

CBER CMC BLA Review Memorandum

BLA STN 125775

**Respiratory Syncytial Virus Vaccine, Adjuvanted
AREXVY**

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1. BLA# 125775

2. GlaxoSmithKline Biologicals SA, U.S. License Number 1617

**3. Respiratory Syncytial Virus Vaccine Adjuvanted
AREXVY**

Also known as RSVPreF3 OA or RSVPreF3

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

Respiratory syncytial virus vaccine is a purified, recombinant RSV-fusion glycoprotein stabilized in the prefusion conformation that is provided as a single dose, preservative-free, lyophilized powder in a 3 mL glass vial. The RSVPreF3 antigen is reconstituted using the liquid adjuvant, AS01E, also provided as a single dose in a 3 mL glass vial. The adjuvant consists of the immune stimulating substances purified *Quillaja* saponin (QS-21) and 3-O-desacyl-4'-monophosphoryl lipid A (MPL) in liposomes made of dioleoyl phosphatidylcholine (DOPC) and cholesterol. The reconstituted RSVPreF3 is administered intramuscularly as a single (0.5 mL) dose containing 120 µg of RSVPreF3 protein immediately following reconstitution. The vaccine is indicated for the active immunization for the prevention of lower respiratory tract disease caused by respiratory syncytial virus in adults 60 years of age and older.

5. MAJOR MILESTONES

Date of submission: September 2, 2022
Filing date: October 31, 2022
Midcycle meeting: December 14, 2022
Midcycle communication: December 20, 2022
Late cycle meeting: February 6, 2023
Late cycle communication: February 15, 2023
VRBPAC: March 1, 2023
ADD: May 3, 2023

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Judy Beeler, OVR, DVP	Module 3 Drug Substance, RSVPreF3 Drug Product RSVPreF3 Appendix 2, Adventitious Agent Safety Evaluation Module 4 Non-clinical pharmacology testing of RSVPreF3 Module 5 Biopharmaceutic studies: Method Validation of RSV clinical assays

Reviewer/Affiliation	Section/Subject Matter
Roberta Lynne Crim, OVR, DVP	Module 3 DS Validation of analytical assays DP Validation of analytical assays Regional Information Comparability Protocols Environmental Assessment Reference Product Designation Request Module 4 Non-clinical pharmacology testing of RSVPreF3 Module 5 Biopharmaceutic studies: Method Validation of RSV clinical assays
Ewan Plant, OVR, DVP	Module 5 Biopharmaceutic studies Influenza hemagglutination inhibition (HI) assays
Marina Zaitseva, OVR, DVP	Module 3 Drug Product AS01E [see separate memo]

7. INTER-CENTER CONSULTS REQUESTED: None requested

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
9/2/2022	STN 125775/0	Original submission
9/30/2022	STN125775/2 (Response to IR #1)	Updated 356h form and iPSP info
10/17/2022	STN 125775/3 (Response to IR#2, from DVP/DBSQC)	CMC information on 1. testing sites performing QC testing updated 2. Bioburden testing [MVR] 3. Endotoxin testing [MVR]
11/4/2022	STN 125775/4 (Response to IR #3, from Clinical/DVP)	CMC: updated 356h form
11/8/2022	STN 125774/5 (Response to IR#4 from DVP)	Responses to questions about 1. test for appearance 2. tests for (b) (4) 3. Provided SOPs for handling and shipping clinical samples.

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Date Received	Submission	Comments/ Status
11/22/22	STN 125775/7 (Response to IR#5, DBSQC)	Responses to questions about 1. Methods used to qualify the sterility test 2. Additional information pertaining to the endotoxin test.
1/3/23	STN 125775/12 (Response to IR#11 from DVP)	Response to CMC questions about the manufacture and testing of the DS
3/20/23	STN 125775/27 (Response to IR#27 from DVP/CMC Biostatisticians)	Responses to CMC questions about the manufacture and testing of the DP.
4/3/23	STN 125775/34 (Responses to IR#32 from DVP)	Responses to CMC questions pertaining to clinical data to support lower limit for IVRP assay.
4/5/23	STN 125775/35 (Responses to IR#33 from DVP)	Responses to CMC questions pertaining to filters used during manufacture of RSVPreF3 (b) (4) DP
4/7/23	STN125775/36 (Responses to IR#37 from DVP)	Responses to CMC questions pertaining to the lot release protocol sent in conjunction with comments from DBSQC.
4/14/23	STN125775/38 (Responses to IR#40 from DVP)	Responses to CMC question from DVP pertaining to reporting categories for Comparability protocols.
4/21/23	STN125775/42 (responses to IR#44 from DVP)	Response to request for clarification of date of manufacture and dating period for shelf life.

Date Received	Submission	Comments/ Status
4/25/23	STN125775/44 (responses to IR#46) from DVP	Response to second request for additional clarification statement on date of manufacture of the DP and shelf-life dating period.

9. REFERENCED REGULATORY SUBMISSIONS

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
IND 018540	RSVPreF3 OA	GSK	NA	IND for RSVPreF3 with AS01 _E adjuvant for older adults
(b) (4)	(b) (4)	GSK	NA	(b) (4)
DMF (b) (4)	Stopper (b) (4) gray Section 3.2.P.7 Vial stoppers (b) (4)	(b) (4)	Yes	Permission to cross reference DMF STN (b) (4)
BB-MF (b) (4)	MPL manufacturing facility information	GSK	Yes	MPL manufacturing (b) (4)
BBMF (b) (4)	QS21 manufacturing facility information	GSK	Yes	See appendix 3.2.A.1 in BB-MF (b) (4) and annual report SN 23 current through June 2022.
DMF (b) (4)	Rubber compound (b) (4) for vial stoppers	(b) (4)	Yes	Rubber compound for vial stoppers.

10. REVIEWER SUMMARY AND RECOMMENDATION

This review memo covers the Module 3, CMC information for the RSVPreF3 component, Module 4, non-clinical studies assessing vaccine immunogenicity and Module 5, validation of clinical assays used to support clinical efficacy endpoints.

This memo does not cover the CMC information for the adjuvant which is reviewed and recommended in a separate memo. However, the executive summary includes a section describing the adjuvant.

A. EXECUTIVE SUMMARY AND RECOMMENDATIONS

Chemistry Manufacturing and Controls (CMC)

The RSVPreF3 (b) (4) drug product (DP) are manufactured at the GSK facility in (b) (4), Belgium. (b) (4) release testing occurs at GSK, (b) (4) Belgium, (b) (4)

(b) (4) Release testing of the DP occurs at the GSK facilities in (b) (4) (b) (4) Rixensart in Belgium, GSK (b) (4), and at the GSK facility in (b) (4).

The RSVPreF3 antigen is produced using a Chinese Hamster Ovary (b) (4) (CHO-(b) (4)) cell (b) (4)

The manufacturing process for the RSVPreF3 DP consists of the following steps: (b) (4)

(b) (4) Sterile filtration (b) (4) Lyophilization; (b) (4) Visual Inspection of filled vials (b) (4) Labeling, Packaging, and Storage. (b) (4)

(b) (4). RSVPreF3 is aseptically filled into 3 mL, Type-(b) (4) clear glass vials with grey, siliconized, bromo-butyl rubber stoppers. Following lyophilization, flip-off aluminum caps and polypropylene covers are applied, and capped vials are inspected. RSVPreF3 final containers are labeled and packaged together with AS01_E final containers in the GSK facilities in (b) (4), Belgium, (b) (4). Final containers are stored protected from light at 5±3°C with a proposed shelf-life of 24 months. The date of manufacture (DOM) for both the RSVPreF3 antigen DP and AS01_E adjuvant DP is based on the date of filling. The expiry date for RSVPreF3 and AS01_E is the earliest of the two dates once the two final containers are co-packaged.

RSVPreF3 (b) (4) DP are manufactured under cGMP conditions.

The (b) (4) DP manufacturing processes went through (b) (4) process upgrades (b) (4) through clinical and commercial development. Comparability of the (b) (4) DP clinical and commercial lots was shown by the ability to meet release specifications and by characterization tests that compared RSVPreF3 (b) (4), stability studies, (b) (4) studies. The commercial manufacturing process is supported by Process Performance Qualification studies that showed consistent manufacture of RSVPreF3 based on (b) (4) DP in-process and release acceptance limits with comparability of critical quality attributes and characterization test results for (b) (4) DP lots that fell within comparability ranges determined using data derived from Phase 3 clinical lots. Alternatively, non-numeric results for PPQ lots were compared to results obtained for Phase 2 and Phase 3 clinical lots and found to be similar. Additionally, in-process parameters that were scale-dependent fell within the range set by multiple development and engineering lots manufactured using the (b) (4) commercial process with ongoing monitoring to support and refine the product control strategy. In summary, the process is well-controlled, and all commercial lots met the specified operating ranges across all process steps.

Provided by Dr. Marina Zaitseva: The AS01_E Adjuvant System contains equal amounts, 25 µg of each per 0.5 mL dose of the vaccine of two immune enhancers: MPL (3-O-desacyl-4'-monophosphoryl lipid A) and QS-21 combined with liposomes. MPL represents a detoxified endotoxin obtained from the *Salmonella minnesota* and QS-21 is a saponin purified from the bark of the South American tree *Quillaja saponaria* Molina. Liposomes are composed of two lipids, DOPC (dioleoyl phosphatidylcholine) and cholesterol; the liposomes are suspended in a phosphate buffer. AS01_E is provided in a single-dose vial. The pharmaceutical form of AS01_E Adjuvant is an opalescent, colorless to pale brownish liquid. AS01_E adjuvant (b) (4)

Nonclinical studies indicated that both MPL and QS-21 are required (b) (4)

Clinical Assays for Case Confirmation and Immunogenicity Endpoint Assessments

To assess clinical trial endpoints, GSK developed clinical assays to use for case confirmation and to measure immune responses following immunization. Quantitative Reverse Transcription-Polymerase Chain Reaction (RT-qPCR) assays used to detect RSV-A and RSV-B infections in Phase 3 clinical trials were performed in the GSK Clinical Laboratory Science, (b) (4), Belgium. RSV-A and -B neutralization assays used to measure serum neutralization antibody levels were performed at GSK Clinical Laboratory Science, (b) (4), Belgium. The RSVPreF3-specific IgG enzyme-linked immunosorbent assay (ELISA) that measured antigen-specific IgG responses in human sera was performed at (b) (4). An Intracellular Cytokine Staining assay for 10 immune relevant parameters (ICS 10P) was used to evaluate polypositive CD4+ and CD8+ T cell responses at GSK Clinical Laboratory Science, Rixensart, Belgium.

Provided by Dr. Ewan Plant: For co-administration studies with influenza vaccine, the four hemagglutination inhibition (HI) assays used to measure HI antibody responses were conducted by (b) (4). The hemagglutination inhibition (HI) assay is used to assess the antibody response elicited by quadrivalent influenza vaccine co-administered with RSVPreF3 vaccine. The assay is acceptable for detection and quantification of influenza antibody response. Antibody response is used as a correlate of protection for the influenza vaccine. The sponsor uses the information to support labeling that describes that the coadministration of seasonal influenza vaccine with RSVPreF3 does not adversely affect immunogenicity of either vaccine. The HI assay is validated for the four types of influenza antigen included in quadrivalent influenza vaccines (H1N1, H3N2, and influenza B Victoria and Yamagata lineages).

All clinical assays were validated and considered suitable for their intended purposes to evaluate the immunological responses in humans following immunization with RSVPreF3 antigen adjuvanted with AS01E.

Non-clinical Pharmacology Studies

Several nonclinical studies in mice evaluated the immunogenicity of RSVPreF3 antigen and supported the selection and justification of inclusion of the adjuvant. AS01E adjuvanted RSVPreF3 elicited CD4+ and CD8+ T cell responses and RSV neutralizing antibody responses effective against both laboratory and contemporary RSV-A and -B strains. AS01E adjuvanted RSVPreF3 antigen induced higher antibody responses than unadjuvanted, (b) (4)

[REDACTED]

B. RECOMMENDATION

I. APPROVAL.

We recommend approval of Respiratory Syncytial Virus Vaccine, Adjuvanted.

II. COMPLETE RESPONSE (CR)

Not Applicable

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Roberta Lynne Crim LPRVD, DVP, OVRR		
Ewan Plant, LPRVD, DVP, OVRR		
Judy Beeler LPRVD, DVP, 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		

μg Microgram

MVR	Method Validation Report
NA	Not Applicable
Nab	Neutralizing antibody
(b) (4)	
NLT	Not less than
NMT	Not more than
(b) (4)	
PCR	Polymerase chain reaction
PDE	Permissible Daily Exposure
PDL	Population doubling level
(b) (4)	
PE	Process evaluation
(b) (4)	
PM	Process monitoring
(b) (4)	
PPQ	Process Performance
(b) (4)	
QC	Quality Control
QD	Quality Decision
QR	Quality Release
QS-21	Quillaja Saponin
(b) (4)	
RNA	Ribonucleic acid
(b) (4)	
RSD	Relative Standard Deviation
RT-qPCR	Quantitative Reverse Transcription-Polymerase Chain Reaction
RVLPs	Retrovirus like particles
(b) (4)	
SST	System Suitability Tests
(b) (4)	
TRA	Technical Risk Assessment
(b) (4)	
ULOQ	Upper Limit of Quantitation
(b) (4)	
USP	United States Pharmacopeia
(b) (4)	
WFI	Water for injection
(b) (4)	

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Module 3

3.2.S DRUG SUBSTANCE

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

(b) (4)



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

3.2.P DRUG PRODUCT

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

The Drug Product (DP) RSVPreF3/AS01_E vaccine is a preservative-free, sterile, liquid suspension of 0.5 mL for intramuscular injection with a target concentration of 120 µg of RSVPreF3 protein per dose. The vaccine consists of two components, RSVPreF3 antigen and AS01_E adjuvant system, with each provided as separate mono-dose preparations.

The trimeric RSVPreF3 protein stabilized in a pre-fusion conformation is a white cake or powder lyophilized preparation. The antigen is filled using a (b) (4) 120 µg/dose is delivered following reconstitution, withdrawal, and injection. Immediate packaging materials include 3 mL, Type- (b) (4) clear glass vials with grey, siliconized, bromo-butyl rubber stoppers with flip-off aluminum caps and polypropylene covers.

The AS01_E Adjuvant System is a pale brownish liquid suspension. Immediate packaging materials include 3 mL, Type- (b) (4) clear glass vials with grey, chloro-butyl, siliconized rubber stoppers with aluminum flip-off caps and polypropylene covers. The adjuvant is filled at (b) (4) 0.5 mL of vaccine is administered following dose preparation.

Liquid AS01_E Adjuvant System is used to reconstitute the RSVPreF3 lyophilized antigen immediately prior to administration and the reconstituted liquid suspension is opalescent, colorless to pale brownish. The composition of RSVPreF3/AS01_E Reconstituted Vaccine (RV) is presented in below.

Table 16. Nominal composition of RSVPreF3 DP (mono-dose)

Ingredients	Quantity per 0.5 mL dose ^{1,2}	Function	Reference Standard
Active substance			
RSVPreF3 antigen	120 µg	(b) (4)	
Excipients			
Trehalose dihydrate	14.7 mg	(b) (4)	
Polysorbate 80	0.18 mg	(b) (4)	
Potassium dihydrogen phosphate (KH ₂ PO ₄)	(b) (4)	(b) (4)	
Dipotassium phosphate K ₂ HPO ₄	0.26 mg	(b) (4)	

Ingredients	Quantity per 0.5 mL dose ^{1,2}	Function	Reference Standard
AS01 _E components			
3-O-deacyl-4'-monophosphoryl lipid A (MPL) ³ of (b) (4)	25 µg	(b) (4)	
Purified Quillaja saponin (QS-21)	25 µg	(b) (4)	
Dioleoyl phosphocholine (DOPC)	500 µg	(b) (4)	
Cholesterol	125 µg	(b) (4)	
Sodium chloride	4.4 mg	(b) (4)	
Disodium phosphate anhydrous (Na ₂ HPO ₄)	0.15 mg	(b) (4)	
Potassium dihydrogen phosphate	(b) (4)	(b) (4)	
Water for injection	0.5 mL	(b) (4)	

¹AS01_E Final Container (b) (4)

0.5 mL is administered.

(b) (4)

Please see the CMC adjuvant review memo for details pertaining to manufacture and quality control testing of the AS01_E adjuvant. The remainder of this review focuses on the manufacture and quality control testing for the RSVPreF antigen DP component.

³The form of MPL in AS01_E consists of (b) (4) documented by Marina Zaitseva, Larry Callahan and Frank Switzer during review.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Product

The RSVPreF3^{(b) (4)} differs from the RSVPreF3 DP only in terms of the (b) (4) of the RSVPreF3 antigen. The buffer and excipients used to (b) (4) in the manufacture of the DP are identical to the (b) (4). No new excipients are added to the DP.

3.2.P.2.1.2 Excipients

Excipients, concentrations, and functions are described in **Table 21** above.


Reviewer's assessment: See Components Table with known UNII codes in Section 6.0, Table 52 for a complete listing of all ingredients used in the manufacturing process.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

Adjustments were made to the components listed below during product development for DP processes 2.2, 2.3. and 2.4 (described under DP Development):

(b) (4)



Process Evaluation Studies:

Study design: (b) (4) of RSVPreF3 DP (b) (4) were produced from (b) (4) (b) (4) as outlined in **Table 17** below and tested in a series of (b) (4) different evaluations and then assessed for (b) (4) to determine which of the (b) (4) had the lowest percentage of (b) (4) following each test (**Table 18**)

(b) (4)

(b) (4)

RSVPreF3 antigen (b) (4)

Based on the results of immunogenicity and acceptable tolerability, the 120 µg dose of RSVPreF3 given with AS01_E adjuvant was selected for further clinical testing.

AS01_E Adjuvant system:

- (b) (4)
See the review of AS01_E DP for more details.
- DP formulations are compared below in **Table 19**.

Table 19. Comparison of Nominal Clinical (b) (4) versus Commercial (b) (4) Formulations of the RSVPreF3 DP Components for 120 µg/dose presentations following reconstitution

(b) (4)

Reviewer's assessment: A comment was sent to the sponsor in IR#27 on March 13, 2023, requesting a Table comparing the nominal composition per dose for clinical DP lots manufactured using Process (b) (4) for comparison with the composition per dose for DP manufactured using process (b) (4). We also requested information on the volumes used to reconstitute each dose. The sponsor provided responses on March 20, 2023. Table 24 above was updated to show the nominal compositions for the high dose (i.e., 120 µg RSVPreF3 per dose) of DP manufactured using processes (b) (4) (b) (4). For Process (b) (4) lots, the reconstitution volume was (b) (4) and the administration volume was 0.5 mL. For Phase 3 clinical trials, a whole content/prescribed volume approach was used that included a reconstitution volume of approximately (b) (4) and administration volume of 0.5 mL. The sponsor also notes that

the (b) (4) between processes (b) (4) and processes (b) (4) differ due to the change in the target (b) (4) implemented as of process (b) (4) (target (b) (4) changed from (b) (4) to (b) (4)). The response is complete and acceptable. Differences in the nominal composition of the reconstituted vaccine are noted, however, the differences are small, and the data support the comparability of RSVPreF3 doses administered across the clinical program and all clinical data accrued across the clinical program support the commercial dose.

A second comment was also sent in IR#27 on March 13, 2023, asking the sponsor to confirm the trehalose concentration per dose for the (b) (4) commercial product as the information provided in the submission of February 6, 2023 indicated the concentration of trehalose in the reconstituted nominal dose was 14.7 mg/dose. In contrast, we estimated a concentration of (b) (4) mg trehalose when the vial was reconstituted using (b) (4) (the target volume used to fill the adjuvant vial). The sponsor provided a complete response in amendment 27 on March 20, 2023. The reconstitution volume, withdrawal volume and vaccine administration volumes were provided in detail for each step. This included the quantity of trehalose per vial, concentration of trehalose following reconstitution of the cake, withdrawal, and concentration of trehalose in the syringe (taking into account hold-up in the vial and hold-up in the syringe) and administration of the 0.5 mL dose. When all factors are considered, the quantity of trehalose per dose is 14.7 mg as stated in the BLA.

3.2.P.2.2.2 (b) (4)

The DP is filled using a target dose of 120 µg (b) (4) of RSVPreF protein/vial. This formulation was tested throughout Phase 3 and is supported by safety data from these clinical trials.

3.2.P.2.2.3 Physicochemical and Biological Properties

The physical and biological properties of the RSVPreF3 DP are identical to those described for the (b) (4) and are reviewed under item 3.2.S.3.1 Elucidation of Structure and other Characteristics. The (b) (4) of the RSVPreF3 DP is (b) (4) and (b) (4)

Reviewer's assessment: *In IR#27 sent to the sponsor on March 13, 2023, we requested the (b) (4) of RSVpreF3 DP. The sponsor responded on March 20, 2023, with the following information: (b) (4)*

All responses are acceptable.

Manufacturing Process Development

The (b) (4) is stored at the DP manufacturing site in (b) (4), Belgium, between (b) (4). The DP manufacturing process consists of the following steps: (b) (4) Sterile Filtration and Filling, (b) (4) Lyophilization, (b) (4) Visual Inspection (b) (4) Labeling, Packaging, and Storage.

Additional information pertaining to each step is given below under Section 3.2.P.3 Manufacture. Initially, manufacture of DP encompassed vaccines for (b) (4) older adults (b) (4) . However, the (b) (4)

Information below describes DP lots supplied to support clinical testing in (b) (4) older adults (OA) (b) (4) across the (b) (4) DP processes:

(b) (4)

The differences between clinical and commercial manufacture of RSVPreF3 DP using Process (b) (4) , respectively, are minor and are summarized below.

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

(b) (4)

Reviewer's assessment: The manufacturer made (b) (4) process upgrades to their original process for the manufacture of the RSVPreF3 DP. The main change is the (b) (4)

(b) (4) GSK facility accompanied by (b) (4). Other minor changes were made to (b) (4)

(b) (4) DP lots used for non-clinical and clinical testing are comparable to each other and to the DP lots manufactured using the current (b) (4) commercial process. The analytical strategy for release was similarly updated. RSVPreF3 DP lots met the acceptance criteria in place at the time of release. Although there were minor changes in release criteria with process upgrades, all lots were of a similar quality and the results of the QR testing support product comparability.

See **Appendices 10A, 10B and 10C** for a complete summary of all RSVPreF3 DP lots, along with AS01_E, diluent, and placebo lots used during clinical testing.

3.2.P.2.4 Container Closure System

RSVPreF3 DP is dispensed into 3 mL, type (b) (4) clear glass vials with a grey bromo-butyl rubber stopper covered by an aluminum flip-off cap with a polypropylene plastic cover. Protection from light is afforded by the opaque secondary packaging. Additional information about compatibility, protection from light, container closure integrity, and performance is given under section 3.2.P.7 Container Closure System below.

Type (b) (4) glass vials are inert and resistant to hydrolysis by the treatments employed to assess extractables and leachables. In contrast, rubber stoppers were subjected to a safety evaluation for extractables and leachables as described below.

Study design for extractables: Rubber stoppers were exposed to the following conditions:

[illegible]


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

3.2.P.2.5 Microbiological Attributes

RSVPreF3 is a sterile, adjuvanted, preservative-free vaccine. Sterility is assured by the following procedures and precautions:

- RSVPreF3 is manufactured according to GMPs under controlled environmental conditions to minimize bioburden and assure sterility. Production areas are monitored, and equipment is cleaned and sterilized using validated methods.


RSVPreF3 (b) (4)



- Filling and lyophilization operations were extensively validated using media fill simulations.
- The suitability and integrity of the container closure system was monitored and verified throughout stability testing and shelf life.
- The adjuvant, AS01_E, is sterile. See Dr. Zaitseva's review of the adjuvant for manufacturing details.
- RSVPreF3/AS01_E reconstituted vaccine must be administered within 4 hours of preparation to maintain integrity of the preF antigen and sterility of the reconstituted vaccine.

Reviewer's assessment: *RSVPreF3 is manufactured using a validated aseptic process that controls bioburden and in-process controls and Quality Release testing assure that the RSVPreF3 DP and AS01_E DP final containers are sterile. Studies support use within four hours of reconstitution. (See section below).*

3.2.P.2.6 Compatibility with AS01_E

Compatibility between RSVPreF3 and AS01_E was evaluated using a series of studies including: 1) interactions between RSVPreF3 and AS01_E assessed using (b) (4)  2) compatibility following reconstitution using quality release testing; 3) characterization of additional CQAs following reconstitution and 4) in-use stability studies following reconstitution. The CMC review of the adjuvant also discusses the studies that support compatibility between the RSVPreF3 antigen and AS01_E adjuvant; please see this review memo for additional details. Below is a brief synopsis of the testing and main conclusions.

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

and stored at 5±3°C. Accordingly, time of use is limited to 4 hours at 5±3°C following reconstitution with AS01_E adjuvant. See the separate review memo for AS01_E DP for additional details.

3.2.P.3 Manufacture of RSVPreF3 DP

3.2.P.3.1 Manufacturer(s)

The names, addresses, and responsibilities of the manufacturers involved in the manufacture, testing, QA release, of the RSVPreF3 DP are listed in the **Table 24** below:

Table 24. Facilities involved in the Manufacture, Testing, and Warehousing of Commercial or Developmental DP Lots

Site name	Address	Responsibilities
Commercial Lots		
GlaxoSmithKline SA (b) (4)	GlaxoSmithKline Biologicals SA (b) (4) Belgium	<ul style="list-style-type: none"> Formulation, filling, and lyophilization of RSVPreF3 DP Labelling, packaging, and visual inspection FC Quality Control and Stability testing of RSVPreF3 FC Quality control testing of Final Product¹ Warehouse operations
(b) (4) GlaxoSmithKline Vaccine (b) (4)	(b) (4)	<ul style="list-style-type: none"> Labelling and packaging Quality control testing of Final Product QA release of Final product Warehouse operations
GlaxoSmithKline (b) (4)	GlaxoSmithKline (b) (4)	<ul style="list-style-type: none"> Labelling and packaging Quality control testing² of Final Product Warehouse operations
GlaxoSmithKline (Rixensart)	GlaxoSmithKline Biologicals Rue de L'Institut 89 1330 Rixensart Belgium	<ul style="list-style-type: none"> QA release of Final product
(b) (4)	(b) (4)	<ul style="list-style-type: none"> Warehouse operations
(b) (4)	(b) (4)	<ul style="list-style-type: none"> Warehouse operations
Development lots		
GlaxoSmithKline SA (b) (4)	GlaxoSmithKline Biologicals SA (b) (4) Belgium	<ul style="list-style-type: none"> Formulation, filling, and lyophilization of RSVPreF3 DP Quality Control and Stability testing of RSVPreF3 FC
GlaxoSmithKline (Rixensart)	GlaxoSmithKline Biologicals Rue de L'Institut 89 1330 Rixensart Belgium	<ul style="list-style-type: none"> Quality Control and Stability testing of RSVPreF3 antigen development batches. QA release

¹ Final product: combo box containing RSVPreF3 antigen and AS01_E with QC testing limited to post packaging identity test.

² QC testing of the final product limited to post packaging identity test which confirms the product in the vial matches the information on the label.

3.2.P.3.2 Batch Formula

The targeted size of a commercial lot is approximately (b) (4) vials corresponding to the maximum capacity of each of the freeze dryers. To guarantee the appropriate amount of antigen in each vaccine vial (120 µg/0.5 mL dose), a (b) (4)

(b) (4)

batches were manufactured as part of the PPQ study (b) (4) and were formulated for the Older Adult vaccine program to contain the final commercial RSVPreF3 vaccine antigen concentration of (b) (4) batch (b) (4) was formulated for use in the (b) (4). Quality Standards for RSVPreF3Lyo are not included in the table below but are described in **Table 16**.

(b) (4)

3.2.P.3.3 Description of Manufacturing Process

The process used to manufacture RSVPreF3 DP consists of the following steps: (b) (4)

(b) (4) Sterile Filtration and Filling, (b) (4) Lyophilization, (b) (4) Visual Inspection (b) (4) Labeling, Packaging, and Storage. A description of the manufacturing steps is given in Table 31 below (prepared from information in the BLA and from the blank Master Batch Records).

A flow diagram illustrating the process used to manufacture RSVPreF3 DP is in **Appendix 9** and a description of the manufacturing process for the DP is given below in **Table 26**.

Table 26. Description of the Manufacturing Process for RSVPreF3 DP

Process	Description
---------	-------------

(b) (4)

Process Steps		Description
		(b) (4)
Lyophilization	Lyophilization	
Capping	Capping, Inspection, Storage	
Labelling and Packaging	Transportation	
Labelling	Labelling	
Packaging	Packaging	
Storage	Storage	

(b) (4)

(b) (4)

(b) (4)

(b) (4) . The responses are clear and acceptable.

We also asked for clarification of th (b) (4) were described in the BLA. The sponsor clarified that the duration allowed for (b) (4)

The sponsor also noted that during process development they evaluated (b) (4)

was defined as a Critical Process Parameter for RSVPreF3 DP and if there is any change in the limit for routine manufacture, the change would be submitted to the BLA for approval. The response is clear and acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates

(b) (4)

(b) (4)

(b) (4)


(b) (4)

3.2.P.3.5 Process Validation and/or Evaluation

Process Performance Qualification (PPQ) study assessed CQAs and CPAs at the commercial scale to assure the manufacturing process is robust and that the resulting product meets quality attributes during routine commercial manufacture using the new facility, utilities, equipment, trained personnel, process, control procedures, and components. PPQ is used to confirm process design, control strategy and proficiency of operations at the commercial scale by comparing (1) DP produced using the new

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

(b) (4)



(b) (4)

Quality Release tests for the Final Container: All (b) (4) FC PPQ lots met the acceptance criteria for the (b) (4) process. In addition, as explained below, all quality release test results for the PPQ lots were within the (b) (4) comparability ranges. A single (b) (4) result was seen for (b) (4) characterization test, which was justified. Details are discussed below and are summarized in **Table 31**.

Additional Characterization tests on FC: The following additional characterization tests were used to evaluate all FC PPQ lots using (b) (4) and are included in

5 Pages were determined to be not releasable: (b)(4)

(b) (4)

[REDACTED]

(b) (4)

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

No new excipients are introduced into the RSVPreF3 DP that are not in the RSVPreF3

(b) (4)

They are purchased from qualified commercial suppliers and comply with (b) (4) requirements.

AS01_E adjuvant is supplied as a liquid in a separate vial and is used to reconstitute the lyophilized RSVPreF3 antigen. Manufacture and control of AS01_E is reviewed by the DVP adjuvant reviewer.

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

RSVPreF3 DP excipients are tested per (b) (4) methods and conform with (b) (4) requirements. The analytical procedures used for DP excipients are performed as specified in the applicable (b) (4). No additional validation studies are required.

3.2.P.4.4 Justification of Specifications

Excipients used in the RSVPreF3 DP conform with (b) (4) requirements.

3.2.P.4.5 Excipients of Human or Animal Origin

There are no excipients of human or animal origin used in the manufacture of RSVPreF3 DP.

3.2.P.4.6 Novel Excipient

There are no novel excipients used in the manufacture of RSVPreF3 DP.

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 tests, specifications, and justification for specifications for the RSVPreF3 Final Container (following reconstitution with WFI) and for Final Product (one vial each of RSVPreF3 antigen and AS01_E adjuvant) for clinical testing and commercial use are shown below in **Tables 34 and 35**, respectively. Changes in analytical procedures and release specification during development of the DP manufacturing process were discussed in section 3.2.P.2.3 Manufacturing Process Development under the section describing Analytical Changes in CQAs and were summarized in **Table 22**.

Table 34. Evaluation of DP Release Tests, Specifications and Justifications for Phase 3 Clinical Lots and PPQ Batches

Attribute	Test Method	Justification for Specification	Phase 3 Clinical Lot Acceptance Criteria	PPQ Lots and Final Acceptance Criteria
Description	In house test according to (b) (4)	(b) (4)	Same as Final Acceptance Criteria	White cake or powder. Clear, colorless liquid after reconstitution with WFI. (b) (4)
(b) (4)				

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Attribute	Test Method	Justification for Specification	Phase 3 Clinical Lot Acceptance Criteria	PPQ Lots and Final Acceptance Criteria
Identity	In house (b) (4)	(b) (4)	Same as Final Acceptance Criteria	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
RSVPreF3 content	In house (b) (4)	(b) (4)	(b) (4)	(b) (4)
Endotoxin content	(b) (4)	(b) (4)	(b) (4) Same as Final Acceptance Criteria	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
RSVPreF3 (b) (4)	In house (b) (4)	(b) (4)	(b) (4)	(b) (4)
PS80 Content	In house (b) (4)	(b) (4)	(b) (4)	(b) (4)
Trehalose Content	In house (b) (4)	(b) (4)	Same as Final Acceptance Criteria	(b) (4)
Sterility (b) (4)	(b) (4)	(b) (4)	Same as Final Acceptance Criteria	No growth

*k-factor of 3.368 was updated in amendment 27 response to IR#27 Question 9

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Table 35. RSVPreF3 Final Product Release Specifications (after labeling operations are completed)

Tests ¹	Acceptance criteria
Identity RSVPreF3 by (b) (4)	(b) (4)
(b) (4)	(b) (4)

Tests ¹	Acceptance criteria
	(b) (4)

(b) (4)

1. Tests performed on Finished Product for purpose of identification only (to comply with 21 CFR requirements).

(b) (4)

Reviewer's assessment: *The sponsor provided justifications for the specifications for release of RSVPreF3 FC. All specifications for release were acceptable except for (b) (4). The potency of the vaccine dose is determined based on (b) (4)*

With respect to the IVRP (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

Release testing on the Final Container

For routine release of RSVPreF3 Final Containers (FC), quality release (QR) tests are performed as shown in **Table 35 above**. DBSQC will provide the primary review of the validation of these (b) (4) tests, however, RSVPreF3-specific test methods are also reviewed below.

The following QR tests are performed for release of DP and many are used for stability testing also so we have included information pertaining to assay validation for the in-house tests.

(b) (4)

Reviewer's assessment: *In the original BLA submission, the test for Description was listed as an in-house test in Section 3.2.S.4.2 Analytical Procedures, Overview and Section 3.2.P.5.2 Analytical Procedures, Overview. However, in Section 3.2.P.5.6 Justification of Specifications, it was listed as a (b) (4) test. An Information Request for clarification was sent to GSK on October 26, 2022. In Amendment 005 (sequence 008), dated November 8, 2022, GSK stated that Description is an in-house test performed according to (b) (4)*

Although it is an in-house test, a Method Validation Report was not provided since GSK considers this a "simple test" since it does not require a complex sample preparation and qualitatively measures a physico-chemical property by visual inspection only. This response is acceptable.

(b) (4)

Reviewer's assessment: *In the original BLA submission, a verification report was not provided for the (b) (4) test method. An Information Request for clarification was sent to GSK on October 26, 2022, requesting the verification report. In Amendment 005 (sequence 008), dated November 8, 2022, GSK stated that in alignment with (b) (4) Verification of (b) (4) Procedures, basic (b) (4) procedures performed routinely are exempt from the requirement of provision of verification reports, unless there is an indication that the (b) (4) procedure is not appropriate for the article under test. I agree with GSK's position that the test for (b) (4) falls under this exemption and no verification report is necessary. This response is acceptable.*

(b) (4)

DBSQC will review this test.

Reviewer's assessment: *In the original BLA submission, a verification report was not provided for the (b) (4) test method. An Information Request for clarification was sent to GSK on October 26, 2022, requesting the verification report. In Amendment 005 (sequence 008), dated November 8, 2022, GSK stated that in alignment with (b) (4)*

(b) (4)
I agree with GSK's position that the test for (b) (4) falls under this exemption and no verification report is necessary. This response is acceptable.

Identity and in vitro relative potency RSVPreF3 (b) (4) : This is an in-house release test used to evaluate the identity and potency of RSVPreF3 Drug Product FC and Final pack (Identity only) that is also part of the **stability testing** program.

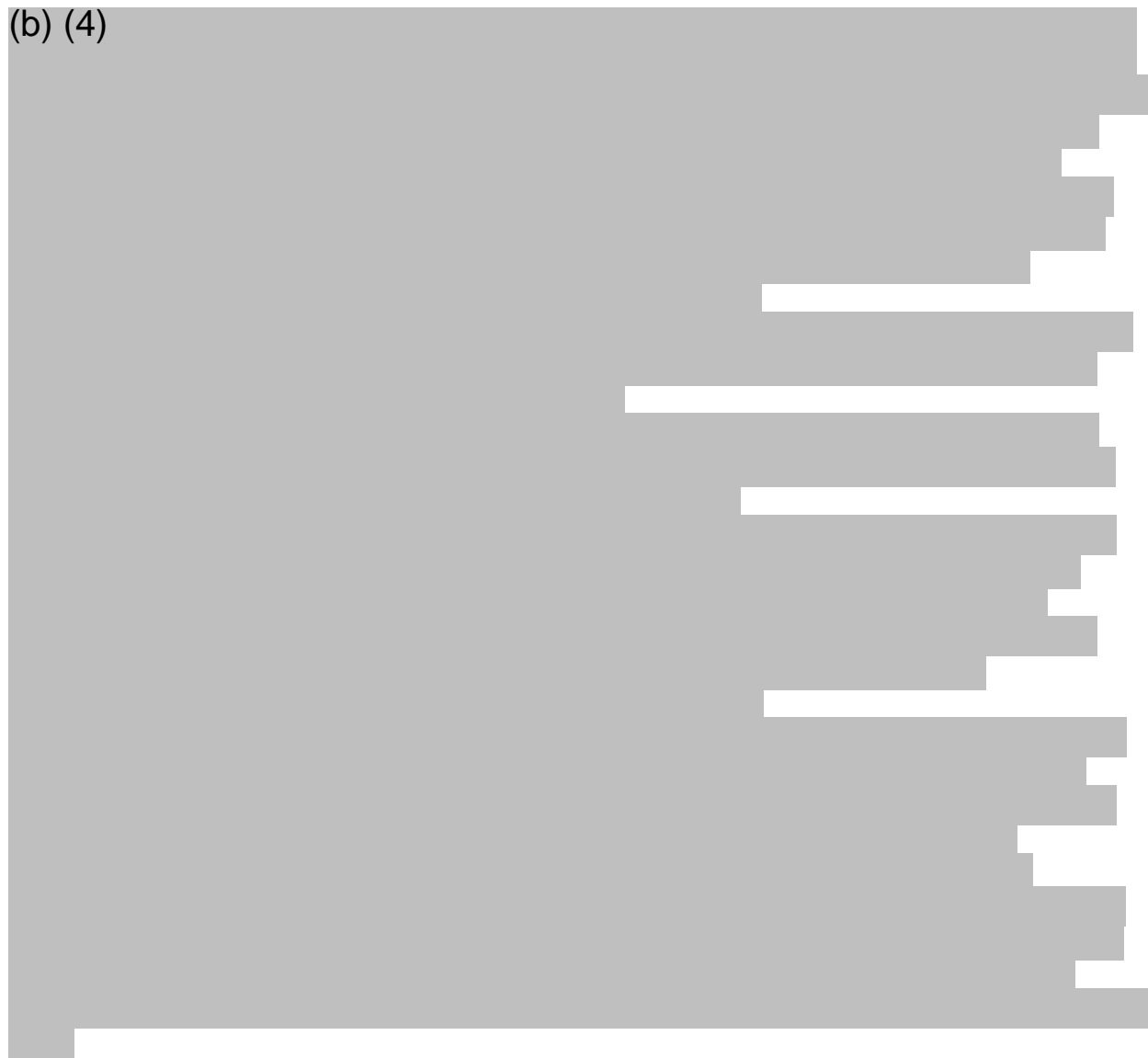
The method is identical to the method described for the (b) (4). However, this method was also validated using DP.

Reviewer's assessment: *Following review of the Method Validation Report for Identity and in vitro relative potency RSVPreF3 by (b) (4) submitted in IND 18540 amendment 71 (for (b) (4) DP), an IR letter was sent on June 15, 2022, asking for clarification since the range was reported in either ng/mL or µg/mL. The sponsor responded in IND 18540 amendment 187, dated November 25, 2022, with an updated Method Validation Report (v3) listing the correct units (µg/mL). This updated report also needs to be submitted to the BLA for accuracy purposes as requested in IR#27 sent to the sponsor on March 13, 2023. On March 20, 2023, the sponsor submitted their response in amendment 27 to the BLA. The acknowledged that RSVPreF3 is (b) (4) and submitted the corrected Method Validation Report to section 3.2.R in the BLA.*

(b) (4)

The sponsor also responded to Question 4 in IR#8 issued on November 28, 2022, and provided the following information in amendment 32 received on March 31, 2023 including 1) the results of identity testing performed as part of the (b) (4) protocol testing at GSK (b) (4) and at GSK (b) (4) described above and 2) the SOPs for the (b) (4) for Identity and IVRP for each site (b) (4). Documents were reviewed and are satisfactory. The response is complete and acceptable.

(b) (4)



(b) (4)



(b) (4)

[Redacted]

Endotoxin content (b) (4) : This is a (b) (4) release test that is performed on RSVPreF3 DP FC. DBSQC will review this test.

(b) (4)

[Redacted]


Trehalose content (b) (4) : This is an in-house release test that is performed on RSVPreF3 DP FC. DBSQC will review this test.

Sterility test (b) (4) : This is a (b) (4) release test that is performed on RSVPreF3 DP FC that is also part of the **stability testing** program. DBSQC will review this test.

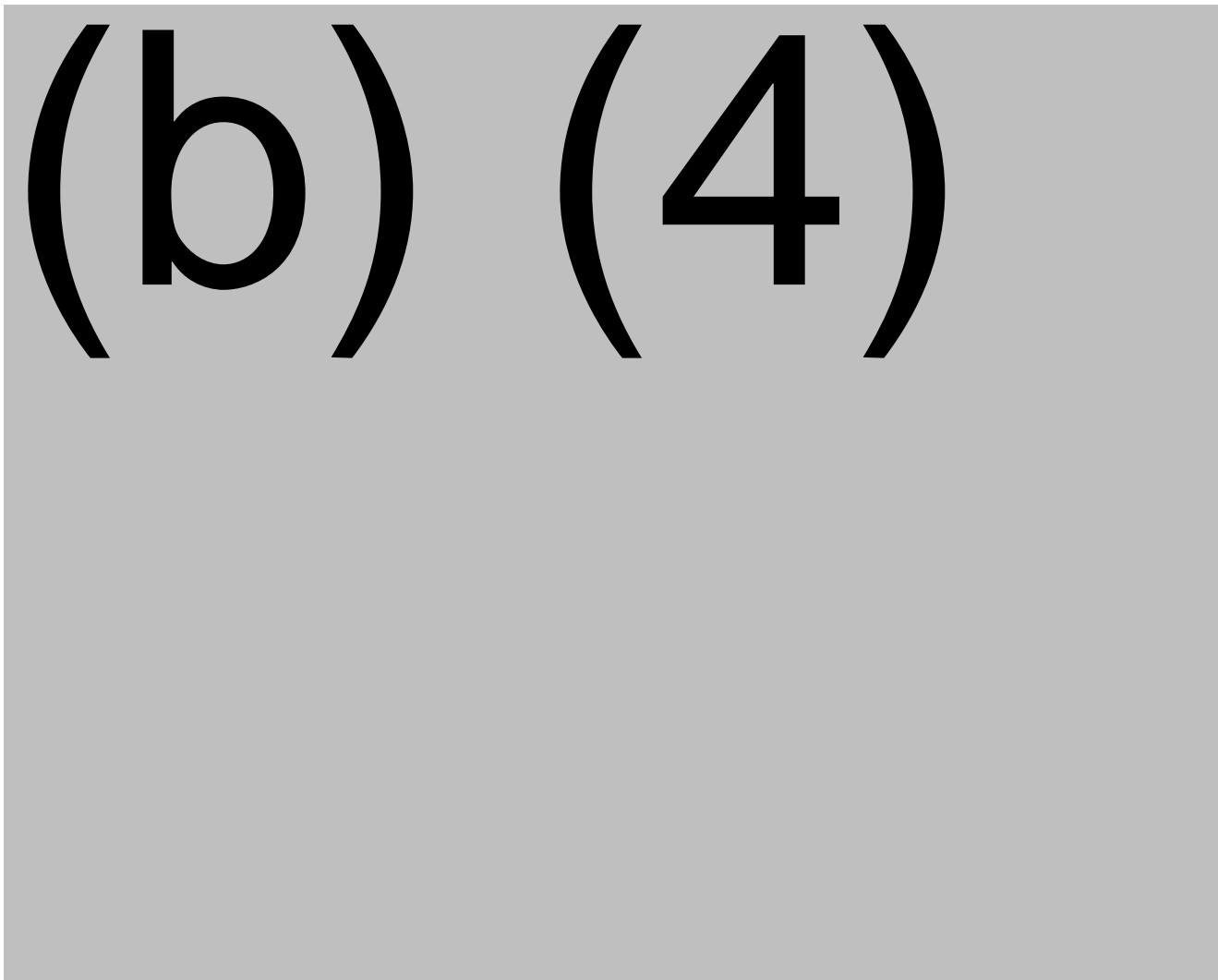
Overall Reviewer's Assessment: *The analytical RSVPreF3 DP FC release and stability tests were adequately validated and shown to be suitable for their intended use.*

3.2.P.5.4 Batch Analyses

(b) (4)




(b) (4)



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


(b) (4)

A large rectangular area of the document is redacted with a solid grey fill. The redaction covers approximately the top third of the page content, starting below the header and ending above the section header. The text "(b) (4)" is printed in the top left corner of this redacted area.

(b) (4)

3.2.P.7 Container Closure System

The container closure system for RSVPreF3 Lyo is a clear Type ^{(b) (4)} 3 mL glass vial that meets (b) (4)

A rectangular area of the document is redacted with a solid grey fill, located directly below the paragraph describing the container closure system.

A diagram of the vial is in **Appendix 13**.

Vials are stoppered with grey, Bromobutyl, type ^{(b) (4)} rubber stoppers sterilized by the manufacturer using (b) (4) prior to shipping. Stoppers meet (b) (4)

(b) (4)

Stoppers are (b) (4)

The stoppered vial is covered by a colored, polypropylene flip-off cap affixed on top of an aluminum cap. Flip-off caps are not sterilized.

Information on stoppers and caps was provided in the submission and included:

1. Letter of Authorization from (b) (4), to FDA allowing GSK to cross reference DMF (b) (4)
2. Letter of Authorization from (b) (4), to FDA giving GSK permission to cross reference MF STN (b) (4) describing the gray rubber stoppers, (b) (4) under Section 3.2.P.7

The manufacturers of the type (b) (4) glass vials are listed below. Representative Certificates of Analyses were submitted and reviewed.

(b) (4)

(b) (4)

Extractables and leachables assessment for the container closure system is described above in Section 3.2.P.2.4. The suitability of the container closure systems is reviewed under stability studies in Section 3.2.P.8.

3.2.P.8 Stability

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

The proposed shelf life of the RSVPreF3 DP is 24 months when stored at 2 to 8°C. The DP must be stored in the original packaging to protect it from light. The shelf-life claim is based on data obtained from long term stability studies for Process (b) (4) RSVPreF3 DP lots. Given that the RSVPreF3 FC and AS01_E FC are presented as two independent vials, the expiry date is determined by whichever component expires first.

Additional supportive data are provided by the following studies

(b) (4)

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

(b) (4)

Reviewer's assessment: These data support the proposed shelf life of 24 months at 5±3°C and further validate a (b) (4)

These studies also support the storage of RSVPreF3 reconstituted with AS01_E for up to 4 hours stored at 5±3°C or at 25°C (b) (4). The data also indicate RSVPreF3 FCs can tolerate temporary storage at 25°C (b) (4) (b) (4)

Reviewer's assessment: IR#44 was sent to the sponsor on April 20, 2023, requesting them to specify the date of manufacture (DOM) and to define the proposed shelf-life with respect to the DOM for RSVPreF3 (b) (4) RSVPreF3 and AS01_E Drug Products (DP).

The sponsor provided responses in amendment 42 (SN 45) on April 21, 2023, which showed stability data tables listing the dates of actual manufacture for (b) (4)

RSVpreF3 and AS01_E Product lots. Since the sponsor did not identify the manufacturing step that defined the date of manufacture per 21CFR610.50, IR#46 was sent on April 24, 2023, asking them to update Section 3.2.P.8 Stability for the RSVPreF3 DP and AS01_E DP with statements that defined the date of manufacture used as the beginning of the dating period for shelf-life for each.

The sponsor submitted a secure email on April 24, 2023, asking if the following statement was sufficient: "The shelf-life is calculated as from the manufacturing date corresponding to the day of start of filling of RSVPreF3 or AS01_E Final Container lot".

CBER agreed that this statement was sufficient. The sponsor formally submitted the change to the BLA in amendment 44 (SN47) on April 25, 2023. The response is complete and acceptable.

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

For commercial lots, (b) (4) (b) (4) will be followed for commercial stability for up to 24 months at 5±3°C. Testing will occur (b) (4) and include description, (b) (4) RSVPreF3 in vitro relative potency (b) (4) sterility test (b) (4) RSVPreF3 (b) (4) and container closure integrity test.

Additional supportive stability testing studies are planned or ongoing as listed below:

- Cumulative stability study to support storage at 5±3°C for up to (b) (4) months of RSVPreF3 FC lots manufactured from RSVPreF3 (b) (4) stored between 24 (b) (4) (Planned study).
- Long term stability study for (b) (4) RSVPreF3 FC lots stored at 5±3°C for up to (b) (4) months. (Study ongoing).
- Long term stability study for (b) (4) RSVPreF3 FC lots stored at 5±3°C for up to (b) (4) months to support maximal (b) (4). (Study ongoing).

- Accelerated stability study to determine the rate of change for RSVPreF3 properties over time for FC held at (b) (4) for up to (b) (4) days (Study ongoing).
- (b) (4) Study ongoing).
- In use stability protocol to support the storage of RSVPreF3/AS01_E reconstituted vaccine for 4 hours at 25°C (b) (4) or 4 hours at 5±3°C using RSVPreF3 FC and AS01_E FC stored at 5±3°C for (b) (4) months. (Planned).

Reviewer's assessment: On April 18, 2023, we contacted Damaris Lopez Rosario (DMPQ) recommending that (b) (5), (b) (7)(E) . Dr. Lopez Rosario indicated by e-mail that (b) (5), (b) (7)(E)

3.2.A Appendices for Facilities, Adventitious Agent Safety Evaluation and Novel Excipients

3.2.A.1 Facilities and Equipment





We defer to DMPQ for the review of the facilities and equipment.

3.2.A.2 Adventitious Agents Safety Evaluation

(b) (4)


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

(b) (4)



3.2.R.3 Environmental Assessment or Claim of Categorical Exclusion

The sponsor has requested a categorical exclusion from the Environmental Assessment pursuant to 21CFR 25.31(c). This product is a recombinant vaccine consisting of two components: purified RSVPreF3 antigen and AS01_E Adjuvant System. The RSVPreF3 antigen is an engineered RSV F protein purified from CHO-^{(b) (4)} cells and contains the following (b) (4)



. The RSVPreF3 antigen is filled into single-use vials and lyophilized. AS01_E liquid adjuvant is also filled into single use vials and is used to reconstitute the vaccine antigen in the clinic just prior to immunization. The 0.5 mL dose is administered intramuscularly with a needle and syringe. The proposed indication is for active immunization for the prevention of respiratory disease caused by respiratory syncytial virus in adults 60 years of age and older.

The authentic RSV-F prefusion protein and the (b) (4) are both found naturally in the environment. The RSVPreF3 vaccine is non-infectious, and its use will not significantly alter the concentration or distribution of the substance, its metabolites or degradation products in the environment and therefore does not require an environmental assessment.

Reviewer's Assessment: *We support the request for a categorical exclusion for this product, RSVPreF3 with AS01_E.*

3.2.R.4 Reference Product Designation Request

The sponsor has requested reference product exclusivity since there are currently no licensed biological products that are structurally related to AREXVY. The CMC reviewers recommend that the request be granted, with a period of exclusivity of 12 years.

Reviewer's Assessment: *Reference Product Exclusivity is recommended.*

Receipt date of BLA Sep 2, 2022

CMC review completed Dec 12, 2022

DVRPA review completed Dec 12, 2022

ADRAM meeting originally scheduled Mar 21, 2023, rescheduled for April 17, 2023, rescheduled for May 1, 2023.

3.2.R.5 Labeling Review

Full Prescribing Information (PI):

Dosage Forms and Strengths: AREXVY is a suspension for injection supplied as a single-dose vial of lyophilized antigen component to be reconstituted with the accompanying vial of adjuvant suspension component. A single dose after reconstitution is 0.5 mL.

Description: AREXVY is a sterile suspension for intramuscular injection. The vaccine is supplied as a vial of lyophilized recombinant respiratory syncytial virus glycoprotein F stabilized in pre-fusion conformation (RSVPreF3) as the antigen component, which must be reconstituted at the time of use with the accompanying vial of AS01E adjuvant as the adjuvant suspension component. The lyophilized antigen component is a sterile white powder. The adjuvant suspension component is an opalescent, colorless to pale brownish sterile liquid supplied in vials.

After reconstitution, each 0.5 mL dose is formulated to contain 120 mcg of the recombinant RSVPreF3 antigen, 25 mcg of MPL, and 25 mcg of QS-21. Each dose also contains 14.7 mg of Trehalose, 4.4 mg of sodium chloride, 0.83 mg of potassium dihydrogen phosphate, 0.26 mg of dipotassium phosphate, 0.18 mg of polysorbate 80, 0.15 mg of disodium phosphate anhydrous, 0.5 mg of DOPC, and 0.125 mg of cholesterol. After reconstitution, AREXVY is a sterile, opalescent, colorless to pale brownish liquid. AREXVY contains no preservative. Each dose may also contain residual amounts of host cell proteins ($\leq 2.0\%$) and DNA (≤ 0.80 ng/mg) from the manufacturing process.

Clinical Pharmacology: AREXVY induces an immune response against RSVPreF3 that protects against LRTD caused by RSV.

How Supplied/Storage and Handling:

Before reconstitution: Adjuvant suspension component vials: Store refrigerated between 2° and 8°C (36° and 46°F). Store in the original package in order to protect vials from light. Do not freeze. Discard if the adjuvant suspension has been frozen.

Lyophilized RSVPreF3 antigen component vials: Store refrigerated between 2° and 8°C (36° and 46°F). Store in the original package in order to protect vials from light. Do not freeze. Discard if the antigen component has been frozen.

After reconstitution: Administer immediately or store in the refrigerator between 2°C and 8°C (36°F to 46°F) or at room temperature [up to 25°C (77°F)] for up to 4 hours prior to use. Protect vials from light. Discard reconstituted vaccine if not used within 4 hours. Do not freeze. Discard if the vaccine has been frozen.

Carton and Container Label: We reviewed the product information for RSVPreF3 provided on primary and secondary container label and note that all information provided is accurate and acceptable.

4.0 Non-clinical Studies

This section contains a summary of the four pharmacological non-clinical studies covering the selection and justification of adjuvant, characterization of the immune response following vaccination and impact of (b) (4) on immunogenicity in naïve mice. Please see review by Nabil Al-Humadi for toxicology studies and review by Marina Zaitseva for adjuvant-specific (AS01, QS-21 and MPL) non-clinical studies.

Table 45. Overview of Non-clinical Studies

Study Type	Study Number	Test system Mice	IND amendment
Justification of need for adjuvant and adjuvant selection justification	20160092-0094	(b) (4)	OS Amendment 26 (v2)
Immunogenicity – proof of concept	20170126-0174	(b) (4)	OS Amendment 26 (v4)
Immuno-characterization of Phase 1/2 GMP lots	COV 0100-18	(b) (4)	OS
Support to process Characterization (b) (4) impact)	20180258	(b) (4)	Amendment 31 Amendment 37 (v2)

(v2) refers to Version 2 of the original report and contains minor editorial changes only

(v4) refers to Version 4 of the original report and contains minor editorial changes and additional cross neutralization data as requested by CBER.

4.1 Comparative Immunogenicity Studies for Adjuvant Selection

(b) (4)

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

5.0 Clinical Assays and Validation of Clinical Assays for Study Endpoints

Clinical assays include an RSV-A and -B Quantitative Reverse Transcription-Polymerase Chain Reaction (RT-qPCR) for case confirmation in the pivotal Phase III efficacy trial. Four additional RSV-specific clinical assays were used to assess primary and secondary immunogenicity endpoints. Vaccine induced humoral responses were evaluated by: RSV-A and -B neutralization assays and RSV PreF3-specific IgG enzyme-linked immunosorbent assay (ELISA). RSV-F specific CD4+ and CD8+ T cell responses were evaluated by Intracellular Cytokine Staining assay based on 10 parameters (ICS 10P). Four hemagglutination inhibition (HAI) assays specific to each influenza strain included in the FLU-QIV vaccine were used to measure responses following co-administration of the QIV vaccine with RSVPreF3/AS01E vaccine. The validation reports for RSV-specific assays are covered in this review. The validations for the Influenza HAI assays were reviewed by Ewan Plant.

Reviewer's comment: In the original BLA submission, the handling and storage of biological samples (nasal swabs, sputum, serum and/or PBMCs) was not described. An Information Request was sent to GSK on October 26, 2022, requesting additional information describing the handling and shipping of clinical samples from the study to testing sites. In Amendment 005 (sequence 008), dated November 8, 2022, GSK provided the requested information.

GSK laboratories perform the RT-qPCR, RSV-A/RSV-B neutralization assays and ICS-10P assays performed in the GSK Clinical Laboratory Science, (b) (4), Belgium. The anti-IgG RSVPreF3 ELISA is performed at (b) (4). Investigator Manual & Shipping Instructions were sent to all clinical sites and provide the detailed instructions for handling, storage and shipping of biological samples.

(b) (4)

. This response is acceptable.

5.1 RSV-A and RSV-B quantitative Reverse Transcription-Polymerase Chain Reaction (RT-qPCR)

This assay is used to detect the presence of RSV genome in nasal and nasopharyngeal swabs for case confirmation in the Phase 3 efficacy trial. Testing is performed at GSK Clinical Laboratory Science, (b) (4), Belgium.

(b) (4)

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

(b) (4)

Reviewer's assessment: *The sponsor demonstrated the RSV ICS 10P assay has been fully validated and is suitable for its intended purpose.*

5.5 Review of Influenza HI Assay and Validation

The HI assay is used to evaluate the humoral immune response of an influenza virus vaccine used in RSVPreF3 OA coadministration studies.

Summary of Recommendation: The Hemagglutination Inhibition (HI) assay is used by the sponsor to assess the antibody response toward quadrivalent influenza vaccine co-administered with the RSV vaccine. Antibody response is used as a surrogate of protection for the influenza vaccine to assess effectiveness of the influenza and RSV vaccines to support vaccine coadministration. The standard operating procedure for the HI assay is acceptable. The HI assay detects antibodies that bind influenza virus and is validated for the four types of influenza antigen included in quadrivalent influenza vaccines (H1N1, H3N2, and influenza B Victoria and Yamagata lineages). There are minor issues with assay validation for the Yamagata lineage, but overall, the assay was found acceptable for detection and quantification of influenza antibody response.

Submission and Review:

(b) (4)

The HI assay was used to assess the humoral response to influenza vaccination for a co-administration study using FLU-QIV with RSVPreF3 OA in study RSV OA=ADJ-007 described in 214488 (RSV OA=ADJ-007): A Phase 3, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with FLU-QIV vaccine in adults aged 60 years and above (submitted in Section 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication) and in Integrated Analysis of Efficacy (in Section 5.3.5.3 Reports of Analyses of Data from more than one study).

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

(b) (4)

Reviewer's Overall Assessment of Clinical Assays Described in Module 5: All five RSV-specific clinical assays have been validated and are suitable for their intended purposes to confirm RSV cases (RT-qPCR) and evaluate the immunological responses (neutralization and binding antibody assays and intracellular cytokine staining assays) in humans following immunization with RSVPreF3 antigen adjuvanted with AS01_E. The HI assays have also been validated and are suitable for their intended use.

6.0 Components Information

Table 52. Components Table

Components	Contained in Final Product	UNII Code
RECOMBINANT RESPIRATORY SYNCYTIAL VIRUS PRE-FUSION F PROTEIN (RSVPREF3 ANTIGEN)	Y	(b) (4)
TREHALOSE DIHYDRATE	Y	
SODIUM CHLORIDE	Y	
POTASSIUM DIHYDROGEN PHOSPHATE	Y	
DISODIUM PHOSPHATE, ANHYDROUS	Y	
DIPOTASSIUM PHOSPHATE	Y	
POLYSORBATE 80	Y	
WATER FOR INJECTION	Y	
AS01E ADJUVANT	Y	

1,2-DIOLEOYL-SN-GLYCERO-3- PHOSPOCHOLINE	Y
CHOLESTEROL	Y
QUILLAJA SAPONIN (QS-21)	Y
MONOPHOSPHORYL LIPID A (b) (4)	Y

(b) (4)

(b) (4)

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

Appendix 13. Diagram of vial

