

CBER CMC BLA Review Memorandum

BLA STN 125768

**Respiratory Syncytial Virus Vaccine
ABRYSV0**

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Ewan Plant, DVP, OVR, CBER
Eric Peng, DBPAP, OVR, CBER**

1. **BLA#:** STN 125768

2. **APPLICANT:** Pfizer Inc. **U.S. LICENSE NUMBER:** 2001

3. **NON-PROPRIETARY NAME:** Respiratory Syncytial Virus Vaccine
PROPRIETARY NAME: ABRYSV0

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

- a. **Pharmacological category:** Biologic-device combination
- b. **Dosage Form:** The vaccine is supplied as a sterile, white, preservative-free, lyophilized powder in a single-dose 2mL vial that is reconstituted with sterile water (diluent) provided in a 1mL prefilled syringe using a vial adapter.
- c. **Strength:** A single dose to be administered after reconstitution is 0.5 mL. 120 micrograms (mcg) of stabilized prefusion F protein (60 mcg (b) (4) and 60 mcg (b) (4))
- d. **Route of administration:** Intramuscular injection
- e. **Indication:** For the prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age by active immunization of pregnant individuals

5. **MAJOR MILESTONES**

Application received:	21-Dec-2022
Filing Action:	16-Feb-2023
Midcycle Meeting:	11-Apr-2023
Midcycle communication:	19-Apr-2023
VRBPAC	18-May-2023
Late cycle Meeting:	23-Jun-2023
Action due date:	21-Aug-2023

6. **CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Christian Sauder, OVRD/DVP	Module 1: 1.4.1 (Letter of Authorization), 1.4.2. (Statement of Right of Reference); 1.14 (Labeling) Module 3: Drug Substance, Drug Product, Appendices, Regional Information
Judy Beeler, OVRD/DVP	Module 4: 4.2.1.1. Primary Pharmacodynamics Module 5: 5.3.1.4. Reports of Bioanalytical and Analytical Methods for Human Studies: RSV assays

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Ewan Plant, OVRD/DVP	Module 5: 5.3.1.4. Reports of Bioanalytical and Analytical Methods for Human Studies Influenza Virus assays (Consult CMC reviewer)
Eric Peng, OVRD/DBPAP/LRSP	Module 5, section 5.3.1.4. DTP assays (Consult CMC reviewer)

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations
Andrea Gray/CBER	1mL prefilled glass syringe, vial adapter	YES

8. SUBMISSIONS REVIEWED

Date Received	Submission	Comments/ Status
11-Nov-2022	STN 125768/0	Original Submission-Part 1
21-Dec-2022	STN 125768/01	Original Submission-Part 2
31-Jan-2023	STN 125768/03	Draft carton and Container labels
17-Mar-2023	STN 125768/08	In response to IR #6 CMC DTP-6 assay (03 Mar 2023)
23-Jun-2023	STN 125768/30	In response to IR #26 CMC (06 Jun 2023)
28-Jun-2023	STN 125768/33	In response to IR #25 labeling (12 Jun 2023)
06-Jul-2023	STN 125768/35	In response to IR #30 CMC (28 Jun 2023)

9. REFERENCED REGULATORY SUBMISSIONS

Submission Type & #	Holder	Referenced Item	LoA	Comments / Status
DMF (b) (4)	(b) (4)	2 mL glass vial (borosilicate)	Yes	^e
DMF STN (b) (4)		Pharmaceutical Closure (Stopper) (Elastomeric Formulations, Coatings and Films) (b) (4)	Yes	^e
(b) (4)		Pharmaceutical closure (Stopper) (b) (4)	Yes	^e
(b) (4)		Pharmaceutical closure (Stopper), (b) (4)	Yes	^e
(b) (4)		(b) (4)	Yes ^c	^e
(b) (4)		Pharmaceutical closure (Stopper), (b) (4)	Yes ^c	^e
DMF STN (b) (4)		Piston ⁹ (Plunger) Elastomeric Formulations, Coatings and Films)	Yes	^e
DMF (b) (4)		VIAL (b) (4) 2mL (borosilicate)	Yes	^e
DMF (b) (4)		2mL (b) (4) vials (aluminosilicate glass)	Yes	^e
DMF (b) (4)		1mL (b) (4) Type (b) (4) borosilicate Glass Syringe with plastic rigid tip cap luer lock connection	Yes	^e
DMF STN (b) (4)	(b) (4)	Syringe tip cap elastomer (b) (4)	Yes	^e
DMF (b) (4)		1mL (b) (4) Type (b) (4) borosilicate glass syringe with (b) (4) cap Luer lock connection	Yes	^e
510(k) (b) (4)		Vial Adapter	N/A	Reviewed by Andrea Gray
510(k) (b) (4)		Vial Adapter	N/A	Reviewed by Andrea Gray
DMF (b) (4)	(b) (4)	Cell culture media (b) (4)	Yes	See 3.2.S.2.3. for review

(b) (4)

c = The letters of authorization for (b) (4) and (b) (4) were provided in BLA 125769 Amd 12 (January 10, 2023)

d = the Pfizer term "plunger stopper" and the supplier term "Piston (Plunger)" are considered synonymous (See BLA125769 Amd 26 (February 20, 2023))

e = No DMF review required, information pertinent to container closure is provided in the BLA; Device components (syringe, stopper, vial adapter) were reviewed by Andrea Gray (CBER). Please refer to her review memo.

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Abbreviations: CC= container closure, Inc. =Incorporated; RS= Ready to Sterilize. LoA= Letter of Authorization/ Letter of Cross-reference.

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

This BLA (STN 125768) is for a vaccine intended for the prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age by active immunization of pregnant individuals.

The proposed commercial name of the vaccine is ABRYSV0. The vaccine is also referred to as RSVpreF in this memo. The product in this BLA is the same as the product in the recently approved BLA 125769 for use of ABRYSV0 in adults; therefore, all CMC information in this BLA is the same as that in BLA 125769.

The vaccine is supplied as a vial of lyophilized recombinant RSV F glycoproteins from RSV subtypes A and B stabilized in the prefusion conformation (RSVpreF A and preF B). The lyophilized RSVpreF antigen is a sterile white powder that is reconstituted at the time of use with sterile water diluent supplied in a prefilled syringe using the vial adaptor supplied in the package. Each dose of ABRYSV0 is 0.5 mL. After reconstitution, the vaccine is formulated to contain 120 µg of RSV stabilized prefusion F proteins (60 µg RSVpreF A and 60 µg of RSVpreF B antigen per 0.5 mL). Each 0.5 mL of ABRYSV0 also contains 0.11 mg tromethamine, 1.04 mg tromethamine hydrochloride, 11.3 mg sucrose, 22.5 mg mannitol, 0.08 mg polysorbate 80, and 1.1 mg sodium chloride. After reconstitution, ABRYSV0 is a sterile, clear, and colorless solution. ABRYSV0 contains no preservatives. The vaccine is to be administered intramuscularly using the provided syringe. A needle is not provided in the package.

The date of manufacture for ABRYSV0 is defined as not later than the date when aseptic filling is initiated.


This review encompasses: (1) chemistry manufacturing and control (CMC), (2) clinical assays used for assessment of clinical study endpoints and (3) pre-clinical effectiveness studies. Please note that in Amendment 35, submitted on July 06, 2023, the sponsor confirmed that the quality information in Module 1, Module 2 section 2.3, and Module 3 submitted to BLA STN 125768 (Maternal) is identical to BLA STN 125769 (Older Adult). Therefore, this memo is the same as the memo for STN 125769; except for the information covering the assay used to measure Tdap immune responses in concomitant administration studies of Tdap and RSV vaccines.

Chemistry Manufacturing and Control (CMC)

The drug substance (DS) (also referred to as (b) (4) or bulk drug substance, BDS) manufacturing and release testing takes place in (b) (4). The Drug Product (DP) RSVpreF and the sterile water diluent manufacturing and primary packaging occurs at the Pfizer facility in (b) (4). DP release testing takes place at Pfizer facilities in (b) (4) (for Diluent and RSVpreF) and (b) (4) (for RSVpreF). DP secondary packaging operations are conducted at facilities located at (b) (4).

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

(b) (4)

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B. RECOMMENDATION

I. Approval

We recommend approval of this BLA.

The following results from ongoing studies will be reviewed in post-approval annual reports and inspections:

- Stability and leachables studies.
- Container closure integrity (b) (4) study for aluminosilicate vials.

The comparability protocols submitted for (b) (4) used in the manufacture of (b) (4), for reprocessing of (b) (4) and for alternate filters ((b) (4)) for DP processing were found acceptable and results from the validations will be provided in the annual report as they become available.

II. COMPLETE RESPONSE (CR)

Not Applicable

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Christian Sauder LPRVD, DVP, OVRR		
Judy Beeler LPRVD, DVP, OVRR		
Ewan Plant LPRVD, DVP, OVRR		
Eric Peng LRSP, DBPAP, OVRR		
Zhiping Ye Laboratory Chief LPRVD, DVP, OVRR		
Sara Gagneten DVP, OVRR		
Robin Levis Deputy Division Director, DVP, OVRR		
Jerry Weir Division Director DVP, OVRR		

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The following abbreviations are used throughout the document

aa	amino acid
(b) (4)	
Amd	Amendment
appr.	Approximately
AQL	Acceptable quality limit
ARD	Analytical Research and Development
AT	Ambient temperature (18-25 °C)
AVI	Automated Visual Inspection
BLEF	Break loose force and extrusion force
BDS	Bulk Drug Substance
BDP	Bulk Drug Product
CC	Container Closure
CCI	Container Closure integrity
CCS	Container Closure System
CD	Chemically defined
(b) (4)	
CFU	Colony Forming Unit
(b) (4)	
CHO	Chinese hamster ovary
(b) (4)	
CMA	Critical material attribute
CoA	Certificate of Analysis
CoC	Certificate of Conformance
CP	Comparability Protocol
CPD	Cumulative Population Doublings
CPE	Cytopathic effect
CPP	Critical Process Parameter
CQA	Critical quality attribute
CRM	Clinical reference material
CTM	Clinical trial material
D; d	Day(s)
DoE	multivariate Design of Experiments
DOM	Date of manufacture
DP	Drug Product
DS	Drug Substance
(b) (4)	
EOP	End of Production
(b) (4)	
(b) (4)	
FCC	Food Chemicals Codex
(b) (4)	
FMEA	Failure Modes and Effects Analysis
(b) (4)	
(b) (4)	
HA	hemagglutination
HAD	hemadsorption
HAP	Hamster antibody production
HCl	Hydrochloric Acid
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	
IPC	In process control
IPT-C	In-process test for control
IPT-M	In-process test for monitoring
(b) (4)	

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(b) (4)	
KH ₂ PO ₄	(Mono) Potassium phosphate
L	Liter(s)
(b) (4)	
(b) (4)	
LIVCA	Limit of in vitro cell age
LLOQ	Lower limit of quantitation
(b) (4)	
LoA	Letter of Authorization
LOD	Limit of Detection
LRV	log ₁₀ reduction value
MA	Material Attribute
(b) (4)	
MALS	Multi-angle light scattering
MAP	Mouse antibody production
MCB	Master cell bank
MFAT	Multi-factor at a time
(b) (4)	
m	month(s)
(b) (4)	
MVI	Manual Visual Inspection
(b) (4)	
NaCl	Sodium Chloride
NaOH	Sodium hydroxide
Na ₃ PO ₄	Sodium phosphate
NF	National Formulary
NMT	not more than
NOR	Normal operating range
NTU	nephelometric turbidity unit
(b) (4)	
OFAT	One factor at a time
PAR	Proven acceptable range
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
(b) (4)	
PE	Polyethylene
(b) (4)	
PFS	Prefilled syringe
PFU	Plaque forming unit
PGS	Pfizer Global Supply
(b) (4)	
PP	Process parameter
PPA	Process Performance Attributes
PPQ	Process Performance Qualification
PQ	Process Qualification
(b) (4)	
PV	Process Validation
QA	Quality attribute
qPCR	quantitative polymerase chain reaction
qrt-PCR	quantitative real-time PCR
QTPP	quality target product profile
RH	relative humidity
RM	Reference material
RP	Relative potency/prefusion
RPH	Relevant Process History
RT	Reverse Transcription
RVLP	Retrovirus-like particle
(b) (4)	
RWCB	Renewal Working cell bank
SCT	Safety Clearance threshold
(b) (4)	
(b) (4)	

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SME	subject matter expert
SWD	Sterile water diluent
TCV	Temperature Controlled Vehicle
Tdap Vaccine	Tetanus, Diphtheria, and Acellular Pertussis Vaccine
TDI	Total daily intake
(b) (4)	
TOR	Time out of refrigeration
TS	Test sample
(b) (4)	
ULD	Unit load Devices
(b) (4)	
UV	Ultraviolet
VOI	Volume of injection
VRF	Virus retaining Filtration
WCB	Working cell bank
WFI	Water for injection

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Manufacturers

Facilities and manufacturing sites involved in DS and DP manufacturing, storage and testing are shown in the table below.

Table 1. DS, DP, and primary packaging Manufacturers

Responsibility	Site(s)
DS	DS
	(b) (4)
DP RSVpreF	DP RSVpreF
DP Manufacture	
Primary Packaging	(b) (4)
Secondary Packaging	
Testing ^t	
Stability sample storage	
DP Diluent (Sterile Water)	DP Diluent (Sterile Water)
DP Manufacture	
DP testing	(b) (4)
Primary packaging	
Secondary Packaging	
Stability sample storage	
Glass Vials ^s	Glass Vials ^s
M. Borosilicate glass vials	(b) (4)
M. Aluminosilicate glass vials	
Aluminosilicate vial processing	
Vial Stopper^s	Vial Stopper^s
Manufacture	(b) (4)
Crimp seal ^t	Crimp seal ^t
Manufacture	(b) (4)
Glass Syringe^s	Glass Syringe^s
Manufacture	(b) (4)
Sterilization	
Manufacture	
Sterilization	
(b) (4) Syringe Tip Cap Assembly	(b) (4) Syringe Tip Cap Assembly
Tip Cap (b) (4) production ^s	(b) (4)
Luer Lock Adapter ^t	
Rigid Cap ^t	
(b) (4)	
Tip Cap (b) (4) production ^s	
Luer Lock Adapter ^t	
Rigid Cap ^t	
Syringe Plunger Stopper ^s	Syringe Plunger Stopper ^s
Manufacture ^t	(b) (4)
Processing ^t	
Sterilization	
Vial Adapter ^s	Vial Adapter ^s
Manufacture	(b) (4)
Plunger rod ^t	Plunger rod ^t
Manufacture	(b) (4)
Finger grip (Backstop) ^t	Finger grip (Backstop) ^t
Manufacture	(b) (4)

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(b) (4)

l = Vial stoppers and Tip Cap (b) (4) are made by (b) (4) ;
Crimp seals are made by (b) (4)
m = Note that DS is stored at the following (b) (4) locations of (b) (4)

(b) (4)

s = Component has direct DP contact; t = Component does not have direct DP contact
Abbreviations: (b) (4) ; M.= manufacture; Inc. = incorporated; Ass. = Assembly

Module 3





3.2.S Drug Substance-RSV (b) (4)

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

(b) (4)

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(b) (4)



3.2.P Drug Product- RSVpreF (= PF-06928316)

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

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

The target strength of the DP is 120 µg/vial; it is designed to deliver a 60 µg dose of each prefusion protein, equivalent to 120 µg dose of total protein in a 0.5 mL injection. The DP does not contain preservatives and is single use. Prior to use, the lyophilized DP is reconstituted in the vial using a prefilled syringe containing sterile water diluent (SWD) using a vial adapter. The DP is reconstituted with (b) (4) of SWD, and the entire content is withdrawn to enable a dose of 0.5 mL for IM administration (equivalent to a 120 µg dose of total protein in a 0.5 mL volume of injection). RSVpreF vaccine is a combination product consisting of a lyophilized DP vial, a fully assembled diluent (sterile

water) prefilled syringe, and a 13 mm vial adapter in a secondary package. The final composition of the reconstituted DP is shown in Table 25 below.

Table 25: Composition of reconstituted DP (prepared vaccine) and nominal dose

Ingredient	Grade/Quality Standard	Function	Composition of reconstituted DP (mg / vial) ^a	Nominal Amount of Dose (mg / dose) ^a
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)		(b) (4)
Tris-base ^b	(b) (4)	Buffer component		0.11
Tris-HCl ^c	In-house specification	Buffer component		1.04
Sucrose	(b) (4)	Cryoprotectant		11.3
Mannitol		Bu king agent		22.5
PS80		Surfactant		0.08
NaCl		Tonicifier		1.10
WFI		Solvent		q.s. to 0.5 mL

a = Each vial contains (b) (4) of solution after reconstitution with SWD and vial adapter which will then be withdrawn in the same prefilled syringe of SWD to enable a volume of injection of not less than 0.5 mL.

b = also known as Trometamol or Tromethamine

c = also known as Tromethamine HCl and Trometamol HCl. HCl (b) (4)

Abbreviations: q.s. = quantum satis (as much as is sufficient); PS80= Polysorbate 80

3.2.P.2 Pharmaceutical Development (RSVpreF)

3.2.P.2.1 Components of the Drug Product

Drug Substance

(b) (4)

Excipients

DP excipients, concentrations, and rationale for use are listed in Table 26 below:

(b) (4)

3.2.P.2.2 Drug Product

Formulation Development

The main objectives during formulation development were to find excipients and conditions to control two key stability indicating critical QAs: (b) (4) (as a measure of aggregation) and prefusion content (potency). (b) (4)

(b) (4)

(b) (4)

One page has been determined to be not releasable: (b)(4)

System volume: Studies were performed to support the target BDP fill volume established at (b) (4) mL to allow for a label claim volume of injection of 0.5 mL after reconstitution with diluent.

Overages: No overage is included in the DP.

Physicochemical and Biological Properties Physical solution properties of the (b) (4) (b) (4), lyophilized DP, and reconstituted DP were measured and used to support manufacturing development. The (b) (4) of the (b) (4) reconstituted DP was determined to be (b) (4) approximately (b) (4) at a protein concentration of (b) (4) at (b) (4); and approximately (b) (4), respectively. The (b) (4) formulation consists of (b) (4) Tris to obtain a target (b) (4). The (b) (4) for the (b) (4) lyophilized DP at the target moisture content was measured as (b) (4).

Reviewer's assessment: *I agree that the formulation development studies demonstrate that the lyophilized DP formulation stabilizes the active protein ingredients when the lyophilized DP is stored at 2-8°C after manufacture using the commercial process.*

3.2.P.2.3 Manufacturing Process Development

Quality attributes (QAs) This section describes the rationale for defining CQAs. QAs of DP were identified and assessed for criticality.

DP attributes included in the Control Strategy for release without further assessment for criticality included: Appearance (before reconstitution), residual moisture, reconstitution time, clarity, coloration, (b) (4), identity, protein concentration, uniformity of dosage units, (b) (4), endotoxin, sterility, container closure integrity. In addition, PS80 concentration is considered a QA due to its low risk to impact efficacy or safety (Please also refer to section 3.2.P.2.2.4). The following additional DP QAs were designated CQAs and are included in release testing:

- Relative preF content (potency): Directly linked to product efficacy
- (b) (4): They may potentially impact product efficacy.
- (b) (4) content.

(b) (4)

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

(b) (4)

3.2.P.2.4 Container Closure System

The CCS for the commercial lyophilized DP is described in section 3.2.P.7. The RSVpreF vaccine combination product consists of a lyophilized DP vial, a fully assembled diluent PFS, and a 13 mm vial adapter in a secondary package. The selection of the primary packaging materials for use with the lyophilized DP was made based on results of various physicochemical, biological and functional tests of the components that meet compendial requirements. Suitability of the primary packaging components was demonstrated based on the following considerations: Safety of materials of construction, protection, and performance.

Safety of Materials of Construction: The elastomeric stopper meets (b) (4) regarding biological tests (Biological reactivity tests) and (b) (4) requirements for chemical testing for elastomeric closures. The glass vials are manufactured with either borosilicate or aluminosilicate glass that meet the (b) (4) requirements for chemical testing for Type (b) (4) glass containers.

Extractables: Controlled extraction studies for product contact elastomeric closure materials present in the DP CCS were evaluated for the selection of potential leachable compounds. The extractable studies were performed at accelerated conditions using model solvents to generate extractable compounds and elements that may also migrate into the DP under labeled storage conditions. An initial controlled extraction study on the chlorobutyl rubber stopper material was used to generate a list of potential leachable compounds and elements. (b) (4)

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

(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)

The release and stability specification for DP is provided in Table 44 below. The tests performed for stability assessment are indicated. The same acceptance criteria are applied to both release and stability.

Table 44: Drug product specifications

Quality attribute	Analytical procedure	Acceptance criteria
Appearance (before reconstitution)	(b) (4)	(4)
Residual moisture		
Reconstitution time		
Clarity		
Coloration		
Visible particulates		
(b) (4)		
(b) (4)		
Protein concentration		
(b) (4) content		
(b) (4) content		
Uniformity of dosage units ^a		
PS80 concentration ^a		
Identity ^a		
Relative perfusion content (potency)		
(b) (4)		
(b) (4)		
(b) (4)		
Endotoxin ^c		
Sterility ^d		
Container closure integrity ^b		

CBER CMC BLA Review Memo BLA 125768 ABRYSSVO/Respiratory Syncytial Virus Vaccine

a = the test is not performed on stability samples

b = Test not performed at release; only performed (b) (4) on stability

c = Test performed at release and the end of shelf life. Release testing uses the (b) (4) method, and stability testing used the (b) (4) method (b) (4) sterility testing).

d = Test performed at release and the end of shelf life. (b) (4) sterility test, which is performed in accordance with the (b) (4) with the exception of incubation duration and detection method, may also be used.

Abbreviation: (b) (4)

EU= endotoxin units.

Reviewer's comment: In Query 9, IR#47 (BLA 125769, 07 Apr 2023), referring to module 3.2.P.5.4 Batch Analysis, the sponsor was asked to describe the sampling plan for routine quality release testing of the final DP container. In Amd 50 (BLA 125769, 17 Apr 2023) the sponsor responded that for PV and routine commercial DP release testing, samples for content uniformity and endotoxin are taken (b) (4) of the filling after capping of the vials. Furthermore, sterility samples are taken at regular intervals across the lot (b) (4). All other DP samples for routine quality testing are collected (b) (4) capping. Although the sponsor's response did not include information on the number of vials collected for the different release tests the response is acceptable. For DP release, the number of vials is generally dictated by the amount of sample needed for each test.

In Query 10, IR#47 (BLA 125769, 07 Apr 2023) with respect to module 3.2.P.3.1. Manufacturer(s), Table 3.2.P.3.1-1., the sponsor was asked to list the site(s) where quality release testing of the DP batches is carried out and which specific tests are performed at the respective sites. An updated table 3.2.P.3.1-1 was provided in Amd 50 (BLA 125769, 17 Apr 2023). The information provided is included in Table 1. The sponsor's response is acceptable.

Justification of Specifications:

(b) (4)

(b) (4)

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

Vial: Vials are made of Type (b) (4) borosilicate glass BG or aluminosilicate glass (AS). The vials consist of clear and colorless glass. The vial has a 2 mL nominal fill volume and 13 mm crown diameter. The vial meets (b) (4) test requirements in (b) (4) for glass containers. The vials are sterilized and (b) (4) (see section 3.2.P.3.3.). See Table 1 for manufacturing site information

Reviewer's comment: In Query 11, IR#26 (BLA 125769, 30 Jan 2023), the sponsor was informed that according to module 3.2.P.7. Container Closure System (RSVpreF), Table 3.2.P.7-2 (Vial Manufacturing Sites), (b) (4), are the (b) (4) manufacturing sites for the 2 mL Borosilicate glass vials. However, in addition to the LoA for (b) (4) vials manufactured in (b) (4) provided in module 1.4.1. (Letter of Authorization), a LoA for (b) (4) vials manufactured by (b) (4) was also provided ((b) (4)). In IR#26, the sponsor was asked to clarify all the manufacturing sites for (b) (4) borosilicate glass vials used in DP manufacture. The sponsor clarified in Amd 28 (BLA 125769, 13 Feb 2023), that the LoA for (b) (4) vials manufactured by (b) (4) was added incorrectly to Module 1.4.1. and that LoA (b) (4) was removed from Module 1.4.1. The manufacturing sites for borosilicate glass vials are correctly listed in Section 3.2.P.7., Table 3.2.P.7-2 ((b) (4)). The answer is acceptable.

Borosilicate and aluminosilicate vial dimensions are provided. (b) (4)

Quality control includes visual identification (performed per lot), check of critical dimensions of vials (on minimum (b) (4)). The manufacturer's certification is accepted per lot for test for Type (b) (4) Glass.

Vial Stopper: The vial stopper is a 13 mm synthetic chlorobutyl lyophilization stopper composed of (b) (4) elastomer. It has a fluoropolymer film (ethylene tetrafluoroethylene) coated on the product surface and on the non-product contact surface. The area of the stopper right under the flange and right at the top of the plug portion of the closure is covered with a cross linked silicone coating. The elastomer formulation meets (b) (4) requirements. See Table 1 for stopper manufacturers.

(b) (4)
Quality control includes visual identification, critical dimension check (on minimum (b) (4) (Manufacturer's certification is accepted per lot).

Crimp Seal: The crimp is a 13 mm flip-off design constructed of aluminum with a polypropylene tamper-evident flip-off cap that has no embossing. See Table 1 for manufacturing site. Quality control includes visual and physical inspections that are performed per lot.

Secondary Packaging components: RSVpreF vaccine combination product is packed in thermoformed blister packs and cardboard cartons with a package insert or instructions for use.

3.2.P.8 Stability

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

Stability information for DP stored under long-term condition of $5 \pm 3^\circ\text{C}$, accelerated condition of (b) (4), as well as (b) (4) conditions are provided. Long-term stability studies are ongoing with DP manufactured using the commercial process. (b) (4) DP lots have been enrolled in ongoing primary stability studies and (b) (4) DP lots are enrolled in supportive stability studies. Primary stability refers to the formal stability studies from which stability data are submitted for the purpose of establishing a shelf-life. Supportive stability refers to additional data relevant to product stability and shelf-life support. A summary of the DP lots used for primary and supportive stability studies is shown in Tables 50 and 51.

Table 50: Summary of DP primary stability studies

(b) (4)

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

(b) (4)

Shelf life and Conclusion:

The DOM is defined as not later than the date when aseptic filling is initiated. The expiry date is calculated (b) (4)

(b) (4). The stability data presented provide rationale and justification for the DP shelf-life claim of 18 months when stored at the recommended temperature of 2-8°C. The shelf-life claim is based on 18 months of stability data from a primary stability lot of DP as well as 15 months of stability data from (b) (4) primary lots of drug product stored at $5 \pm 3^\circ\text{C}$. Data accumulated from the (b) (4) supportive lots stored at $5 \pm 3^\circ\text{C}$ further demonstrate that QAs remain in conformance with the commercial stability acceptance criteria throughout the claimed shelf life. The accelerated condition supports temporary temperature excursions from the recommended storage condition. These data demonstrate that excursions above the recommended storage condition up to (b) (4) are allowable for up to 6 months. In addition, the data demonstrate that DP is stable through:

(b) (4)

Future shelf-life updates will be submitted as an annual report.

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

Post-approval, a minimum of (b) (4) lot of DP will be enrolled in the commercial stability program at the long-term storage condition of $5 \pm 3^\circ\text{C}$ each year that DP is

manufactured. The QAs to be tested are identical to those used for release testing as shown in Table 44, except for omission of tests for (b) (4), identity, PS80, and uniformity of dosage units. Acceptance criteria are identical to those used for release testing. (b) (4)

Reviewer's assessment -Stability: *The documentation provided by the sponsor is acceptable as submitted. The reviewer agrees with the sponsor's proposed DP shelf-life claim of 18 months when stored at the recommended temperature of 2-8°C.*

3.2.P Drug Product -Diluent

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


The sterile water diluent (abbreviated here as SWD) is designed to reconstitute lyophilized DP using a vial adapter to obtain the final RSVpreF vaccine. The diluent is supplied at (b) (4) target fill volume in a 1 mL glass syringe with Luer lock adapter, plunger (=stopper) and tip cap with cap cover. To ensure that a **volume of reconstitution of (b) (4)** can be achieved, there is an (b) (4). The entire content from the reconstituted DP vial delivered using the syringe is **≥ 0.50 mL**. After the lyophilized DP is reconstituted, at least 0.5 mL Volume of injection (VOI) is required for administration. The (b) (4) volume of diluent ensures the reconstituted vaccine meets the required volume of injection (VOI). A confirmatory study was conducted to show that at least 0.5 mL VOI can be delivered in a worst-case scenario where reconstitution is performed using a DP vial and diluent PFS filled at their respective lower reject limits (see below). The reject limit for SWD during syringe filling is set at (b) (4) and the QC release test of volume expelled from diluent PFS is (b) (4).

3.2.P.2. Pharmaceutical Development (Diluent)

(b) (4)

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

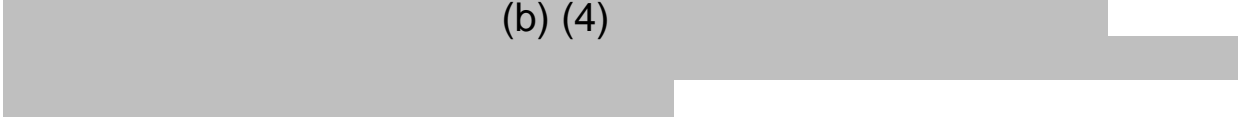
(b) (4)

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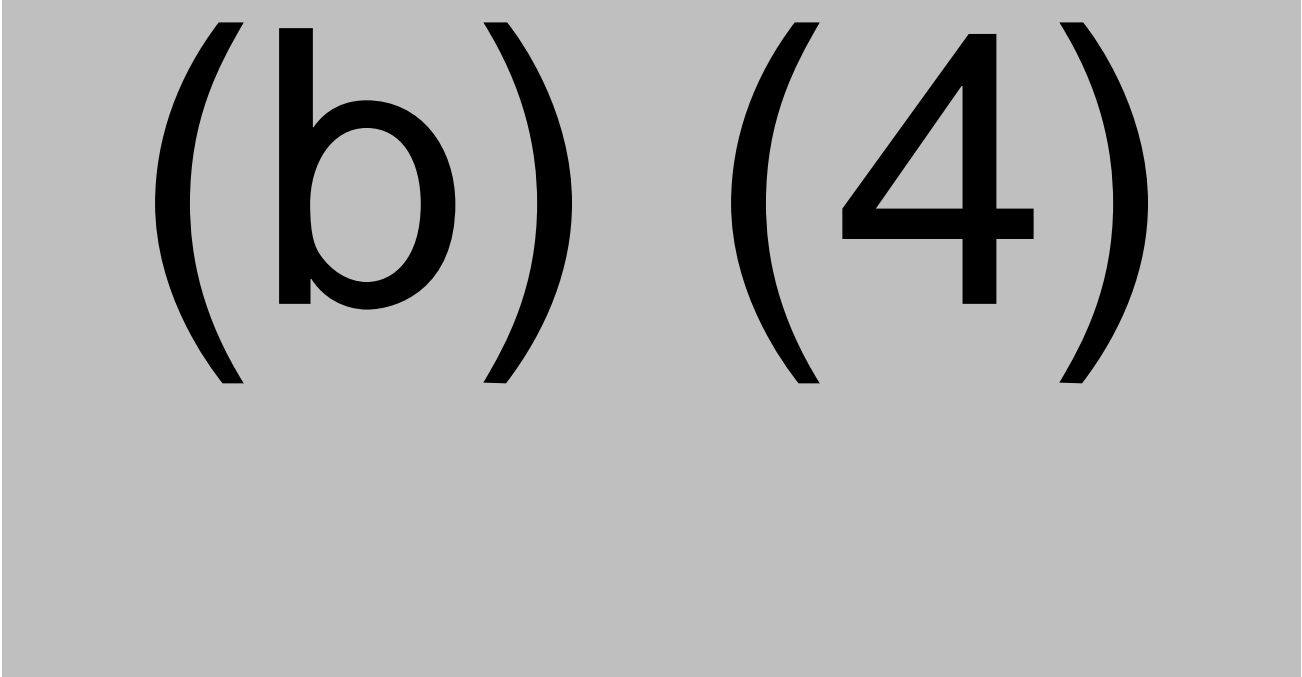
3.2.P.5. Control of Drug Product (Diluent)

3.2.P.5.1. Specifications

(b) (4)

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(b) (4)

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

(b) (4)

3.2.P.8. Stability Summary and Conclusion (Diluent)

Data from stability studies for SWD stored at (b) (4) long-term storage conditions, $5 \pm 3^{\circ}\text{C}$, (b) (4), as well as (b) (4) conditions are provided. Primary stability studies are ongoing with SWD manufactured using the commercial process. (b) (4) Phase 3 and (b) (4) PV lots of SWD are on primary stability. Primary stability refers to the formal stability studies from which stability data are submitted for the purpose of establishing a shelf life. A summary of the SWD lots used for primary stability studies is shown in Table 64. The syringes were placed in a (b) (4) for the duration of the study.

Analytical procedures used in the Stability Monitoring Program: The assessed stability attributes were (b) (4)

The methods are the same as those used for release testing, with the addition of CCI (Table 61). For the (b) (4) were analyzed. Testing for (b) (4) in injections included test for (b) (4)

(Acceptance criteria: Report results (particles / container)).

Protocol of testing under long-term storage conditions (b) (4): The stability protocols for SWD clinical and PV lots stored long-term at $5 \pm 3^{\circ}\text{C}$, (b) (4) (clinical lots only) and (b) (4), are provided and include annual measurements up to (b) (4) months, with shorter time intervals in the first 18 months ((b) (4)).

Protocol of testing at the accelerated condition: To study the effects of temporary excursions above the recommended temperature, (b) (4) primary lots of SWD were stored under the accelerated storage condition of (b) (4) .

(b) (4)

(b) (4)

Results of Stability Data

Data availability for each lot under stability is indicated in Table 64.

Summary of Stability Data at the Long-Term Storage Condition 1 and 2: Results from stability studies on SWD stored at the long-term conditions of $5 \pm 3^{\circ}\text{C}$ (b) (4), are provided for (b) (4) phase 3 clinical lots and (b) (4) PV lots. Data remain within the commercial stability acceptance criteria. Overall, the data generated to date at both conditions indicate that there have been no significant changes in terms of quality of the sterile water diluent.

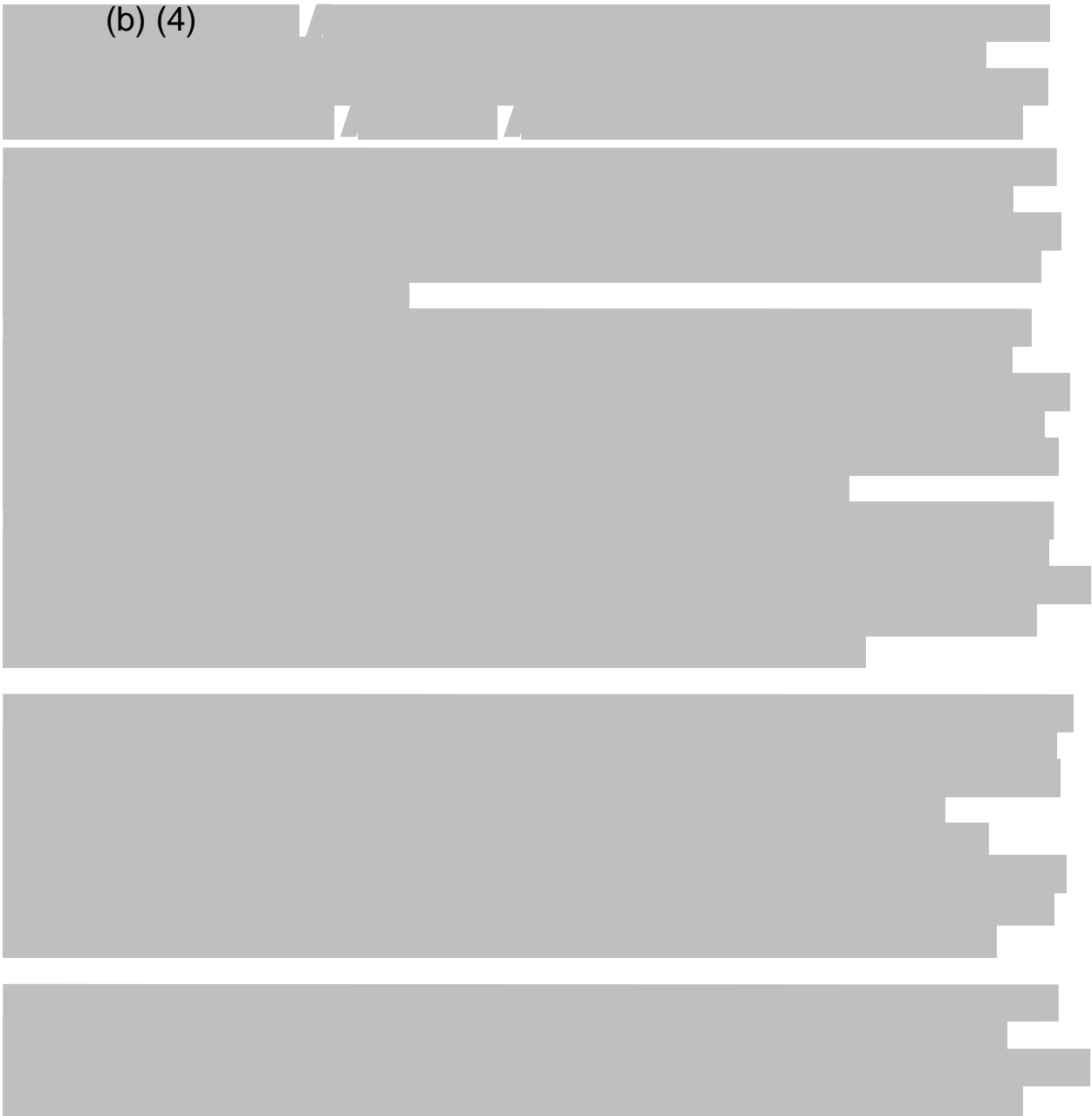
Reviewer's note: While all results met the acceptance criteria, the number of (b) (4) per container not only varies considerably within each lot over time, with no obvious trending, but also varies from lot to lot. For instance, Lot (b) (4) stored at (b) (4) displayed (b) (4)

it was decided that no further action was necessary.

Summary of Stability Data at the Accelerated Storage Conditions: Results from stability studies on SWD stored at the accelerated storage condition of (b) (4) are provided for (b) (4) primary lots. All results were within commercial acceptance criteria.

(b) (4)

(b) (4)



Reviewer's assessment: *The stability data are acceptable*

- *The stability data support the SWD shelf-life claim of 24 months when stored at the recommended temperature of 2 - 32°C.*
- *Future shelf-life updates will be submitted as an annual report.*
- *The accelerated condition supports temporary temperature excursions from the recommended storage condition. The data demonstrate that excursions above the recommended storage condition up to (b) (4).*

In addition, the data demonstrate that SWD is stable through:

(b) (4)



(b) (4)



3.2.A Appendices

3.2.A.1 Facilities and Equipment: Reviewed by DMPQ

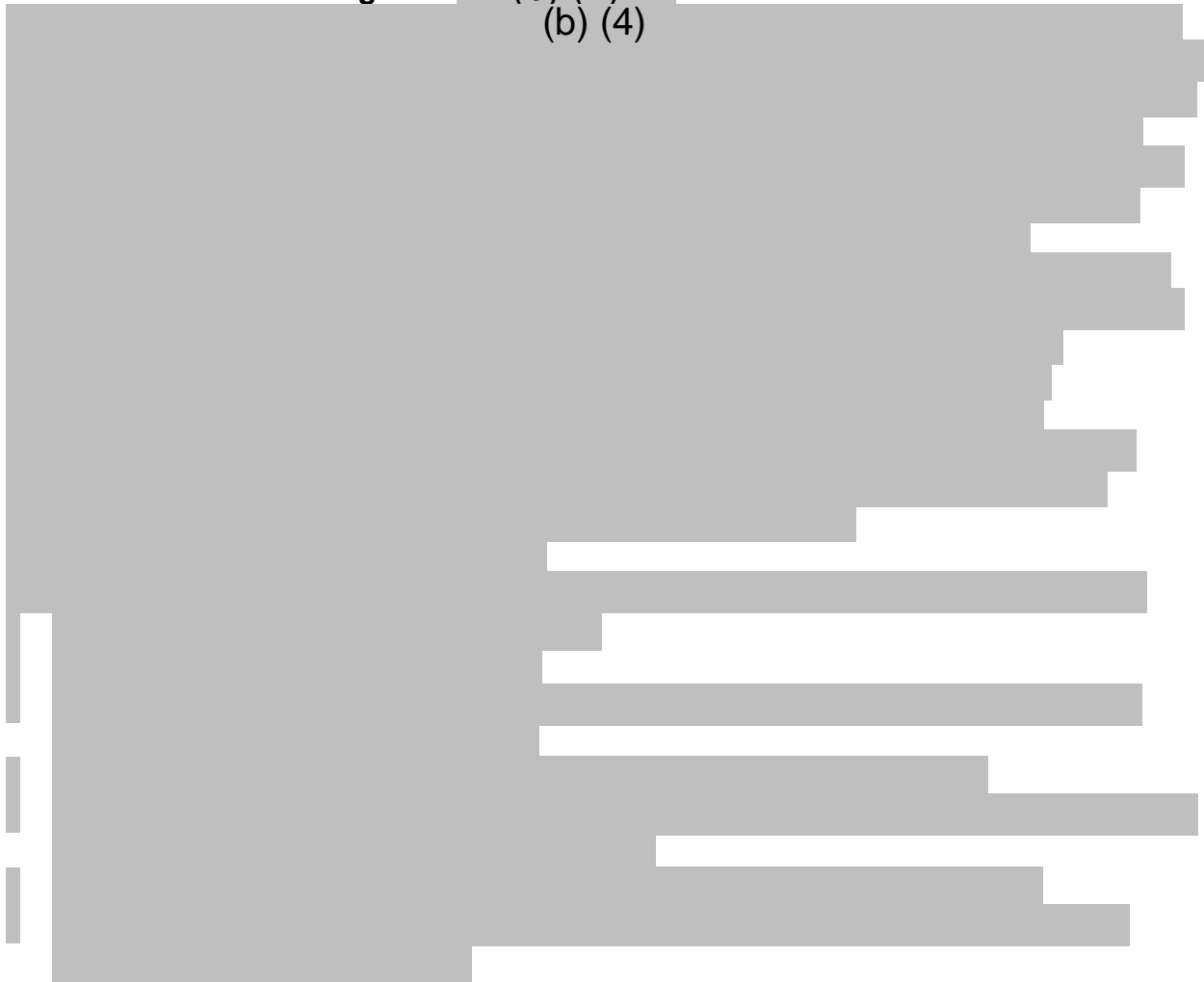
3.2.A.2 Adventitious Agents Safety Evaluation

Multiple mechanisms, procedures, and assays are used to minimize the entry of adventitious agents into the process stream and detect those agents that may enter the process stream. The adventitious agent control program includes the engineering systems of the facility and vessels, the control of the raw materials used in the process, various filtration steps to control microbial load in media, buffers and the process stream, and in-process and environmental testing to monitor the level of adventitious agents in and around the process stream. Furthermore, several steps in the DS downstream processes are designed for the robust elimination of potential adventitious agents, and the capacity of these steps to remove and/or inactivate virus has been evaluated.

Non-viral adventitious agents-


(b) (4)

(b) (4)



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

(b) (4)



B. Reference Product Designation Request

In module 1.3.5.3. a **notice of claimed exclusivity** was provided by the sponsor. The sponsor requests a determination that the licensure of Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine constitutes the “first licensure” of Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine and that Pfizer Inc. is entitled to exclusivity from the date of licensure pursuant to section 351(k)(7) of the Public Health Service Act. The sponsor states that there are no licensed biological products that are structurally related to Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine for which Pfizer Inc. or one of its affiliates, licensors, predecessors in interest, or related entities are the current or previous license holders. Accordingly, consistent with Section 351(k)(7)(C) of the Public Health Service Act, FDA’s licensure of Respiratory Syncytial Virus Stabilized Prefusion F Subunit Vaccine under 351(a) will constitute the “first licensure” of Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine.

a. Pursuant to Section 351(k)(7)(A), no approval of an application submitted under Section 351(k) for which Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine is the **reference product** can be made effective until 12 years after the date of licensure of Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine.

b. Pursuant to Section 351(k)(7)(B), no application under Section 351(k) for which Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine is the

reference product can be submitted until 4 years after the date of licensure of Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine.

Reviewer's assessment: *Form T-846.02 (Reference Product Exclusivity Period Determination Review) was filed and reference product designation was not recommended, since the applicant already submitted a request for Product Exclusivity in BLA 125769 for the identical product. A product license was issued on 31 May 2023 for a different indication (immunization of older adults).*

Lot release protocol

The Lot Release Protocol was reviewed and requests for adding testing for (b) (4) and the relative prefusion content (b) (4) were sent to DBSQC to be sent to the sponsor.

C. Labeling Review:

CMC product reviewer input was provided on the text for the following sections of the Prescribing Information (PI): Dosage Form and Strengths (3); Description (11), Clinical Pharmacology (12) and How Supplied/Storage and Handling (16).

Carton and Container Label:

Carton and Container labels were reviewed and corrected. Edits were discussed and agreed upon with DVRPA upper management.

Reviewer's comment: *All edits to Prescribing information, Carton and Container labels were discussed with DVRPA reviewers and OVRP management and agreed upon. Comments were relayed to the sponsor in several communications. The revised versions of the labeling items are acceptable.*

Module 4: Nonclinical Study Reports

4.2.1.1. Primary Pharmacodynamics

Non-clinical pharmacology studies

The information in this section summarizes the in vitro and in vivo non-clinical studies performed to assess the design, selection, and characterization of RSV-A and RSV-B prefusion F proteins based on consensus sequences derived from subtype A (Ontario) and B (Buenos Aires) contemporary strains, additional structural characterization of the RSV-preF A proteins, in vivo studies to demonstrate immunogenicity in mice, cotton rats and non-human primates, and the selection the vaccine construct for clinical development. The non-clinical studies also show the ability of post-immunization sera to neutralize a panel of contemporary RSV-A and RSV-B clinical isolates and compare the ability of prefusion versus post-fusion forms of RSVF to adsorb neutralizing activity from post-immunization sera. The 10 study reports submitted in support of licensure are listed in the table below. Studies were previously reviewed under IND 17931. Brief narrative summaries of each study follow.

CBER CMC BLA Review Memo BLA 125768 ABRYSVO/Respiratory Syncytial Virus Vaccine

Table 70. Summary of non-clinical studies reported in Module 4.

Study	Study number	Test System	Route of administration	Reviewed under IND 17931 Amd #
Design screening and selection of RSVF vaccine candidates	VR-VTR-10914 ^a	In vitro	NA	Original submission
Structural characterization of (b) (4)	VR-VTR-10880 ^a	In vitro	NA	Original Submission
Immunogenicity of prefusion constructs in mice	VR-VTR-10385 ^a	Mice	IM	Original submission
Immunogenicity of prefusion candidates in cotton rats	VR-VTR-10386 ^a	Cotton rats	IM	Original submission
Immunogenicity of prefusion candidates in rhesus macaques	VR-VTR-10388 ^a	NHPs	IM	Original submission
Immunogenicity of prefusion monovalent and bivalent formulations in cotton rats	VR-VTR-10387 ^a	Cotton rats	IM	Original submission
Evaluation of safety efficacy and immunogenicity of candidate vaccines in the RSV cotton rat model	VR VTR-10390 ^b	Cotton rat	IM	Original submission
Evaluation of safety efficacy and immunogenicity of candidate vaccines in the RSV cotton rat model Study #2	VR-VTR-10938 ^b	Cotton rat	IM	BLA
Assessment of RSV Prefusion RSV Immune Sera Neutralizing Activity Against Laboratory and Clinical Strains.	VR-VTR 10391 ^c	Cotton rat, NHPs, Human	IM	Original submission
Characterization of Human Serum Neutralizing activity by Adsorption against prefusion and post-fusion RSV-F protein conformations	VR-VTR-10879 ^c	Humans	NA	BLA

a= these studies pertain to antigen design, selection, and characterization

b = these studies pertain to Efficacy assessment in cotton rats

c = these studies pertain to Serology testing using post-immunization serum

(b) (4)

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

(b) (4)

Evaluation of safety, efficacy, and immunogenicity of candidate (b) (4) vaccines in the RSV cotton rat model VR VTR-10390 (b) (4) Study

Method: Cotton rats (10/group) were immunized IM with (b) (4) 30 µg + (b) (4) 30 µg /no adjuvant, (b) (4) 30 µg + (b) (4) 30 µg + alum, FIRSV (Formalin-inactivated RSV) lot 100, or mock immunized with PBS buffer alone [2 groups with one challenged and then other not challenged with live RSV]. Another group was infected with RSV-A2 intranasally on Day 0 only. Animals were immunized on day 0 and 28 and then challenged with a crude lysate of RSV-A2 (10⁵ PFU) on day 49 with lungs and noses harvested 5 days later. Lung tissues were processed and scored for pathology (blinded to group assignment) by (b) (4). Virus replication in noses and lungs was measured by (b) (4) assay on HEp-2 cell monolayers and reported as pfu/gm tissue. Sera were collected at week 5

after two immunizations (or after RSV infection on Day 0) and tested for neutralizing antibodies in RSV-A and -B neutralization assays. (b) (4) antigens used for immunization were derived from an experimental lot produced using (b) (4) cells.

Results:

Serology testing: All animals given (b) (4) developed neutralizing antibodies against RSV-A and RSV-B virus with ND₅₀ GMTs of 5223 and 3291 against A and B viruses, respectively, in the unadjuvanted group and GMTs of ~40,000 against both RSV-A and RSV-B viruses in the group given (b) (4) with adjuvant. Mock immunized animals remained seronegative, and animals given FIRSV had little functional antibody detected [ND₅₀ GMT of 23 and 24 against RSV-A and RSV-B viruses, respectively]

Virus replication post-challenge:

RSV A2 replication in the nose: Animals given (b) (4) with adjuvant did not have any detectable virus in the nose. In contrast, 7/10 animals given (b) (4) without adjuvant shed 4-6log₁₀ PFU/gm nasal tissue and 3/10 were virus free. All mock immunized and FIRSV immunized and challenged cotton rats shed 6log₁₀ PFU/gm nasal tissue. Mock immunized animals who were not challenged were virus free as expected.

RSV A2 replication in the lungs: The lungs of all animals given (b) (4) with or without adjuvant had no detectable virus replication after challenge. Virus was detected in 3/10 [GMTs ~4log₁₀] cotton rats given FIRSV Lot 100 and in 10/10 mock immunized animals [5log₁₀ PFU/gm tissue].

Histopathology scores after a live RSV challenge:

Alveolitis: Alveolitis scores were 1 and 2 in 10/10 animals given FIRSV. Alveolitis scores of 1 were detected in 2/10 animals given 847A+847B without adjuvant while scores were all 0 in 10/10 given (b) (4) with alum. No alveolitis was detected in the mock immunized group.

Total histopathology scores: Total sum of lung scores (alveolitis + peribronchiolitis + perivascularitis + interstitial pneumonia) were high for animals given FIRSV [range 6-10, mean, 6.4] while the total sum scores observed in both groups given (b) (4) with or without adjuvant were like the scores observed in the mock immunized group.

Reviewer's assessment: The challenge test in cotton rats provided proof-of-concept that the immune response elicited by immunization with (b) (4) provided protection against a live RSV challenge and evidence of vaccine efficacy. However, the test did not provide a valid assessment of the ability of bivalent preF vaccine to predispose to enhanced respiratory pathology because there was little to no virus replication in the lungs after challenge. A valid test for ERD requires some virus breakthrough in the lung after challenge. This is generally achieved by dose de-escalation or by waiting for serum neutralization titers to fall below a protective level prior to the live virus challenge. It is our opinion that these results were inconclusive. The group given (b) (4) with adjuvant had very high serum neutralizing antibody titers prior to challenge and no detectable virus replication in the lungs after challenge. The total absence of virus replication in the lungs post-challenge invalidates the study

as a safety test for ERD. Also, the product intended for use in the clinic was not tested but instead the study used preF antigen expressed using (b) (4) cells which was a very early, crude lot. Since all adult humans have been exposed many times to RSV over their lifetime, they are not at risk for enhanced disease and the effectiveness data were sufficient to support clinical development. However, the study was not valid for assessing ERD risk and as such does not support progressing with clinical testing of the (b) (4) vaccine in an RSV naïve infant population. Pfizer was made aware of the need for a valid test for ERD prior to testing their vaccine in an RSV-naïve infant population.

Evaluation of safety efficacy and immunogenicity of candidate vaccines in the RSV cotton rat model Study #2 VR-VTR-10938 ((b) (4) Study)

Method: Cotton rats [10/group] were immunized IM with (b) (4) 30 µg + (b) (4) 30 µg /no adjuvant, (b) (4) 30 µg + (b) (4) 30 µg + AL(OH)₃, (b) (4) 30µg + (b) (4) 30 µg + CpG adjuvant, with FIRSV lot 100, or FI mock preparation or given PBS buffer alone (2 groups with one challenged and then other not challenged with live RSV). Another group was infected with RSV A2 (10⁵ PFU, intranasally) on day 0 only. Animals were immunized on day 0 and 28 and then challenged with a crude lysate of RSV-A2 (10⁵ PFU) on day 49 with lungs and noses harvested 5 days later. Tissues for pathology were processed and scored (blinded to group assignment) by (b) (4). Virus replication in noses and lungs was measured by (b) (4) assay on HEp-2 cell monolayers and reported as pfu/gm tissue. Sera were collected at week 5 after two immunizations and tested for neutralizing antibodies in RSV-A and RSV-B neutralization assays. (b) (4) and (b) (4) **antigens used for these immunizations were manufactured using the CHO cell expression system and purified using a process representative of the process used to manufacture the product used in the first in human trials.**

Results

Serology testing: Serum neutralizing antibody titers against RSV-A and RSV-B viruses were determined prior to challenge. Animals given PBS or FIRSV had GMTs <30 against both RSV-A and RSV-B. Animals infected with RSVA2 on day 0 had GMTs of 563 and 114 against RSV-A and RSV-B, respectively. Animals immunized with two doses of (b) (4) had GMTs of 3388 and 1581 against RSV-A and RSV-B respectively. Animals in the groups given adjuvanted RSVpreF vaccines had the highest GMTs of all, with titers of 48931 and 53784 in the group given (b) (4) with Al(OH)₃ and 38519 and 40607 in the group given (b) (4) with CpG adjuvant against RSV-A and RSV-B strains, respectively.

Virus replication post-challenge

RSV A2 replication in the nose

Animals in the groups given RSV-A2 on Day 0 and animals immunized with (b) (4) adjuvanted with either Al(OH)₃ or CpG were completely protected and had no detectable virus replication in the nose after challenge. Likewise, the mock immunized group that was not challenged with live virus was also virus free. All cotton rats in the group given PBS or given FIRSV had GMTs >10⁶ PFU /gm nasal tissue after challenge. In contrast nine of 10 animals in the group immunized with (b) (4) without adjuvant had virus replication in the nose after challenge but titers were lower with a GMT of ~10^{4.5} PFU/gm tissue.

RSV A2 replication in the lungs

No virus replication was detected in the lungs of cotton rats immunized with (b) (4) without adjuvant or with (b) (4) with either Al(OH)₃ or CpG adjuvant. Likewise, animals infected with RSV-A2 on Day 0 were also completely protected and no virus was detected in the lungs after re-challenge. In contrast, all animals given PBS on days 0 and 28 replicated virus in the lungs after challenge as did 2 of 10 cotton rats immunized with FIRSV.

Histopathology scores after a live RSV challenge:

Alveolitis: Alveolitis scores were lowest in the animals given PBS with or without a subsequent live virus challenge as expected and scores were highest (range 1-3, mean ~2) in the group immunized with two doses of FIRSV prior to challenge. Scores were 1 or lower in animals infected with RSV-A2 on day 0 prior to challenge. Mean scores were low (<1) among the animals given (b) (4) with or without adjuvant albeit single animals in each group had alveolitis scores of 2 that over-lapped with scores seen in the FIRSV group.


Total lung score: Mean total lung score (MTLS) was highest in the group immunized with FIRSV (MTLS ~7) followed by the group infected with RSVA2 (MTLS~4) and then the groups immunized with (b) (4) with or without adjuvant (MTLS~ 2.5 in each group) and scores were lowest among the mock immunized group (MTLS ~1).

Reviewer's assessment: *In this experiment, (b) (4) antigens used to immunize cotton rats were manufactured from CHO cells using a method comparable to that used for clinical lots tested in Phase 1 trials. The study demonstrated that immunity elicited in response to (b) (4) vaccine protects lungs against a live RSV challenge and, if administered with adjuvant, the immunity against infection was increased and there was no virus replication in the nose after virus challenge. However, the study is not a valid test for enhanced disease since there was no virus breakthrough in the lungs of the animals given (b) (4) after challenge. Virus breakthrough in the lungs is needed to assess priming for vaccine-associated ERD. As noted above, adults are not at risk for ERD since they have experienced multiple RSV infections over their lifetime. However, the study does not support advancing clinical testing into RSV naïve children at this time, since these children are at risk for ERD if cytokine responses are misdirected by vaccine priming prior to the first natural RSV infection.*

(b) (4)

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

(b) (4)



Module 5: Clinical Study Reports

5.3.1.4. Reports of Bioanalytical and Analytical Methods for Human Studies

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


This section reviews the following clinical assays:

- RT-qPCR for the Detection of RSVA and RSVB using (b) (4) for RSV Case Confirmation.
- (b) (4) Assay for the Detection of Functional Antibodies to Respiratory Syncytial Virus in Serum.
- Hemagglutination Inhibition (HI) Assay and (b) (4) Assay methods and validations to evaluate the immune response to influenza virus vaccine
- Assays to measure antibody responses to Tdap vaccine

RT-qPCR for the Detection of RSV A and RSV B using (b) (4) for Case Confirmation.

VR-TM-10281: Test Method for RT-qPCR for the detection of RSV A and RSV B using (b) (4), approved 17FEB2022

(b) (4)



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

(b) (4)

Diphtheria, Tetanus, and acellular Pertussis serological (DTP-6) assay

Reports of Biopharmaceutic Studies

My (EP) review addresses the Diphtheria, Tetanus, and acellular Pertussis serological (DTP-6) assay used for the evaluation of immune responses for Phase 2b study C3671004, a placebo-controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of a respiratory syncytial virus (RSV) vaccine when administered concomitantly with Tetanus, Diphtheria, and acellular Pertussis vaccine (Tdap) in healthy nonpregnant women 18 through 49 years of age. Pfizer did not provide information on the assay validation status, SOPs, or performance data in the initial submission for BLA 125769. The SOPs and performance data were submitted to Amd 125769/0.12 (10 Jan 2023). The validation report for the DTP-6 assay was provided in Amd 125768/01 (21 Dec 2022).

The DTP-6 assay is a Luminex-based assay used to detect IgG antibodies specific to Diphtheria toxoid (DTd), Tetanus toxoid (TTd), Pertussis toxin (PTx), and pertussis antigens Pertactin (PRN), (b) (4), and Filamentous Hemagglutinin (FHA). (b) (4) performed the initial validation at the (b) (4) location in 2010, and the assay was transferred to the (b) (4), location in 2015. Pfizer provided documents pertaining to the validation and method transfer under Section 5.4 of Amd 125769/0.12:

- VR-ECD-10041 – Validation of the Pertussis Toxin (PTx), Filamentous Hemagglutinin (FHA), Pertactin (PRN), (b) (4), Diphtheria Toxoid (DTd), and Tetanus Toxoid (TTd) IgG Serology Assay (DTP-6 IgG); dated August 09, 2010.
- (b) (4) Statistical Report – Qualification of the (b) (4) Laboratory for Performing the Diphtheria, Tetanus and Pertussis (DTP) Six-Valent IgG Luminex Immunoassay (DTP-6 IgG); dated April 15, 2015.
- (b) (4) Scientific Summary – Technology Transfer of the Diphtheria, Tetanus and Pertussis (DTP) Six-Valent IgG Luminex Immunoassay (DTP-6 IgG); dated April 16, 2015.

Pfizer also provided the assay protocol: VSDVAC 13 Version 3.03 DTP (PTx, FHA, PRN, (b) (4), DTd and TTd) Total IgG Assay (DTP-6 IgG).

The version used to test clinical study samples was provided in Amd 125769/0.46 (17 Mar 2023): VSDVAC 13 Version 3.00.

(b) (4)

Assay validity parameters are described on pages 19 and 20 of the assay method document (Version 3.03). The LLOQ and ULOQ ((b) (4)) for each antigen are below (LLOQ/ULOQ, respectively):

- PTx (EU/mL) – (b) (4)
- FHA (EU/mL) – (b) (4)
- PRN (EU/mL) – (b) (4)
- (b) (4) – (b) (4)
- DTd (IE/mL) – (b) (4)
- TTD (IU/mL) – (b) (4)

Responses to (b) (4) were not evaluated in study C3671004.

(b) (4)

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