.2.P.3.5 Process Validation and/or Evaluation

(b) (4)

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

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)

Pfizer lists 22 quality attributes as specifications for RSVpreF DP tested at release and throughout shelf life. DP endotoxin and sterility methods are (b) (4) validated, and specification is set at (b) (4) and "no growth detected" respectively. These tests are performed at release and at the end of shelf life.

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

Sterility testing is performed at release and end of shelf life, and container closure integrity testing by (b) (4) is performed (b) (4) during stability testing to demonstrate the integrity of the container closure over product shelf life. The review of CCIT can be found in section 3.2.P.7.

3.2.P.5.4 Batch Analyses

A total of (b) (4) batches of RSVpreF DP were manufactured at Pfizer (b) (4) including (b) (4) lots to support PPQ and (b) (4) confirmatory lot. All of the PPQ batches were tested against 22 quality attributes, including, those tests under DMPQ purview with acceptance criteria defined the same as in 3.2.P.5.1 Specifications and met acceptance criteria.

> ***Reviewer's comment:*** *Pfizer reports no out-of-specification (OOS) results for bacterial endotoxin or sterility at release for any of the PPQ batches. The acceptance criteria for the quality attributes under DMPQ purview did not change from the reported commercial acceptance criteria. This information appears acceptable.*

3.2.P.7 Container Closure System

The container closure system for the drug product includes the drug vial, vial adapter and pre-filled diluent syringe, all packaged together. The drug product is filled into 2mL (b) (4) Type (b) (4) glass vial with 13mm chlorobutyl rubber lyophilization stopper, aluminum seal, and plastic snap-off cap. The vial adapter is a sterile, plastic disposable device in a blister package (Class II medical device, 510(K) number (b) (4)
Minimum volume of injection is 0.5mL.

For the RSVpreF Vaccine product, Pfizer stated that they followed the streamlined approach for combination products as described in 21 CFR 4.4(b)(1). The approach was based on compliance to the drug CGMP regulation and the selected provisions of the device Quality System Regulation (QSR) regulation 21 CFR 820. The drug delivery system was designed in accordance with 21 CFR 820.30.
The container closure system parts for the drug product are listed below:

Component	Description	Reference to monograph	Manufacturer
Vial 2 ml	Colorless glass with a high hydrolytic resistance	(b) (4)	
Lyophilization Stopper 13 mm Grey	Chlorobutyl rubber, coated; (b) (4)		
Vial Seal	13 mm aluminum vial seal with tamper-evident polypropylene flip off cap		
Vial Adapter	13 mm Sterile, plastic fluid transfer device, in a blister package		

Preparation of the container closure

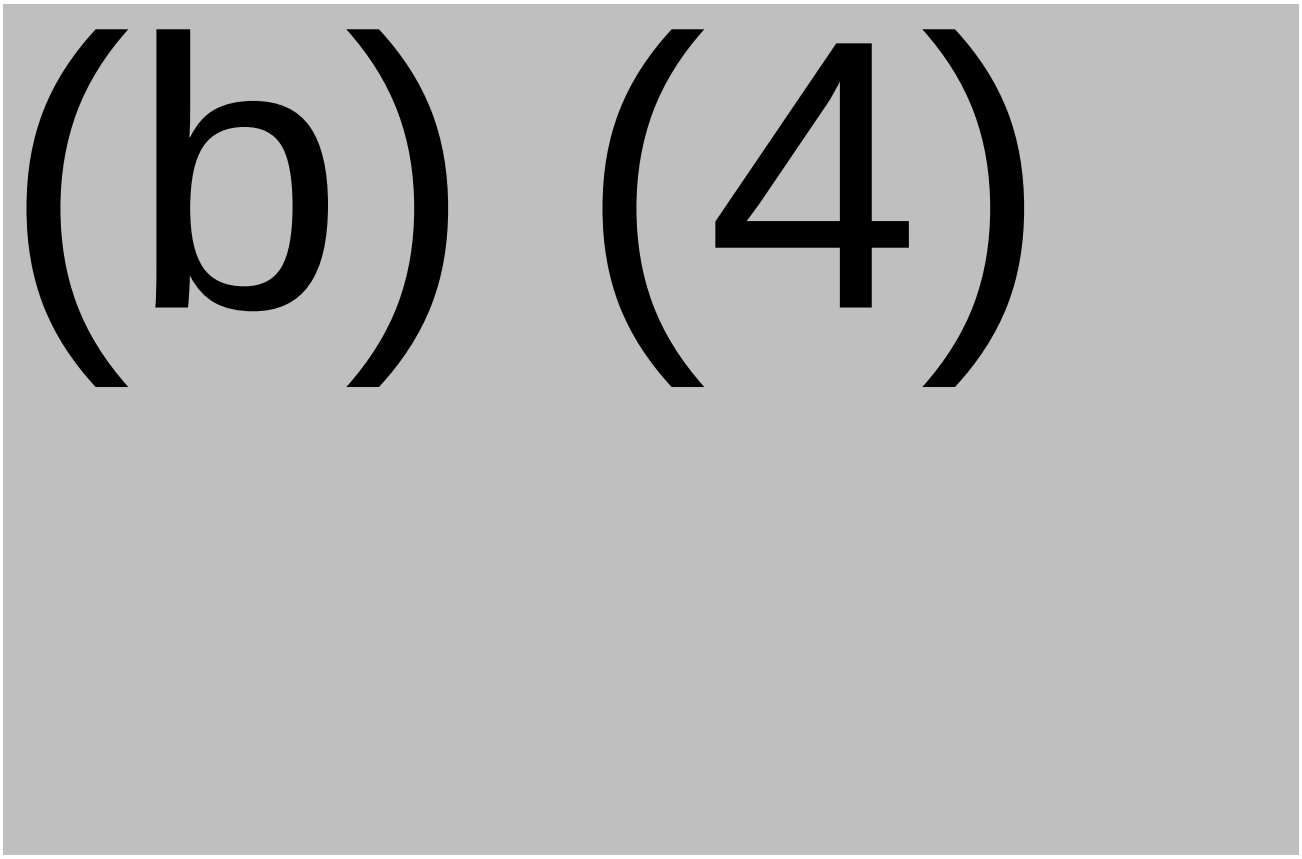
Vials are cleaned by (b) (4) Afterwards the vials are (b) (4) (b) (4) Rubber stoppers are sterilized by (b) (4) prior to filling. All cleaning and sterilization processes mentioned are validated.

Container Closure Integrity Testing

Pfizer provided the CCIT of RSV DP vials method qualification and verification which included both (b) (4) Pfizer indicates CCIT by (b) (4) (b) (4) method will be performed for stability studies.

The report provides for the detection of container defects of (b) (4) and the establishment of (b) (4) detection limit. Method defect qualification was carried out by performing (b) (4) separate assay runs on RSV Drug Product vials. All system suitability and assay acceptance criteria were met for the (b) (4) runs. No (b) (4)

was observed in any of the test vials; for the (b) (4) defect, a minimum of (b) (4) vials must be positive for (b) (4) (the (b) (4) defect qualification run is for information purposes only).



3.2.P.8 Stability

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

Evaluation of the acceptability of the stability data and the overall plan is deferred to the assigned OVRR reviewer. Pfizer committed to submit CCIT, sterility and endotoxin long-term stability data annually through the end of shelf life for (b) (4) batch to support drug product shelf life. Data provided for stability for these quality attributes under DMPQ purview meet the established commercial stability specification described in section 3.2.P.5.1 above.

3.2.P DRUG PRODUCT (DILUENT)

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

The sterile water diluent, presented in a 1-mL glass prefilled syringe (PFS) is single use, and is manufactured at the Pfizer (b) (4) facility. The facility is designed as multi-product manufacturing facilities, which is approved and regularly inspected for compliance to CGMPs by FDA. The water diluent (b) (4) filling volume) is used for reconstitution

of the lyophilized RSVpreF Vaccine drug product before intramuscular administration. The composition of the diluent solution is water for injection (WFI) and complies with (b) (4) (b) (4) is filled into clean and sterilized syringes on the Disposable Syringe (b) (4)

The RSVpreF vaccine is provided in a kit comprising the lyophilized drug product (DP) in a 2 mL glass vial; a terminally sterilized 1 mL standard glass PFS containing sterile water diluent for reconstitution; and a 13 mm vial adapter. The vial adapter is an individually packaged, sterile, commercially available medical device purchased from (b) (4) The kit is defined as a co-packaged (biologic/device) combination product. All components of the diluent PFS are commercially available. Pfizer provided drug master file (DMF) references for each sterile water diluent contact component.

3.2.P.2.5 Microbiological Attributes

Refer to container closer section 3.2.P.7 below.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The following Facilities are associated with the manufacture of RSVpreF Vaccine diluent:

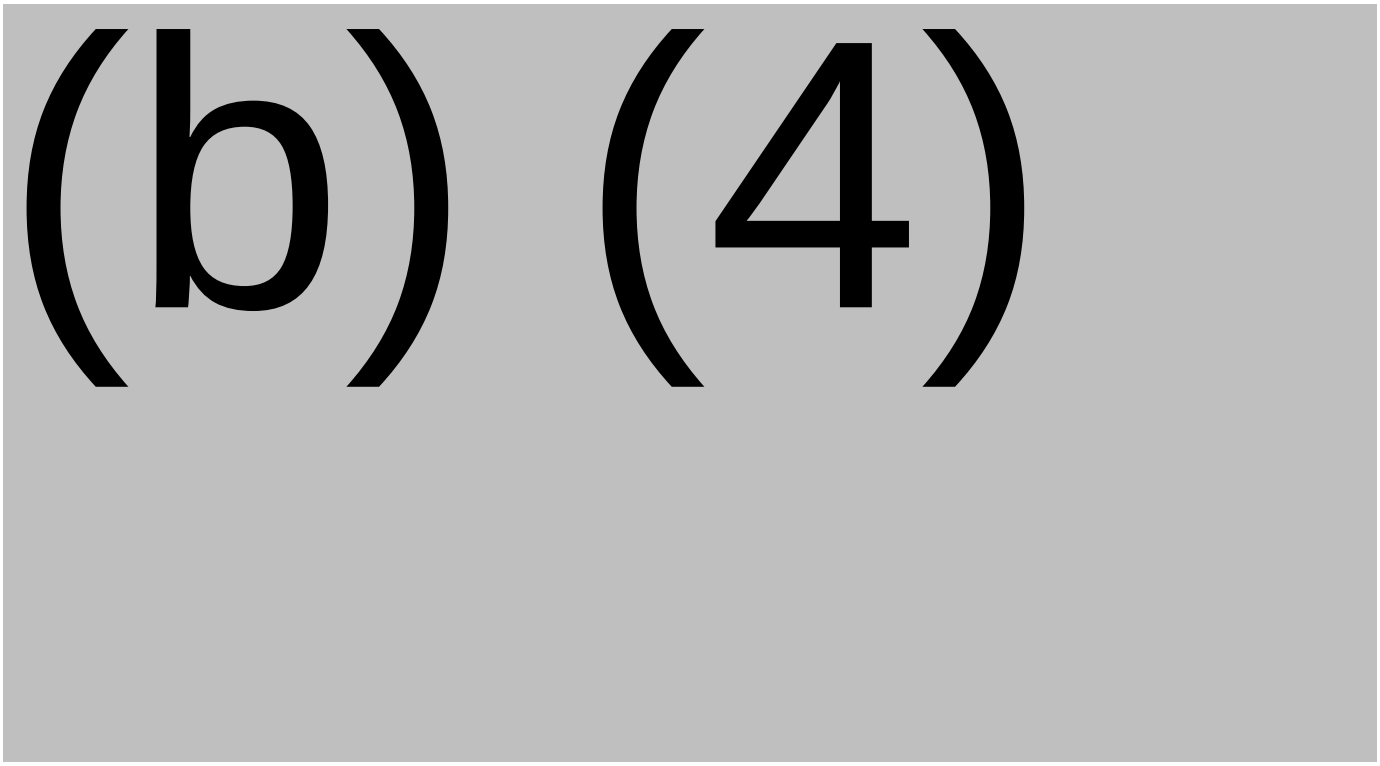
Name/Address	FEI number	Responsibility
Pfizer (b) (4)	(b) (4)	• Manufacture of the Diluent (formulation and filling) • Testing of in-process samples • Quality Control testing of finished product including release testing (microbiological test and stability samples) • Visual inspection of diluent • Packaging

3.2.P.3.3 Description of Manufacturing Process

Pfizer (b) (4) performs the manufacturing process described below for the RSVpreF diluent.

(b) (4)

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



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)
For quality attributes under DMPQ purview (endotoxin, sterility, and CCI), the specifications for the RSVpreF diluent are the same for the RSVpreF DP that is described in section 3.2.P.5 (RSVpreF) above.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures
The CCIT method validation is described in section 3.2.P.7 for RSVPreF drug product.

3.2.P.5.4 Batch Analyses
All (b) (4) diluent PV lots met the following release criteria:

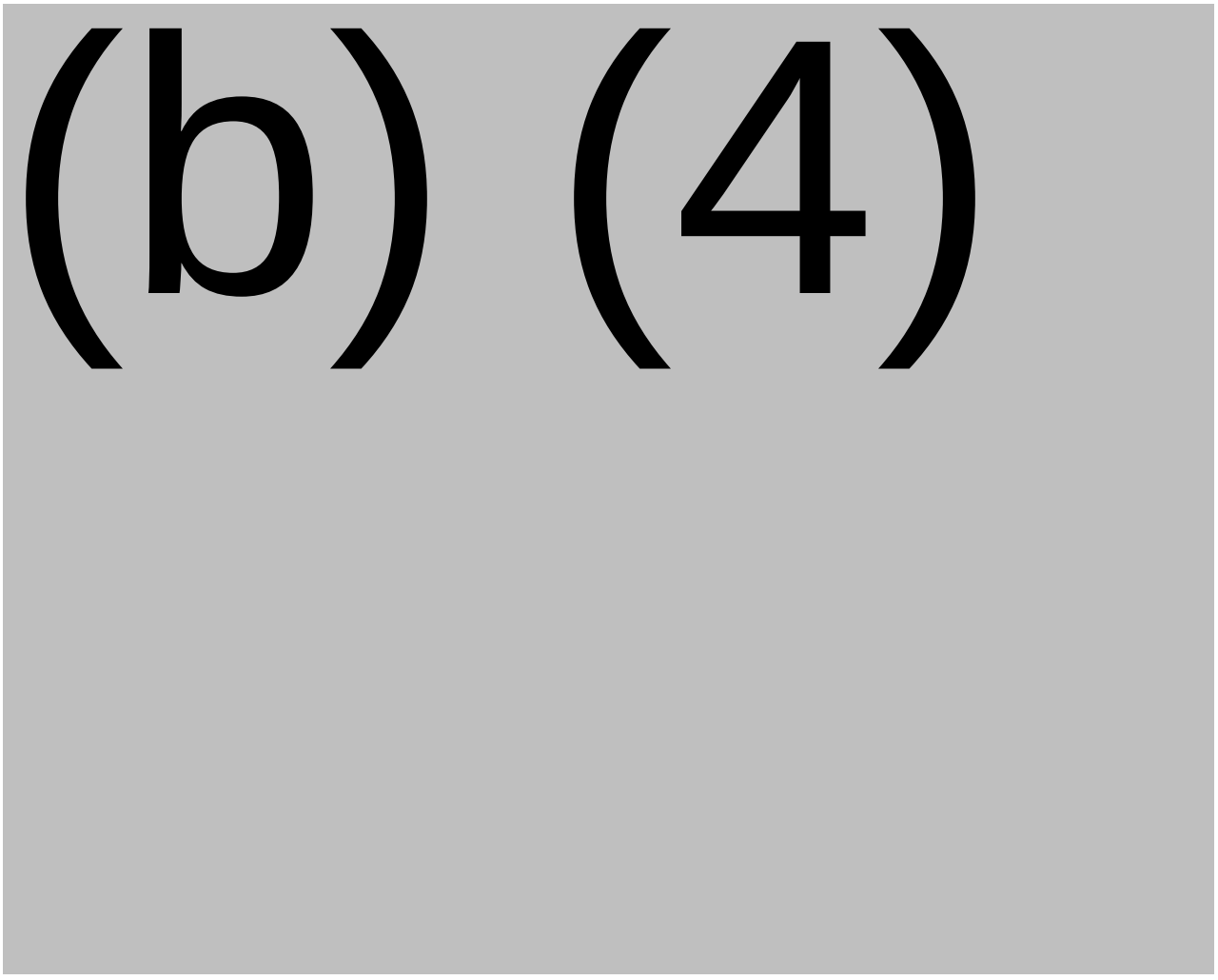
- Appearance: Clear, colorless, essentially free of visible particles
- Extractable volume: (b) (4)
- Endotoxin: (b) (4)
- Sterility: No growth detected

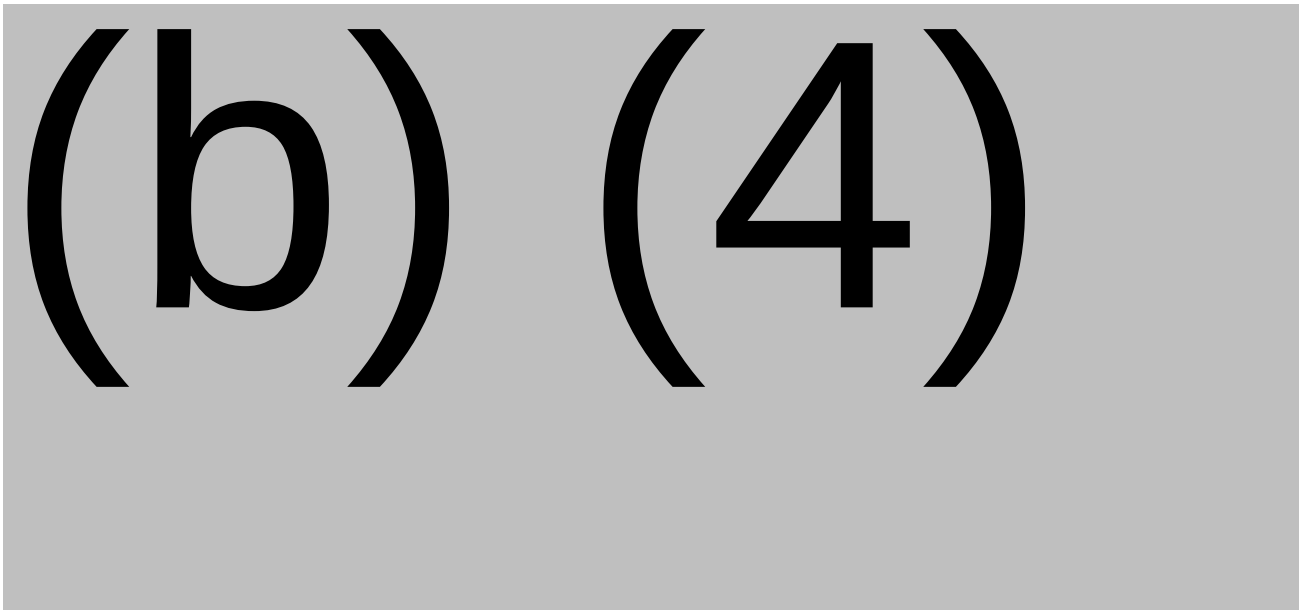
Additionally, PFS from the (b) (4) PV lots met expanded release testing for (b) (4) (b) (4)

3.2.P.7 Container Closure System
The container closure system for the sterile water diluent consists of a 1 mL type (b) (4) glass syringe barrel (b) (4) with rigid cap, a bromobutyl rubber tip cap

(b) (4) a 1-3 mL polypropylene plunger rod, and chlorobutyl rubber plunger stopper (b) (4) The sterilization of syringes is performed with (b) (4) according to (b) (4) (b) (4) The syringes are received ready-to-use, washed, siliconized, and sterilized in tubs. Sterilization of the plunger stopper is performed by (b) (4) according to (b) (4) The plunger stoppers are received washed, siliconized, sterilized, and ready to use. The RSVpreF vaccine combination product consists of a lyophilized DP vial for reconstitution, a fully assembled diluent prefilled syringe (PFS), and a 13 mm vial adapter in a secondary package. The drug product kit is regulated as a combination product in accordance with 21 CFR 3.2(e). Pfizer adhered to current Good Manufacturing Practices (cGMP) for combination products, 21 CFR Part 4.4(b), subpart A. A streamlined approach was used integrating the specific device Quality System Regulation (QSR) provisions.

The qualification of the container closure system was performed by (b) (4) container closure integrity testing and (b) (4) container closure testing. Testing was performed on both syringe/plunger stopper combinations.





3.2.P.8 Stability

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

Pfizer provided stability data for (b) (4) process validation lots of sterile water diluent on ongoing stability studies. Data provided for the quality attributes under DMPQ purview meet the established commercial stability specification.

3.2.A APPENDICES

The following table includes a full listing of all facilities associated with the BLA submission.

Facility Manufacturing/ Testing activities	**Inspection? Waiver? Not required?**	**Compliance check required for approval?**	**RMS-BLA entry required?**	**CMO**	**Comments**
(b) (4)	Waiver	Yes	Yes	No	DMPQ VAI, (b) (4)
(b) (4) DP Manufacturing (fill/finish, PFS diluent terminal sterilization), DP testing, Primary and secondary packaging	Waiver	Yes	Yes	No	DMPQ NAI (b) (4)
(b) (4) Primary and Secondary Packaging (co-package combination product)	Waiver	Yes	Yes	No	DMPQ NAI (b) (4)

Facility Manufacturing/ Testing activities	**Inspection? Waiver? Not required?**	**Compliance check required for approval?**	**RMS-BLA entry required?**	**CMO**	**Comments**
(b) (4)	Waiver	Yes	Yes	No	ORA NAI (b) (4) CBER
(b) (4)	Not required	No	Yes	Yes	
(b) (4)	Not required	No	Yes	No	
(b) (4)	Not required	No	Yes	Yes	

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	CMO	Comments
(b) (4)	Not required	No	Yes	Yes	
(b) (4)	Not required	No	Yes	Yes	
(b) (4)	Not required	No	No	Yes	

(b) (4)

32 pages have been determined to be not releasable: (b)(4)