DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: October 17, 2017

To: The File STN 125614

FromROM: Shuang Tang, DVP
Product reviewer

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Sponsor: GlaxoSmithKline (GSK) Biologicals

Subject: CMC Review of Original BLA STN125614

Product: Zoster Vaccine Recombinant, Adjuvanted (Shingrix, also referred to as HZ/su or gE/AS01B

Submission Date: October 21, 2016

Action Date: October 21, 2017

Abbreviations: (b) (4) ELISA: Enzyme-linked immunosorbent assay; (b) (4) gE: Glycoprotein E; VZV: Varicella-Zoster Virus, (b) (4) DS: Drug substance; DP: Drug product; (b) (4) ; SD: Standard deviation; (b) (4) .

Contents

1 Executive Summary

This BLA (STN 125614) is for a varicella zoster virus (VZV) recombinant vaccine adjuvanted with AS01B. The proposed commercial name of the vaccine is Shingrix, also referred as HZ/Su or gE/AS01B in this memo. Shingrix consists of 50 µg of the recombinant (b) (4) -truncated VZV glycoprotein E (gE) antigen presented as a lyophilized preparation in monodose vials. The AS01B adjuvant is provided in separate monodose vials (0.5 mL/dose). The AS01B adjuvant contains 50 µg of each of the immuno-enhancers QS-21 and MPL combined with liposomes. The content of the AS01B vial is used to reconstitute the content of the gE vial immediately prior to injection. The vaccine is intended for prevention of herpes zoster (shingles) in adults aged 50 years and older. The vaccine is to be administered intramuscularly in two doses (0.5 mL each) separated by 2 to 6 months.

This review encompasses: (1) all relevant quality-related information in the BLA (Module 3 of the CTD format), (2) clinical assays (including the VZV (b) (4) qPCR assay, human beta-actin qPCR assay, anti-gE ELISA, gE specific intracellular cytokine staining assay, and (b) (4) (b) (4) described in 5.3.1.4 Reports of bioanalytical and analytical methods for human studies), (3) CMC-related pre-clinical studies (Module 4 of the CTD format) and (4) CMC-relevant portions of amendments 05, 11, 12, 15, 17, 28, 30, 35, 37, 38, 39, 44 and 54. Quality-related information on the AS01B adjuvant is reviewed by other DVP reviewers.

The (b) (4) manufacturing and the gE drug product manufacturing occur at GSK's commercial facility located at (b) (4), Belgium. Labelling, QC testing and packaging operations are conducted at the facilities located at (b) (4), Belgium and (b) (4) . QA release is performed at the facilities at (b) (4) and Rixensart, Belgium.

The process for the manufacture of (b) (4)

The process for drug product formulation involves two major steps: (b) (4) into 3 mL type (b) glass containers followed by lyophilization. The lyophilized gE containers are capped and inspected. The gE final container drug product expiry is 36 months at 2-8°C. The gE final container is labeled and packaged together with AS01B final container at the facilities located at (b) (4) and (b) (4), Belgium.

The gE (b) (4) drug product are manufactured under cGMP and the manufacturing process went through (b) (4) through the clinical and commercial development. The batch scales for the (b) (4)

(b) (4) . Manufacturing site changes occurred during the process upgrades. In addition to the changes in the manufacturing scale and facility, there were minor changes made for manufacturing process upgrades. The clinical study material used in the US was manufactured using (b) (4) . The Phase III efficacy gE final container lot was manufactured using (b) (4) , and the (b) (4) consistency gE final container lots were manufactured using (b) (4) . The product quality of the gE (b) (4) drug product manufactured using (b) (4) remained comparable as evaluated by release specification tests, comprehensive characterization tests, stability studies, viral clearance studies and non-clinical immunogenicity bridging studies. Critical process parameters, critical process attributes, and critical quality attributes were identified through evaluation of the manufacturing process for (b) (4) drug product during the Phase III clinical development and commercial development. The control limits of the identified critical parameters were enforced in the manufacturing of the commercial consistency gE (b) (4) drug product (using (b) (4)).

The capability to produce gE (b) (4) product of consistent quality was ascertained by comprehensive assays, including the potency gE by (b) (4) (which is stability indicating, and is capable of detecting subtle changes induced by environmental stresses), host-cell protein by (b) (4) (used to determine residual CHO cell impurity), purity gE by (b) (4) (which is also stability indicating and is used to determine the purity of gE antigen), protein content by (b) (4) (used to determine the gE content per dose), relative abundance of gE sequence heterogeneity by (b) (4) , and endotoxin by (b) (4) method (used to ensure the drug product is free of bacterial endotoxin contamination). Quality is also established by long-term stability data generated using the potency gE by (b) (4) assay, sterility tests, water content test, container and closure integrity test. The proposed shelf life of 36 months at 2-8^{o}C for the gE final container is supported by stability data from a total of (b) (4) Phase III efficacy and consistency gE final container lots. Stability testing for the three commercial consistency lots (b) (4) is ongoing and the data through the (b) (4) interval appear satisfactory. The ongoing sequential stability studies (which empirically challenge the worst-case storage of (b) (4) up to (b) (4) for input (b) (4) lots, maximal (b) (4) for final container lots, then assessment of the final container drug product throughout the expiry period) highlight the inherent stability of properly formulated gE antigen.

(b) (4) has been established and carefully characterized to be genetically stable, which ensures consistent quality for future production, and to be free of adventitious agents using extensive in vitro and in vivo analytical methods. Removal of impurities and process residuals for the gE antigen was demonstrated to be comparable between the different manufacturing developmental processes. Protein purity for gE antigen as assessed by (b) (4) . Residual host-cell DNA is (b) (4) DNA per vaccine dose, and residual host-cell protein is (b) (4) per dose for the commercial batches. A cumulative reduction factor of (b) (4) for the relevant model virus (b) (4) is achieved by the gE purification steps using worst-case conditions. The risk of CHO retrovirus-like particles in a vaccine dose was evaluated and less than (b) (4) retrovirus-like particle per (b) (4) doses would be expected. Thus, the gE purification steps provide adequate assurance for impurity removal and virus safety of the vaccine.

The following review issues were encountered and resolved:

- A major exception occurred in the manufacturing of the commercial consistency gE final container lots. Although meeting the release specifications and other in-process monitoring tests, the commercial consistency gE final container lots were identified to contain higher level of (b) (4) The root cause studies demonstrated that (b) (4) , widely used to (b) (4) in gE antigen in partially stoppered vials. Note: A different sterilization mechanism ((b) (4)) was used in the manufacturing of the gE final container clinical lots. Product impact studies concluded that higher levels of (b) (4) of the gE antigen do not significantly impact gE antigen in terms of the immunogenicity, antigenicity, safety or secondary and tertiary structure of the gE antigen. The results from corrective and preventative action lots manufactured by lowering the (b) (4) level prior to starting filling from (b) (4) and covering the worst-case conditions concluded that the level of (b) (4) is reduced by (b) (4) ; however, a relative higher than clinical lots level of gE (b) (4) may not be avoidable. GSK proposed to establish a (b) (4) continuous aseptic filling operation using the adjusted process with residual (b) (4) concentration prior to starting the filling operations set at (b) (4) for the future commercial production. The exception, investigation as well as corrective and preventative actions were submitted to CBER during the IND Phase and discussed extensively between GSK and CBER in the Type C meetings held on December 5, 2015 and April 14, 2016. During the Type C meetings, CBER agreed with GSK's proposal of establishing a control limit of (b) (4) and recommended to test (b) (4) on the first (b) (4) commercial lots. CBER also recommended measuring the (b) (4) level in vials filled with water for injection and recommended re-qualifying the aseptic filling operation. In Amendment 05, GSK concluded that the maximum residual (b) (4) content is lower than (b) (4) in water filled vials, which is below the threshold of toxicological concern of (b) (4) specified in the EMA's guideline. Also, re-qualification of the aseptic filling operation by (b) (4) was satisfactory. In Amendment 038, GSK submitted lot-release information of (b) (4) commercial lots manufactured using the (b) (4) continuous filling operation (served as additional process validation). The (b) (4) level of these lots ranged from (b) (4) after storage for (b) (4) days at (b) (4) (used to estimate the maximum (b) (4) level at the end of shelf life), suggesting consistent quality is obtained through the corrective and preventative actions.
- The information related to the source and qualification of the (b) (4) , 3 mL glass vials and stoppers for drug product was requested on April 6, 2016 and June 27, 2016. GSK provided the requested information in Amendment 17 on April 20, 2017, and Amendment 30 on July 12, 2017. GSK's responses are acceptable.
- The statistical reviewer and I noticed inconsistencies for manufacturing-related analytic assays, e.g., the acceptance criteria for the internal control used in the gE content by

(b) (4) for lot release samples and for in-process samples appeared to be significantly different from each other, acceptance criteria in the SOP appeared to be different from the validation report for the gE by (b) (4) and the (b) (4) content by (b) (4) (requested on July 24, 2017). In addition, the validated range for gE final container used the amount of gE, while in the BLA, the specification of gE antigenicity used a ratio of gE content by (b) (4) and protein content by (b) (4). In Amendment 035 (dated Aug 11, 2017), GSK indicated that the gE (b) (4) for release samples and for in-process samples were validated in different laboratories despite both sharing the same reagents. With increased experience, GSK decided to enforce the strict acceptance criterion for the internal control for future testing. GSK also indicated that acceptance criteria might be changed due to drift of experimental conditions and reagents, as a result of continuous review of life cycle of analytical methods. Such changes may eventually trigger revalidation of the method. GSK also submitted the new validation range by transforming the gE content by (b) (4) to a ratio and indicated that the validation report will be updated in the (b) (4). GSK's responses are acceptable.

Final Recommendation:

I recommend approval of this BLA. (b) (4)

2 Introduction

This original BLA by GlaxoSmithKline (GSK) Biologicals is for a Zoster Vaccine with tradename Shingrix. This is a subunit vaccine consisting of recombinant varicella zoster virus (VZV) glycoprotein E (gE) as antigen, combined with GSK's proprietary adjuvant system AS01B. The gE protein is provided in a lyophilized form in monodose vials (50 μg/dose). The AS01B (liquid) adjuvant system is provided in separate monodose vials (0.5 mL/dose). The content of the AS01B vial is used to reconstitute the content of the gE vial immediately prior to injection. The gE antigen is purified from the culture supernatant of CHO cells stably expressing the truncated VZV gE lacking the membrane anchor and carboxyterminal domain. The AS01B adjuvant system contains 50 μg of each of the immuno-enhancers QS-21 (Quillaja saponaria Molina, fraction 21) and MPL (3-O-desacyl-4'-monophosphoryl lipid A) combined with liposomes.

SHINGRIX is designed to induce strong cellular and humoral immune responses in individuals with pre-existing immunity against VZV and who are at increased risk of developing herpes zoster (HZ). The proposed indication is: SHINGRIX is a non-live, recombinant vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older.

The vaccine is to be administered intramuscularly in two doses (0.5 mL each) separated by 2 to 6 months.

3 Drug Substance

3.1 General Description

(b) (4)

3.2 Manufacturing Sites and Contract Laboratories

GlaxoSmithKline Biologicals SA

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4 Drug Product

4.1 General Description and Composition

Shingrix drug product (DP) is a lyophilized sub-unit vaccine with a nominal composition of 50 µg/dose of recombinant gE antigen in a monodose vial using a 3-mL glass vial capped with a (b) (4) rubber stopper and (b) (4) cap. Prior to use, Shingrix DP is combined with a 0.5 mL/dose of GSK's adjuvant system AS01B supplied in a separate monodose vial. Nominal composition of one vial of gE FC is shown in Table 9. Nominal composition of one vial of gE FC reconstituted with one vial of AS01B adjuvant is shown in Table 10. The gE antigen is the active ingredient and the rest of the components are inactive ingredients.

Table 9. Nominal Composition of the Lyophilized gE FC

Ingredients	Quantity (per 0.5 mL dose)	Function	Reference
Active Substance			
gE	50 µg	Antigen	In house
Excipients			
Sucrose	20 mg	Stabilizer (b) (4)	(b) (4)
Polysorbate 80 (PS80)	0.08 mg	(b) (4)	(b) (4)
Sodium Dihydrogen phosphate dihydrate ($NaH_2PO_4.2H_20$)	0.160 mg	Buffering agent	(b) (4)
Dipotassium phosphate (K2HPO4)	0.116 mg	Buffering agent	(b) (4)

Table 10. Nominal Composition of gE/AS01B Reconstituted Vaccine (vial)

Ingredients	Quantity (per 0.5 mL/dose)	Function	Reference
Active substance			
gE	50 µg	Antigen	In house
Excipients			
Sucrose	20 mg	Stabilizer ((b) (4))	(b) (4)
Polysorbate 80 (PS80)	0.08 mg	(b) (4)	(b) (4)
3-O-desacyl-4'-monophosphoryl lipid A (MPL)	50 µg	Immuno-enhancer	(b) (4)
Purified Quillaja Saponin (QS-21)	50 µg	Immuno-enhancer	In house
Dioleoyl phosphatidylcholine (DOPC)	1 mg	Liposomes membrane constituent	In house
Cholesterol	0.25 mg	Liposomes membrane constituent (b) (4)	(b) (4)
Sodium chloride (NaCl)	4.385 mg	Tonicity agent	(b) (4)
Sodium Dihydrogen phosphate dihydrate ($NaH_2PO_4.2H_20$)	0.160 mg	Buffering agent	(b) (4)
Dipotassium phosphate (K_2HPO_4)	0.116 mg	Buffering agent	(b) (4)
Disodium phosphate anhydrous (Na_2HPO_4)	0.15 mg	Buffering agent	(b) (4)

4.2 Manufacture Sites and Contract Laboratories

GlaxoSmithKline Biologicals s.a.
(b) (4)
Belgium

(b) (4)

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
1330 Rixensart
Belgium

The gE drug product (DP) is formulated, filled and lyophilized at GSK's commercial facility at (b) (4), Belgium. Labelling, QC testing and packaging operations are conducted at the facilities located at (b) (4), Belgium. QA release is performed at the facilities at (b) (4) Rixensart, Belgium.

4.3 Pharmaceutical Development

Development of a Lyophilized Formulation
The (b) (4) gE FC lot ((b) (4)) was a liquid formulation filled in monodose vials (0.25 mL/dose) supplied with separate AS01B monodose vials. The gE FC lot ((b) (4)) was stored at (b) (4) and the AS01B vials were stored at (b) (4). This (b) (4)(b) (4) formulation gE FC was used in the initial, Phase I/II clinical trial (EXPLO-CRD-004). A lyophilized formulation (0.5 mL/dose prior to lyophilization) was then developed and used for the following clinical trials. Both lyophilized gE FC and AS01B adjuvant vials are stored at (b) (4).

Reviewer's Comment
The (b) (4) formulation of gE antigen was not used in the US clinical trials. The lyophilized formulation of gE likely improves the long-term stability and reduces the reconstitution time.

Dosage Selection
(b) (4) different gE dosages ((b) (4), 50 μg and (b) (4)) were evaluated in a Phase II clinical trial (Zoster-003). These (b) (4) dosages were obtained by reconstituting the gE lyophilised FC with different amounts of AS01B. For example, 1 vial of gE FC (50 μg gE/vial) was mixed with (b) (4) vials of AS01B (0.5 mL/vial) and 0.5 mL of reconstituted vaccine (RV) containing a gE dosage of (b) (4) was used for injection. Similarly, (b) (4) vials of gE FC (50 μg gE/vial) were mixed with (b) (4) vial of AS01B (0.5 mL/vial) and 0.5 mL of RV containing a gE dosage of (b) (4) was used for injection. There was no change to the actual gE dosage during the manufacturing process.

Change of Excipients

Use of sucrose: In the lyophilized formulation, sucrose was included in the formulation as a (b) (4).

Use of polysorbate 80 (PS80): PS80 ((b) (4)) was included in the formulation in (b) (4) to (b) (4). Addition of PS80 significantly (b) (4).

Reviewer's Comment

PS80, the most common polysorbate used in the formulation of protein biopharmaceuticals, is an amphipathic, non-ionic surfactant composed of fatty acid esters of polyoxyethylene sorbitan. The manufacturing change by addition of PS80 was submitted to the FDA for review during the IND phase. An immunobinding study suggested that there is no change for the immunogenicity of gE as evaluated by the potency gE on a mouse assay. In Amendment 15 (dated March 30, 2017), GSK indicated that a (b) (4) *PS80 with* (b) (4) *commercial gE manufacturing.*

Additional excipient changes: Dipotassium phosphate (b) (4) (K_2HPO_4.(b) (4)) was added during formulation of gE (b) (4) batches (b) (4) Starting from batch (b) (4), dipotassium phosphate (b) (4) (K_2HPO_4 (b) (4)) (b) (4) dipotassium phosphate (K_2HPO_4). K_2HPO_4.

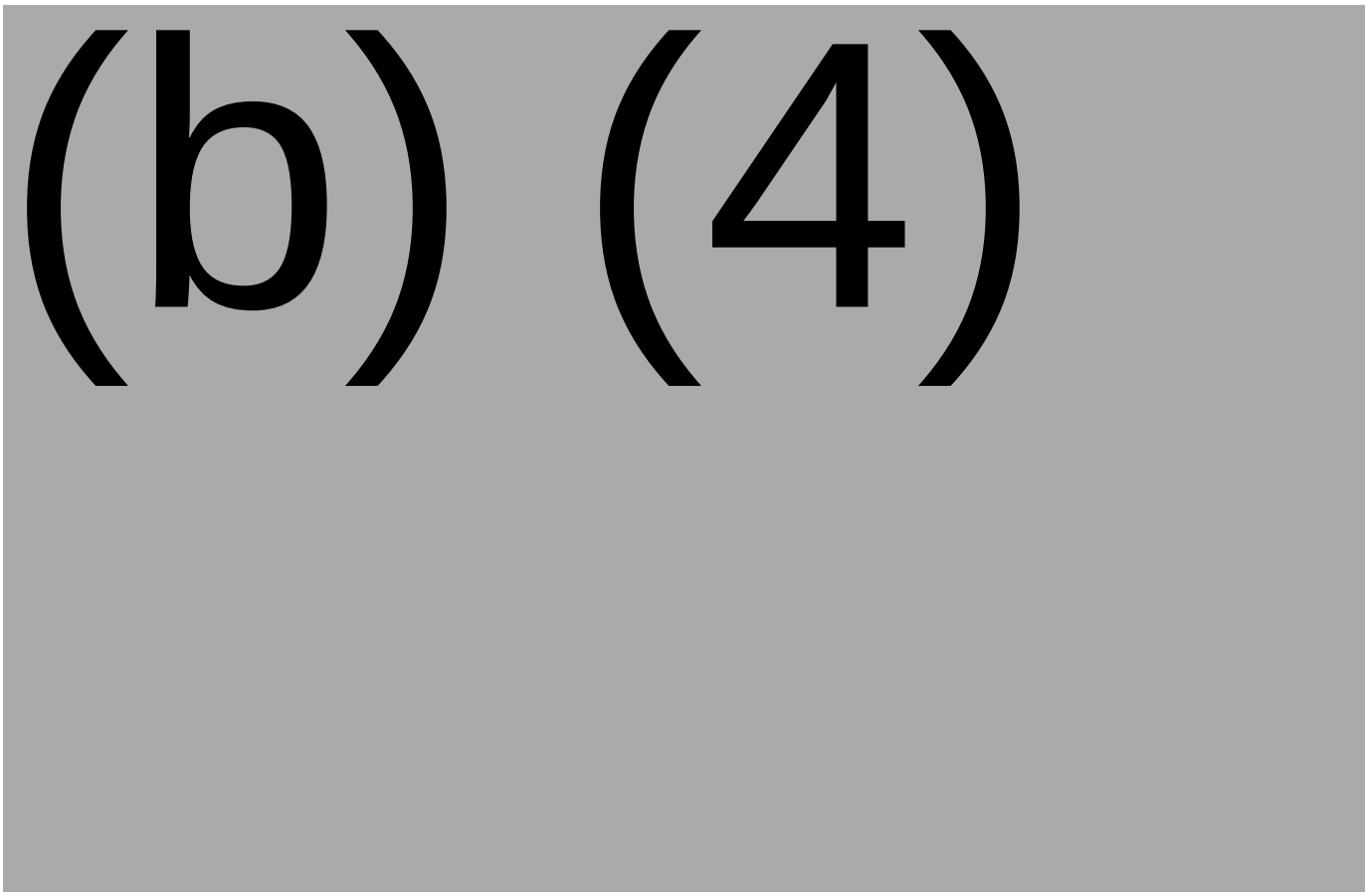
Selection of the AS01B adjuvant: Use of AS01B as adjuvant for gE antigen was supported by non-clinical studies (see Section 5.1) and clinical studies. AS01E containing a half-dose form of AS01B in 0.5 mL was developed and tested in the clinical study, but was not selected for further development.

Dose Overage

A (b) (4) concentration overage (corresponding to a target concentration of (b) (4) µg/dose) is applied during the formulation of gE (b) (4) to compensate for vaccine loss due to reconstitution, withdrawal and injection of the final vaccine. The same overage is applied to other lyophilized vaccines produced by GSK.

Development History of the gE FC

Development of the gE FC was associated with the development history of gE (b) (4), which experienced (b) (4) upgrades (Section 3.6). In addition to the changes of lyophilized formulation in (b) (4) and new excipients including sucrose, PS80 and dipotassium phosphate as discussed above, the major differences between the processes related to the manufacture of gE (b) (4) gE FC are in the (b) (4) for the formulation, filling and lyophilization. Other changes include use of (b) (4) since (b) (4), changes of the (b) (4). The major process changes related to gE (b) (4) gE FC are listed in Table 11.



Key gE FC and gE/AS01B lots used in Clinical Studies
A total of (b) (4) lots gE FC and gE/AS01B RV manufactured using (b) (4) have been used in the clinical studies as shown in **Appendix G**.

Compatibility of gE/AS01B RV
The compatibility between the gE DP and the AS01B adjuvant was assessed to show whether there are interactions between the gE antigen and the AS01B adjuvant and whether different AS01B lots are interchangeable in combination with a gE DP lot.

Lack of interaction between the gE DP and AS01B adjuvant: The gE antigen and AS01B liposomes (b) (4) of reconstituted gE/AS01B RV mixture in a sucrose gradient, suggesting that the gE antigen is less likely to be physically associated or chemically linked to the AS01B adjuvant. In addition, the (b) (4) of gE/AS01 B reconstituted vaccine lots and corresponding AS01B lots are comparable, suggesting that reconstitution of the gE antigen is less likely impacted AS01B quality.

The gE antigen lots and AS01B adjuvant lots are interchangeable: Each of (b) (4) gE FC lots ((b) (4)) were combined with (b) (4) AS01B FC lots ((b) (4)), respectively, generating (b) (4) different

gE/AS01B RV lots. These RV lots were analyzed by a series of tests including potency gE on mice, potency gE by (b) (4) , general safety test on guinea and on mice, (b) (4) and description test. The statistical analysis performed for the quantitative tests showed comparability of the results, demonstrating the interchangeability of AS01B lots being used in the gE/AS01B reconstituted product, which supports QC release testing on the gE and AS01B separate FCs.

Reviewer's Comment
During the IND phase, a specific combination of a gE FC lot of an AS01B lot was released by QC release tests including potency gE on mice. The interchangeability study plan and proposed new QC release strategy on the gE/AS01B RV were previously reviewed and concurred by the FDA in a Type C meeting correspondence dated April 29, 2014. The compatibility study results support the new QC release strategy on the gE/AS01B RV.

4.4 Manufacturing Process and Process Controls

Manufacturing Process
The manufacturing of gE (b) (4) consists of formulation, filling and lyophilization, labelling and packaging as illustrated in Table 12.

(b) (4)

Table 12. Manufacturing Process of gE Drug Product

Process Steps		Descriptions
(b) (4)		
Filling and Lyophilization	Preparation of Vials	(b) (4)
	Preparation of Vial Stoppers	
	Aseptic Filling Operations	
	Lyophilization	
	Capping, inspection and storage	
Labeling and Packaging	Transportation	
	Labelling	Vials are labelled automatically on a labelling machine. Labels are overprinted with lot number and expiry date and then affixed to the vials.
	Packaging	The labelled vials are introduced into a cardboard box and visually inspected and placed in grouping boxes. The packaged gE final product is stored at 2-8°C and remains quarantined prior to QA release.

(b) (4)

(b) (4)

(b) (4)

Batch Formula

The targeted size of commercial lot is approximately (b) (4) vials corresponding to the capacity of each of the (b) (4) . In order to guarantee the appropriate amount of antigen (50 µg of lyophilized gE) in each vaccine dose, a (b) (4) concentration overage (corresponding to a target concentration of (b) (4) µg/dose) is applied during the formulation of gE (b) (4) to compensate for vaccine loss due to reconstitution, withdrawal and injection of the final vaccine. The same overage is applied to other lyophilized vaccines produced by GSK. The batch formulas for representative commercial gE (b) (4) are provided below in Table 14. Note: (b) (4) , targeting the maximal (b) (4) lot size, was manufactured by (b) (4) .

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Similar to the control of (b) (4), in-process quality decision (QD) tests and in-process monitoring (PM) tests were used in the gE DP manufacturing.

QD tests: QD tests have defined acceptance criteria and are used to demonstrate that the process is controlled. Particulate matter by visual inspection test is used as an (b) (4) quality decision (QD) test for the gE FC after capping. The acceptance criterion is free from extraneous visible particulates after reconstitution with water for injection. All the (b) (4) commercial batches met the acceptance criterion for the particulate matter by visual inspection test.

PM tests: PM tests that are used to evaluate process consistency and performance, and also for data collection (to be used in case of investigation). PM tests include a bioburden test and pH test for the gE (b) (4) prior to the (b) (4) and a container closure integrity test (CCIT) for gE FC. Although classified as PM test, the CCIT test does have an acceptance criterion ((b) (4)).

4.5 Process Validation and/or Evaluation

Design of the Process Validation Study
CQAs and CPAs for the manufacturing of the gE FC were identified. CQAs were established based on the potential impact on the purity, contaminants, structure, immunogenicity, safety, and physical description. CPAs were established based on the potential impact on yield. Critical process parameters (CPPs) were also identified through technical risk assessment based on potential impacts on the CQAs and CPA. CPPs for the manufacturing of (b) (4) gE FC are shown in **Appendix J and Appendix K**, respectively. Thus, in addition to tests on the CPAs and CPAs including PD tests, PM tests and release tests, control of CPPs during the manufacturing process ensures the process consistency and quality. Process validation is used to confirm the CPPs, CQAs and CPAs.

(b) (4) commercial PPQ batches ((b) (4)) produced at (b) (4) commercial facility in November 2014 were used to manufacture (b) (4) gE FC lots ((b) (4)). The batch size of Batch (b) (4) is approximately (b) (4) of that of Batches (b) (4)). The history of gE commercial PPQ batches are listed in Table 16.

(b) (4)

The consistency ranges used to assess the consistency among the (b) (4) FC PPQ batches were established using the arithmetic mean of historical values (b) (4) standard deviations (SD). SD

was calculated using data from (b) (4) Phase III clinical efficacy lots and (b) (4) Phase III clinical consistency lots (a total of (b) (4) lots). Similarly, (b) (4) were also calculated. The methodology of establishment of (b) (4) has been introduced in Section 3.5. The PPQ results were evaluated against the comparability and consistency ranges.

Validation Results

Critical process parameters (CPPs) and batch records
All the (b) (4) PPQ batches were performed within the predefined operating ranges. CPPs were maintained within the operating ranges for all PPQ batches. (b) (4) representative executive batch record for gE (b) (4) batch (b) (4) and gE FC Lot (b) (4) (in French) was included in the submission. Step-by-step process parameters including CPP targets and limits were comprised in the record template. Executive data were also included in the records. The executive batch record appears properly signed and QC reviewed.

Process measurements and monitoring tests for the gE (b) (4)
Bioburden of gE (b) (4) is very low for all the (b) (4) batches (less than (b) (4)). The (b) (4) of these (b) (4) batches prior to (b) (4) is consistently at (b) (4). (b) (4) yield (CPA) for all (b) (4) batches is close to (b) (4).

QC release tests for the gE (b) (4)
All the (b) (4) PPQ gE (b) (4) met the QC release specification ((b) (4)).

Process measurements and monitoring tests for the gE FC
Fill volume is consistent within the same lot and between lots based on (b) (4) measurements and no vials were rejected. All the (b) (4) lots passed the visual inspection and container closure integrity test.

QC release tests for the gE FC
All FC PPQ lot results are within the acceptance criteria. In addition, when applicable, results are within the pre-established consistency and comparability ranges (Table 17).

Table 17. QC-release Testing Results of gE FC PPQ Lots

Tests	Acceptance Criteria	Consistency range	Comparability ranges		Results			
		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Description	White cake or powder. Clear to opalescent, colorless liquid after reconstitution with water for injection	(b) (4)						
pH	(b) (4)							
Osmolality	(b) (4)							
Identity gE by (b) (4)	(b) (4)							
Protein content by (b) (4)	(b) (4)							
Endotoxin content by (b) (4)	(b) (4)							
Water content by (b) (4)	(b) (4)							
Polysorbate 80 content by (b) (4)	(b) (4)							
Sucrose content by (b) (4)	(b) (4)							
Potency gE by (b) (4)	(b) (4)							
Sterility test (b) (4)	(b) (4)							
Sterility test (b) (4)	(b) (4)							
General safety - (b) (4)	(b) (4)							
General safety - (b) (4)	(b) (4)							

Characterization Tests

The FC PPQ lots were further characterized using different analytical techniques including (b) (4) The characterization results are provided in Table 18. The testing results for description, (b) (4) PPQ lots are within historical range ((b) (4)) established by (b) (4) clinical batches.

Table 18. Characterization Tests Results of gE FC PPQ Lots

(b) (4)

Exceptions

Two exceptions were identified in the characterization testing results.

(b) (4)

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Corrective and Preventive Action (CAPA)

Following identification of the root cause analysis and impact analysis, GSK has taken a CAPA in order to adequately control the (b) (4) and have added assurance of the product quality. The CAPA measures include the focus on the following three area:

(b) (4)

(b) (4)

(b) (4)

Reviewer's comment

(b) (4)

Additional Validations

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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Table 19. Batch analysis data for gE Final Container Commercial Consistency Lots

Tests/Procedures	Acceptance Criteria	Results
Final Container Lots		(b) (4)
QC Release Tests		
Description	White cake or powder. Clear to opalescent, colorless liquid after reconstitution with water for injection	(b) (4)
pH	(b) (4)	
Osmolality	(b) (4)	
Identity gE by (b) (4)	(b) (4)	
Protein content by (b) (4)	(b) (4)	
Endotoxin content by (b) (4)	(b) (4)	
Water content by (b) (4)	(b) (4)	
Polysorbate 80 content by (b) (4)	(b) (4)	
Sucrose content by (b) (4)	(b) (4)	
Potency gE by (b) (4)	(b) (4)	
Sterility test (b) (4)	(b) (4)	
Sterility test (b) (4)	(b) (4)	
Characterization Test		
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	

There were four environmental (EM) monitoring deviations during the validation period in March 2017. Deviation reports were included in the submission. All the deviations appeared to be related to the training of operators and the action is awareness of operator or staff. The

absence of impact on the product or the (b) (4) aseptic filling operations was concluded for each deviation.

Deviation 200547229: This deviation is related to invalid (b) (4) in class (b) (4) area. The possible root cause is a counting error at final reconciliation, which was reported as conform while there was a missing test.
Deviation 200548159: This deviation is related to (b) (4) out of action limit in class (b) (4) area. The investigation highlighted two possible root causes: contamination from class (b) (4) area with insufficient sanitation of the gloves while passing to class (b) (4) area or contamination in class (b) (4) area following a previous intervention (removal of incorrectly positioned vials).
Deviation 200550885: This deviation is related to (b) (4) invalid (exposure) in (b) (4) area. (b) (4) invalid. The operator closed the (b) (4), which is not in accordance with the procedure in (b) (4) area.
Deviation 200547888: This deviation is related to (b) (4) out of action limit for water for injection sampling point. Two potential root causes are false positive due to presence of (b) (4) residues on the operator's gloves or false positive due to the presence of (b) (4) residues at the outside of the (b) (4) vial.

Reviewer's Comment

- (b) (4) *of the aseptic filling session by using the* (b) (4) *continuous filling operation likely reduces the potential exposure of gE antigen with the* (b) (4) *provided the aseptic filling condition is maintained during the* (b) (4) *period.*
- *Data submitted including aseptic filling qualification in 2005 and requalification in 2016, product-impact study as a result of* (b) (4) *filling time, and manufacture of the 4 commercial gE FC lots using the* (b) (4) *continuous filling operation support the* (b) (4) *of the filling time to up to* (b) (4) *under aseptic condition.*
- *The lot-release data for the* (b) (4) *commercial lots are satisfactory.*
- *The* (b) (4) *levels for* (b) (4) *for the* (b) (4) *commercial lots range from* (b) (4) *at release and* (b) (4) *after storage for* (b) (4). *Although still higher than that for the clinical lots, the* (b) (4) *levels in the* (b) (4) *lots after storage for* (b) (4) *are lower than the 2014 commercial PPQ lots (ranged* (b) (4)*) and the subsequent CAPA lots (ranged* (b) (4)*) as indicated in the Type C meeting held on April 6, 2016, suggesting that the additional CAPA is effective in reducing the* (b) (4). *As discussed above,* (b) (4) *at such a level (*(b) (4) *at the end of shelf life) is not likely to impact negatively the immunogenicity of gE.*
- *Since the commercial PPQ gE FC lots and subsequence CAPA gE FC lots will not be released to the market, the* (b) (4) *commercial lots manufactured under the* (b) (4) *continuous aseptic filling operation will be the* (b) (4) *commercial lots to be released to the market.*

4.6 Control of Excipient

All excipients used to manufacture gE drug product, sucrose, polysorbate 80 (PS80), sodium dihydrogen phosphate dihydrate and dipotassium phosphate (both used for phosphate buffer solution), are widely used excipients, therefore not considered as novel. No excipients of human or animal origin are used in the manufacture of the drug product. Dipotassium phosphate, sodium dihydrogen phosphate dehydrate, and sucrose were all from commercial suppliers. The specification and testing method for the above excipients comply with (b) (4). PS80 ((b) (4)) used in gE drug product for the clinical trials was purchased from commercial suppliers and complies with the current editions of the (b) (4) . A new pharmaceutical grade of PS80, PS80 ((b) (4)), was introduced in 2016. Certificates of analysis of PS80 ((b) (4)) The manufacturing process of PS80 ((b) (4)) included an (b) (4) step and thus is (b) (4) than the PS80 ((b) (4)). The specifications and testing methods for PS80 ((b) (4)) comply with the USP. Both PS80 ((b) (4)) and PS80 ((b) (4)) are stable over a period of 36 months.

AS01B adjuvant: AS01B adjuvant supplied in a separate vial is considered as non-active vaccine component. The manufacturing and control of the AS01B is reviewed by DVP adjuvant reviewer.

4.7 Control of Drug Product

Drug Product Specifications

For routine release of DP lots, quality control (QC) tests are performed at the FC and Final Product levels. Release specification for the gE (b) (4) is sterility by sterility test in (b) (4) as shown in Table 15 (described in Section 4.4). The release specifications for the gE FC and the gE final drug product are listed in Table 20 and Table 21, respectively.

Table 20. gE Final Container Release Specifications

Tests	Acceptance Criteria
Description	White cake or powder. Clear to opalescent, colorless liquid after reconstitution with water for injection
pH	(b) (4)
(b) (4)	(b) (4)
Identity gE by (b) (4)	(b) (4)
Protein content by (b) (4)	(b) (4)
Endotoxin content by (b) (4)	(b) (4)
Water content by (b) (4)	(b) (4)
Polysorbate 80 content by (b) (4)	(b) (4)
Sucrose content by (b) (4)	(b) (4)
Potency gE by (b) (4)	(b) (4)
Sterility test (b) (4)	(b) (4)
Sterility test (b) (4)	(b) (4)

Table 21. gE Final Product Release Specification

Tests	Acceptance criteria
Identity gE by (b) (4)	(b) (4)
Identity Cholesterol by (b) (4)	(b) (4)

Justification of the Specifications:

Description: The visual aspect of the gE FC reconstituted with water for injection is determined by comparing samples to the (b) (4)

(b) (4)

(b) (4)

Protein content by (b) (4): (b) (4)

Endotoxin content by (b) (4) method: (b) (4)

Water Content by (b) (4) : (b) (4)

PS80 content by (b) (4) : (b) (4)

Sucrose content by (b) (4): (b) (4)

Potency gE by (b) (4): (b) (4)

Reviewer's Comment, Information Request and Teleconferences

- *It is not clear which QC release tests are to be conducted at the* (b) (4) *facility and whether the QC release assays are validated in the* (b) (4) *facility. Thus, an Information Request letter was sent on April 6, 2017. In Amendment 17 (dated April 20, 2017), GSK indicated that one release test for the gE final container vaccine (Identity gE by* (b) (4) *) and one release test for the AS01B Adjuvant System (Identity Cholesterol by* (b) (4) *) will be performed at the* (b) (4) *facility.*

Analytical Method Transfer Reports for the technical transfer of these two tests from GSK's (b) (4) site to GSK's (b) (4) site are targeted for completion by the end of April 2017 and will be available for inspection at the (b) (4) site.

- *There are inconsistencies between SOP9000037069 and the descriptions in the justifications regarding to the definition of potency gE by (b) (4). The justification section defines potency gE by (b) (4) in the footnote of a table. Additionally, the justification section explains that the potency specification is aligned with the specification for (b) (4) with a proposed acceptance limit "mean(b) (4)" (i.e., Ratio gE (b) (4)/Protein is between (b) (4)). An Information Request sent to GSK on September 8, 2017. On GSK's draft response dated September 13, 2017, GSK acknowledge the error.*
- *A teleconference request was also included in the same Information Request dated September 8, 2017 sent for discussion on the release specification of potency gE by (b) (4). In preparation for the teleconference, GSK submitted a draft response on September 13, 2017 and informed CBER that GSK proposed different acceptance criteria for the potency gE by (b) (4) specification in different regions in response to requests from different jurisdictions. During the teleconference between CBER and GSK, GSK agreed to tighten the acceptance criteria for the potency gE by (b) (4) from (b) (4) (after reconstitution with (b) (4) buffer) to (b) (4) (after reconstitution with (b) (4) buffer) (b) (4) as a part of global harmonization effort. During the above referenced teleconference, GSK agreed that all Shingrix final container lots released in the US will meet the tightened specification of "(b) (4) after reconstitution with (b) (4) buffer" (b) (4). The summary of the teleconference was also submitted to Amendment 45 (dated September 22, 2017). GSK's response is acceptable.*

The sterility test (b) (4)

Identity gE by (b) (4) and Identity Cholesterol by (b) (4) for the gE/AS01B final product: The gE final product package contains both gE FC and AS01B adjuvant. The gE final product package can be released at both GSK's (b) (4). The release specifications for the final product include the identity gE by (b) (4) test for the gE FC and identity cholesterol by (b) (4) for the AS01B adjuvant vial. The gE final release tests ensure that the final product package contains both gE FC and AS01B FC.

Reviewer's Comment

- *According to the Type C meeting correspondence dated April 29, 2017, CBER concurred with GSK's release strategy on product release of the gE FC, AS01B FC and gE final drug product without tests on the reconstituted vaccines, provided the results of the planned compatibility studies and other characterization studies support independent*

release of the gE FC and the AS01B FC lots. The compatibility study results indeed support the independent release of the gE FC and AS01B FC (Section 4.3). Thus, the gE FC and the AS01B FC lots can be released independently. No tests for lot release will be performed on the reconstituted vaccine.

- *According the Type C meeting correspondence dated April 29, 2017, CBER concurred that the in vivo potency gE on mice may be replaced by an in* (b) (4) *potency assay for the release of commercial material. The in* (b) (4) *potency assay on mice was used as a release test for both gE FC and gE/AS01B RV for all clinical lots. Due to the high intrinsic variation (*(b) (4) *) and the nature of the in* (b) (4) *potency assay in mice, the in* (b) (4) *potency gE by* (b) (4) *appears to be more sensitive to stress conditions. The in* (b) (4) *potency assay will be used as a characterization test for bridging studies when needed.*
- *The potency gE by* (b) (4) *is the ratio of the gE content by* (b) (4) */protein content by* (b) (4)*. A wider release specification of the gE content by* (b) (4) *µg/dose) was used to release the gE FC and gE/AS01B RV used in the clinical studies. In the Type C Pre-BLA CMC meeting held on April 30, 2014, CBER agreed that the in* (b) (4) *potency assay may be replaced by an in* (b) (4) *potency assay for the release of commercial material, and recommended that the release specification for the in* (b) (4) *gE* (b) (4) *potency assay of* (b) (4) *µg/dose be further defined according to accumulated manufacturing and stability data. As systemic control of the product quality, process consistency and stability, GSK's proposal using the mean* (b) (4) *range to calculate the release specification (*(b) (4) *after reconstitution with* (b) (4) *buffer) for potency gE by* (b) (4) *is acceptable.*
- *Although listed as a characterization test,* (b) (4) *test by* (b) (4) *will be measured for the first* (b) (4) *commercial lots. CBER concurred with the GSK proposed acceptance limit for the* (b) (4) *level* (b) (4) *at release or after* (b) (4) *).*

4.8 Validation of Analytic Procedures

Identity of gE by (b) (4) and potency gE by (b) (4) was reviewed in Section 3.11. Analytical assays including protein content by the (b) (4) assay, endotoxin content by (b) (4) method, PS80 content by (b) (4), sucrose content by (b) (4) and sterility tests were reviewed by DBSQC reviewers.

4.9 Reference Standards

There is no international standard available. A gE FC development lot (Lot (b) (4)) is used as reference standard (see Section 3.12 for detail).

4.10 Batch Analysis

Batch analysis data on three gE commercial consistency lots are presented in the BLA and the batch analysis data for all clinical lots were also reviewed during the IND phase. All (b) (4) PPQ batches ((b) (4)) met release specification for sterility. The (b) (4) gE FC lots ((b) (4)) manufactured from the

three (b) (4) batches between Nov 5, 2014 and Dec 5, 2014 at Building (b) (4) and Building (b) (4) met the release specification (Table 22). It should be noted that CBER concurred with GSK's previous request that general safety tests will no longer be included in the release test for the subsequent commercial lots. QC release testing results for additional gE FC lots ((b) (4) manufactured during the same campaign as the PPQ batches using (b) (4) batches ((b) (4)) were also provided as secondary validation. (b) (4) batches ((b) (4)) were used to manufacture both the commercial consistency gE FC lots and secondary validation gE FC lots. gE (b) (4) batch (b) (4) met the specification of sterility. All secondary validation lots also met release specifications for final FCs.

Table 22. Batch Analysis Data for gE FC Commercial Consistency Lots

Tests	Acceptance criteria	Results
Final Container		(b) (4)
Description	White cake or powder. Clear to opalescent, colorless liquid after reconstitution with water for injection	
pH	(b) (4)	
Osmolality	(b) (4)	
Identity gE by (b) (4)	(b) (4)	
Protein content by (b) (4)	(b) (4)	
Endotoxin content by (b) (4)	(b) (4)	
Water content by (b) (4)	(b) (4)	
Polysorbate 80 content by (b) (4)	(b) (4)	
Sucrose content by (b) (4)	(b) (4)	
Potency gE by (b) (4)	(b) (4)	
Sterility test (b) (4)	(b) (4)	
Sterility test (b) (4)	(b) (4)	
General safety - (b) (4)	(b) (4)	
General safety - (b) (4)	(b) (4)	

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

4.12 Container-Closure System

The formulated vaccine is filled and lyophilized in 3 mL vial containers (type (b) (4) uncolored glass, sterilized by (b) (4)), sealed with (b) (4) stoppers ((b) (4) type (b) (4) rubber, sterilized by (b) (4)) and secured with flip-off caps. Both the container and stopper meet (b) (4) requirements. The flip-off caps (Colored (b) (4) top fixed on a (b) (4) varnished cap. The flip-off caps are not in contact with the product and are thus not (b) (4). An extractable study was performed on the (b) (4) rubber stoppers using (b) (4) . This study is not relevant for inert containers such as Type I glass vials due to their (b) (4) studies. Extractable compounds using the (b) (4) method include (b) (4) . The calculated worst-case level of each extractable compound per dose using (b) (4) method is below the threshold of toxicological concern (TTC) TTC ((b) (4)) intake specified in the (b) (4) guideline. The (b) (4) method is considered an extreme extraction condition. The calculated worst-case level of extractable per dose for more than half of the extractable compounds extracted by (b) (4) was below the TTC of (b) (4). For extractable compounds with amount above the TTC of (b) (4), further toxicological assessment was performed based on the available literature data for compounds with CAS registry numbers, and the toxicological assessment concludes that these compounds are below established permissible daily exposure (PDE). Leachable studies are performed over a (b) (4) period on gE FC lot (b) (4) filled in Type (b) (4) glass vials closed by (b) (4) rubber stopper and (b) (4). Available leachable testing results for gE FC samples after storage at (b) (4) and for (b) (4) months indicated that all extractable compounds are very low ((b) (4)) and thus are below the TTC of (b) (4).

Reviewer's Comment and Information Request

The information related to the glass vial and (b) (4) *rubber stopper used in the gE DP was not described in detail in the submission. Thus, an Information Request was sent to GSK on June 27, 2017. In Amendment 30 (dated July 12, 3027), GSK indicated that the 3 mL Type* (b) (4) *glass vial containers are supplied from* (b) (4) *Glass. The different suppliers of glass vials may be used interchangeably; however, the glass vials are tested according to the same in-house quality control procedure. These 3 mL glass vial containers have been used in* (b) (4) *different GSK US-licensed vaccines. The same* (b) (4) *rubber stopper is currently used in three GSK US-licensed vaccines. The GSK's response is acceptable. In the Information Request of June 27, 2017, CBER also inquired whether the leachable study was performed on the gE FC development lots and whether there are updates for the ongoing leachable study. GSK indicated that leachable study was not performed on the gE FC development lots and the next time point for the ongoing study are expected for end 2018 and end 2020, respectively. GSK's response is acceptable.*

4.13 Stability of Drug Product

A shelf-life of 36 months at 2-8°C is claimed for both gE FC and AS01B FC. The shelf-life is calculated as from the manufacturing date (i.e., filling date). The storage conditions are the following: “Store in a refrigerator (2-8°C); Do not freeze; Store in the original package in order to protect from light.” Since the gE/AS01B vaccine is presented as two independent vials of gE FC and AS01B FC, the expiry date of the dual presentation will be determined by whichever component expires earlier. In Amendment 28 (dated July 6, 2017), the long-term stability for these Phase III consistency lots were updated with data for up to the (b) (4) tested.

4.13.1 Accelerated Stability Study of gE FC

Accelerated stability studies (for up to (b) (4) days at (b) (4) and for up to (b) (4) months at (b) (4)) were performed to further define the gE FC stability profile. The accelerated stability studies ((b) (4)) for all stability lots are complete and the testing results are satisfactory (Table 23).

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

4.13.2 Long-term Stability Study of gE FC

To support the proposed shell life of the gE FC, long-term stability studies (storage for up to [redacted]) were performed on the gE FC lots, the AS01B FC lots, and the gE/AS01B RV. Cumulative stability studies were designed to support the shelf-life of FC lots produced with [redacted] stored at [redacted] months. [redacted] studies were performed to further define the gE FC stability profile and provide data that may be supportive of a [redacted] excursion. The long-term stability tests include [redacted]

All stability studies including long-term stability study for storage at [redacted] months, [redacted] (supportive of a [redacted] excursion at [redacted]) for all [redacted] efficacy lots ([redacted]) manufactured using [redacted] are complete, and all testing results met pre-specified specifications. The long-term stability study and [redacted] study for Phase III consistency lots ([redacted]) manufactured using [redacted] are still ongoing. The stability testing results up to [redacted] for the above two stability studies are satisfactory.

[redacted] phase III consistency gE FC lot ([redacted]) manufactured using [redacted] was followed in the long-term stability study and is used to support the maximal holding time of gE [redacted] before filling activities). The study is still ongoing and the testing results through [redacted] met pre-specified specifications.

[redacted] Phase III consistency gE FC lots ([redacted]) manufactured using [redacted] were followed in a long-term stability study to support the long-term storage of gE FC lots formulated with gE [redacted] stored at [redacted]. The study is ongoing, and the data through [redacted] are available and meet pre-specified specifications.

[redacted] Phase III consistency gE FC lots ([redacted]) manufactured using [redacted] were followed in the long-term stability study and are used to support the long-term storage of gE FC lots formulated with gE [redacted] stored at [redacted] months. The study is still ongoing and the data through [redacted] are available and met pre-specified specifications.

[redacted] PPQ lots ([redacted]) manufactured using [redacted] were followed on a long-term stability study and [redacted] study. The studies are ongoing, and the data through [redacted] are satisfactory. Two PPQ lots ([redacted]) manufactured using [redacted] were followed on the ongoing long-term stability study and are used to support the maximal gE [redacted]. The stability-testing results through [redacted] are satisfactory.

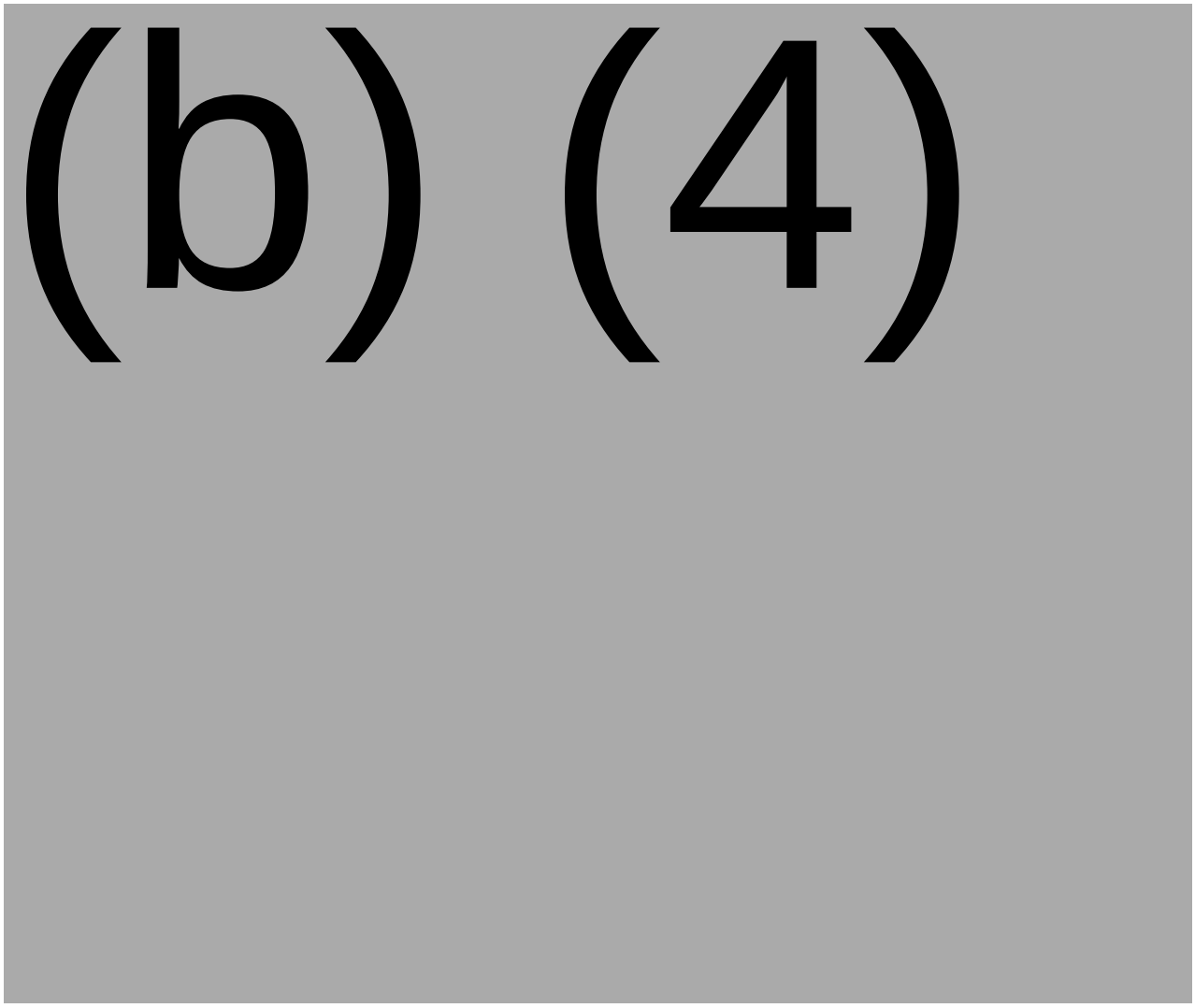
There were two out-of-trend exceptions found during the stability studies. The first one is that increased values of [redacted] in the gE FC vials were found in both long-term stability

testing and in accelerated testing (e.g., Phase III efficacy lots). The (b) (4) values are likely due to the progressive release of (b) (4) from the vial stopper. The trend is, however, considered acceptable, as all results ((b) (4)) remained well below the upper specification limit ((b) (4)). The second out-of-trend exception is that a statistically significant (b) (4) for decrease was also observed for the test "(b) (4) " in the Phase III Efficacy lot (b) (4) followed in a long-term stability study. This is likely due to the inherent variability of the immunological response of (b) (4). The trend is considered acceptable as (i) all values remained within the acceptance limits over time, and (ii) no significant trend was observed for the other gE FC lots followed in stability studies.

Reviewer's Comment
The increased (b) (4) values were demonstrated in both long-term stability testing and in accelerated testing in different lots. The (b) (4) values reached a plateau quickly after storage and did not increase further in either condition, suggesting this phenomenon is less likely due to leaking of the container and closure system, but is rather due to releasing of (b) (4) from components inside the FC (e.g., stopper).

4.13.4 Long-term Stability Study of gE/AS01B RV

(b) (4) Phase III efficacy lots ((b) (4)), (b) (4) Phase III consistency lots ((b) (4)) and (b) (4) commercial consistency lots ((b) (4)) were matched with the dedicated AS01B FC lot and followed by long-term stability study ((b) (4)), and in-use stability ((b) (4) for the reconstituted vaccine after long-term storage). A (b) (4) was also performed on the six Phase III lots. The key long-term stability tests performed on the gE/AS01B reconstituted vaccines include (b) (4) . The progress of all these stability lots is indicated in Table 24. All stability results for the stability studies of gE/AS01B RV met pre-specified specifications, except for the description test carried out on (b) (4) (in long-term conditions) and (b) (4) (in the (b) (4) study) at the (b) (4) time point. Investigations confirmed that the presence of trace amounts of (b) (4) (identified as the root cause for the observed (b) (4)), has no impact on the stability of the product or safety concern.



4.13.5 In-use Stability Study of gE/AS01B RV

In-use stability studies ((b) (4) storage at (b) (4) post-reconstitution with AS01B adjuvant) were performed on the stability lots after long-term storage at (b) (4), 36 months, (b) (4) to support the temporary storage of gE/AS01B after reconstitution prior to injection in the clinic. The key analytical procedures used in the in-use stability studies include (b) (4) . The in-use stability studies for the (b) (4) Phase III efficacy lots are completed, and all the tested parameters met the acceptance criteria, except for the (b) (4) test carried out on lot (b) (4) . The out-of-specification result was linked to the presence of a (b) (4) within the reconstituted vaccine. Corrective actions were also undertaken during (b) (4) reduce the potential occurrence of (b) (4) within the vaccine. There was no stability impact. Thus, the testing results support the in-use stability ((b) (4) after reconstitution with the AS01B of the Phase III efficacy gE FC lots after long-term storage at (b) (4) . The in-use stability studies for the (b) (4) Phase III

consistency lots are ongoing and the available testing results met pre-specified specifications throughout a storage period of (b) (4). The in-use stability studies for the (b) (4) commercial-consistency lots are ongoing and currently only the testing results on Time (b) (4) is available. In conclusion, the in-use stability studies appear to support the use of reconstituted vaccine after (b) (4) throughout the proposed 36-month shelf life of the gE FC at the long-term storage condition.

Reviewer's Comment

- *A shelf life of 36 months for the gE FC and AS01B FC at the 2-8°C is claimed in the BLA, while the long-term stability studies were designed to support a storage of gE FC, AS01B and gE/AS01B at (b) (4). Indeed, the testing results from the long-term stability study results for the Phase III efficacy gE FC lots and gE FC/AS01B FC lots were satisfactory through (b) (4). The testing results from the long-term stability study results for the Phase III consistency gE FC lots and gE/AS01B lots are satisfactory through (b) (4). Cumulative stability studies used to demonstrate that the shelf life of gE (b) (4) does not negatively impact the shelf life of the gE FC are still ongoing. The ongoing long-term stability results on Phase III consistency gE FC lots formulated with gE (b) (4) are satisfactory through the 36-month interval at 2-8°C. In addition, the ongoing long-term stability results on Phase III consistency gE FC lots formulated with gE (b) (4) stored at (b) (4) are satisfactory through the (b) (4) interval.*
- (b) (4) *studies demonstrated the gE FC or gE FC/AS01B FC lots are stable in a (b) (4) such as at (b) (4) for a short period of time. The in-use stability studies support the use of reconstituted vaccine after (b) (4) throughout the proposed 36 months shelf life of the gE FC at the long-term storage condition. The long-term stability study for the commercial consistency (PPQ) gE FC lots is still ongoing and the data through a (b) (4) interval are acceptable.*
- *It should be noted that increased levels of (b) (4) in the PPQ gE FC lots were revealed; however, extensive in vitro as well as in vivo studies indicated that increased level of (b) (4) does not likely negative impact the product quality. Furthermore, CAPA including use of lowered (b) (4) prior to filling, use of the acceptance criteria established for the level of gE (b) (4) indeed provide additional assurance to the product quality of the further commercial lots. Thus, I agree that the stability study data provided support a shelf-life of 36 months for the gE FC and AS01B FC at the 2-8°C.*

4.14 Comparability Protocols

To support future manufacturing changes for gE (b) (4) DP, GSK submitted three comparability protocols including (b) (4) is reviewed in Section 3.5.3 and 3.9. Comparability protocol for (b) (4) gE FC is reviewed in Section 3.12. Comparability protocol for (b) (4)

(b) (4)

Reviewer's Comment:
The three comparability protocols are acceptable.

5 CMC-Related Non-Clinical Studies

The nonclinical studies included pharmacology, pharmacokinetics, and toxicology studies on gE/AS01B and key components including AS01, QS-21 and MPL. This memo covers nonclinical studies related to adjuvant justification and selection, comparison of routes of administration, support to manufacturing development.

(b) (4)

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

(b) (4)

6 Clinical Assays

Clinical assays including PCR VZV and PCR beta actin used to confirm zoster cases in clinical samples, anti-gE ELISA used to measure the humoral immune responses, gE CMI used to measure the cell mediated immune response, (b) (4) , and (b) (4) assay were used in different phases of the clinical studies. All the assays used in the Phase III studies were validated and the full validation reports and standard operating procedures (SOPs) for these assays are provided. The validation reports and SOPs of key assays used in the Phase III trials including PCR VZV, PCR beta actin, anti-gE ELISA and gE specific intra-cellular cytokine staining (ICS) assay are covered by this review. The (b) (4) used in the Phase II trial is also covered in this review. The validation of the (b) (4) assay was reviewed by other DVP reviewers.

Reviewer's Comment
To clarify usage of the clinical assays in the clinical study, an Information Request was sent on February 21, 2017. In the Information Request, CBER requested GSK to provide a table that correlates the clinical assays included in this section with the corresponding clinical study. CBER also requested GSK to provide the phase of the study, the endpoint measured (primary, secondary, and exploratory), the time period when the clinical samples were tested and which version of each assay was used, and whether testing results from the clinical assays were reported to CBER in a previous IND submission or in the BLA submission. In Amendment 11 (dated March 2, 2017), GSK provided related information. In Amendment 12 (dated March 8, 2017), GSK provided cross-reference for the (b) (4) *assay. GSK's response is adequate. I found that the clinical assays under this review, including PCR VZV, PCR beta actin, anti-gE ELISA, gE specific intra-cellular cytokine staining (ICS) assay and* (b) (4) *, are suitable for their intended use in testing clinical samples in the supportive clinical studies.*

6.1 GSK Anti-gE ELISA

The GSK anti-gE ELISA is used to quantitatively determine antibodies to gE VZV glycoprotein in human serum samples obtained from gE/AS01B clinical trials (Phase I/II, and Phase III). Briefly, gE is (b) (4)

(b) (4)

Assay Validity Criteria

Results from a plate or positive control are not valid unless the assay validity criteria are met. The assay validity criteria are listed in Table 25. The assay validity criteria in the updated validation report remain the same as those in the original reports, except that the CV on the (b) (4) of the GSK (b) (4)

(b) (4)

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

(b) (4)

(b) (4)

Reviewer's Comment

The immunogenicity studies of pivotal trials suggest that more than (b) (4) *of subjects of the trials are already* (b) (4) *with a* (b) (4) *confidence interval of* (b) (4) *for the placebo control group in study Zoster-006 and* (b) (4) *with a* (b) (4) *confidence interval of* (b) (4) *for the placebo control group in study Zoster-022. The gE specific antibody response is used as exploratory endpoint in the pivotal trials and a primary endpoint for lot consistency studies. The anti-gE ELISA was adequately validated, and I recommend use of the anti-gE* (b) (4) *in measuring the gE specific antibody response in clinical samples.*

6.2 GSK gE specific Intra-cellular Cytokine Staining (ICS) Assay

The VZV gE specific ICS assay is intended for use in Phase III studies to measure the cell-mediated immune (CMI) response induced by gE/AS01B. This assay provides information on the frequency of CD4+ T cells responding to the gE antigen that produce molecules involved in immunity: such as interferon-γ (IFN- γ), interleukin-2 (IL-2), tumor necrosis factor-α (TNF-α) and the costimulatory molecule CD40L. The current standard procedure is described in the SOP 9000005533. (b) (4)

Dose Range

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

(b) (4)

(b) (4)

(b) (4)

7 Pre-Approval Inspection

No pre-approval inspection is planned for this BLA.

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